Australian Government

Department of Health and Ageing

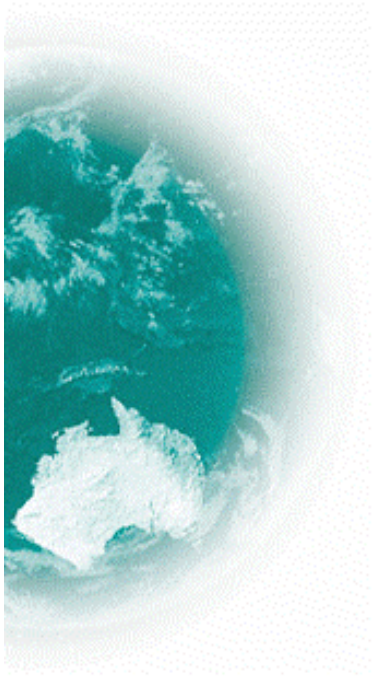
Therapeutic Goods Administration

Australian Public Assessment Report for Indacaterol

Proprietary Product Name: Onbrez Breezhaler/Arbeela Breezhaler

Submission No: PM-2009-00350-3-5

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd



October 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	2 July 2010
Active ingredient(s):	Indacaterol (maleate)
Product Name(s):	Onbrez Breezhaler, Arbeela Breezhaler
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Limited 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Inhalation powder, hard capsule
Strength(s):	150 and 300 µg
Container(s):	Blister packs
Pack size(s):	Pack of 10 capsules and a Breezhaler device Pack of 30 capsules and a Breezhaler device Pack of 60 capsules and two Breezhaler devices 2 x (30 capsules and a Breezhaler device). Not all pack sizes may be marketed.
Approved Therapeutic use:	Onbrez Breezhaler/Arbeela Breezhaler is a long-acting β_2-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease. (See "Clinical Trials").
Route(s) of administration:	Oral inhalation route only using the Breezhaler inhaler
Dosage:	The recommended dosage is the once-daily inhalation of the content of one 150 µg capsule using the Breezhaler inhaler. The maximum dose is 300 µg once-daily.
ARTG Number (s)	160172, 160176, 160177 & 160178

Product Background

Chronic obstructive pulmonary disease (COPD) is considered a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual subjects. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

The pathophysiology of COPD involves both inflammatory and bronchoconstrictive components and so it is expected that glucocorticosteroids (GCS) and bronchodilator therapy would be beneficial. The spirometric classification of COPD severity includes four stages: Stage I mild, Stage II moderate, Stage III severe and Stage IV very severe (Table 1).

Table 1: Spirometric severity of chronic obstructive pulmonary disease based on postbronchodilator FEV_1

Stage I	Mild	FEV_1/FVC <0.70 FEV_1 ≥80% predicted
Stage II	Moderate	FEV_1/FVC <0.70 50% ≤ FEV_1 <80% predicted
Stage III	Severe	FEV_1/FVC <0.70 30%≤ FEV_1<50% predicted
Stage IV	Very Severe	FEV_1/FVC <0.70 FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO2) <8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) >6.7 kPa (50 mm Hg) while breathing air at sea level.

Indacaterol is a new chemical entity which is a long acting beta-adrenergic agonist (LABA) which can only be used as monocomponent therapy in chronic obstructive pulmonary disease. This submission concerns two trade names for indacaterol - Onbrez Breezhaler and Arbeela Breezhaler. It will be designated as Onbrez in this AusPAR

The proposed indication for indacaterol is:-

Onbrez Breezhaler is a long-acting beta2-agonist indicated for long-term, once daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease (COPD)

The recommended dosage of Onbrez Breezhaler is the once-daily inhalation of the content of one 150 µg Onbrez capsule using the Breezhaler inhaler. The dosage should only be increased on medical advice. Once-daily inhalation of the content of one 300 µg Onbrez capsule, using the Breezhaler inhaler, has been shown to provide additional clinical benefit to some patients. The maximum dose is 300 µg once-daily.

Regulatory Status

Similar applications to the current Australian submission have been made in Canada, Switzerland and the European Union (EU) (as Onbrez Breezhaler) and USA (as ArcaptaNeohaler). Onbrez Breezhaler was approved in the EU on 30 November 2009 and in Switzerland on 21 May 2010 with the indication:

Maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD)

The main difference from the current submission is that in the proposed Australian product information “airflow obstruction” is replaced with “airflow limitation”.

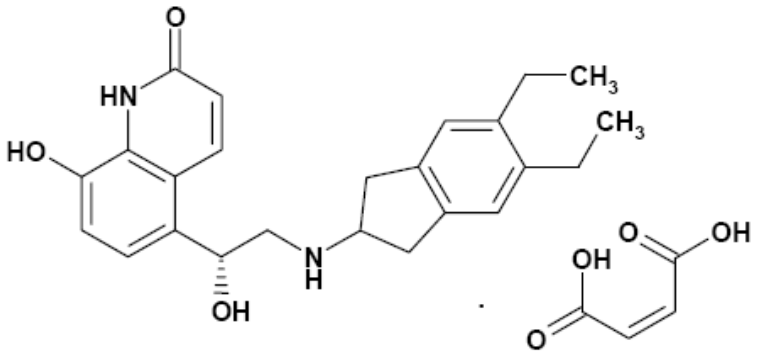
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Indacaterol is a long acting beta-2 agonist (LABA). Indacaterol has one chiral centre and the pure *R* enantiomer is used. It shares limited structural similarity with 2-amino-1-hydroxy-1-phenylethyl amines such as salbutamol and salmeterol:

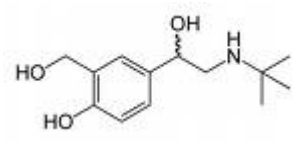


indacaterol maleate

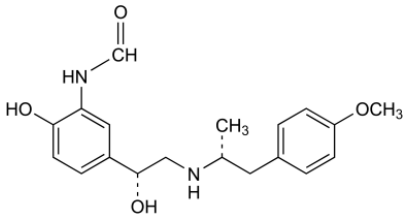
(R)-5-[2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate

Company Code QAB149

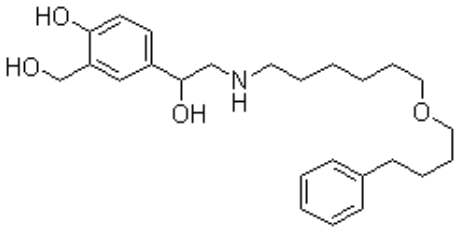
Maleate salt: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$ MW 508.56 (free base: 392.49)



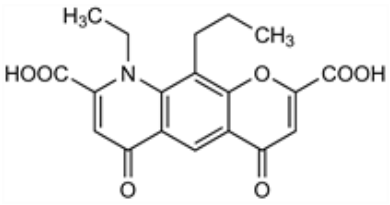
salbutamol



eformoterol



salmeterol



nedocromil

Indacaterol maleate is synthetic. Impurity levels in recent batches have been fairly low. Drug substance aspects are acceptable.

Drug Product

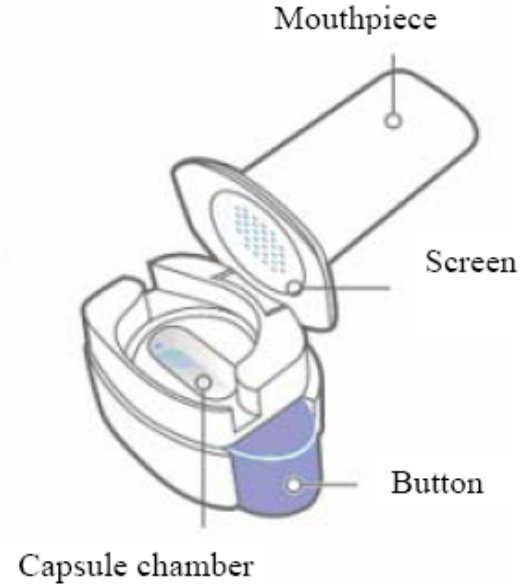
Inhalation powder, hard capsules

The Onbrez inhalation powder consists of a simple mixture of lactose and indacaterol maleate presented in clear, hard, gelatin capsules. Capsules are presented in blisters, packed in a carton together with an inhalation device. Packs of 10 (sample), 30 and 60 capsules, are proposed; the 60 pack is presented as a multipack of 2 x (30 capsules and one device).

The 150 µg and 300 µg capsules contain the drug and 24.8 mg and 24.6 mg lactose monohydrate respectively with either 0.78% w/w drug or 1.56% w/w drug on the lactose 'carrier'. Indacaterol is weakly bonded to the lactose as agglomerates. This bonding has to be strong enough to withstand processing, storage and transport, yet weak enough to allow mechanical disaggregation and dispersion during inhalation via the device. The lactose particles are relatively large: it is intended that the lactose is largely deposited in the mouth and throat, not delivered to the lungs.

The capsules contain 194 µg or 389 µg of indacaterol maleate which corresponds to 150 µg or 300 µg of indacaterol base. Doses are labelled in terms of the indacaterol free base content in the capsules (not delivered dose), in keeping with current Australian labelling rules. When used with the inhalation device provided, under controlled *in vitro* conditions the capsules allow delivery to the mouth of 120 µg or 240 µg indacaterol base (that is, 80%). The dose then delivered to the lung as an aerosol powder is estimated in product testing as the 'fine particle dose' showing slight non-linearity *in vitro*. The 'lung dose' *in vivo* is affected by inspiratory flow.

Breezhaler Device



The inhaler uses two manually pushed needles to puncture the capsule when it is inside the device. The capsule fits only loosely into the chamber, and it moves around during inhalation.

The 'specific resistance' of a dry powder inhaler device determines the flow rate at which the patient can inhale through it. The *Breezhaler* device has a low specific resistance (similar to *Rotahaler* or *Spinhaler;* compared with a high resistance device, for example *Turbuhaler*).

The *Breezhaler* device was developed from the *Novartis Aeroliser* (used with eformoterol capsules). One model was used in phase II studies. Another model was used throughout Phase III studies, including pivotal clinical studies and the dose finding part of the study B2335S. The two models are very similar and have equivalent operating parts (for example, piercing the capsule, and dimensions of device parts which are relevant for dose delivery).

The design of the device allows for some adventitious inhalation of gelatin fragments. This has not been quantified; Novartis claims that the absence of related adverse event reports, including for placebo inhalers, indicates that there is not a problem clinically.

An equilibration of the filled capsules is achieved after storage for a specified time and temperature/humidity. Batch release testing is performed after equilibration.

On prolonged storage, a temperature dependent change in the aerosol is observed. The capsules are somewhat sensitive to high humidity, but protected by aluminium-aluminium blister packaging.

The TGA considered that the submitted data justified a 12 month capsule shelf life.

Bioavailability

Bioavailability data are generally not useful for assessing formulation performance of locally acting products because they confound oral and pulmonary drug delivery. Study CQAB149B2103 did include data allowing an estimation of the absolute bioavailability of 300 µg of inhaled indacaterol (about 43% n=4).

Quality Summary and Conclusions

Registration was recommended with respect to chemistry and biopharmaceutic aspects, but with a 12 month shelf life.

III. Nonclinical Findings

Introduction

The nonclinical data submitted in support of the registration of indacaterol maleate as a new clinical entity were comprehensive and generally well presented, including the sponsor's written and tabulated summaries. Pivotal pharmacokinetic and toxicological studies were quality-assured and performed to contemporary standards and in compliance with Good Laboratory Practice (GLP).

Pharmacology

Primary pharmacology

Indacaterol was shown to be a potent agonist of the recombinant human β_2-adrenoceptor with high intrinsic activity. Its binding affinity for the β_2-receptor was intermediate between that of eformoterol and salbutamol. *In vitro*, the drug was shown to inhibit electrically-stimulated contraction in the isolated guinea-pig trachea and human bronchi, and carbachol-contracted human small airways. Its potency in these systems was similar to that of salbutamol and salmeterol, and it had a relatively fast onset of activity (comparable to the other agents) together with a prolonged duration of action (about 6–12 hours; comparable to salmeterol).

Indacaterol was efficacious against 5-HT-induced bronchoconstriction in guinea pigs *in vivo*. The 80% effective dose (ED_{80}) dose (intratracheal [IT] administration) was similar to eformoterol and 15–80 times less than that for salmeterol or salbutamol, associated with an 18-hour duration of action (compared with 12 hours for salmeterol and 4 hours for eformoterol and salbutamol). After five successive days of IT treatment, indacaterol inhibited bronchoconstriction by about 60% at doses of 0.006–0.06 µg/kg/day, compared with similar efficacy at 0.06–0.6 and 0.0006 µg/kg/day for salmeterol and eformoterol, respectively. In rhesus monkeys, a single 12.5 µg/kg inhalational dose of indacaterol inhibited methacholine-induced bronchoconstriction by about 80, 70 and 25% at 15, 165 and 285 min post-administration.

Secondary pharmacodynamics

Indacaterol was screened for activity against a panel of 82 receptors in radioligand binding assays. Its most potent secondary targets were the α_{1A}- (rat) and α_{1D}- (human) adrenoceptors, with K_i values (≥0.20 µM) almost 38- and 17-times higher than at the human β_2-adrenoceptor. Its β-adrenoceptor subtype selectivity was comparable to that of eformoterol. Based on the modest activity and low systemic exposure achieved after inhalational administration these secondary actions are not considered to be of clinical relevance.

In other experiments, indacaterol showed weak excitatory activity at the Transient Receptor Potential A1 (TRPA1) non-selective cation channel (recombinant human; expressed in CHO cells), as did salmeterol, salbutamol and eformoterol. TRPA1 is expressed by vagal neurons innervating the lung, and it has been suggested that activation of TRPA1 may mediate the respiratory response to environmental irritants. Activation of guinea-pig lung vagal C-fibres (which can induce cough) was observed with the maleate salt of indacaterol at 100 µM, but not 10 µM. The estimated local concentration of indacaterol in patients receiving a 400 µg dose (higher than the maximum proposed dose of 300 µg) was ≤6.0 µM. Thus, considering the drug's potency to produce these effects, they are considered unlikely to be of clinical relevance.

In conscious guinea pigs, indacaterol elicited a weak but statistically significant cough response and about a 50% increase in airway resistance when administered via the inhalational route as a nebulised 2.0 mg/mL solution in 100% ethanol, but not at 1.0 mg/mL in the same vehicle, 1% N-

methylpyrrolidone or 1% cyclodextrin. Eformoterol caused similar cough and airway responses at 0.20 mg/mL in 100% ethanol. The relevance of the findings is uncertain given that therapeutic use will entail inhalation of indacaterol as a dry powder in lactose rather than as a nebulised aerosol in liquid vehicle.

Safety pharmacology

Specialised safety pharmacology studies were conducted to assess effects on the nervous, respiratory and cardiovascular systems. All studies were GLP compliant apart from an *in vivo* cardiovascular/ respiratory safety study in monkeys. In central nervous system (CNS) safety studies, indacaterol did not cause any apparent acute pharmacological or neurobehavioural effects in mice at 2000 mg/kg orally (PO) at an estimated relative exposure based on C_{max} >100 or rats at 0.5 mg/kg by inhalation at an estimated exposure ratio of about 30. However, signs consistent with acute neurotoxicity (decreased locomotor activity, impaired righting reflex, hypothermia, ataxia, muscle tremors and salivation) were observed in single-dose toxicity studies in rats at 50–200 mg/kg subcutaneously (SC) and/or dogs at 100 mg/kg PO. Exposure ratios are not calculable but peak blood drug levels would have greatly exceeded the clinical C_{max}. Excessive salivation occurred during inhalational dosing in some repeat-dose dog studies, but there were no other related signs of neurotoxicity, and the finding is consistent with a response to administration of powder. There were no significant effects on respiratory system parameters in rats at 2000 mg/kg PO or in rhesus monkeys treated by inhalation at 12.5 µg/kg.

Indacaterol produced concentration-dependent inhibition of the hERG K^+ channel in transfected HEK293 cells. The IC_{50} was 3.1 µM , ~1400-times the clinical C_{max} at the maximum recommended human dose. In dogs, a single 0.35 mg/kg dose of indacaterol by inhalation caused long-lasting tachycardia and decreased P width and PR and QTc intervals; blood pressure was unchanged. Serum drug concentrations were not measured, but a C_{max} of about 4.5 ng/mL (5-fold higher than the clinical value) is expected to have been attained based on data from Study 0220065. In rhesus monkeys, a 12.5 µg/kg dose of indacaterol by inhalation caused a 13% increase in heart rate, declining to a 5% increase within 100 minutes; there was no accompanying effect on blood pressure. Serum indacaterol levels were not measured in the study and exposure can not be estimated. The increase in heart rate was about half and two-thirds of that elicited by 1.2 µg/kg eformoterol and 5.5 µg/kg salmeterol by inhalation; salmeterol also produced 7–8% decreases in systolic and diastolic blood pressure.

Pharmacokinetics

The methods of analysis of indacaterol and its metabolites in biological matrices were well documented, and the design, conduct and reporting of most pharmaco- and toxicokinetic studies were adequate. However, in the toxicokinetic component of several repeat-dose toxicity studies, indacaterol was detected above the lowest level of quantification (LLoQ) (0.10 ng/mL in rat and dog serum, and 0.20 ng/mL in 50 µL of mouse serum) in samples from control animals. The sponsor noted that toxicokinetic blood samples obtained during pre-clinical studies via the inhalational route are highly prone to *ex vivo* contamination by the test drug because it is difficult to restrict environmental exposure of the animals and equipment in the laboratory area during or after the dosing procedure. The case supporting *ex vivo* contamination of control serum during analysis is considered to be plausible and consistent with the raw data presented in the respective studies.

Indacaterol was rapidly absorbed in laboratory animal species and humans following inhalational administration, with the time to maximal plasma concentration (T_{max}) values typically 0.25–1 hour. Absorption following intratracheal, PO and SC administration was also rapid (T_{max}, 0.5–3 hours). Absorption and bioavailability were high (80–90%) in rats following bolus intratracheal administration, but systemic exposure via nasal inhalation dosing (the method used in pivotal repeat-dose toxicity and carcinogenicity studies) was only about 10–15% as extensive per unit dose. Oral absorption of indacaterol was rapid and moderately extensive (20–70%) in laboratory species,

but due to an extensive first-pass effect, PO bioavailability of the parent drug was negligible in rodents (0–1%) and moderate in dogs (33%). By contrast, SC absorption was essentially complete in rats and high (>70%) in rabbits, and bioavailability was 67–100% and 51% in the respective species. In humans, the absolute bioavailability by the inhalational route was 43%; the bioavailability of an oral dose was 46% relative to an inhalational dose.

Systemic exposure in animals was generally dose-proportional. Less than dose-proportional exposure was evident in mice following inhalation at doses ≥5 mg/kg and following PO administration, and to a modest degree in rats following inhalational and SC dosing. C_{max} and the area under the plasma concentration time curve (AUC) following inhalational administration in humans were highly dose-proportional over the range studied (150–600 µg/day). A sex difference in exposure to indacaterol was observed for mice, with exposure tending to be higher in females treated via the inhalational and PO routes, although the margin between the sexes was not constant. Serum half-lives for indacaterol were not given for laboratory animal species following inhalational administration. Following intravenous (IV) administration, circulating levels of the parent drug declined biphasically, with terminal half-lives of about 6, 8, 11 and 20 hours in the mouse, rat, rabbit and dog, respectively. The plasma drug half-life in healthy human subjects after inhalational administration was about 75 hours.

Protein binding by indacaterol was high in rat, dog and human plasma (91, 93 and 96% in the respective species). Volume of distribution was also high in mice, rats, rabbits, dogs and humans. Accordingly, widespread tissue distribution of radioactivity was observed after administration of ^{3}H-indacaterol to rats (intratracheal, PO and IV routes) and dogs (IV). Distribution was rapid. The trachea, lung and renal cortex had the highest levels of radioactivity after intratracheal administration. Radioactivity declined to low or background levels in most tissues by 24 hours post-dose. Entry to the CNS and distribution to the testis was very limited. Indacaterol was shown to be a substrate for P-glycoprotein in experiments with Caco-2 cell monolayers.

Metabolism of indacaterol was found to primarily involve:

- Monohydroxylation of the benzylic carbons to produce two diastereomers (P26.9 and P30.3). This pathway was catalysed *in vitro* by human cytochrome P450 (CYP)s 1A1, 2D6 and 3A4; mouse, rat and human liver microsomes; human hepatocytes and rat and dog liver slices. The pathway was active *in vivo* in rats, rabbits, dogs and humans.
- Glucuronidation of the phenolic oxygen (generating the metabolite P37), catalysed *in vitro* by human UGT1A1 and by rat, dog and human liver slices, and active *in vivo* in humans, mice, rats, rabbits and dogs.
- Glucuronidation of the diethyl-indanylamine nitrogen (generating P37.7), detected in rat and dog liver slices *in vitro* and in mice, rats, dogs and humans *in vivo*.
- Oxidative cleavage to form diethyl-indanylamino-acetic acid (P38.2), produced *in vitro* by human hepatocytes and rat and dog liver slices. The pathway was active in rats, dogs and humans *in vivo*.
- N-dealkylation forming diethyl-indanylamine (P39), produced *in vitro* by human hepatocytes and rat and dog liver slices, and by rats, dogs, rabbits and humans *in vivo*.
- Glucuronidation of the phenolic oxygen together with monohydroxylation of the benzylic carbons (forming P19), seen in rat and dog liver slices *in vitro* and dogs and humans *in vivo*.

A further 20 minor metabolites were detected: three were apparently formed only *in vitro*. Fifteen were produced by laboratory species but not humans, and two (P26 and P31.6) were found only in human excreta (that is, not detected in plasma/serum). The uniquely human metabolites together accounted for only about 4% of the administered dose. There was pronounced inter-species

variation in the relative activities of the six primary metabolic pathways. N-glucuronidation (forming P37.7) was more extensive in mice than other laboratory species and humans, while O-glucuronidation (generating P37) was more extensive in mice, rats and rabbits than in dogs and humans. The remaining pathways were most active in humans. Due to the hepatic first-pass effect, there was also marked route-dependency in mice, rats and dogs. Compared with PO dosing, treatment via other routes caused greater exposure to indacaterol and less exposure to the O-glucuronide metabolite, P37. Exposure to metabolites P19, P26.9, P30.3, P37 and P38.2 at the highest doses tested in rats and dogs in inhalational studies of ≥4-weeks duration (rats: 8.5 mg/kg/day; dogs: 1.0 mg/kg/day) is estimated to be 1.1–1058-times (rats) and 2.6–22-times (dogs) higher than in humans at the maximum recommended dose of 300 µg/day. *In vitro* studies with human liver microsomes and hepatocytes indicated a low potential for indacaterol and/or its metabolites to covalently bind to cellular proteins.

Excretion of indacaterol and its metabolites was primarily via the faeces for all species and routes studied (mouse: PO, IV; rat: intratracheal, PO, IV, SC; dog: PO, IV; rabbit: IV, SC; human: inhalation; PO). Biliary excretion was demonstrated in rats. The extent of faecal excretion was roughly similar in the laboratory animal species (60–90%) and humans (85%). Unchanged drug was a minor component in urine, but the major component in faeces.

Comparisons of the pharmacokinetic profiles of indacaterol in the laboratory animal species used in the pivotal repeat-dose toxicity studies (rats and dogs) indicate that sufficient similarities exist to allow them to serve as appropriate models for the assessment of indacaterol toxicity in humans.

Pharmacokinetic drug interactions

Indacaterol did not inhibit CYP2C9, 2E1 or 3A4/5 at ≤100 µM in human liver microsomes, and displayed only very weak inhibition of CYPs 1A2, 2C8, 2C19 and 2D6. The IC_{50} values (5–50 µM) are >2000-times the clinical C_{max} at the maximum recommended human dose, and the drug is therefore considered unlikely to act as a clinically significant enzyme inhibitor.

Studies in humans showed increased exposure to indacaterol with co-administration of ketoconazole (a strong inhibitor of CYP3A4 and P-glycoprotein), verapamil (P-glycoprotein inhibitor) and erythromycin (a moderate inhibitor of CYP3A4). This interaction is consistent with the *in vitro* data identifying the drug as a substrate for CYP3A4 and P-glycoprotein.

Relative exposure

Relative exposure levels achieved in the toxicology studies have been calculated based on animal:human serum area under the concentration time curve from time zero to 24 hours ($AUC_{0\text{-}24\,h}$) values for indacaterol with reference to a human value obtained at the maximum recommended dose of 300 µg/day. The C_{max} in humans at this dose was 0.86 ng/mL (Study CQAB149B2339).

Toxicology

Acute toxicity

Inhalational doses up to 3.1 mg/kg (as powder) and 3.7 mg/kg (liquid aerosol) produced no mortality or clinical signs in rats; exposure in the animals is estimated to have been about 15- and 40-times the clinical AUC and C_{max} at the maximum recommended human dose. Maximum non-lethal doses for other routes/species were >1600 mg/kg PO and 5 mg/kg SC in mice, 100 mg/kg SC in rats, and >10 mg/kg PO in dogs. SC administration to rodents at ≥50 mg/kg caused decreased locomotor activity, abdominal distension, postural hunching and/or impaired righting reflex, and rats given 200 mg/kg SC died showing additional signs including hypothermia, ataxia and laboured respiration. The C_{max} and AUC attained at these doses would have exceeded clinical exposure by >100-fold. In dogs, PO dosing had no apparent effect at 0.01 mg/kg, but at ≥0.1 mg/kg caused sinus tachycardia, peripheral vasodilation and decreased mean arterial blood pressure, accompanied by

increased respiratory rate at ≥1 mg/kg, and emesis and dry mouth at 10 mg/kg. At 100 mg/kg PO, dogs also displayed hypothermia, decreased locomotor activity, ataxia, muscle tremor, lacrimation, salivation and ventricular premature complexes; they were sacrificed after developing marked renal injury (proximal tubule necrosis, dilatation and cast formation) about 24 hours post-treatment.

Repeat-dose toxicity

Studies of up to 3 months duration were conducted in mice, 6 months in rats and 9 months in dogs using the inhalational route. Shorter studies by other routes (PO, SC or IV) were also submitted, and higher exposure than with inhalational administration was achieved. The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with ICH guidelines.

Major toxicities

The major targets for indacaterol toxicity identified in the studies were the cardiovascular system, respiratory tissues, liver, kidney and GI tract, with some effects on skeletal muscle and haematology also seen.

Progressive cardiomyopathy, a common age-related finding in rodents characterised by fibrosis, minor inflammatory cell infiltrates and myocardial degeneration/necrosis, was increased in incidence with treatment at 0.62 and 2.1 mg/kg/day in the 2-year rat inhalational carcinogenicity study (relative exposure, 7–14); its severity was minimal to mild. Cardiovascular findings in other rodent studies were limited to increased absolute and/or bodyweight-relative heart weight, which was observed at high systemic exposures in mice following oral administration in the 6-month carcinogenicity study (relative exposure, 30–106), and in rats after intravenous or inhalation administration (relative exposure, ≥15). There were no associated histological lesions in these studies, and no cardiovascular findings in the pivotal 6-month repeat-dose toxicity study in rats (≤3.1 mg/kg/day by inhalation; relative exposure, ≤12).

Cardiovascular effects in dogs were more pronounced. During and after inhalational administration, animals displayed peripheral vasodilation (seen as reddened ears, skin and gums), and subjectively increased heart rate and force, and carotid pulse. Electrocardiogram (ECG) monitoring revealed dose-related tachycardia, with heart rates increasing up to 3-fold compared with baseline or control values. Tachycardia persisted for up to 24 hours post-dosing. Tachycardia and reddening of skin were also observed following IV dosing (at ≥0.1 mg/kg/day). The lowest inhalational dose at which tachycardia (as assessed by ECG) occurred was 0.10 mg/kg/day, associated with a C_{max} 2.3-times the clinical value. Moderation of indacaterol-induced clinical signs and tachycardia was evident with continued treatment, and no or negligible differences from control were seen by Week 7 or later. Cardiac lesions in inhalational studies in dogs comprised focal myocardial degeneration (relative exposure, 26), fibrosis (relative exposure, ≥37), necrosis (relative exposure, 6) and haemorrhage (relative exposure, 26), and inflammation (relative exposure, 5). Myocardial degeneration/fibrosis was also observed with IV treatment (relative exposure, 18). The lesions did not exceed slight or moderate severity, and are consistent with findings for other β-agonists, occurring secondary to repeated or prolonged stimulation of the heart. There were no cardiac lesions in dogs treated at 0.3 mg/kg/day by inhalation in the pivotal 9-month study (relative exposure, 2).

Indacaterol caused numerous changes in respiratory tissues of mice and rats that were exposed repeatedly by nasal inhalation. Olfactory/respiratory epithelial atrophy was observed in the nasal cavity of mice treated at ≥10 mg/kg/day for 2 weeks (markedly severe at 30 mg/kg/day) and ≥1.5 mg/kg/day for 3 months (minimal to mild). There were also findings of inflammatory cell foci/infiltration (≥5 mg/kg/day), debris and exudate (30 mg/kg/day) and accumulation of proteinaceous globules (1.5 mg/kg/day) in the mouse nasal cavity, and squamous metaplasia in the larynx (≥10 mg/kg/day; minimal) and alveolar macrophage accumulation in the lung

(30 mg/kg/day; minimal). In rats, reversible inflammation, focal degeneration, atrophy and hyperplasia of the olfactory epithelium occurred at doses ≥3.0 mg/kg/day in repeat-dose studies of 4 or 13 weeks duration; rhinitis (at ≥0.62 mg/kg/day) and olfactory epithelial atrophy (2.1 mg/kg/day) were observed in the 2-year carcinogenicity study. Squamous metaplasia/ hyperplasia of the larynx and squamous hyperplasia of the pharynx developed at ≥0.9 mg/kg/day, and squamous metaplasia of the respiratory epithelium of the nasal cavity as well as inflammation and haemorrhage in the larynx were observed at 20 mg/kg/day. Froth-filled trachea were observed at ≥0.21 mg/kg/day, lymphocytic infiltration of the trachea at 3.1 mg/kg/day and tracheitis at 16 mg/kg/day. Alveolar macrophage accumulation and type 1 pneumocyte proliferation were observed in the lungs of rats treated at 3.1 mg/kg/day. Mice and rats exhibited gasping, irregular, laboured and/or crackling respiration post-dosing at 30 mg/kg/day and ≥16 mg/kg/day in the respective species. In inhalational studies in dogs, isolated cases of inflammation and hyperplasia in upper respiratory tract tissues and accumulation of foamy macrophages in the lungs were observed with treatment at ≥0.10 mg/kg/day for 3 months. Oedema of the nasal turbinates was recorded in dogs in a 4-day pilot study (at 1 mg/kg/day or with escalating doses up to 1.6 mg/kg/day). An oral inhalation system was used in dogs, which is closer to the intended method of drug deliver in humans cf. the nasal system used in mice and rats. The respiratory tract effects in the animal studies are consistent with a response to irritation, and were reversible. The local doses at which they occurred are very much greater than will occur in patients. The No Observable Effect Level (NOEL) for effects on the respiratory system established in the pivotal 9-month dog study was 0.10 mg/kg/day, which is more than 16-times higher than the maximum recommended human dose in a 50 kg patient (0.006 mg/kg) on a mg/kg basis.

Hepatocellular vacuolation, together with large increases in serum aspartate transaminase (AST) and alanine transaminase (ALT) (about 4–8-times) and a modest increase in alkaline phosphatise (ALP) (75%), were observed at 3000 mg/kg/day PO in the mouse (2-month study; relative exposure, ≥79). By contrast, there were no effects on the liver or signs of hepatotoxicity in mice treated by inhalation (dosing up to 30 mg/kg/day for 2 weeks [relative exposure, ≤67] or ≤5 mg/kg/day for 3 months [relative exposure, ≤52]), and no treatment-related liver histological abnormalities were observed in rats (relative exposure, ≤12 in the pivotal study with administration by inhalation and ≤49 in a 2-week IV study). Statistically significant, but slight, increases in serum ALP/ALT/AST were observed inconsistently in rats. In dogs, formation of glycogen-containing vacuoles throughout the periportal regions of the liver occurred in all repeat-dose studies (IV and inhalational routes), irrespective of duration. The lowest inhalational dose that caused the effect consistently was 0.02 mg/kg/day (relative exposure, 0.9). There were no accompanying changes in serum enzymes, except for elevated ALT activity, which was seen at 0.9 mg/kg/day in a 4-day inhalational study (relative exposure, 26). Periportal fibrosis accompanied the glycogen accumulation in a 3-month inhalational study at 1.1 mg/kg/day (relative exposure, 56). This was minimally severe, and not observed at slightly lower exposure ratios (≤42) over 3 months, or in the pivotal 9-month dog study at the highest dose tested (0.31 mg/kg/day; relative exposure, 11). Hepatotoxicity in the mouse following a large oral dose is consistent with the rodent liver's massive exposure to the drug on first pass by this route. Findings of increased levels of glycogen in periportal hepatocytes of treated dogs (fasted overnight prior to termination) are consistent with mediation by β-adrenoceptor activation (glucagon receptor down-regulation and stimulation of lipolysis).

Renal injury was evident in mice treated at ≥1000 mg/kg/day PO (2 month study; relative exposure, ≥79), with tubular basophilia, degeneration, dilatation and fibrosis and cast formation (up to markedly severe) observed. At 3000 mg/kg PO, blood urea and creatinine levels were massively increased (by 4–4.5-times and about 12–24-times, respectively); smaller increases were present at lower doses in the study. With inhalational administration, focal tubular basophilia occurred in male mice treated at 30 mg/kg/day for 2 weeks (estimated relative exposure, about 50) and the incidence

of chronic progressive nephropathy was more than doubled with treatment at 5 mg/kg/day for 3 months (relative exposure, 29). In rats, renal tubule vacuolation occurred at 8.1 mg/kg/day in males in a 4-week inhalational study (relative exposure, 41); there were no treatment-related renal lesions observed in the 2-week IV study (relative exposure, ≤49), and no evidence of renal dysfunction or injury in rat inhalational studies of 3 months to 2 years duration (relative exposure at the highest doses 12–18). While renal injury followed administration of a single oral dose of 100 mg/kg (see *Acute toxicity*), no treatment-related renal lesions were found in dogs in repeat-dose inhalational studies (relative exposure, ≤11 in the pivotal 9-month study [≤0.31 mg/kg/day] and ≤56 in 3-month studies [≤1.1 mg/kg/day]). Given the high exposure margins, and considering also that the most pronounced effects were observed in mice, in which renal elimination of the drug is a more significant pathway compared with humans, the data do not indicate any significant hazard of renal toxicity in patients.

Mice treated with indacaterol at 100–3000 mg/kg/day PO for 2 months displayed GI tract lesions. These comprised dyskeratosis of the gastric limiting ridge, gastric erosion, hyperplasia and inflammatory cell infiltration, and goblet cell depletion and leukocytic infiltration in the caecum; intestinal necrosis was observed at 3000 mg/kg/day only. Glandular erosion, inflammation, hyperplasia, hyperkeratosis and dyskeratosis were found in the stomach of mice treated PO at 100–600 mg/kg/day in the 6-month carcinogenicity study. Gastrointestinal (GI) changes did not develop in rodents or dogs dosed SC, IV or by inhalation. The findings are consistent with local irritation associated with very high local concentrations of the drug in the GI tract; they are not considered to be predictive of a hazard to patients.

Increased body weight gain was commonly observed in the repeat-dose studies, particularly in rodents, and visible enlargement of skeletal muscle mass was noted in the 6-month and 2-year studies in rats (inhalational doses ≥0.31 and ≥0.21 mg/kg/day, respectively). Increased muscle mass was not associated with histopathological changes. The finding is consistent with the known anabolic effect of β_2-adrenoceptor agonists.

Statistically significant decreases in red blood cell indices (count, haematocrit and/or haemoglobin concentration) were seen in a number of the repeat-dose studies in rats and dogs, but the finding was not consistently observed, and there were no associated histological changes. Increased white blood cell count, observed in the 2-week, 4-week and 6-month inhalational studies in rats, was associated with inflammation of the respiratory tract. Haematology parameters were unaffected in the pivotal 9-month dog study (≤0.31 mg/kg/day by inhalation; relative exposure, ≤11).

Studies examining the toxicity of indacaterol in combination with the experimental muscarinic antagonists NVA237 and QAT370 and the glucocorticoid steroid mometasone furoate were conducted in rats and dogs. Administration was by inhalation; studies with NVA237 and QAT370 were of 2-weeks duration, and 13-weeks duration for mometasone. No novel or additive toxic effects were observed apart from an additive increase in heart rate in dogs treated with indacaterol and NVA237 in combination.

Genotoxicity

The potential genotoxicity of indacaterol was investigated in a bacterial reverse mutation assay and in assays for chromosomal aberrations in cultured Chinese hamster V79 cells and in the bone marrow of rats. Concentrations used in the *in vitro* assays were appropriate (limited by cytotoxicity), and the dose used in the *in vivo* test (2000 mg/kg/day SC) was sufficient to produce signs of systemic toxicity; distribution to the bone marrow had been shown in the rat. The assays were appropriately conducted and validated, and all returned negative results.

Carcinogenicity

The carcinogenic potential of indacaterol was investigated in a 6-month study by the oral route in transgenic mice and in a 2-year inhalational study in rats. Group sizes were appropriate. The sponsor did not provide a justification for the use of the PO route rather than the clinical (inhalational) route in the transgenic mouse study. However, its use appears to have allowed higher systemic exposure levels to be achieved, and in the absence of proliferative lesions in the respiratory tract in the rat study, is considered acceptable. Dose selection was appropriate and exposure ratios were adequate (relative exposure, ≤49 and ≤106 in male and female mice, and ≤14 in rats).

Indacaterol was not carcinogenic in CB6F1/TgrasH2 mice (≤600 mg/kg/day PO). In rats, the drug produced ovarian leiomyoma at 2.1 mg/kg/day (observed in 2/50 animals; relative exposure, 14), associated with focal hyperplasia of the ovarian smooth muscle. The NOEL for carcinogenicity in the rat was 0.62 mg/kg/day (relative exposure, 7). Leiomyoma of the ovary is recognised to be a class effect of β_2-adrenoceptor agonists in the rat (Jack *et al.*, 1983), and has also been observed with salbutamol, salmeterol, terbutaline, and eformoterol.[1] It is believed to result from prolonged and intense activation of β_2-adrenoceptors of the mesovarial smooth muscle, causing muscle relaxation and, in turn, smooth muscle proliferation. Development of the tumour can be inhibited by co-administration of the β-adrenoceptor antagonist propranolol. Despite widespread clinical use, there is no evidence of tumourigenic activity for β-adrenoceptor agonists in humans. The finding of ovarian leiomyoma in indacaterol-treated rats is therefore not considered to indicate a carcinogenic hazard to patients.

Reproductive and developmental toxicity

Studies assessing the effects of indacaterol on fertility, embryofetal and postnatal development in rats and embryofetal development in rabbits were submitted. Study design was appropriate and high exposure levels were achieved at the maximum doses administered.

Placental transfer of ^{14}C-indacaterol-derived radioactivity was demonstrated in the rat, with significant fetal exposure observed. Indacaterol and seven of its metabolites were excreted into rat milk within 1 hour of maternal SC dosing. Milk:plasma $AUC_{0\text{-}24h}$ ratios were 2.9 for the parent drug and 1.3 for total radioactivity. A human infant consuming 1 litre of breast milk per day was estimated to receive 0.09% of the mother's dose.

Male and female fertility were unaffected in rats at SC doses ≤2 mg/kg/day (relative exposure, ≤114 in males and ≤86 in females). No adverse effects on embryofetal development were observed in rats treated with indacaterol at ≤1 mg/kg/day SC (relative exposure, ≤43). In rabbits, an increased incidence of a skeletal variation (full supernumerary rib) and retarded ossification (frontal and metacarpal bones) were observed at 3 mg/kg/day SC (relative exposure, 248), a maternotoxic dose. There was no effect on embryofetal development in the rabbit at 1 mg/kg/day SC (relative exposure, 98). No teratogenicity was observed in either species. The findings justify placement of indacaterol in Pregnancy Category B3. No novel or additive embryofetal toxicity was observed with indacaterol and the experimental muscarinic antagonist NVA237 in combination in a study in rats.

Pups of rats treated at ≥0.3 mg/kg/day SC displayed reduced postnatal bodyweight gain (≤10%), which diminished post-weaning. Pups would have been exposed to indacaterol *in utero* and through the consumption of maternal milk. A learning deficit was evident in the male offspring of rats treated at 1 mg/kg/day (the high-dose level; relative exposure, 37), with the number of animals successfully completing the acquisition/learning phases of a passive avoidance test markedly reduced; a smaller reduction in the water M-maze test was also seen; there were no similar findings in females at this dose. Treatment at 1 mg/kg/day was also associated with a reduction in fertility of

[1] Jack D *et al.* Beta-adrenoceptor stimulants and mesovarian leiomyomas in the rat. Toxicology 1983; 27: 315–320.

the offspring. Postnatal survival and other developmental parameters were not affected by treatment. Relative exposure at the NOEL for effects on fertility and learning in the rat postnatal development study (0.3 mg/kg/day) is 15, and 5 at the NOEL for suppression of postnatal bodyweight gain (0.1 mg/kg/day).

Immunotoxicity

Effects on the immune system were seen in some of the repeat-dose studies in rodents at excessively high dose levels. Thymic atrophy occurred at high incidence in mice treated at 3000 mg/kg/day PO in a 2-month study (relative exposure, 286), together with lymph node depletion/necrosis and lymphoid depletion in the spleen. No effects on the immune system were apparent in the 3-month inhalational study (relative exposure, ≤52) or 6-month PO carcinogenicity study (relative exposure, ≤118) in mice. In rat inhalational studies, thymus weights were reduced at about 17 mg/kg/day (relative exposure, 34), but no effects were evident with treatment at ≤3.1 mg/kg/day for 6 months (relative exposure, ≤12) or ≤2.1 mg/kg/day for 2 years (relative exposure, ≤14). Immunotoxicity was not seen in indacaterol-treated dogs (relative exposure, ≤111 in a 2-week IV study; ≤56 in 3-month and ≤11 in 9-month inhalational studies). Consequently, indacaterol is not expected to adversely affect the immune system in patients.

Local tolerance

No specific local tolerance studies were conducted. Localised swelling, hardening, scabbing, inflammation, alopecia, ulceration and/or hyperkeratosis of the skin around injection sites were noted following SC administration in mice, rats and rabbits. In several studies, there was also discolouration or deposition of gelatinous masses underneath the skin, sometimes accompanied by discolouration, necrosis or degeneration of fibre in the underlying muscle. Darkening of IV injection sites occurred in dogs. There was evidence of irritation with the vehicles alone, but dose-related increases in the intensity of local reactions to indacaterol sometimes occurred despite the use of a constant injection volume.

Antigenicity

Indacaterol was not a dermal sensitiser by cutaneous application and did not elicit pulmonary airway sensitisation with administration by the inhalational route in studies in guinea pigs. However, indacaterol was classified as a weak lymph node activator and skin sensitiser in local lymph node assays in BALB/c mice.[2]

Phototoxicity

Indacaterol was classified as probably phototoxic in an *in vitro* phototoxicity evaluation in Balb/c 3T3 cells according to the Organisation for Economic Co-operation and Development (OECD) criteria. Based on low systemic exposure and anticipated distribution to the skin and eyes, no clinically relevant phototoxicity is expected in patients however.

Nonclinical Summary and Conclusions

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies, demonstrating potent β_2-adrenoceptor agonism *in vitro* and long-lasting inhibition of bronchoconstriction *in vivo*, support the drug's use for the proposed indication.
- Secondary pharmacodynamic and safety pharmacology studies identified no clinically relevant concerns. Tachycardia observed in dogs and monkeys after a single inhalational dose is consistent with excessive β-adrenoceptor stimulation from high systemic exposure.

[2] BALB/c is an albino, laboratory-bred strain of the house mouse from which a number of common substrains are derived.

- The toxicological profile of indacaterol was similar to that of other β_2-adrenoceptor agonists in most respects. Findings of cardiotoxicity in the nonclinical species are consistent with exaggerated pharmacology. Respiratory tract findings are considered to reflect a response to irritation and occurred at local doses very much greater than will occur in patients. Glycogen accumulation in the dog liver is consistent with mediation by β-adrenoreceptor activation. Large margins of exposure exist at the NOELs for other hepatic lesions and for renal injury established in the pivotal studies in the rat (12-fold) and dog (11-fold). GI tract lesions were only observed with PO dosing, and are consistent with a response to local irritation stemming from exposure to very high local concentrations of the drug not relevant to administration by the clinical route. Anabolism by indacaterol is recognised to be β_2-adrenoceptor-mediated. Haematological changes, observed in some of the studies, are not anticipated in patients based on their absence in the pivotal dog study (relative exposure, ≤11) and secondary association with inflammation.
- Ovarian leiomyoma developed in rats treated with indacaterol at 14-times the clinical dose (based on AUC) for 2 years. This occurred in the context of ovarian smooth muscle hyperplasia. Other β_2-adrenoceptor agonists are known to cause ovarian leiomyoma in the rat, and its development is consistent with smooth muscle proliferation in response to prolonged β_2-adrenoceptor-mediated relaxation of mesovarial smooth muscle cells. The finding is not considered to be of clinical relevance. Relative exposure at the NOEL for carcinogenicity in the rat is large (7) and no carcinogenicity was observed for the drug in transgenic mice (relative exposure, ≤106). Indacaterol is not genotoxic.
- Reproductive and developmental toxicity studies revealed effects on skeletal development in the rabbit and impaired postnatal body weight gain, fertility and learning in the offspring of treated rats. Margins of exposure at the NOELs for these effects are large to very large (5–98), indicating a limited risk in clinical use.
- There are no nonclinical objections to the registration of Onbrez for the proposed indication.

IV. Clinical Findings

Introduction

The clinical development programme consists of 7 Phase III studies involving over 6000 patients in over 30 countries. Six of these studies were in COPD patients only (studies **B2335S, B2334, B2346, B2305, B2307** and **B2340**) and one study evaluated safety of indacaterol in asthma patients (not proposed indication) to provide safety data following probable off-label use of indacaterol for asthma **(B2338).**

Although the initial Phase I and II studies used different devices for indacaterol administration, all of the Phase III studies used the Concept1 (Breezhaler) device intended for marketing in Australia. Subjects have been exposed to single doses of indacaterol up to 3000 μg and in repeat dose Phase III studies, doses up to 600 μg once-daily for up to 52 weeks have been investigated in COPD and asthma patients.

Pharmacokinetics

Introduction

Pharmacokinetic information has been collected from 36 clinical studies from healthy volunteers, patients with COPD and asthma patients. In the different studies indacaterol was administered via the inhaled route of administration using either single dose dry powder inhaler (SDDPI) devices, a pressurized metered dose inhaler (pMDI) device, or a multi dose dry powder inhaler (MDDPI) device. The development of the pMDI and the MDDPI was discontinued and the device used currently in the development program is an SDDPI variant called Concept1. All the Phase III studies used the Concept1 (Breezhaler) device intended for marketing in Australia.

Pharmacokinetic (PK) data after inhalation via Concept1 was collected in studies in healthy subjects **(A2307, A2311, B2103, B2216, B2220** and **B2339),** in patients with COPD **(B2212, B1202, B2346, B2334** and **B2335S)** and in asthmatic patients **(A2228, B2338)**. Some studies in healthy subjects have used other routes of administration such as the oral route by swallowing inhalation capsules **(A2106, A2214** and **A2223)** and an intravenous infusion in study **B2103**. There were three drug interaction studies in healthy subjects **(A2311, B2216** and **B2220).** Studies in special patient populations evaluated effect of hepatic impairment **(A2307)** and UGT1A1 genotype **(A2221)** on pharmacokinetics of indacaterol. Ethnic differences between Japanese and Caucasian subjects were addressed in healthy subjects **(A2215)** as well as in asthmatics **(A2219).** Information about covariates that may have an impact on pharmacokinetics such as age, gender, body weight, body mass index and race were investigated using a population PK modelling approach with pooled pharmacokinetic data from studies B2212, A2228,B2334, B2335S and B2338.

Pharmacokinetic sampling times were adequate to meet objectives of the individual PK studies. In all PK studies, indacaterol was determined in serum prepared from the blood samples using a validated LC-MS/MS method. The lower limit of quantification (LLOQ) was 10 pg/mL.

Pharmacokinetics in healthy subjects

Bioavailability study

B2103 was an open-label, single-dose, two-period crossover study in 24 healthy volunteers conducted in two parts to compare the pharmacokinetics of indacaterol when dosed in the morning and in the evening, and determination of the absolute bioavailability of indacaterol. Overall, these results suggest similar exposure to indacaterol upon inhalation in the morning or evening.

The disposition of indacaterol after intravenous administration to 4 subjects in Part 2 was characterized by an extensive distribution (mean volume of distribution [Vz]: 2557 L), a moderate systemic clearance (CL) (mean CL: 23.3 L/h) and a long terminal elimination phase ($t_{1/2}$)(mean $t_{1/2}$: 76 hours). The absolute bioavailability of an inhaled indacaterol dose was 43.2% [24.0] (mean [%CV]) based on inhalation and infusion exposure data from four subjects.

Pharmacokinetic and initial tolerability studies in healthy subjects

B149A1101 was a randomized, double-blinded, placebo-controlled study to investigate the safety, tolerability and PKs of indacaterol in 12 healthy Japanese male subjects. Indacaterol was rapidly absorbed and reached its maximum serum concentration between 15 and 30 minutes after each inhalation. Mean C_{max} of indacaterol in serum increased 1.5 times from Day 1 to Day 7 and mean AUC $_{0\text{-}24h}$ increased 2.3 times. The apparent terminal half-life was on average 71.2 hours. Renal excretion was a minor clearance pathway for indacaterol as only 1.1% and 3.2% of the dose on day 1 and 7, respectively was excreted in the urine. **A2106** was a randomized, open label, cross-over study to assess the absorption, distribution, metabolism and excretion of indacaterol following a single oral or inhaled dose in 4 healthy male subjects. Systemic exposure to indacaterol was higher following inhalation compared to oral administration with higher mean C_{max} and mean $AUC_{0\text{-}48h}$. Hence, relative bioavailability of the oral dose compared to the inhaled dose was only 46%. Following an inhaled dose of indacaterol via the Aerolizer device, T_{max} for each subject occurred at 0.25 hours compared with the more variable time to peak serum concentrations (0.5 – 2 hours) in the same subjects following the oral dose.

Only a minor portion of the dose (<1-3%) was found in the urine as indacaterol and indacaterol glucuronide following both inhaled and oral routes of administration. Following the inhaled and oral doses, the ratio of indacaterol/ indacaterol glucuronide in urine was in the range of 1.5:1 to 3:1.

Faecal excretion accounted for 39.7 – 87.0% of the inhaled indacaterol dose. Following the oral dose, faecal excretion accounted for 14.2 – 62.9% of the dose. The percent dose of indacaterol and

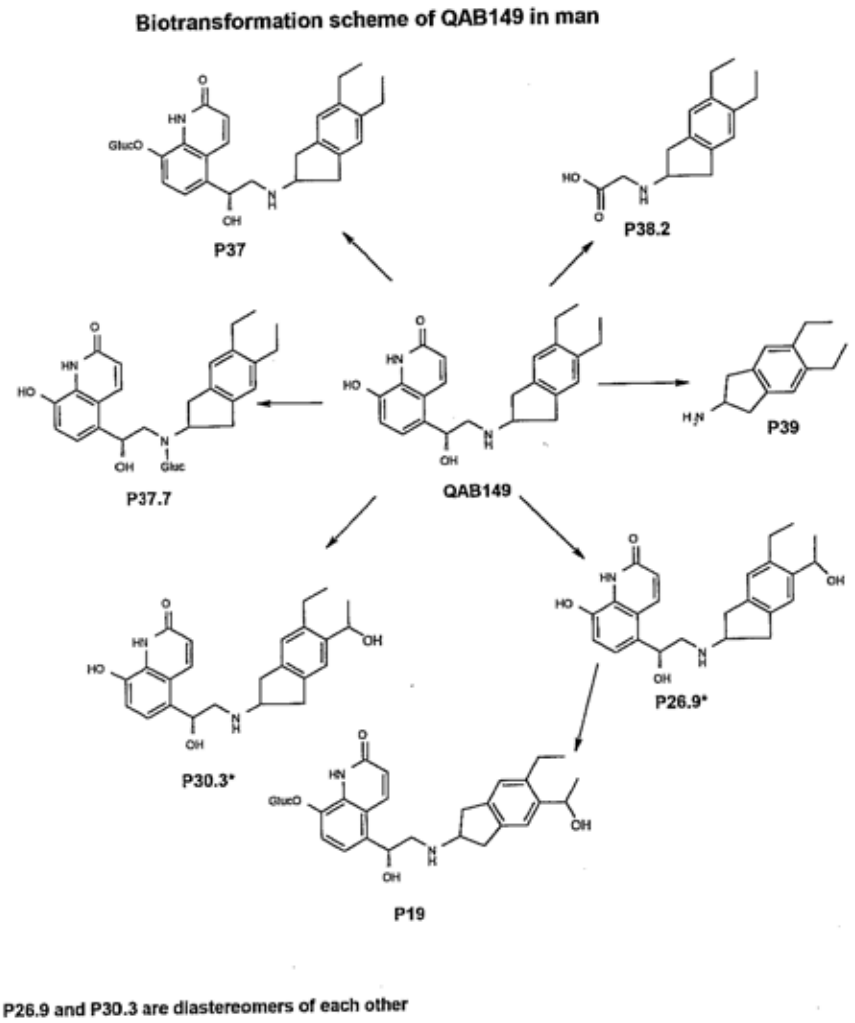
indacaterol glucuronide recovered in the excreta collected up to 168 hours was: 41.4 – 90.3% (inhaled route) and 15.4 - 64.0% (oral route).

A2214 was an open-label study in four adult healthy male volunteers to assess the PKs and metabolism of a single oral 800 μg dose of [14C]-labelled indacaterol. The radioactivity was primarily excreted via the faecal route (average of 45.1% of dose in faeces). The renal excretion route was minor, accounting for only 8.9 % of dose. Consistent with the results of study **A2214**, the major metabolites of indacaterol identified were P19 (glucuronide conjugate of P26.9), P26.9 (hydroxylation of one of the benzyl carbons in the diethyl-indane moiety), P30.3 (diastereoisomer of P26.9), P37 (phenolic O-glucuronide conjugate), P37.7 (N-glucuronide conjugate at the diethyl-indanylamine nitrogen), P38.2 (diethyl-indanylamino-acetic acid metabolite formed from oxidative cleavage), and P39 (diethyl-indanylamine metabolite resulting from N-dealkylation). The largest contributor to serum radioactivity was indacaterol itself (32.5% of AUC_{0-24h}). Other serum metabolites included P19 (5.8%), P26.9 (12.4%) and P37 (4.2%). Maximum serum radioactivity levels were observed within 2-4 hours. The terminal half-life of elimination of total radioactivity was 116.8±24.2 hours. Indacaterol achieved its maximum systemic levels (C_{max}) within 1-3 hours. Based on the metabolites characterized in human excreta and in serum, a general biotransformation scheme for indacaterol is proposed in Figure 1. The primary metabolic reactions observed included: (1) Hydroxylation of the benzylic carbon in the diethyl-indanyl moiety; this pathway lead to the formation of the diastereometric metabolites P26.9 and P30.3 which together accounted for 25.3 % of the excreted dose. (2) Both N- and O- glucuronidation; this pathway lead to the formation of metabolites P19, P37 and P37.7. Although these metabolites only accounted for 1.35% of the excreted dose, they represented a significant fraction of the drug-related material found circulating in the serum AUC pool (the exact percentage could not be calculated due to the co-elution of P37.7 with P38.2). (3) Oxidative cleavage, which lead to the formation of metabolites P38.2 and P39 which together accounted for 2.7% of the excreted dose.

The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. CYP3A4 appeared to be the predominant isoenzyme responsible for hydroxylation of indacaterol. The hydroxylated metabolites P26.9 and P30.3 were found to have similar in vitro affinity to human beta-2-receptors. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays and are not expected to contribute significantly to pharmacological activity of indacaterol.

Analysis of urine samples from PD study **2211** provided evidence that stereochemical conversion of indacaterol (the pure R-enantiomer) to the S-enantiomer in vivo does not happen to any significant extent.

Figure 1: Study CQAB149A2214



Pharmacokinetics in COPD patients

A2105 was a single-centre, randomized, double-blind, placebo controlled, parallel group study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics (PD) of multiple inhaled doses of indacaterol (by pMDI) in 12 patients with mild (Stage I) to moderate (Stage IIa) COPD (see Table 1), Indacaterol was absorbed rapidly following inhalation and the median T_{max} was between 0.5 and 1 hours. The mean C_{max} was similar on all sampling days. Mean AUC of indacaterol increased by about 60% from Day 1 to Day 14. The average apparent total body clearance following multiple dosing was between 131 and 159 L/h. No firm inference could be made as to whether steady-state had been reached by Day 7. Urinary excretion of total indacaterol amounted to 1.0 to 1.6% of dose and of the total indacaterol excreted about 50 to 60% was excreted as unchanged drug.

B2201 was a randomized, double-blind, placebo controlled, parallel group, multicentre study in 163 patients with moderate COPD. Its primary objective was to assess the safety, tolerability of 28 days treatment with indacaterol (400 µg [68 patients] or 800 µg [67 patients] once daily) delivered via an SDDPI device, compared to placebo (28 patients). Trough levels of indacaterol in serum indicate that steady state was reached between 2 and 3 weeks of treatment. The 1.55 to 1.79-fold increase in 1 hour post-dose levels of indacaterol suggest moderate accumulation after 4 weeks of indacaterol treatment.

B2202 was an open-label, dose escalation study to assess the safety and tolerability of incremental doses of indacaterol (400, 1000, 2000 and 3000 µg via an SDDPI device) in 18 adults with mild-to-moderate COPD. Indacaterol was rapidly absorbed with median T_{max} of 30 minutes for the 400, 2000, and 3000 µg dose and 17 minutes for the 1000 mg dose. The maximum serum concentration (C_{max}), AUC $_{0-24}$ and $AUC_{0-\infty}$ all increased with dose, suggesting dose-proportionality. The mean apparent terminal elimination half-life of indacaterol was 12.3 hours for the 400 µg dose and ranged from 50.2 to 63.5 hours for the higher dose levels. In study **B2202** involving 18 patients with moderate COPD, mean changes (from pre-dose) in QTc(F) showed a trend to increase from 400 µg QAB149 to 3000 µg QAB149 dose of ~13 milliseconds (ms) at 40 minutes post dose. Mean changes (from pre-dose) in heart rate showed a trend to increase from 400 µg QAB149 to 3000 µg QAB149 dose from <3 beats per minute (bpm) to ~14 bpm respectively within 2 hours post dose.

B2205 was a randomized, double-blind, parallel group, multicentre, multiple dose (7 days), dose-ranging study to assess the efficacy and safety of four doses of indacaterol delivered via an MDDPI and one dose delivered via a SDDPI device in 635 patients with moderate-to-severe COPD. In a subset of patients, sparse samples for pharmacokinetics were collected on Day 1 and Day 7. Systemic exposure increased about 8- to 9-fold between the 50 µg and the 400 µg doses and mean accumulation ratios between Day 1 and Day 7 for AUC_{0-4h} ranged between 1.7 and 3.0.

In the Phase IIb, randomized, double-blind, single dose, active and placebo controlled, multicentre, five period crossover, dose-ranging study **B2212** in 51 COPD patients, indacaterol (by SDPPI) was systemically available shortly after the oral inhalation. Peak serum levels could in most cases be observed at the first sample time point (scheduled at 30 minutes post-dose), resulting in median T_{max} of 0.58, 0.59, and 0.58 hours in the 150 µg, 300 µg and 600 µg dose-group, respectively. Exposure (C_{max} and AUC_{0-24}) increased with increasing doses, but dose-proportionality across the entire dose range (dose range points =4) could not be concluded from the statistical analysis.

The Phase II, single-dose, crossover study involving 45 Japanese COPD patients, peak serum indacaterol levels following oral inhalation (by SDPPI) of 150 µg, 300 µg and 600 µg) could in most cases be observed at the first sample time point (scheduled at 15 minutes post-dose), resulting in median T_{max} of 0.33 hours in all dose-group. C_{max} increased with increasing doses but dose-proportionality across the entire dose range could not be concluded from the statistical analysis; however, AUC_{0-24h} increased with increasing doses and dose-proportionality across the entire dose range could be concluded.

In the QTc study **2339,** 68% of subjects had all serum samples assayed for the parent drug and 30 % subjects had trough (pre-dose) and peak (0.33 hours post-dose) Day 14 concentrations of indacaterol measured. The median T_{max} of indacaterol was 15 minutes in all dose groups, both on Day 1 and Day 14. Dose proportionality over the entire dose range of 150 µg to 600 µg was demonstrated for peak exposure (C_{max}) of indacaterol on Day 1 and Day 14 and for total exposure (AUC_{0-24}) on Day 14.

Effect of intrinsic factors on indacaterol pharmacokinetics

Hepatic/ renal impairment

A2307 was an open-label, parallel-group study to assess the impact of mild and moderate hepatic impairment on the pharmacokinetics of single inhaled doses of indacaterol. A total of 16 patients with mild or moderate hepatic impairment were matched with 16 healthy volunteers. Mean systemic exposures (AUC_{0-24}, AUC_{0-168} and $AUC_{0-\infty}$) were similar between each subject group. The AUC ratios of the mild and moderate hepatically impaired subjects to matched controls ranged from 0.87 – 1.12. For C_{max} the ratios ranged from 0.77 – 0.98, and for Ae_{0-24} they were close to unity. The mean apparent terminal elimination half-life of indacaterol was similar in all treatment groups and ranged between 71.1 and 79.6 hours.

Indacaterol pharmacokinetics were not evaluated in subjects with renal impairment, but this is not likely to be of significance as <1% of the drug is excreted renally.

Effect of race

A2215 was a randomized, double-blind, 5-period within-subject placebo-controlled single dose escalation study (400 to 2000 μg) to assess the safety and tolerability of indacaterol dry powder inhaler (RS-01) in 22 Caucasian and 20 Japanese healthy male subjects. For Japanese and Caucasian subjects, the serum concentration increased rapidly following drug administration and reached a maximal level approximately 15 minutes post-dose, followed by a steep decrease up to 4-8 hours after inhalation; thereafter the decrease slowed down.

Effect of genetic variants of UDPGT

A2221 was an open label, multiple dose, single-centre study to compare the pharmacokinetics of indacaterol in 24 healthy subjects with genetic variants of uridine diphosphate (UDP) glucuronosyltransferase 1 enzyme (UGT1A1 enzyme); the purpose of this study was to investigate whether subjects who are homozygous for the genetic variant A(TA)7TAA in the gene encoding the enzyme UDP-glucuronosyltransferase demonstrate reduced clearance of indacaterol, resulting in elevated systemic concentrations of indacaterol following multiple doses compared with subjects who are homozygous for the genetic variant A(TA)6TAA. On Day 1, concentration-time profiles were similar in both genotype groups, but by Day 14, there were minor differences in C_{min}, C_{avg}, C_{max} AUC_{0-24} between the genotype groups; mean exposure was 1.2-fold higher in the A(TA)7TAA group than the A(TA)6TAA group, and indacaterol accumulation was slightly higher in the A(TA)7 TAA group The terminal elimination half-life of indacaterol determined from the serum concentrations up to 168 hours after the last dose on Day 14 were similar; the effective half-life for indacaterol accumulation, calculated from the AUC accumulation ratio, was 42.3 hours for the A(TA)6TAA genotype group and 51.6 hours for the A(TA)7TAA genotype group. Overall, there were no significant differences in indacaterol pharmacokinetic parameters between the UGT1A1 genotype groups.

Effect of extrinsic factors on indacaterol pharmacokinetics (Drug interactions)

A2311 was an open-label, single-dose, two period, single sequence crossover study to assess the pharmacokinetic interaction of indacaterol (300 μg via inhalation) with the potent CYP3A4 inhibitor ketoconazole in healthy adult subjects. Systemic exposure to indacaterol was statistically significantly ($p<0.001$) higher after co-administration with ketoconazole as compared with the administration of indacaterol alone. AUC's (that is, AUC_{0-24}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$) were approximately doubled and C_{max} increased about 30 to 40%. Median time to maximum serum concentration (T_{max}) was delayed by 15 minutes when indacaterol was co-administered with ketoconazole. The terminal elimination half-lives of indacaterol were similar for both treatments: on average, 63.2 hours for indacaterol alone and 69.4 hours for indacaterol + ketoconazole.

B2216 was an open-label, single-dose, two-period, single sequence study to assess the pharmacokinetic interaction of indacaterol (300 μg via inhalation) with steady-state verapamil in 12 healthy adult Indian subjects. Verapamil is a dual substrate and moderate inhibitor of both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Co-administration of verapamil with a compound such as indacaterol that is also a CYP3A4 substrate and low affinity P-gp substrate could result in either inhibition of indacaterol metabolism, reduced P-gp efflux, or a combination of both effects. Co-administration of a single dose of indacaterol with verapamil at steady state resulted in a statistically significant increase of systemic exposure to indacaterol, as compared with a single dose of indacaterol given alone. The C_{max} of indacaterol increased by 53%, AUC_{0-24} by 100%, $AUC_{0-tlast}$ by 47% and $AUC_{0-\infty}$ by 35%. Median T_{max} increased from 0.25 to 1.0 hour post dose when indacaterol was co-administered with verapamil as compared with indacaterol given alone.

B2220 was an open-label, two-period, single sequence study to assess the pharmacokinetic interaction of a single-dose of indacaterol (300 µg via oral inhalation) with multiple, daily doses of the moderate CYP3A4 inhibitor erythromycin ethylsuccinate in healthy adult subjects. Co-administration of a single dose of indacaterol with erythromycin at steady state resulted in increased systemic exposure to indacaterol. The C_{max} of indacaterol increased by 15% and AUC_{0-24}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ increased by 44 to 61%. However, C_{max} was virtually unaffected by co-administration of erythromycin, being 0.25 hours for indacaterol alone and 0.27 hours for indacaterol + erythromycin.

No other drug interaction studies were conducted between indacaterol and other oral/inhaled medications commonly used in COPD.

Population Pharmacokinetic analysis

Indacaterol-containing arms of five Phase II and Phase III clinical studies (A2228, B2212, B2334, B2335S, B2338) were pooled to generate a pharmacokinetic analysis dataset for modelling. The influence of covariates on exposure was characterized using two distinct approaches. In the first, a population pharmacokinetic model was developed using the software program NONMEM and used for investigating covariate effects on area under the curve at steady state (AUCτ). Owing to doubts about the model's ability to provide reliable estimates of peak concentrations (it was impossible to reliably characterize an absorption component due to a lack of data in the absorption phase) another approach of empirical linear mixed-effects modelling was used to investigate covariate effects directly on the observed peak and trough concentrations. Indacaterol exposure increases nonlinearly with age; the peak concentration increases by an average of 41% between 48 and 78 years (90% age range) in COPD patients and by an average of 21% between 16 and 69 years (90% age range) in asthma patients. AUCτ increases by an average of 23% between 48 and 78 years (Table 2). There is a less-than-linear increase in exposure with increasing age. In the empirical models for C_{max} and C_{min} in COPD, the effect of age in both models was similar**.** Using the full pharmacokinetic model, CL/F decreased nonlinearly with increasing age, thus driving an increase in average exposure, quantified as AUCτ.

Table 2: Covariate Effects in the Final model

Parameter	Estimate (% RSE)	95% Confidence Interval*	Interpretation with respect to exposure
Age on CL/F ($\theta_{Age,CL/F}$)	-0.425 (11.9)	-0.524 ; -0.326	Average exposure increases nonlinearly with age, by approximately 23% between 48 and 78 years
BMI on V_c/F ($\theta_{BMI,Vc/F}$)	0.256 (27.3)	0.119 ; 0.323	No effect on exposure
Body weight on F ($\theta_{Weight,F}$)	-0.312 (15.0)	-0.404 ; -0.220	Average exposure decreases nonlinearly with body weight, by approximately 21% between 50 kg and 107 kg
Gender on F ($\theta_{Sex,F}$)	1.07 (2.02)	1.03 ; 1.11	Average exposure is 7.0% greater in the typical female patient
Indication on F ($\theta_{Ind,F}$)	1.17 (2.47)	1.11 ; 1.23	Average exposure is 17.0% greater in the typical asthma patient
Race on F (Black patients, $\theta_{RaceB,F}$)	-0.151 (44.6)	-0.283 ; -0.0191	Average exposure may be reduced by 15% in the typical Black patient

* Derived from NONMEM-provided standard errors

Indacaterol exposure decreases nonlinearly with body weight; peak concentration decreases by an average of 25% between 50 and 107 kg (90% weight range) in COPD patients and by an average of 27% between 52 and 110 kg (90% weight range) in asthma patients. AUCτ decreases by an average

of 21% between 50 and 107 kg (Table 2). Similar effects of body weight were observed on C_{max} and C_{min}. Age and weight were not significantly correlated.

Indacaterol exposure was greater in female COPD patients, although this difference was unlikely to be clinically significant; peak concentration and AUCτ were 11% and 7% greater, respectively in female COPD patients compared with male COPD patients. AUCτ was an average of 17% greater in asthma patients than in COPD patients. Indacaterol exposure is lower (by an average of 30%) in Black asthma patients, although the number of Black subjects was small. No statistically significant effect of race on indacaterol exposure was found in COPD patients, although a trend towards reduced AUCτ in Black patients was noted.

The clinical implications of age, gender and body weight on indacaterol exposure appeared to be small and due to the overall dose linearity observed for indacaterol at therapeutic doses, it appears to be unlikely that any of these effects warrant dose adjustment.

Pharmacokinetic summary

After oral inhalation from an SDDPI device such as Concept1 (which is the proposed marketing device for administering indacaterol), indacaterol was rapidly absorbed and achieved peak serum levels (C_{max}) in the majority of subjects within the first 30 minutes. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 hours. Data from the multiple dose inhalation studies (A2221 and B2339) suggested that the effective half-life for accumulation was in the range of 40 to 52 hours which was consistent with the observation that steady state was achieved between 12 and 14 days of once daily (od) dosing.

The increase in steady state indacaterol AUC and C_{max} was dose-proportional in the dose range of 150 µg to 600 µg and there was no change in the clearance of indacaterol following repeated once-daily dosing via Concept1 (study B2339); following 14 days once daily dosing, there was a 3-fold increase in systemic exposure (Day 14/Day 1 AUC ratios were 2.9 to 3.5) and 2-fold increase in C_{max} (1.7 to 1.9).

There was no clinically meaningful difference in systemic exposure when comparing indacaterol dosing via Concept1 in the morning versus evening.

After intravenous administration, serum clearance was moderate (23.3 L/h), and a large volume of distribution was observed (Vz=2557 L) (study B2103). Relative bioavailability of an oral dose compared to an inhaled dose was 46% (Study A2106). The bioavailability data suggest that systemic exposure to indacaterol after inhalation is due to both pulmonary and intestinal absorption.

Since indacaterol is an inhaled drug, a formal food effect study was not conducted. In the pivotal studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake.

Indacaterol is highly bound to plasma and serum proteins. The in vitro human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively. In vitro protein binding results were consistent with ex-vivo protein binding measurements. Indacaterol had an in vitro blood-to-plasma concentration ratio of 1.2.

Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. In a human absorption/distribution/metabolism/excretion (ADME) study A2223, the majority of the orally administered radioactive dose was excreted into faeces and only a minor fraction (<2%) was found in the urine. Mass balance in the human ADME study was complete.

The primary metabolic pathways of indacaterol in humans involved monohydroxylation, O and N-glucuronidation, and both C- and N-dealkylation. After oral administration of indacaterol in the

human ADME study A2223, unchanged indacaterol was the main circulating component in human serum, accounting for 32.5% of the total drug-related AUC_{0-24h}. The contribution of individual metabolites to the total drug-related AUC_{0-24h} in human serum ranged from 4.2% to 12% with the hydroxylated metabolite P26.9 being the most prominent. The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic-O-glucuronide. CYP3A4 appeared to be the predominant isoenzyme responsible for hydroxylation of indacaterol. The hydroxylated metabolites P26.9 and P30.3 were found to have similar in vitro affinity to human beta-2-receptors. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays and are not expected to contribute significantly to pharmacological activity of indacaterol.

Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in C_{max} (B2216). Co-administration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C_{max} (B2220). Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and C_{max} respectively (A2311). Given the safety data of study B2339 and of the pivotal studies (which both confirmed safe use of a 600 μg dosage regimen), the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 150 μg or 300 μg.

Inhibition of the key contributors of indacaterol clearance, that is, UGT1A1 (study 2221), CYP3A4 and P-gp (studies A2311, B2220 and B2216) appear to have no clinically relevant impact on the clinical safety of therapeutic doses of indacaterol.

Indacaterol pharmacokinetics shows no difference between Japanese and Caucasian subjects (study 2215)]. Further exploration of ethnic factors as covariates of systemic exposure in COPD patients and patients with asthma was done using a population PK modelling approach. Ethnic factors/ race did not appear to have any significant impact on systemic exposure to indacaterol after inhalation via Concept1, although interpretation was limited due to majority of subjects being Caucasians and inadequate representation of other ethnic subgroups. The population PK analysis indicated that within the COPD analysis population the systemic exposure increased with increasing age (41% increase in peak exposure and 23% increase in steady state AUC_{0-24h} within the age range of 48 to 78years), decreased with increasing body weight (C_{max} by 25% and AUC_{0-24h} decreased by 21%, when body weight increased from 50 to 107 kg) and female COPD patients had on average 7%-11% higher systemic exposure than males. However, none of these minor changes appear to warrant a change in dosing regimen.

Mild and moderate hepatic impairment did not alter indacaterol pharmacokinetics or protein binding significantly (study A2307). The effect of severe hepatic impairment on indacaterol pharmacokinetics was not evaluated. Since renal clearance plays a very minor role in elimination of indacaterol, a study in renally impaired subjects was not conducted.

Pharmacodynamics

Pharmacodynamics in COPD patients

Introduction

The bronchodilator effects of indacaterol were investigated in COPD patients treated with up to 3000 μg indacaterol in single dose and 800 μg in repeated dose studies.

Common endpoints were trough FEV_1 to characterize the bronchodilator effect of indacaterol at the end of the 24 hours dosing interval and peak FEV_1.

Two short term efficacy studies (B**2212** and B**2205)** in patients with COPD characterized the bronchodilator effects of indacaterol over 24 h. These studies helped to determine the doses

evaluated in the Phase III clinical development program. Further studies in COPD patients focused primarily on safety/ tolerability and secondary PD effects of indacaterol **(B2202, B2217, B2201** and A**2105),** but these also included spirometric measurements for the assessment of bronchodilation. One study included a comparison of the bronchodilator effects on inspiratory capacity with those on FEV_1 **(B2211).** Study B**2318** investigated the effect of indacaterol on dynamic hyperinflation, exercise tolerance and dyspnoea in patients with COPD.

Three other studies were undertaken as part of the efficacy program for Phase III clinical Development (studies **B2307, B2305** and **B2340**).

Bronchodilator effects of indacaterol following single dose administration

Study B2212

B2212 was a Phase IIb, randomized, double-blind, double-dummy, active (formoterol 12 μg bd) and placebo controlled, multicentre, 5 period crossover, dose-ranging study to assess the bronchodilatory efficacy and safety of single doses of indacaterol 150 μg, 300 μg and 600 μg delivered via single dose dry powder inhaler (SDDPI) versus placebo in 51 patients with moderate to severe COPD. The study included patients aged 40-65 years and required to have a clinical diagnosis of COPD according to the GOLD Guidelines and a history of characteristic COPD symptoms (such as cough, sputum production, dyspnoea), and additionally meet the following criteria:[3]

- Smoking history of at least 10 pack years,[4]
- FEV_1 at Visit 1 and Visit 2 <65% of the predicted normal value and at least 0.75 L and a prebronchodilator FEV_1/FVC at Visit 1 and Visit 2 < 70%.

The primary efficacy endpoint (24 hour post-dose, trough FEV_1) for the mITT population was statistically significantly greater for all doses of indacaterol compared with placebo ($p< 0.001$). The least squares mean (LSM) difference to placebo was greatest with indacaterol 600 μg (180 mL), although that with indacaterol 300 μg was similar (170 mL) (Table 3). An exploratory analysis of treatment contrasts showed that the trough FEV_1 for indacaterol 600 μg was statistically significantly greater than that for formoterol 12 μg (LS mean difference of 50 mL) and indacaterol 150 μg (LS mean difference 40 mL). The treatment contrast between indacaterol 300 μg and formoterol 12 μg was also statistically significantly in favour of indacaterol. An analysis of covariance of 24 hours post-dose log-transformed (trough) FEV_1 for the mITT population also showed similar results. The results in the per protocol population were consistent with the results of the primary analysis in the mITT population, although differences between active treatments were not statistically significant in the PP population.

[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) produce guidelines and other resources about the diagnosis, prevention, and management of COPD.

[4] 1 pack year was defined as 20 cigarettes per day, every day, for one year, or 10 cigarettes a day for two years, or 40 cigarettes a day for six months etc.

Table 3: Study B2212

Analysis of covariance of 24 h post-dose (trough) FEV_1 (L) (modified ITT population)

	n	LSMean	SE	95% CI*	p-value*	SS 95% CI**	SD p-value (2-sided)**
Treatment Effect							
Indacaterol 600 µg	50	1.46	0.014	(1.43, 1.49)			
Indacaterol 300 µg	49	1.45	0.015	(1.42, 1.48)			
Indacaterol 150 µg	47	1.42	0.015	(1.39, 1.45)			
Formoterol 12 µg	50	1.41	0.014	(1.38, 1.43)			
Placebo	48	1.28	0.015	(1.25, 1.31)			
Treatment Contrast (Primary Analysis)							
Indacaterol 600 µg-Placebo		0.18	0.021	(0.14, 0.22)	<0.001	(0.13, 0.23)	<0.001
Indacaterol 300 µg-Placebo		0.17	0.020	(0.13, 0.21)	<0.001	(0.12, 0.22)	<0.001
Indacaterol 150 µg-Placebo		0.14	0.020	(0.10, 0.18)	<0.001	(0.09, 0.19)	<0.001
Treatment Contrast (Secondary / Exploratory Analysis)							
Indacaterol 600 µg-300 µg		0.01	0.020	(-0.03, 0.05)	0.5690		
Indacaterol 600 µg-150 µg		0.04	0.020	(0.00, 0.08)	0.0428		
Indacaterol 600 µg-Formoterol 12 µg		0.05	0.020	(0.01, 0.09)	0.0089		
Indacaterol 300 µg-150 µg		0.03	0.020	(-0.01, 0.07)	0.1382		
Indacaterol 300 µg-Formoterol 12 µg		0.04	0.020	(0.00, 0.08)	0.0426		
Indacaterol 150 µg-Formoterol 12 µg		0.01	0.020	(-0.03, 0.05)	0.5925		
Formoterol 12 µg-Placebo		0.13	0.020	(0.09, 0.17)	<0.001		

*95% CIs and p-values are calculated without multiplicity adjustment
** SS 95% CIs are based on a single step Dunnett procedure implemented using % SimIntervals SAS macro. The SD p-values are based on stepdown Dunnett procedure implemented using % SimTests SAS macro

Analysis of FEV_1 by time point showed that all doses of indacaterol, and formoterol 12 µg, had higher FEV_1 values than placebo at all time points (up to 24 hours post-dose) with no major differences between active treatment groups. Changes in FEV_1 from baseline were sustained until the 23 hour 45 minute time point for all indacaterol doses, particularly the two highest doses. All active treatments had statistically higher standardized AUC (0.5-4 hours) of FEV_1 than placebo (LS mean difference of 0.15 L, 0.22 L and 0.23 L for the indacaterol 150, 300 and 600 µg doses versus placebo). There was no significant difference between treatments in time to peak FEV_1. Analysis of covariance for % change from baseline in FEV_1 showed that all active treatments had significantly greater changes than placebo at all time points. The same was true for % change from baseline in FVC.

Overall, results from the single-dose Phase II study 2212 showed that all evaluated doses of indacaterol (150 µg, 300 µg and 600 µg) were associated with statistically significantly greater 24 hour post-dose (trough) FEV_1 than placebo. The differences were also clinically relevant, 180 mL for indacaterol 600 µg, 170 mL for indacaterol 300 µg and 140 mL for indacaterol 150 µg. The active control, formoterol 12 µg, was also associated with a clinically relevant and statistically significant increase in 24 hour post-dose (trough) FEV_1 relative to placebo. Exploratory analyses on 24 hour post-dose (trough) FEV_1 suggested that indacaterol 300 µg and 600 µg were more effective than the 150 µg dose, and more effective than formoterol 12 µg, although these results should be interpreted with caution as they were only exploratory and the study was not powered to detect differences between active treatments.

Study B1202

B1202 was a randomized, double-blind, placebo controlled, four-period crossover, multicentre, dose-ranging study that assessed the efficacy and safety of three single doses of indacaterol (150, 300 and 600 µg) delivered via Concept1 in 45 Japanese patients with COPD.

The primary efficacy analysis showed that all doses of indacaterol were associated with statistically significant ($p<0.001$) and clinically relevant increases compared with placebo in standardized FEV_1 AUC (22-24 hours). Standardized (with respect to time) FEV_1 AUC (22-24 hours) (LS means) for

placebo, indacaterol 150 µg , 300 µg and 600 µg were 1.33, 1.45, 1.48 and 1.49L, respectively. An exploratory analysis showed that the two higher doses (600 µg and 300 µg) of indacaterol were also statistically significantly more effective than the 150 µg dose. The results in the PP population were consistent with the results in the mITT population

All indacaterol doses had a statistically significantly greater standardized FEV_1 AUC (0-24 hours) than placebo, but the 150 µg dose had a statistically significantly lower standardized FEV_1 AUC0-24 hours than the higher doses (300 µg and 600 µg).

Overall, the 300 µg and 600 µg doses of indacaterol were associated with sustained efficacy in terms of improvements in FEV_1 and other pulmonary function measurements (for example, FVC), but the improvements reached plateau at the 300 µg dose. The 150 µg dose of indacaterol, while showing clinically relevant and statistically significant differences to placebo, appeared to be less effective than the 300 µg and 600 µg doses in terms of standardized FEV_1 AUC $_{22\text{-}24h}$ (trough) and peak FEV_1.

Bronchodilatory effects following multiple dosing

Study B2205

B2205 was a Phase II, randomized, double-blind, placebo-controlled, parallel group, multicentre, multiple dose (7 days), dose-ranging study to evaluate the bronchodilatory efficacy of indacaterol in 635 patients with moderate to severe COPD in terms of FEV_1 standardized area under the curve (AUC) between 22 and 24 hours on Day 1 of treatment. Patients took the study medication for 7 days and were assessed on Day 1 both pre-treatment and then up to 24 hours post first dose, then again on Day 7. A minimum of a 1-week washout period between the completion of the core protocol and the first day of dosing in the open label treatment period (tiotropium bromide 18 µg) was included to minimize the possibility of carry-over from the randomized treatment period. The 8-day, open-label tiotropium bromide treatment phase was added as an amendment to enable comparison of indacaterol with an established therapy for COPD.

The primary efficacy variable was the standardized AUC of FEV_1 calculated between 22 and 24 hours post-dose on Day 1 of treatment. The AUC values were significantly higher in all indacaterol MDDPI groups compared to placebo, with the largest difference seen between the 400 µg dose and placebo. The differences between the 400 µg dose and the 100 µg dose, and between the 400 µg dose and the 50 µg dose were also statistically significant. The AUC value for the 400 µg SDDPI group was higher than for all other treatment groups and this was statistically significant compared to placebo, 200 µg MDDPI, 100 µg MDDPI and 50 µg MDDPI groups. There was a notable and rapid increase in mean FEV_1 within the first 2 hours post-dose for the indacaterol treatment groups compared to placebo. This response declined slowly until a further small increase after 22 hours post-dose. All doses of indacaterol were statistically superior to placebo at every time point up to 24 hours post-dose on Day 1 and Day 7. Peak FEV_1 during the first 4 hours of dosing on Day 1 and Day 7 was significantly superior for all indacaterol MDDPI doses compared to placebo on Day 1 and Day 7. In addition, the 400 µg dose values were significantly higher than the 50 µg, 100 µg and 200 µg dose values on Day 1, and significantly higher that the 50 µg and 100 µg dose values on Day 7. The 400 µg SDDPI group peak FEV_1 was significantly higher than placebo on both days. The number of patients with a percentage change from baseline of ≥12% in FEV_1 was noticeably higher in the indacaterol MDDPI groups and SDDPI 400 µg group compared to placebo at all time points on Day 1 and Day 7. The 400µg SDDPI group had the largest number of patients, at a single time point with a change from baseline of ≥12% (71.6 % at 3 hours on Day 1). All doses of indacaterol showed statistically superior results in terms of FVC to placebo at every time point up to 24 hours post-dose on Day 1 and Day 7. The increase in FVC in all indacaterol groups was evident from up to 30 minutes to 4 hours post-dose after which values fell slightly.

The AUC values for all indacaterol treatment groups were higher than the tiotropium values and this was significant for the 400 µg MDDPI group (p=0.0017). The difference in AUC values between the 400 µg SDDPI group and tiotropium group was also statistically significant (p=0.0074).

Overall, this study provided limited evidence for efficacy of indacaterol 400 µg SDDPI over placebo, although interpretation of results was limited by lack of randomisation based on smoking status at baseline and fewer number of current smokers in the indacaterol 400 µg group compared with placebo. A majority of the patients in this study were administered indacaterol using the MDDPI device (which is not the proposed marketing device). The SDDPI dose of 400 µg in this study was similarly effective to the 400 µg MDDPI dose; however, it was not clear if the SDPPI device used in this study was similar to the device used in Phase III clinical trials or the final marketing device. Furthermore, none of the doses proposed for marketing (150 µg and 300 µg) were evaluated in this study.

Study B2201

B2201 was a randomized, double-blind, placebo controlled, parallel group, multicentre study in 163 patients with moderate COPD. Its primary objective was to assess the safety and tolerability of 28 days treatment with indacaterol [(400 µg [68 patients] or 800 µg [67patients] once daily) delivered via a SDDPI device, compared to placebo (28 patients).

Although planned as a safety study, exploratory analysis of FEV_1 and salbutamol use data provided evidence of drug efficacy. When comparing LS means of FEV_1 values between the treatment groups, both doses of indacaterol (400 µg and 800 µg) were statistically significantly superior to placebo at all post-baseline time points and had an adjusted mean difference of ≥ 200 mL. There was an increase in the number of patients not using salbutamol since the previous visit, which was most marked in the indacaterol groups and largest in the 400 µg treatment group.

This 28-day study of multiple dosing with indacaterol showed a marked increase from baseline in FEV_1 for both indacaterol treatment groups (400 and 800 µg) using the SDDPI, with least squares (LS) means of change from baseline ranging from 240 to 320 mL. Treatment contrasts of indacaterol versus placebo were statistically significant for both dose strengths at all visits. The pre-dose FEV_1 measurements on Days 14 and 28 were also over 200 mL above baseline in the indacaterol treatment groups, showing that the treatment effect lasted throughout the 24 hours period.

Overall, this study mainly provided evidence for safety of nearly twice the proposed dose of indacaterol and also provided supportive evidence for bronchodilatory efficacy of indacaterol, although the doses evaluated were not the proposed marketing indacaterol doses.

Collectively, these studies showed that indacaterol provides effective bronchodilation based on spirometric measures of trough FEV_1. The treatment effects compared to placebo (baseline-adjusted) for indacaterol delivered via the Concept1 device ranged from 120 mL up to 250 mL for inhaled doses of 150 µg to 800 µg. Single doses below 150 µg did not appear to provide clinically meaningful bronchodilation over 24 hours. After repeated doses the bronchodilator effect in the dose range above 150 µg ranged from 145 mL up to 350 mL with no clear evidence for a further improvement at doses above 400 µg. Hence, clinically meaningful bronchodilator effects of >120 mL have been observed consistently with inhaled indacaterol doses of 150 µg and higher (irrespective of the device used). The trough bronchodilator effect after 24 hours appears to be more pronounced after repeated dosing.

Across all studies, indacaterol also produced consistent clinically meaningful effects on peak FEV_1. The largest effect was seen in study A2105 where 800 µg inhaled indacaterol resulted in a peak

FEV_1 contrast versus placebo of 350 mL. After single doses the peak FEV_1 treatment contrast versus placebo appeared to be slightly smaller than after repeated doses.

Other pharmacodynamic studies

Indacaterol efficacy data from clinical studies in patients with asthma are included, given previous development of indacaterol monotherapy in asthma prior to the concerns raised regarding LABA-only use in asthma. These studies also support the consistency of bronchodilator responses obtained in COPD.

In study **B2202**, FEV_1 trough changes from baseline were 210, 300, 150 and 220 mL with indacaterol 400 µg, 1000 µg, 2000 µg and 3000 µg, respectively.

In study **A2105,** COPD patients receiving 800 µg indacaterol showed rapid onset of bronchodilator action as shown by spirometry; FEV_1 was clinically meaningful at the first spirometry reading post dose (1 hour) and was maintained through the 14 day clinical phase. The increase in FEV_1 following indacaterol treatment was about 15% greater compared to baseline.

Study **B2211** was an exploratory, double-blind comparison of inspiratory capacity (IC) and FEV_1 in 30 COPD patients following single dose administration of indacaterol and placebo and open label bd administration of formoterol. Both indacaterol 300 µg and formoterol (12 µg bd) showed statistically significant ($p<0.001$) improvements over placebo in FEV_1 maximum effect (E_{max}), FEV_1 (trough) and inspiratory capacity (IC) E_{max}**.** The onset of both maximal change in IC and FEV_1 occurred 1 hour post-dose, which was consistent with a fast onset of action. The maximal change in IC observed with indacaterol was a clinically relevant 380 mL. In this study the FEV_1, E_{max} and IC E_{max} showed a similar treatment response for indacaterol versus placebo (the point estimates for the treatment comparison to placebo based on geometric means of absolute values were 1.19 in both cases). Compared with formoterol, indacaterol 300 µg showed a trend of significantly greater improvement in each of the above parameters (by 4-8% greater), although these results should be interpreted with caution as the study was not powered to detect such differences.

B2318 was an exploratory, Phase III, 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 hyperinflation, subjective breathlessness and health status in 27 patients with COPD. The primary objective of this study was to evaluate the effect of 2 weeks treatment with inhaled indacaterol (300 µg) on isotime and peak exercise IC in patients with COPD. IC was measured at two minute intervals during exercise. Isotime was defined as the time the subject was still exercising in the shortest of all sub-maximal exercise tests whilst peak time was defined as the last measurement taken in the exercise period. Both peak and isotime IC showed statistically significant ($p<0.03$) improvements over placebo on day 14 (0.317 mL for peak and 0.268 mL for isotime).

Effect of indacaterol on heart rate

B2217 was a randomized, double blind, placebo-controlled, cross-over, two-part study to compare the effect of indacaterol (300 µg) and salmeterol (50 µg) on heart rate under exercise and high-dose salbutamol co-administration in patients with COPD. During exercise, no differences in maximal heart rate (HR) were observed between indacaterol and salmeterol. Following high dose salbutamol, there was no observed difference following treatment with a single dose of indacaterol and salmeterol. In addition, no difference in maximal HR was observed following a second dose of salmeterol without an accompanying indacaterol dose. Therefore, despite a second peak in exposure to salmeterol, no differential impact on maximal HR was observed. The incidence of maximum HR increase >10 bpm during exercise was similar for both active treatment groups during exercise in Part 1, being 0.20 for indacaterol (n=26) and 0.16 for salbutamol (n=26). The incidence of maximum HR increase >10 bpm from placebo for both active treatment groups during salbutamol

administration in Part 2 was similar (0.13 for indacaterol versus 0.17 for salmeterol between 0 and 24 hours). Overall, differences in pharmacokinetic profiles for the two long-acting β2-agonists do not appear to have different effect on HR.

In study **B2202**, single doses of indacaterol in COPD patients produced a dose-dependent increase in heart rate up to 3000 μg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm. In the double-blind, placebo-controlled study **B2201**, repeat doses of 400 and 800 μg indacaterol for 28 days produced a maximum heart rate change versus placebo of 2.9 bpm one hour post-dose with the 800 μg dose.

Overall the effects on heart rate appeared to be marginal and inconsistent with doses up to 800 μg indacaterol, so that it is unlikely that doses up to 800μg will produce relevant effects on heart rate. There is an indication of potential heart rate effects at very high overdoses such as 3000 μg indacaterol.

Effect of indacaterol on QTc interval

With doses up to 800 μg in COPD patients there was no suggestion of a clinically meaningful (>10 ms) increase in QTc interval after four weeks of treatment. Any change observed did not appear to be dose-dependent. Study **B2202**, which investigated single doses of indacaterol up to 3000 μg in patients with COPD showed a maximal increase from baseline in QTcF of 9.10 ms at 8 hours after the inhalation of 2000 μg indacaterol.

Changes in blood glucose and serum potassium associated with indacaterol administration in COPD were small, variable and not dose-related (in the therapeutic dose range).

A2339 was a randomized, multiple-dose, placebo and positive-controlled parallel group, Thorough QTc study to evaluate the effects of indacaterol on cardiac safety in 404 healthy subjects.[5] There was no evidence of statistically significant QT prolongation for any of the three indacaterol doses compared to placebo**.** In contrast, all time points from 20 minutes until 24 hours post-dose following dosing with moxifloxacin control demonstrated statistically significant QT prolongation compared to placebo confirming the assay sensitivity of the trial.

Summary of pharmacodynamics

The PD studies showed that indacaterol provides effective bronchodilation based on spirometric measures of trough FEV_1. The treatment effects compared to placebo (baseline-adjusted) for indacaterol delivered via the Concept1 device ranged from 120 mL up to 250 mL for inhaled doses of 150 μg to 800 μg. Doses below 150 μg appeared not to provide clinically meaningful single dose bronchodilation over 24 hours. After repeated doses the effect size in the dose range above 150 μg was from 145 mL up to 350 mL with no clear evidence for a further improvement in bronchodilator response in doses above 400 μg. The 24 hour trough bronchodilator effect appears to be more pronounced after repeated dosing than after a single dose.

Across all studies, indacaterol also produced consistent clinically meaningful effects on peak FEV_1. The largest effect was seen with 800 μg inhaled indacaterol which resulted in a peak FEV_1 contrast versus placebo of 350 mL. There was only a small or no incremental effect for peak FEV_1 with indacaterol doses >300 μg.

Indacaterol 300 μg over 14 days increased inspiratory capacity under peak exercise by 317 mL when compared to placebo. It also demonstrated a statistically significant increase in resting IC,

[5] EMEA. ICH E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, 25 May 2005. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04).

exercise endurance and FEV_1 as well as measures of dyspnoea, which were significantly improved with indacaterol (B2318).

Studies in asthma patients also support the consistency of bronchodilator responses obtained in COPD.

The Thorough QTc study in 404 healthy subjects showed no concerns for pro-arrythmogenic potential for indacaterol in the dose range of 150-600 μg (B2339). With doses up to 800 μg in COPD patients, there was no suggestion of a clinically meaningful (>10 ms) increase in QTc interval after four weeks of treatment (B2302). The effects on heart rate appeared to be marginal and inconsistent with doses up to 800 μg indacaterol, although very high overdoses such as 3000 μg indacaterol could lead to increased heart rate (B2202).

Efficacy

There were six Phase III studies evaluating efficacy and safety of indacaterol in COPD patients. All these studies used the proposed for marketing indacaterol formulation and device (Concept 1). The phase III program includes 3 large, pivotal efficacy and safety studies of up to 52 weeks duration **(B2334, B2335 and B2346)** and 3 small, short-term profiling crossover studies **(B2305, B2307, B2340)** in patients with COPD. All studies were conducted according to Good Clinical Practice (GCP) guidelines with adequate ethics approval. Spirometry equipment and performance of spirometric testing were in accordance with the American Thoracic Society standards (Miller et al, 2005).[6] Three acceptable manoeuvres were performed for each time point. All displaceable volumes were reported in litres (L) at normal body temperature (37° C), ambient pressure, saturated with water vapour. In order to reduce the variability of observations, where possible the same equipment was used and the same staff member evaluated and coached a given patient at each visit throughout the study. In addition the spirometer was calibrated every morning before taking any spirometric measurements for this study.

Pivotal Phase III studies

Overview of pivotal studies

The seamless, adaptive design of pivotal study B2335S provided evidence to support efficacy of both the proposed indacaterol doses (150 μg and 300 μg), while another adequate and well-controlled trial (**B2346**) provided efficacy data for up to (3) months for the 150 μg dose. The 52 week trial **(B2334)** added further efficacy data for the 300 μg dose and provided data to support long-term usage (including extra safety data at 600 μg for 1 year).

The inclusion and exclusion criteria were similar for the 3 pivotal studies and reflected the proposed target population for the intended use of indacaterol. The main inclusion criteria were adult male and female patients with a clinical diagnosis of moderate to severe COPD. The diagnosis of COPD severity is made using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD 2005). The criteria for defining moderate to severe COPD used in the inclusion criteria for the pivotal studies in this submission are shown in Table 1.

Patients with either reversible (although not fully reversible) or non-reversible airway function were enrolled. Although the former usually demonstrate a significant increase in airflow after the inhalation of a β2-agonist, the latter may show improvement in symptoms and functional capacity even in the absence of an obvious spirometric response. Patients were not classified according to reversible or irreversible disease.

The main exclusion criteria were:

- pregnancy,

[6] Miller MR, Hankinson J, Bruanasco V et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-38.

- hospitalization for an exacerbation of airway disease in the prior 6 weeks,
- a respiratory tract infection within prior 6 weeks,
- concomitant pulmonary disease,
- a history of asthma,
- diabetes Type I or uncontrolled diabetes Type 2,
- other serious medical conditions (including cancer with < 5 years survival time)
- patients with QTc > 0.45 seconds for males and > 0.47 seconds for females,
- a history of prolonged QTc intervals, untoward reactions to sympathomimetic amines or inhaled medications,
- those patients unable to maintain regular sleep cycles.

Certain medications also lead to exclusion including:

- long acting anticholinergic agent tiotropium (bromide) within 7 days for Visit 1,
- short acting anticholinergics within 8 hours,
- fixed combinations of β2-agonists and inhaled corticosteroids or long acting β2-agonists within 24 hours,
- short acting β2-agonists within 12 hours,
- or non-modified release theophylline within 72 hours of Visit 1.

Other excluded medications were non-potassium sparing diuretics, non-selective beta-blockers, quinidine-like medications, tricyclic antidepressants, monoaminooxidase inhibitors, terfenadine, astemizole and any other drugs contraindicated for QT prolongation. **Varenicline for smoking cessation was only excluded in study B2346 and use of varenicline in the other 2 pivotal studies was not specified.**

Although patients were randomised according to smoking status in all 3 pivotal studies, tobacco exposure during the study was not monitored and any changes in smoking status were not reported or considered in the analysis. In all 3 pivotal Phase III studies, treatment groups were not stratified according to baseline severity of COPD or prior use of inhaled corticosteroids (ICS), but these were similar in the different treatment groups as discussed in sections below. However the sponsor highlighted that the baseline severity was accounted for in the statistical model.

The trough FEV_1 was the primary efficacy endpoint in all 3 pivotal studies and was an appropriate primary endpoint as it reflects the efficacy of the study drug in COPD over 12 to 24 hours (Donohue 2005).[7] Also, this value reflects morning lung function when patients awaken and symptoms are more noticeable (Gilbert et al 2007). The 24 hour post-dose trough FEV_1 was defined as the average of the 23 hours 10 min and the 23 hours 45 min post-dose values taken in the clinic. **A difference of 120 mL in trough FEV_1 between indacaterol and placebo was considered a clinically important difference for COPD patients by the sponsor, (no explicit definition is provided in the current EU Committee for Medicinal Products for Human Use (CHMP) guidelines (dated Jan 22, 2009). The sponsor provided in a response to the clinical evaluation report literature-based clinical trials results in support of the cut-off of 120 mL as being clinically relevant.**

Apart from 24 hours post-dose FEV_1, other related spirometry outcomes were measured. In addition to these lung function endpoints, a wide range of symptom-related outcomes, covering many aspects of COPD and its effects, were assessed. These included the St. Georges' Respiratory Questionnaire (SGRQ), the transitional dyspnoea index (TDI), COPD exacerbations, use of rescue medication, days of poor control (DOPC) and daytime and night-time symptoms.

[7] Donohue JF. Still looking for answers in COPD. Lancet 2005; 365: 1518-1520.

Pivotal study B2335S

B2335S was a Phase III, 26-week treatment, multicentre, randomized, double-blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group study to assess the efficacy, safety and tolerability of two doses of indacaterol (selected from 75, 150, 300 and 600 µg od) in patients with COPD using blinded formoterol (12 µg bd) and open label tiotropium (18 µg od) as active controls. The study remained blinded to the sponsor throughout both of its recruitment stages. Stage 1 was designed to provide data about the risk-benefit of 4 dose regimens of indacaterol (75, 150, 300 and 600 µg od) in order to select two doses to carry forward into study Stage 2. The dose selection was done by an independent external data monitoring committee (DMC), using unblinded data to which only the DMC had access. Patients were randomly assigned to receive one of the following double-blind, double dummy treatments **(**indacaterol 75 µg od, indacaterol 150 µg od, indacaterol 300 µg od, indacaterol 600 µg od, placebo, formoterol 12 µg bd) or open label tiotropium 18 µg od using an allocation ratio of 1:1:1:1:1:1:1 with stratification for smoking status. Formoterol was included as an active comparator in Stage 1 of the study to make a blinded comparison with a LABA for dose selection. Formoterol was provided as dry powder capsules via an aerolizer device. In order to maintain the blind, Stage 1 of the study was therefore double-dummy with patients in the indacaterol and placebo dose arms also receiving placebo via aerolizer. The marketed drug tiotropium (18 µg od) was selected to compare the safety and efficacy of indacaterol with the current gold standard for COPD. For tiotropium treatment, commercially available tiotropium and a Handihaler device were supplied by the pharmacy. No placebo to tiotropium was available and so blinding of the tiotropium treatment arm was not possible. A total of 1683 patients were randomized to study treatments selected in Stage 1. Overall, 76.7% of patients completed the study as planned. An interim analysis was performed when at least 770 patients (approx. 110 evaluable patients from each of the seven treatment groups) from Stage 1 each completed at least 2 weeks of treatment. The objective of the interim analysis, as part of the intended adaptive design, was only to select the two doses of indacaterol with the optimal risk-benefit profile for stage 2 of the study. Formoterol was not carried forward into Stage 2, as its purpose in Stage 1 was as a bd LABA comparator for dose selection, and the major planned comparison was with tiotropium, a standard COPD therapy.

The selection of the two indacaterol doses to continue into Stage 2 of the study based on these two primary variables was undertaken by the independent Data Monitoring Committee, according to dose selection guidelines outlined in the DMC charter; briefly the guidelines were based upon the following criteria:

• The selected dose needed to be 0.12 L greater than placebo in terms of trough FEV_1 and numerically higher than tiotropium and formoterol.

• The selected dose needed to be numerically higher than tiotropium and formoterol in terms of FEV_1 AUC 1-4 hours.

The DMC were asked to select the lowest dose that met the criteria and the next highest dose (unless the 600 µg dose was selected when the 300 µg dose also had to be chosen).

Stage 1 patients who were receiving either of the selected doses of indacaterol, tiotropium or placebo continued in a "seamless" manner into Stage 2. Patients on the doses not selected (75 µg and 600 µg) or those receiving formoterol were discontinued. In Stage 2, investigator sites re-commenced recruitment for the two chosen indacaterol doses, placebo and tiotropium in a 1: 1: 1: 1 ratio. An additional 285 patients per treatment group were randomized until the total required number of patients (400 per group) had been included. Each patient in the selected dose groups received study drug for a total of 26 weeks irrespective of whether they had commenced in Stage 1 or Stage 2.

Efficacy endpoints and statistical considerations

The primary objective of the study was to demonstrate that at least one of the selected indacaterol doses (150 and 300 μg od) was superior to placebo with respect to 24 hour post dose (trough) FEV_1 after 12 weeks of treatment. The primary variable was analysed using a mixed model. The model contained treatment as a fixed effect with the baseline FEV_1 measurement, FEV_1 prior to inhalation and FEV_1 30 min post inhalation of salbutamol/ albuterol (components of SABA reversibility at Day -14), FEV_1 prior to inhalation and FEV_1 one hour post inhalation of ipratropium (components of anti-cholinergic reversibility at Day -13) as covariates. The standard deviation of 270 mL for trough FEV_1 was based on the weighted average of two Foradil (formoterol) pivotal studies (FOR258C0056 and FOR258C0058) and the results from an indacaterol study B2205.The key secondary objective was to show that at least one of the selected indacaterol doses was not inferior to tiotropium with respect to 24 hour post dose (trough) FEV_1 after 12 weeks of treatment. Non-inferiority was defined as a difference in FEV_1 not less than -55 mL. If the key secondary objective (non-inferiority of at least one indacaterol dose to tiotropium with respect to trough FEV_1 after 12 weeks treatment) was met indacaterol dose(s) were then tested for superiority against tiotropium with respect to trough FEV_1 after 12 weeks treatment. This comparison did not form part of the hierarchical procedure and no adjustment for multiplicity was made. Another important secondary endpoint was the percentage of COPD 'days of poor control' during 26 weeks of treatment. A 'day of poor control' was defined as any day in the Patient Diary where a score ≥ 2 (that is, moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, colour of sputum, breathlessness).

The primary analysis population for the primary and important secondary efficacy endpoints was the ITT population. The PP population was also used for supportive analysis of trough FEV_1 (superiority comparison). The primary analysis population for the key secondary efficacy endpoint (non-inferiority comparison of trough FEV_1 versus tiotropium) was the PP population.

Other secondary endpoints included:-

Spirometry measures- Trough FEV_1 at Day 2 and after 2 and 26 weeks treatment, FEV_1 and FVC during 12 hours post morning dose, Peak FEV_1 during 4 hours post morning dose, FEV_1: AUC (5 min – 4 hours), FEV_1: AUC (5 minutes – 11 hours 45 minutes) measured in a sub-set of patients, FEV_1 and FVC trough response over 26 weeks, FEV_1 and FVC early response over 26 weeks;

COPD exacerbations- Time to first COPD exacerbation, COPD exacerbation rates;

Symptoms- TDI Focal Score after 4, 8, 12, and 26 weeks treatment;[11] Percentage of nights with 'no night-time awakenings' over 26 weeks; percentage of days with no daytime symptoms,[8] Percentage of 'days able to perform usual daily activities' over 26 weeks (was defined from the diary data as any day where the patient was not prevented from performing their usual daily activities due to respiratory symptoms); percentage of patients with a clinically important improvement of at least 1 unit in the focal TDI score;

Rescue medication - daily rescue use, that is, number of puffs over 26 weeks; Daytime and night-time rescue medication use (number of puffs) over 26 weeks, Daily, daytime and night-time rescue medication use (number of puffs) at approximately 4 weekly intervals , Percentage of 'days with no rescue use' over 26 weeks);

[8] A day with 'no daytime symptoms' was defined from the diary data as any day where the patient had recorded in the evening no cough, no wheeze, no production of sputum and no feeling of breathless (other than when running) during the past 12 hours (approx 8 am to 8 pm).

Health-related quality of life:- Total SGRQ score after 4, 8, 12 and 26 weeks treatment;[9] Percentage of patients with a clinically important improvement of at least 4 units in the total SGRQ score after 4, 8, 12 and 26 weeks treatment; EuroQol after 12 and 26 weeks treatment and a health state assessment from 0 (worst possible health state) to 100 (best possible health state);[10]

Exploratory endpoints included:-BODE index after 12 and 26 weeks treatment[11]; COPD quality of life questionnaire.

Other secondary efficacy variables and time points were analysed for the ITT population only, unless stated otherwise and treatment comparisons for these endpoints were made without an adjustment for multiplicity.

For the testing of non-inferiority of indacaterol with respect to tiotropium, a non-inferiority margin of 55 mL was used.

Patient disposition and baseline demographics

From the four treatment groups continued into Stage 2, 416, 416, 415 and 418 patients in the indacaterol 150 µg od, indacaterol 300 µg od, tiotropium and placebo groups were treated and were included in the Safety and ITT populations for analysis.

Discontinuations from the study occurred more frequently for placebo patients than for the indacaterol or tiotropium treated patients (22.6%, 18.4%, 21.2% and 30.8%, for the indacaterol 150 µg, indacaterol 300 µg, tiotropium, and placebo groups, respectively) and the most common reasons for discontinuation were adverse events (6.9%, 6.2%, 4.0%, and 10.8%, respectively), and withdrawal of consent (6.9%, 5.3%, 4.8%, 8.7%, respectively). In addition, more patients receiving placebo withdrew due to unsatisfactory therapeutic effect compared to the indacaterol and tiotropium treatment groups (1.0%, 2.2%, 2.1%, 4.0%, respectively).Major protocol deviations (those which excluded ITT patients from the per-protocol population during Stage 2 of the study) occurred slightly more frequently for the tiotropium group than for the indacaterol treatment groups.

Patient demographics and disease characteristics were comparable across the treatment arms, and represented the target population of patients with moderate to severe COPD and a smoking history of at least 20 pack years. Treatment groups continued into Stage 2 of the study were comparable in terms of baseline demographics. The mean age of patients in the study was 63.6 years, with 47.5% aged 65 years or older. The majority of patients were male (62.8%), Caucasians (84%) with mean body mass index (BMI) of 26.7 kg/m^2 (24.6% patients were classified as obese with BMI > 30 kg/m^2). Just over half of the patients were ex-smokers, with the remaining patients being active smokers. The median number of pack years (total years of smoking multiplied by cigarette packs smoked per day) for all patients was 43.0. The median duration of COPD was 5.1 years (range 0 - 67.6 years) and approximately two-thirds of patients (65.9%) had a duration between 1 and 10 years. Slightly more than a third of patients were using ICS at baseline (37.5%). The majority of patients had moderate to severe COPD according to the GOLD 2005 guidelines (95%). Baseline disease severity and spirometry values were similar in all treatment.

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[9] The St. George's Respiratory Questionnaire (SGRQ) was used to provide health-related quality of life measurements during the course of the study. The test is a composite of three domains with a total score of 0 to 100 with a higher score indicating poorer health.

[10] EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with 3 categories (no problem, moderate problem, severe problems.

[11] BODE index is a composite measure of COPD severity and has a differential prediction of outcomes. It is a total score of 4 domains scores with the total score ranging from 0 to 10. Higher BODE index scores indicate a higher risk of death.

Mean compliance with the device (SDDPI used to deliver indacaterol 150 μg and 300 μg or placebo, Handihaler device used to deliver tiotropium) was high (over 96% for all treatment groups).

Primary efficacy results

In Stage 1, following the dose selection guidelines, the reference value for trough FEV_1 was 0.14 L (tiotropium versus placebo difference) and for FEV_1 AUC (1-4 hours) was 0.22 L (formoterol versus placebo). The lowest dose to surpass these reference values was the indacaterol 150 μg dose, with the next highest dose being the 300 μg.

In Stage 2, after 12 weeks of treatment, both indacaterol 150 μg (1.46L) and 300 μg (1.46L) produced statistically significant greater improvement in trough FEV_1 compared with placebo (1.28L)($p<0.001$, based on a two-sided significance level of $p<0.0125$ and 98.75% confidence intervals entirely higher than 0 L). The difference of 180 mL over placebo for both indacaterol 150 μg and 300 μg was well in excess of the pre-defined (by the sponsors) minimum clinically relevant improvement of 120 mL. Results were almost identical for the PP population. The LSM trough FEV_1 at Week 12 for tiotropium (140) was also statistically superior to placebo for both the ITT and PP populations. Sensitivity analyses of the primary efficacy variable without last observation carried forward (LOCF) imputation also revealed consistent statistically significant results in both ITT and PP populations.

The results of the primary efficacy analysis for all subgroups (with at least 20 patients per subgroup (<65 and ≥65 years of age, males and females, Caucasian and Asian race, moderate and severe COPD severity, ex- and current smokers, and ICS use and non-use at baseline) were consistent with those of the overall study population in terms of showing superiority of both indacaterol doses to placebo and non-inferiority of both doses to tiotropium. Statistical superiority of indacaterol 150 μg (n=11) over placebo (n=6) was not shown for the small subgroup of black patients and statistical superiority of both indacaterol 150 μg and 300 μg (n=4 and n=2, respectively) over placebo (n=3) was not shown for the small subgroup of 'other' race patients.

Secondary efficacy results

The LSM percentages of COPD 'days of poor control' (based on patient-reported symptoms captured in the Patient Diary) over 26 weeks of treatment were numerically similar for the indacaterol and tiotropium treatment groups and slightly lower than those for the placebo group (31.5, 30.8, 31.0, and 34.0 for indacaterol 150 μg, indacaterol 300 μg, tiotropium and placebo, respectively), but treatment group comparisons did not show statistically significant differences for either indacaterol dose or tiotropium compared to placebo. A large change with fewer days of poor control from baseline was noted in the placebo group. COPD 'days of poor control' score was broken down to its component symptoms from the patient diaries. The cough and sputum production/colour did not show any significant improvement over placebo with indacaterol or tiotropium; however, wheezing and breathlessness components showed significant improvements over placebo with both indacaterol (150 μg and 300 μg) and tiotropium.

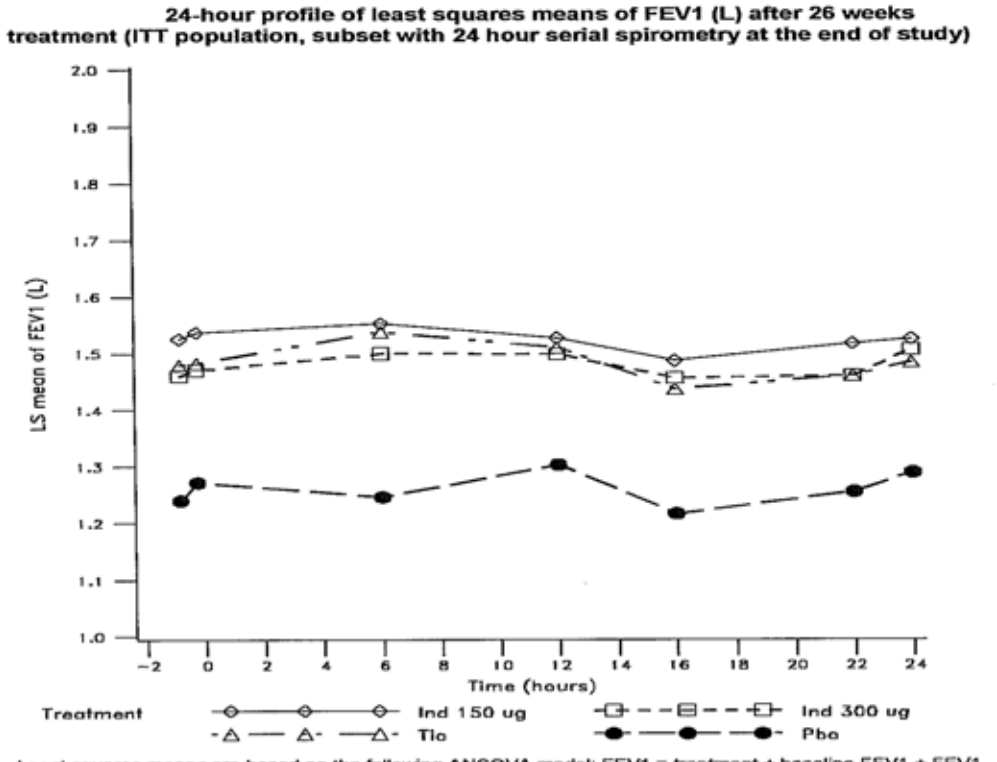
At each time point measured (Day 2, Day 15 and Week 26), indacaterol 150 μg and 300 μg both showed statistically superior improvements in trough FEV_1 compared to placebo (all $p<0.001$). Both indacaterol doses were also shown to be non-inferior to tiotropium at each time point measured (all $p<0.001$, if based on a one-sided significance level of $p<0.025$ and 95% confidence intervals higher than -0.055 L). The improvement in trough FEV_1 at Day 2 was statistically significantly higher for the indacaterol 300 μg dose compared to the indacaterol 150 μg dose suggesting an earlier onset of effect for the indacaterol 300 μg dose, but LSM trough levels were similar for both indacaterol doses at the Day 15 and Week 26 endpoints (although the 300 μg dose remained numerically superior at Week 26). Improvements in LSM trough FEV_1 for the indacaterol dose groups were also comparable to or higher than for the tiotropium group.

At Week 12, Peak FEV_1 in the first 4 hours post-dose and standardized AUC measurements for FEV_1 (between 5 minutes and 4 hours and between 5 minutes and 11 hours 45 minutes) were statistically significantly higher with both indacaterol (150 and 300µg) and tiotropium compared with placebo. A sustained improvement in FEV_1 for both indacaterol doses over placebo, comparable to or slightly better than that shown for tiotropium, is shown over the 12 hours of spirometry measurements. A sustained improvement in FEV_1 for both indacaterol doses over placebo, comparable to that shown for tiotropium, was also shown over the 24 hours of spirometry measurements in a subset of the ITT patient population. A dip in FEV_1 at 16 hours for all treatments probably reflects diurnal variation (Figure 2). Overall, these results suggest maintenance of the bronchodilation across the 24 hour period.

The LS mean increase from baseline in both morning and evening peak expiratory flow (PEF) was statistically significantly higher for both indacaterol groups compared to placebo (all $p<0.001$) and compared to tiotropium (both $p<0.001$ for morning PEF, $p<0.05$ for evening PEF). Analysis of forced vital capacity (FVC) in the ITT population showed similar results to FEV_1. At all days and time points both indacaterol dose groups and tiotropium had statistically significantly greater FVC values than placebo with no statistically significant difference between the indacaterol groups and tiotropium at most time points.

The rates for patients free of COPD exacerbation at 6 months based on Kaplan-Meier estimates were higher for the indacaterol 150 µg and indacaterol 300 µg doses compared with placebo and comparable to that seen for tiotropium. Estimated hazard ratios were in favour of the indacaterol doses and achieved statistical significance for the indacaterol 150 µg group. However, the proportion of patients who experienced at least one COPD exacerbation was similar across treatments. The rate of COPD exacerbations per year were numerically in favour of the indacaterol doses and tiotropium compared to placebo, with statistical significance for the comparison with the indacaterol 150 µg dose.

Figure 2: 24-hour profile of least squares means of FEV_1



Least squares means are based on the following ANCOVA model: FEV1 = treatment + baseline FEV1 + FEV1 reversibility components + smoking status + country + center(country) + error, with center(country) included as random effect.

TDI scores increased from baseline to Week 12 and further to Week 26 for all treatment groups including placebo. At both Week 12 and Week 26, the LS mean scores were greatest for the indacaterol 300 µg treatment group. Both the indacaterol treatment groups had statistically significantly greater scores than placebo at Weeks 12 and 26. At Week 12 the indacaterol 300 µg dose achieved the defined minimal important difference (MID) of 1 point and at Week 26 both doses achieved this MID. LS mean scores were numerically higher for the indacaterol treatment groups compared to tiotropium at Weeks 12 and 26, which reached statistical significance for the indacaterol 300 µg group compared to tiotropium at Week 12 (p=0.046), but not at week 26**.** The percentage of patients with a clinically meaningful improvement in TDI focal score (an increase of 1 or more) ranged from 65.8% to 70.8% in the indacaterol 300 µg treatment group and 56.6% to 62.4% in the indacaterol 150 µg treatment group, compared to 49.9% to 57.3% in the tiotropium group and 39.5% to 46.6% in the placebo group over the course of the study. The difference between indacaterol 300 µg and tiotropium was also statistically significant at all visits (Table 5).

Table 4: Number of COPD exacerbations per patient over 26 weeks

Number of COPD exacerbations (without imputation)	Ind 150 µg N=416	Ind 300 µg N=416	Tio N=415	Pbo N=418
Number per patient - n (%)				
None	344 (82.7)	340 (81.7)	336 (81.0)	327 (78.2)
1	57 (13.7)	60 (14.4)	66 (15.9)	73 (17.5)
2	13 (3.1)	12 (2.9)	11 (2.7)	12 (2.9)
3	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)
≥4	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.7)
Mean (SD)	0.22 (0.525)	0.23 (0.556)	0.23 (0.523)	0.28 (0.625)
Median	0.00	0.00	0.00	0.00
Min - Max	0 - 4	0 - 4	0 - 4	0 - 4
Total number of exacerbations	90	97	95	118
Total number of treatment years	178.55	184.12	180.23	164.88
Rate of exacerbations per year	0.50	0.53	0.53	0.72
Treatment comparisons				
vs. Pbo Ratio of rates	0.67	0.75	0.70	
95% CI	(0.46,0.99)	(0.51,1.08)	(0.48,1.03)	
p-value	0.044	0.125	0.070	
vs. Tio Ratio of rates	0.96	1.06		
95% CI	(0.64,1.43)	(0.71,1.57)		
p-value	0.832	0.781		
vs. Ind 150 µg Ratio of rates		1.11		
95% CI		(0.74,1.65)		
p-value		0.625		

CI = confidence interval
Treatment group comparisons are based on a poisson regression model: log (exacerbation rate) = treatment + smoking status + baseline COPD exacerbation history + country + baseline percentage of days of poor control + FEV1 reversibility components + random effect of center + error.
Ratio of rates <1 favors the treatment group in the numerator of the ratio.

Table 5: The proportion of patients with a clinically important improvement in TDI focal score at Week 12 and Week 26

		Treatment		Treatment difference		
Treatment	N	n (%)	Comparison	Odds Ratio	95% CI	p-value
Week 12						
Ind 150 µg	355	209 (58.9)	Ind 150 µg - Pbo	2.19	(1.58, 3.04)	<0.001
			Ind 150 µg - Tio	1.16	(0.84, 1.59)	0.369
Ind 300 µg	363	239 (65.8)	Ind 300 µg - Pbo	2.89	(2.08, 4.01)	<0.001
			Ind 300 µg - Tio	1.52	(1.11, 2.09)	0.010
			Ind 300 µg - Ind 150 µg	1.31	(0.95, 1.81)	0.095
Tio	360	198 (55.0)	Tio - Pbo	1.90	(1.37, 2.62)	<0.001
Pbo	326	138 (42.3)				
Week 26						
Ind 150 µg	343	214 (62.4)	Ind 150 µg - Pbo	2.16	(1.55, 3.02)	<0.001
			Ind 150 µg - Tio	1.28	(0.92, 1.77)	0.141
Ind 300 µg	353	250 (70.8)	Ind 300 µg - Pbo	2.85	(2.03, 3.99)	<0.001
			Ind 300 µg - Tio	1.68	(1.21, 2.33)	0.002
			Ind 300 µg - Ind 150 µg	1.32	(0.94, 1.83)	0.106
Tio	349	200 (57.3)	Tio - Pbo	1.69	(1.22, 2.36)	0.002
Pbo	309	144 (46.6)				

Logistic regression model: Logit (proportion) = treatment + smoking status + BDI focal score + FEV1 reversibility components + country + random effect of center + error.
Missing data were imputed using LOCF but not by more than 14 weeks.

Compared with placebo, both indacaterol groups had a statistically significantly higher percentage of nights with no night-time awakenings (both $p<0.01$) and percentage of days with 'no daytime symptoms' ($p<0.05$), while tiotropium did not show a statistically significant difference from placebo ($p\geq0.068$). Compared with placebo, the percentage of 'days able to perform usual daily activities' were statistically significantly higher for the indacaterol groups compared with placebo ($p<0.001$), as well as tiotropium ($p=0.011$) groups.

Salbutamol was available for rescue use throughout the study. The change from baseline in the overall LS mean daily number of puffs of rescue medication, and the LS mean daytime and night-time number of puffs of rescue medication all showed statistically significantly greater reductions for the indacaterol groups compared to placebo (all $p<0.001$). Rescue medication was also required statistically significantly fewer times for the indacaterol groups compared to tiotropium ($p=0.001$ and $p<0.001$ for the indacaterol 150 µg and 300 µg groups, respectively, for the mean daily number of puffs of rescue medication). The percentage of days with no rescue medication use was also statistically significantly higher for the indacaterol groups (56.7% and 57.8% for 150 µg and 300 µg indacaterol) compared to placebo (41.8%) (both $p<0.001$) and compared to tiotropium (46.1%) (both $p<0.001$).

Statistically significant ($p<0.01$) differences in LS means for SGRQ total score were seen in favour of both indacaterol dose groups compared to placebo at Week 12 and Week 26. However, the difference in LS means for SGRQ total score was not statistically significant for tiotropium compared to placebo at either Week 12 or 26. Furthermore, indacaterol 150 µg achieved a statistically significant difference compared to tiotropium at both time points ($p<0.05$). The proportion of patients with a clinically important improvement ($\geq$ 4 units) in the SGRQ total score was higher for indacaterol compared to placebo and tiotropium at Weeks 12 (51.9%, 50.1%, 44.9% and 45.0% for indacaterol 150 µg, indacaterol 300 µg, tiotropium and placebo, respectively) and week 26 (57.8%, 52.5%, 47.3% and 45.8%, respectively); the indacaterol 150 µg group achieved

statistical significance against placebo at Week 12 (p=0.031) and Week 26 (p<0.001) and against tiotropium at Week 26 (p=0.009).

EQ-5D category scores showed an improvement (higher percentage of patients with no symptoms/problems) from baseline at Weeks 12 and 26 for both indacaterol doses across all question categories, while improvements for the tiotropium and the placebo groups were more variable.

The BODE index is used to determine the risk of death in COPD patients with a score of 0 to 10 over four domains. A higher score indicates an increased risk of death. Analysis of the BODE index at Week 12 and Week 26 showed both indacaterol treatment groups to have a statistically lower value than placebo (all, p<0.001), indicating that treatment had a positive effect (lower scores have been correlated with a decreased mortality risk). There were no statistically significant differences between the indacaterol 150 μg and 300 μg groups, or between the indacaterol dose groups and tiotropium.

Health care resource utilization information was collected during the study and included details of hospitalizations, emergency room (ER) and unscheduled outpatient visits. Most patients in all treatment groups (approximately 93%) had no hospital admissions during the study and only one patient each in the indacaterol 300 μg, tiotropium and placebo groups had more than 2 admissions. For patients who were hospitalized, the mean duration of hospitalization was lowest for indacaterol 150 μg group and highest for the placebo group. Less than 10% of patients had emergency room visits and mean number of visits was comparable across treatment groups. Only one placebo patient experienced more than 2 emergency room visits. The mean number of unscheduled doctor's visits did not show meaningful differences across treatment groups.

Pivotal study B2346

B2346 was a multicentre, randomized, double-blind, placebo controlled, parallel group study to assess the efficacy and safety of indacaterol (150 μg od) for 12 weeks in 416 patients with moderate to severe COPD. Eligible patients were randomly assigned (randomization ratio 1:1, with stratification for smoking status) to inhaled indacaterol 150 μg od or placebo. Patients were required to take study medication once a day in the morning between 08.00 and 11.00 hours.

Efficacy endpoints and statistical considerations

The efficacy assessments included:

- Spirometry measurements of FEV_1 and FVC,
- Peak expiratory flow (PEF) using a Peak Flow Meter,
- COPD exacerbations,
- St George's Respiratory Questionnaire (SGRQ),
- Symptoms based on patient diary entries and
- Rescue medication use (salbutamol/albuterol).

The primary objective was to demonstrate superiority of indacaterol (150 μg) versus placebo with respect to 24 hours post-dose (trough) FEV_1 after 12 weeks of treatment The secondary objectives were to compare indacaterol (150 μg od) to placebo on spirometry assessments in terms of: trough FEV_1 measured on Day 2; FEV_1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response; the standardized AUC for FEV_1 (5 minutes – 4 hours), (5 minutes – 1 hour) and (1 – 4 hours) on Day 1 and after 12 weeks of treatment.

The exploratory endpoints were: percentage of COPD 'days of poor control', percentage of nights with 'no night-time awakenings', percentage of days with 'no daytime symptoms', percentage of days with 'days able to perform usual daily activities', total score of the St George's Respiratory

Questionnaire (SGRQ), after 4, 8 and 12 weeks, time to first COPD exacerbation, morning (pre-medication) and evening PEF and the use of rescue medication over 12 weeks. The effect of indacaterol (150 µg od) on post inhalation events (especially cough) and the impact of indacaterol (150 µg od) on medical resource utilization were also explored.

The primary variable (imputed with LOCF) was analysed using a mixed model for the ITT population. The model contained treatment as a fixed effect with the baseline measurement, FEV_1 prior to inhalation and FEV_1 30 minutes post-inhalation of salbutamol/albuterol, and FEV_1 prior to inhalation and FEV_1 60 minutes post-inhalation of ipratropium as covariates. The model also included smoking status (current/ex-smoker) as fixed effects with the centre as a random effect. Superiority of indacaterol from placebo was demonstrated if the p-value (2-sided) was less than the 5% significance level and the 95% confidence interval was higher than 0 mL. The study sample size had 90% power to detect a clinically relevant difference of 120ml between indacaterol and placebo groups (assuming a SD of 270ml) at the 5% significance level (2 sided).

Patient disposition and baseline demographics

All randomized patients were also included in the ITT population, with the exception of one patient in the placebo group who was excluded due to the lack of signed informed consent. Patients with major protocol deviations were excluded from the PP population; the PP population included 199 and 182 patients in the indacaterol 150µg and placebo groups, respectively. Discontinuations from the study occurred more frequently for placebo patients (13.2%) compared with indacaterol patients (11.8%), mainly due to protocol deviations - the most common reason for discontinuation (4.4% and. 3.3% for placebo and indacaterol, respectively) - and unsatisfactory therapeutic effect (2.9% and. 0.5% for placebo and indacaterol, respectively). Other common reasons for discontinuation were adverse events and withdrawal of consent. Major protocol deviations (those which excluded patients from the PP population) occurred in almost twice as many patients in the placebo group (10.8%) compared with the indacaterol group (5.7%); high eosinophil count at screening and the use of LABA/ICS ≤48 hours prior to screening occurred in twice as many placebo patients as indacaterol patients, while study medication at < 80% dose occurred with similar frequency in the two groups.

The majority of patients were Caucasian (92.5%), male (52.4%) with mean age of 63 years (>42% were over 65 years of age). All patients were either current smokers or ex-smokers (approximately half and half) with a mean number of pack years (total years of smoking multiplied by the number of cigarette packs smoked per day) of 57. The mean duration of COPD was 6.9 years, with a wide range of duration, from newly-diagnosed to 38.7 years; the placebo group had slightly higher number of patients with duration of COPD of 5 to 15 years. Overall, the treatment groups were comparable and well matched with respect to baseline demographic and disease characteristics.

Primary efficacy results

The least squares mean (LSM) estimate of the trough FEV_1 at Week 12 was statistically and clinically significantly greater for indacaterol 150 µg compared with placebo (1.49 L versus 1.35 L, respectively, p <0.001; diff=0.13L, 95% CI: 0.09 to 0.18). Similar results were observed in the PP primary analysis.

The results of the subgroup comparisons were broadly comparable for those under and at least 65 years of age, males and females, and those with moderate and severe disease. The difference between indacaterol and placebo appeared to be greater in current smokers (LSM difference of 0.17 L) compared to ex-smokers (LSM difference of 0.09 L), and also in patients with no ICS use at baseline (LSM difference of 0.16 L) compared to those with ICS use at baseline (LSM difference of 0.06 L).

Secondary efficacy results

At each time point measured (Day 2, 29, 57, and 84), indacaterol 150 μg showed significantly greater improvements in trough FEV_1 compared to placebo (all, $p < 0.001$).

Peak FEV_1 in the first 4 hours post-dose were significantly ($p < 0.001$) greater with indacaterol 150 μg compared with placebo on Day 1 (LSM difference=0.19 L) and at week 12 (LSM difference=0.16 L). Compared with placebo, indacaterol 150 μg also showed statistically significantly greater standardized AUCs for FEV_1 between 5 minutes and 4 hours, between 5 minutes and 1 hour and between 1 and 4 hours at Day 1 and after 12 weeks of treatment (all, $p < 0.001$); the LSM differences at Day 1 were 0.17 L, 0.16 L, and 0.17 L, respectively. The LSM differences at Week 12 were 0.17 L, 0.18 L, and 0.17 L, respectively. The LSM changes from baseline in both morning and evening PEF were significantly greater with indacaterol 150 μg than with placebo (both, $p < 0.001$).

The percentage of COPD 'days of poor control' (based on patient-reported symptoms captured in the Patient Diary) over 12 weeks of treatment was significantly lower in the indacaterol 150 μg (31.2%) treatment group compared with the placebo (40.2%) group ($p < 0.001$; diff=-9.1, 95% CI: -13.3, -4.8).

The percentage of nights with 'no night-time awakenings' was numerically higher for the indacaterol 150 μg group compared with the placebo group ($p = 0.061$). The percentage of days with 'no daytime symptoms' and the percentage of 'days able to perform usual daily activities' were both significantly higher in the indacaterol 150 μg treatment group compared with the placebo group (both, $p < 0.05$).

The SGRQ total score at Week 12 was significantly lower for the indacaterol 150 μg (43.38) treatment group compared with the placebo (48.13) group, with the difference exceeding the MCID of a 4-point change (diff=-4.75, 95% CI: -7.14, -2.36, $p < 0.001$). Between-treatment comparisons for the LSM changes from baseline in the mean daily, mean daytime, and mean night-time number of puffs of rescue medication showed that patients in the indacaterol 150 μg group required rescue medication significantly fewer times compared with patients in the placebo group (all, $p <0.001$). The percentage of days with no rescue medication use was also significantly higher with indacaterol 150 μg than with placebo ($p < 0.001$). There was no significant difference in the incidence of hospitalizations, emergency room (ER) and unscheduled outpatient visits between the indacaterol and placebo groups.

Pivotal 52-week study B2334

B2334 was a 52-week, multicentre, randomized, double-blind, double dummy, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of indacaterol (300 & 600 μg od) in patients with moderate/ severe COPD, using formoterol (12 μg bd) as an active control Patients were required to take study medication twice a day, (once in the morning via SDDPI device and Aerolizer®, and once in the evening via the Aerolizer only). Treatments were added to the patients' established 'background' COPD treatment, such as daily inhaled corticosteroids; and additionally patients were allowed to use a short acting β2–agonist as rescue medication.

Patient compliance was assessed using the percentage of doses taken over the 52 week treatment period. Mean compliance was high in all treatment groups (greater than 98%).

Efficacy endpoints and statistical considerations

The primary objective was to assess indacaterol (300 and 600 μg od via SDDPI) superiority in patients with COPD compared to placebo with respect to 24 hours post dose (trough) FEV_1 after 12 weeks of treatment. The key secondary efficacy endpoint was the percentage of 'days of poor control' reported over the 52 week randomized treatment period. Other important secondary

endpoints were: the total score of the St George's Respiratory Questionnaire (SGRQ) after 12 weeks treatment, time to first COPD exacerbation during the 52 week randomized treatment period.

Other secondary endpoints were COPD exacerbation rates during the 52 week randomized treatment period, effects on health related quality of life measures, transition dyspnoea index (TDI) focal score after 4, 8, 12, 24, 44 and 52 weeks treatment, trough FEV_1 on Day 2 and after 52 weeks of treatment, peak and trough FEV_1 and FVC on Day 1 and after 12 and 52 weeks treatment.

Other clinical variables which were evaluated included morning (pre-medication) and evening (pre-medication) PEF, clinical symptoms and use of rescue medication over 52 weeks. Exploratory endpoints included effect on the BMI, airflow obstruction, dyspnoea and exercise capacity (BODE) index after 12 and 52 weeks of treatment; to compare formoterol with placebo, indacaterol with formoterol and indacaterol 300 and 600 μg doses with respect to all of the secondary variables above and the trough FEV_1 at Week 12; to explore the impact of indacaterol (300 and 600 μg) on medical resource utilization.

The primary analysis population for efficacy was the modified ITT population. Sensitivity analyses using the full ITT population were performed for the primary and key secondary efficacy variables. The PP population was used for supportive analysis of the primary variable only. For the percentage of COPD 'days of poor control', a difference of 8% was considered clinically important based upon data from prior studies with Foradil. An estimate of 28% for the standard deviation was also based on data from Foradil pivotal studies over 12 weeks, 6 months and 12 months. With these parameters, the number of evaluable patients for safety implied for the comparisons of indacaterol 300 μg and indacaterol 600 μg with placebo at the 5% significance level (2 sided) a power of 93% and 89% respectively in the hierarchical testing procedure. **The study was not powered to detect differences between formoterol and indacaterol.**

Patient disposition and baseline demographics

A total of 2446 patients were screened with 1732 randomized into the study. A total of 129 patients from centres in Egypt were excluded from the modified ITT (mITT) population and modified Safety population due to serious GCP non-compliance and unreliability of data. The main populations for efficacy (mITT) consisted of 405, 396, 400 and 399 patients in the indacaterol 300 μg, indacaterol 600 μg, formoterol and placebo groups, respectively. The highest percentage of patients discontinuing was in the placebo group predominantly due to the withdrawal of consent, adverse events or unsatisfactory therapeutic effect. Adverse events (AEs) were the main reason for discontinuation in the formoterol and indacaterol 300 μg treatment groups. Approximately 13% of mITT patients in each treatment group were excluded from the PP population with an elevated eosinophil count at screening being most common protocol deviation leading to exclusion from PP population.

The majority of the patients were male (80%), Caucasians (90%) with mean age of 63 years (47% were ≥65 years), had moderate to severe COPD (with approximately 50% using inhaled corticosteroids) and the mean duration of COPD was 7 years. The baseline demographics**,** disease characteristics and spirometry measures were similar in all treatment groups.

Primary efficacy results

The LS mean of trough FEV_1 at Week 12 was the same for both doses of indacaterol (0.17 L) and both were significantly greater than placebo (hierarchical testing tested 600 μg only if 300 μg versus placebo was significant). Both doses of indacaterol had significantly greater LS mean trough values than formoterol (which had a significantly higher LS mean trough level compared to placebo). **However, it was not clearly stated if the study was powered to detect a difference between active treatments and if it was a superiority or non-inferiority analysis.** Results for the PP population supported those for the mITT population.

Subgroup primary efficacy analysis revealed that the LSM difference between indacaterol and placebo groups was slightly greater in female patients (compared to males) and those with moderate COPD (compared with severe COPD), although all groups showed clinically relevant treatment differences of >120 mL. However, overall, gender, COPD severity, race and smoking status did not appear to have any significant impact on primary efficacy results.

Secondary efficacy results

The LS mean for 'percentage of days of poor control' for both indacaterol doses was statistically significantly lower than that for placebo. Although the 600 µg dose of indacaterol resulted in a slightly lower LS mean percentage of days of poor control than 300 µg, the difference was not statistically significant (p=0.056). Formoterol treatment resulted in a similar LS mean percentage of days of poor control as 300µg indacaterol and was significantly lower than placebo. However, the decrease in the mean number of days of poor control was much greater in the indacaterol 600 µg treatment group than others (11.1 days), and was the only group also to have more than 50% of patients with a decrease. Patients aged 65 and older, had a higher percentage of days of poor control for all treatment groups than those patients under 65 years, with the exception of the 600 µg indacaterol dose group. Indacaterol 300 µg and formoterol versus placebo did not show a significant difference in LS mean days of poor control in the over 65's. Females showed little difference to males, but did have greater differentiation between the indacaterol 300 and 600 µg treatment groups whilst indacaterol 300 µg versus placebo was not significantly different. In the subgroup of patients with severe COPD and in females only the higher dose of indacaterol (600 µg) was significantly lower than placebo; indacaterol 300 µg and formoterol treatment groups showed no statistical difference compared with placebo in patients with severe COPD. Current smokers reported a higher percentage of days of poor control than ex-smokers in the placebo treatment group and appeared to benefit less from the higher indacaterol dose than ex-smokers.

LS mean scores of SGRQ at Week 12 were lower for indacaterol 300 and 600 µg than for placebo (or formoterol), and the difference versus placebo was statistically significant. At week 12, there was a significant difference (approximately 10%) in the proportion of patients with an improvement of ≥4 units between placebo and active treatment (51.9%, 53.7%, 51.5% and 41.2% for indacaterol 300 µg, indacaterol 600 µg, formoterol and placebo, respectively). By week 52 this difference had increased to approximately 15%.

The percentage of patients with a COPD exacerbation was greatest in the placebo group, with a difference from indacaterol 300 µg of 3.5%. The median event-free time was not estimable from the Kaplan-Meier plot (as there were insufficient events to calculate the median and 75 quartiles). Event free rates were similar for the two doses of indacaterol and were greater than for formoterol or placebo at Month 6. At Month 12 the 600 µg indacaterol group had a slightly higher event free rate than the 300 µg group, both remaining higher than placebo (by 6.1% and 9.7% for the 300 and 600 µg doses, respectively). Both indacaterol doses and formoterol resulted in a hazard ratio of less than one versus placebo (favouring the active treatment), and for the indacaterol comparisons this was statistically significant. The number of exacerbations per patient was similar between treatment groups over the 52 week period, although a slightly higher percentage of patients in the placebo group experienced four or more exacerbations compared to the active treatment groups. The rate of exacerbations per year was greatest in the placebo treatment group. Rates were similar for the two indacaterol groups although slightly lower for the higher dose. Rate ratios indicated that all active treatment groups had lower rates of exacerbation than the placebo group, and for indacaterol 600 µg and formoterol this was statistically significant ($p<0.05$). There was little difference between indacaterol and formoterol treatment groups, whilst the indacaterol 300 µg group versus the indacaterol 600 µg group had a rate ratio which favoured the higher dose, but not significantly so.

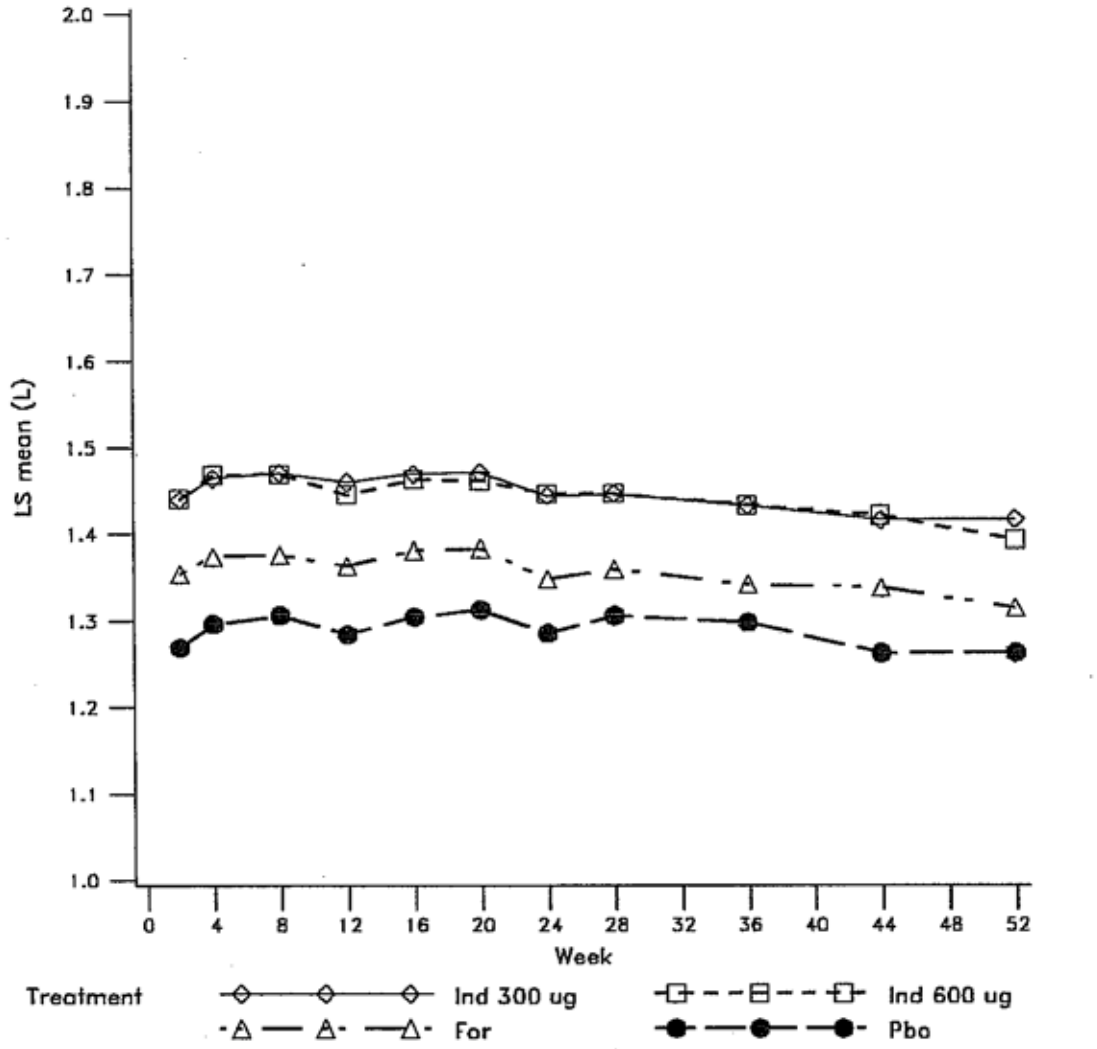
The reduction in trough FEV_1 was maintained over 52 weeks of treatment for all indacaterol and formoterol groups and was consistently greater than placebo (Figure 3). At Week 52, the LS mean

of trough FEV_1 for indacaterol 300 µg was similar to that seen at Day 2. For indacaterol 600 µg there was a small decrease of 0.06 L between Day 2 and Week 52. For the formoterol group, the Week 52 LS mean trough FEV_1 was 0.11 L lower than at Day 2. At both Day 2 and Week 52, the difference between indacaterol and placebo, and indacaterol and formoterol was statistically significant ($p = < 0.05$). At Day 2 the difference between the indacaterol treatment groups was also statistically significant (LS mean difference of 0.04 L), but by Week 52 there was no difference in trough FEV_1 between the dose groups (in fact from Day 15 onwards there was no statistical difference between the two indacaterol dose groups). Peak FEV_1 over the first 4 hours of treatment at Week 12 was greatest in the indacaterol treatment groups (with no difference between doses), and significantly greater than placebo. Formoterol treatment also resulted in significantly greater peak FEV_1 than placebo, with no statistical difference from indacaterol treatments. Peak FEV_1 on Day 1 was similar to Week 12 for all treatment groups, whilst at Week 52 it was slightly lower than Week 12 for the 300 µg indacaterol, formoterol and placebo groups. Results on Day 1 and at Week 52 were similar to Week 12, with both dose groups of indacaterol having significantly greater LS mean AUC's of FEV_1 (5 minutes to 11 hours 45 minutes) than placebo and formoterol. There were no statistical differences between indacaterol dose groups.

TDI scores increased from baseline to Week 12 and further to Week 52 for all treatment groups including placebo. At Week 12, the LS mean scores were greatest for the indacaterol 300 µg treatment group. Both the indacaterol treatment groups had statistically significantly greater scores than placebo and formoterol at Week 12, with LS mean differences versus placebo of over 1.10, and of over 0.40 versus formoterol. Formoterol treatment group scores were significantly greater than placebo at Week 12. At Week 52 the increase from Week 12 was greater for the placebo and formoterol groups than for the indacaterol groups. However, scores were numerically greater for the indacaterol treatment groups, both of which were significantly greater than placebo (as was formoterol). At Week 12 the percentage of patients with an improvement of at least one point in the TDI focal score was 62.9% for indacaterol 300 µg, 58.0% for indacaterol 600 µg, 52.9% for formoterol and 40.2% for placebo. At Week 52, the percentage of patients with an improvement of at least one point was over 9% greater in the indacaterol treatment groups than placebo. The odds ratio for the percentage of patients with an improvement of one point or more favoured indacaterol versus formoterol or placebo at all visits, and the difference between indacaterol (300 or 600 µg) and placebo was statistically significant at all visits, as was the difference between formoterol and placebo. There did not appear to be an increase in the percentage of patients achieving a clinically meaningful improvement between Week 12 and Week 52 for any group.

The percentage of nights with no night-time awakenings was relatively high in all groups and all active treatments resulted in significantly more uninterrupted nights than placebo. The percentage of days with no symptoms was considerably less than the number of nights with no awakenings, as were differences between treatment groups. In the indacaterol 300 µg treatment group there were significantly more days free from symptoms than placebo, and the same was true for formoterol versus placebo. The difference between the indacaterol 600 µg and placebo treatment groups was not statistically significant, although it was numerically greater for indacaterol, as was the mean change from baseline. Compared with placebo, both indacaterol (300 µg and 600 µg) and formoterol had significantly higher mean percentage of days when patients were able to perform usual daily activities.

Figure 3: Least squares means of 15 minutes pre-dose FEV_1 over 52 weeks of treatment (mITT population)



Least squares means are based on the following ANCOVA model:
Pre-dose FEV1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center(country) + error, with center(country) included as random effect.

All active treatment groups decreased the LS mean daily number of puffs of rescue medication taken by more than one, and all differences versus placebo were statistically significant. The mean number of puffs of rescue medication taken at night decreased to a lesser degree than daytime, although all active treatments resulted in significantly lower usage than placebo. Compared with placebo, the LS mean percentage of days where rescue medication was not required was statistically significantly greater for indacaterol (300 and 600 µg) (> 23%) or formoterol (> 5%).

After 52 weeks of treatment, indacaterol (300 µg and 600 µg) and formoterol produced statistically significantly greater increases in morning and evening PEF compared with placebo.

LS mean scores for the SGRQ at Week 12 were lower (better) for indacaterol 300 and 600 µg than for placebo (or formoterol), and the difference versus placebo was statistically significant. The scores for the SGRQ over the 52 week duration of the study show that in the placebo group after an

initial small decrease in score (improvement in health status) scores remained fairly constant. In the formoterol and indacaterol treatment groups, the initial decrease was greater and scores fell over the first 12 weeks of the study. After this, responses for the indacaterol 600 μg and formoterol treatment groups remained relatively constant, whilst there was a further slight fall in the indacaterol 300 μg treatment group. At all assessed time points the active treatment groups had significantly lower scores (better) than placebo. From Week 12 onwards at least 50% of patients in the active treatment groups showed a clinically important improvement (51.9%, 53.7%, 51.5% and 41.2% for indacaterol 300 μg, indacaterol 600 μg. formoterol and placebo, at Week 12 respectively). The percentage of patients with an improvement was significantly greater in the active treatment groups than in the placebo group at all assessed time points.

At all days and time points, the active treatment groups had statistically significantly greater FVC values than placebo (with the exception of the formoterol treatment group on Day 365 at 23 hours 45 min). Analysis of the BODE index at Week 12 and Week 52 showed all active treatments to have a statistically lower value than placebo, indicating that treatment had a positive effect (lower scores have been correlated with a decreased mortality risk). At 52 weeks, both indacaterol treatment groups had a significantly greater LS mean 6-minute walk distance than placebo, as did formoterol (403.1 metres [m], 405.4 m, 403.9 m and 389.6 m for indacaterol 300 μg, indacaterol 600 μg, formoterol and placebo, respectively).

Summary statistics of the total EQ-5D self-rating visual analogue scores (0-100) showed no change for the placebo group, whilst there was an increase for all active treatment groups (Week 52 change from baseline 4.1, 3.5, 5.0, -0.6 for 300 μg indacaterol, 600 μg indacaterol, formoterol and placebo, respectively). Resource utilization data showed similar mean hospital admissions, length of hospital stay, number of emergency room visits and unscheduled doctor's appointments in all of the treatment groups.

Other Phase III studies

The 3 short-term, profiling, crossover, Phase III studies provide information on specific aspects of indacaterol therapy, such as efficacy following evening dosing **(B2305),** its lung function profile throughout 24 hours **(B2340)** and fast onset of effect **(B2307).**

Study B2305

B2305 was a phase III randomized, double-blind, double dummy, placebo controlled, multicentre, 4 treatment, 3 period incomplete block crossover study to assess the efficacy and safety of indacaterol 300 μg od dosed in the evening in 96 patients with moderate to severe COPD, using salmeterol 50 μg bd as active control. The main inclusion and exclusion criteria were similar to those for the pivotal Phase III studies described in the previous sections of this report.

The primary efficacy variable (trough FEV_1) was defined as the mean of the spirometry measurements taken on Day 15 at 23 hours 10 minutes and 23 hours 45 minutes following Day 14 evening study medication intake. The primary analysis which compared PM indacaterol versus placebo (pm), was evaluated in the mITT population and was analysed using an analysis of covariance (ANCOVA) model with the patient as random effect, and period baseline FEV_1, period, treatment group (PM indacaterol, AM indacaterol, salmeterol, placebo), daytime (am, pm), and treatment by daytime interaction as fixed effects, (where daytime refers to the time of the day at which the FEV_1 measurements were taken).

The secondary variables were trough FEV_1 values derived from measurements performed at 23 hours 10 minutes and 23 hours 45 minutes post-evening dose and post-morning dose on Day 14. Other secondary efficacy endpoints included the COPD and asthma sleep impact scale (CASIS), percentage of "nights with no night-time awakenings" and percentage of days with 'no daytime

symptoms'.[11,12,13] In the mITT population, PM indacaterol 300 µg od showed statistically and clinically significant greater 24 hours post-dose trough FEV_1 compared with placebo after 14 days of treatment (treatment difference=200ml, p<0.001). This was supported by the analysis of the primary endpoint in the PP population which also showed statistically significant clinical superiority of PM indacaterol 300 µg od over placebo (treatment difference =170 mL, p < 0.001).

The estimated treatment difference between the LS means for morning trough FEV_1 for indacaterol 300 µg od dosed in the morning and placebo after 14 days of treatment was also clinically relevant (difference of 200 mL, p-value < 0.001).

After 14 days treatment, there was no difference between evening trough FEV_1 for indacaterol 300 µg od dosed in the evening and morning trough FEV_1 for indacaterol 300 µg od dosed in the morning (difference=10 mL, p-value = 0.704).

Compared with placebo, trough FEV_1 was statistically significantly greater following both the evening (diff=90 mL, p=0.002) and morning salmeterol dose (diff=150mL, p<0.001). Furthermore, PM indacaterol evening trough FEV_1 was numerically higher than salmeterol evening trough FEV_1 and the estimated treatment difference was 110 mL (p-value < 0.001); AM indacaterol morning trough FEV_1 was numerically higher than salmeterol morning trough FEV_1 and the estimated treatment difference was 50 mL (p-value = 0.125). **However, these were exploratory efficacy analyses which made no adjustments for multiplicity and therefore, the results should only be regarded as descriptive. Overall, results of this Phase III study suggested that time of administration of indacaterol (evening or morning) was not likely to affect its efficacy in moderate to severe COPD.**

Study B2307

B2307 was a phase III, randomized, double-blind, triple-dummy, placebo controlled, multicenter, 5-period, single-dose complete block crossover study to determine the onset of action of indacaterol (150 and 300 µg) in 89 patients with moderate to severe COPD using salbutamol (200 µg) and salmeterol/fluticasone (50/500 µg) as active controls. The study was conducted in 17 centres in 4 countries in 2008. The primary objective of the study was to assess the possible superiority of indacaterol (150 and/or 300 µg) to placebo on FEV_1 measured 5 minutes post-dose administration. The secondary objectives of the study were to compare the effects of indacaterol (150 and 300 µg) at the 5 minute post-dose time point versus the following treatments: salbutamol (200 µg) and salmeterol/fluticasone (50/500 µg).

The LS mean FEV_1 value at 5 minutes post-dose for indacaterol 150 µg and 300 µg was higher than that for placebo by 100 mL and 120 mL, respectively and statistical and clinical significance was confirmed for both indacaterol doses. The LS mean FEV_1 for indacaterol 300 µg was estimated to be 20 mL higher than for indacaterol 150 µg but the difference was not statistically significant (p = 0.233). The LS mean FEV_1 for either dose of indacaterol was statistically significantly higher than that for salmeterol/fluticasone 50/500 µg (p < 0.001). The indacaterol effects were also marginally

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[11] CASIS was completed at Visit 3 (baseline) and at the end of each treatment period. The CASIS consists of 7 items, each one with a score ranging from 1 to 5. Items 1 to 5 have scores 1 (never), 2 (rarely), 3 (sometimes), 4 (often) and 5 (very often). Item 6 and 7 have scores 1 (very often), 2 (often), 3 (sometimes), 4 (rarely) and 5 (never). Higher scores indicate more sleep impairment. The CASIS total score was calculated based on the sum of item scores which have a range of 7 to 35 which was transformed to a 0 - 100 scale.

[12] A night with "no night-time awakenings" was defined from the diary data as any night where the patient did not wake up due to symptoms. The total number of "nights with no night-time awakenings" over 14 days of a treatment period was divided by the total number of days where diary recordings have been made.

[13] A day with "no daytime symptoms" was defined from the diary data as any day where the patient had recorded in the evening no cough, no wheeze, no production of sputum and no feeling of breathlessness (other than when running) during the past 12 hours (approx 08:00 hours to 20:00 h).

higher than that for salbutamol 200 µg**.** These findings show that indacaterol has a fast onset of action and is at least as effective as salbutamol at 5 minutes post-dose. LS mean values for FEV_1 at 15 minutes, 30 minutes, 1 hour and 2 hours post-dose for either dose of indacaterol were all statistically significantly higher than that for placebo ($p < 0.001$). At 2 hours post-dose, the LS mean FEV_1 value for indacaterol 300 µg was statistically significantly higher than that for salbutamol ($p = 0.005$). At other time points there was little difference between indacaterol and salbutamol regarding FEV_1. At 15 minutes post-dose, the LS mean FEV_1 for both doses of indacaterol was statistically significantly higher than that for salmeterol/fluticasone ($p \leq 0.035$), but these effects were not observed at 1 hour and 2 hours post-dose.

The proportion of patients with an increase in FEV_1 (from baseline to 5minutes post-dose) of at least 10%, 12% and 15% was statistically significantly higher with indacaterol (150 µg and 300 µg) compared with placebo and salmeterol/ fluticasone; however, only indacaterol 300 µg showed a significantly higher proportion of patients with at least 10% and 15% increase in FEV_1 compared to salbutamol.

In the 2009 CPMP guidelines for COPD drugs, reversibility of airway function in adults is defined as FEV_1 of >12% and >200mL 15 minutes after inhalation of a short acting beta2 agonist. The number of patients with an increase of at least 12% and 200 mL in FEV_1 at 5 minutes post-dose was statistically significantly higher in the indacaterol 150 µg/300 µg and salbutamol 200 µg groups compared with both salmeterol/fluticasone and placebo (18.8%, 27.6%, 23.3%, 9.1% and 3.4%, for indacaterol 150 µg, indacaterol 300 µg, salbutamol 200 µg, salmeterol/fluticasone 50/500 µg and placebo, respectively). Neither dose of indacaterol was statistically significantly superior to salbutamol. The proportion of patients showing an increase in FEV_1 of at least 12% and 200 mL between baseline and other post-dose time points (15 minutes, 30 minutes, 1 hour and 2 hours) showed that both doses of indacaterol were statistically significantly superior to placebo at 15 minutes, 30 minutes, 1 hour and 2 hours (all $p < 0.001$) Patients taking indacaterol 300 µg were numerically more likely to achieve an increase in FEV_1 of at least 12% and 200 mL at 15 minutes, 30 minutes and 1 hour compared with patients taking indacaterol 150 µg, salbutamol or salmeterol/fluticasone. However, there were no significant differences between the 3 active treatments (indacaterol, salmeterol/ fluticasone and salbutamol) at 2 hours. Comparisons of the indacaterol doses showed that indacaterol 300 µg performed consistently better than indacaterol 150 µg, although the differences were not consistently statistically significant.

Overall, results from this study confirmed the fast onset of action of indacaterol 150 µg and 300 µg with statistically significant improvements over placebo and similar or slightly greater efficacy to that demonstrated by salbutamol and salmeterol/fluticasone. However, there was no definitive non-inferiority testing for comparing the active treatments and these results must be considered exploratory only.

Study B2340

B2340 was a Phase III, randomized, double-blind, placebo controlled, multicentre, 3-period, 14-day crossover study to determine the 24 hour lung function profile of indacaterol (300 µg od) in 68 patients with moderate-to-severe COPD, using open-label salmeterol (50 µg bd) as active control. The study was conducted at 11 centres in USA, Belgium and Spain in 2008. The study was powered for the primary endpoint (trough FEV_1) and the key secondary endpoint (FEV_1 at each time point). **However, comparisons between indacaterol and salmeterol were not pre-defined and were considered exploratory only.** The study met the primary objective of showing that indacaterol 300 µg od is superior to placebo in terms of 24 hour post-dose (trough) FEV_1 after 14 days of treatment. The LS mean treatment difference for indacaterol minus placebo was a statistically and clinically significant 200 mL ($p<0.001$) in the mITT analysis with similar results in the PP analysis. The trough FEV_1 LS mean treatment difference for indacaterol minus placebo was also statistically

significant after 1 day of treatment. Although the trough FEV_1 LS mean treatment difference for indacaterol minus salmeterol was favourable but not statistically significant for indacaterol after 1 day of treatment, the difference reached statistical significance after 14 days of treatment (treatment difference 90 mL; p = 0.011). The trough LS mean treatment difference for salmeterol *versus* placebo was statistically significant after 1 and 14 days of treatment.

At Day 14, 24 hour serial spirometry was performed. Individual time point analyses of FEV_1 showed that the LS mean treatment difference for indacaterol minus placebo was statistically significant at all post-dose time points evaluated after 14 days of treatment. The difference for indacaterol minus salmeterol was generally statistically significant up to and including 11 hours 45 minutes, with later time points favouring indacaterol but usually not reaching statistical significance. Notably, the treatment difference for indacaterol minus salmeterol was favourable (although not statistically significant) for indacaterol at 14 hours post-dose, 2 hours after the second dose of salmeterol was administered. The LS mean treatment difference for salmeterol minus placebo was statistically significant at all post-dose time points.

Indacaterol showed superiority over placebo and salmeterol in terms of peak FEV_1 in the first 4 hours post morning dose on Day 1, with an LS mean treatment difference for indacaterol minus placebo of 180 mL (p < 0.001) and for indacaterol minus salmeterol of 50 mL (p=0.002). Salmeterol was also superior over placebo, with an LS mean treatment difference for salmeterol minus placebo of 120 mL (p < 0.001). After 1 and 14 days of treatment, the FEV_1 AUC (0-12h) and FEV_1 AUC (0-24h) LS mean treatment differences were statistically significant for indacaterol minus placebo, indacaterol minus salmeterol, and salmeterol minus placebo**. However, it is important to note that the study was only powered to detect differences between indacaterol and placebo and comparisons between indacaterol and open-label salmeterol were only exploratory.**

Summary of efficacy

The pivotal Phase III study B2335S involving 1665 patients with moderate to severe COPD showed that the proposed doses of indacaterol 150 µg and 300 µg were statistically and clinically significantly superior to placebo and non-inferior to tiotropium 18 µg in terms of primary endpoint of trough FEV_1 after 12 weeks treatment with similar results observed after 26 weeks treatment. The improvement in trough FEV_1 at Day 2 was statistically significantly higher for the indacaterol 300 µg dose compared to the indacaterol 150 µg dose suggesting an earlier onset of effect for the indacaterol 300 µg dose, but LSM trough levels were similar for both indacaterol doses at the Day 15 and Week 26 endpoints (although the 300 µg dose remained numerically superior at Week 26). Improvements in LSM trough FEV_1 for the indacaterol dose groups were also comparable to or non-significantly higher than for the tiotropium group at all time-points. At the primary end point (Week 12), both indacaterol 150 µg and 300 µg once-daily treatment groups showed a significantly higher trough FEV_1 value compared to placebo. Superiority of indacaterol (150 µg and 300 µg) to tiotropium (18 µg od) for trough FEV_1 at week 12 was also established in this study. Patients on each indacaterol dose experienced fewer COPD 'days of poor control' (based on patient-reported symptoms captured in the Patient Diary) than those on placebo and similar levels to patients on tiotropium over 26 weeks. Overall, data showing improvement on key and well established symptomatic endpoints in COPD are supportive of the positive effect of indacaterol. The data are favourable for indacaterol versus placebo (and at least comparable to tiotropium) for breathlessness as measured by BDI/TDI, rescue medication use, the risk of COPD exacerbation, percentage of nights with 'no night-time awakenings', days with 'no daytime symptoms', and number of days 'able to perform usual daily activities', morning and evening PEF, and health-related quality of life, as measured by the SGRQ. The reduction in the number of COPD exacerbations and an increase in the time to first exacerbation were statistically significant for the indacaterol 150 µg dose compared to placebo.

Another pivotal Phase III study B2346 involving 416 patients with moderate to severe COPD provided evidence of efficacy in terms of effective bronchodilatation and symptomatic relief with indacaterol 150 μg treatment for 12 weeks.

The long-term efficacy of indacaterol 300 μg and 600 μg was evaluated in study B2334 involving 1732 patients with moderate to severe COPD; 364 patients were exposed for >26 weeks and, of these, 172 patients were exposed for >52 weeks. Spirometric results (FEV_1, FVC and PEF) showed clinically and statistically significant improvements in indacaterol treatment groups compared with placebo and formoterol 12 μg after 12 weeks of treatment and these effects were maintained over 52 weeks of treatment. However, it was not clearly stated if study was powered to detect a difference between active treatments and if it was a superiority or non-inferiority analysis. The main secondary endpoint for proving long-term efficacy was provided by the 'days of poor control' which was significantly lesser in the indacaterol groups compared with placebo. These results were validated by the quantitative quality of life measures SGRQ, TDI and BODE all of which showed indacaterol treatment to have a positive effect on patient's well-being and was statistically significantly superior to placebo. Symptom scores also supported the spirometry and QoL results, but to a lesser degree. The assessment of use of rescue medication showed indacaterol treatment to have a positive effect. Overall, results from this study provided evidence for long-term bronchodilation and symptomatic relief with indacaterol (300 μg and 600 μg) in moderate to severe COPD. However, it is important to note that 600 μg is not the proposed dose for which approval is sought and long-term efficacy of the proposed indacaterol dose of 150 μg was not evaluated.

The efficacy of indacaterol was not affected significantly by age, gender, baseline COPD severity and use of ICS and smoking status. However, there were trends suggesting greater treatment difference between indacaterol and placebo (in trough FEV_1) in females, patients with moderate COPD and those without baseline ICS use.

Results of the Phase III study B2305 involving 96 patients with moderate to severe COPD suggested that time of administration of indacaterol 300 μg (evening or morning) was not likely to affect its efficacy in moderate to severe COPD.

The Phase III study B2307 in 89 patients with moderate to severe COPD provided evidence for the fast onset of action of the proposed doses of indacaterol (150 μg and 300 μg); statistically and clinically relevant bronchodilation was seen from 5 mins post-dose and this was maintained till 2hours post-dose. Exploratory analysis revealed that indacaterol was statistically significantly better than salmeterol/ fluticasone (50/500 μg) and similar to salbutamol (200 μg) at 5 minutes post-dose, but there was no significant difference between the active treatments at 2 hours post-dose.

Another Phase III study involving 68 moderate/severe COPD patients showed that once daily indacaterol (300μg) was an effective bronchodilator throughout the 24h time period and is at least as good as, if not better than, salmeterol, a bd LABA (study B2340). At most of the time points evaluated up to and including 11 hours 45 minutes, indacaterol was also statistically significantly superior to twice-daily salmeterol. Notably, the treatment difference for indacaterol minus salmeterol was favourable (although not statistically significant) for indacaterol at 14 hours post-dose, 2 hours after the second dose of salmeterol was administered. However, the study was only powered to detect differences between indacaterol and placebo and comparisons with salmeterol can only be considered exploratory. The 24 hour lung function profile following administration of proposed dose of 150μg indacaterol was not evaluated.

Safety

Introduction

The safety evaluation plan focuses on the 3 pivotal, phase III, COPD studies B2334, B2335S and B2346 in which 2154 patients received indacaterol (75, 150, 300 or 600 μg od) via the Concept1 device; these 3 studies had designs sufficiently similar to allow pooling for an integrated safety

analysis in patients treated with indacaterol for up to 12 weeks. The combined studies B2334 and B2335S provide an integrated safety analysis over 26 weeks, while study B2334 provides long-term safety data over 52 weeks of treatment. The inclusion and exclusion criteria in the 3 studies included in the key COPD safety populations were the same. In addition, a 26 week asthma study B2338 involving 536 patients is presented for safety evaluation in order to provide a basis for evaluation of safety in the event that indacaterol is prescribed off-label to asthmatics.

Other studies providing safety data included 4 Phase II studies in COPD patients**,** 8 Phase II studies in asthma patients and 25 clinical pharmacology studies including 7 studies in COPD patients**,** 8 in asthmatics and 10 in healthy subjects. There were 5 special safety studies**.** Additional sources of data consisted of a review of serious adverse effect (SAE) reports submitted to the Novartis Integrated Medical Safety (IMS) department (cut-off date: 1 October 2008) from the ongoing trials evaluating indacaterol.

Considering all the completed adolescent/adult studies to date, regardless of duration, device, indication or design and included in the "all treated subjects" population, 6003 subjects were treated with indacaterol and overall exposure to indacaterol was 1555.8 subject years.

The analysis of adverse events (AEs) includes the conditions reported on the AE case report forms (CRFs) and the COPD exacerbation episodes recorded on the CRF specifically designed for reporting these episodes in the pivotal studies. COPD exacerbations were defined as a new onset or worsening of more than one respiratory symptom (that is, dyspnoea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days, plus at least one of the following:-

• documented change or increase in COPD-related treatment due to worsening symptoms (e.g. steroids/antibiotics/oxygen),

• documented COPD-related hospitalizations or Emergency Room visits.

All COPD exacerbations were recorded on the COPD Exacerbation Episode CRF and **not** the AE CRF. 'Worsening of COPD' AEs did not meet the definition of COPD exacerbation and therefore were not reported on the COPD exacerbation CRF.

Treatment emergent AEs were defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first dose of study drug and up to 7 days after the last dose for non-serious AEs, or up to 30 days after the last dose for SAEs.

Adverse effects reported with marketed β2-agonists were carefully evaluated in the safety analysis. Adverse effects reported for other compounds in this class include: anxiety, back pain, chest pain, muscle cramps and myalgia, diarrhoea, dizziness, dyspnoea, headache, insomnia, musculoskeletal pain, nasal congestion, nausea, peripheral oedema, pruritis, rash, rhinitis, sinusitis, throat irritation, tremor, and upper respiratory tract infection. In addition, laboratory abnormalities such as hypokalaemia and hyperglycaemia, and effects on vital signs and ECG intervals (specifically QTc) have been reported for other LABA compounds, and an extensive analysis was done to evaluate these effects in the indacaterol studies.

Safety was assessed in the following main populations (Table 7)

(1) COPD 3-month safety populations
(2) COPD 6-month population
(3) COPD 12-month population
(4) COPD safety population
(5) asthma safety population
(6) Short-term safety population
(7) "all-treated subjects" population

The COPD safety dataset included 4180 patients, 2154 of whom received indacaterol treatment at doses of 75 µg od (N=127), 150 µg od (N=627), 300 µg od (N=853) or 600 µg od (N=547) inhaled via the Concept1 device. The number of patients exposed to indacaterol 150, 300 and 600 µg od for ≥3 months was 363, 756 and 445, respectively, and the corresponding numbers exposed for ≥6 months were 243, 628 and 358. The number of patients exposed to indacaterol 300 and 600 µg od for ≥12 months was 172 and 167, respectively. In the 'all-treated' safety dataset, a total of 9057 subjects were exposed to study drug in the 42 completed studies (11 in healthy volunteers, 16 in COPD patients and 15 in asthmatics); 6003 subjects were treated with indacaterol and overall exposure to indacaterol was 1555.8 subject years.

Table 7: Safety Groupings

Dataset	Studies	N †	Safety topics Subgroup analyses
COPD 3-month safety population	B2346 B2334 (up to day 91) B2335S (up to day 91)	4180	**Main safety topics:** exposure, disposition, demographics, baseline disease characteristics, deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs, ECGs. **Special safety topics with further analyses:** CCV & APTC, DM, HT, bronchospasm, hypersensitivity and photosensitivity AEs; BP, pulse, ECG QTc, potassium, glucose and liver chemistries; PI cough. **Subgroups:** age, sex, race, COPD severity, smoking history, ICS use, history of diabetes mellitus, baseline CCV condition, baseline hyperlipidemia, baseline hypertension, BMI.
COPD 6-month safety population	B2334 (up to day 182) B2335S	3764	As for COPD 3-month safety population, plus Holter monitoring in a subset of patients in study B2335S
COPD 12-month, safety population	B2334	1728	As for COPD 3-month safety population
COPD safety population	B2346, B2334, B2335S	4180	**Main safety topics:** exposure; by visit summaries of changes from baseline for clinical laboratory results, vital signs and ECGs. **Special safety topics with further analyses:** by visit & time point summaries and treatment comparisons of BP, pulse, ECG QTc, potassium and glucose; liver chemistries; PI cough. **Subgroups:** age, sex, race, COPD severity, smoking history, ICS use, history of diabetes mellitus, baseline CCV condition, baseline hyperlipidemia, baseline hypertension, BMI.
Asthma safety population	B2338	805	**Main safety topics:** exposure, disposition, demographics, baseline disease characteristics, deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs, ECGs. **Special safety topics with further analyses:** by visit & time point summaries and treatment comparisons of BP, pulse, ECG QTc, potassium and glucose; liver chemistries; PI cough; Holter monitoring in a subset of patients.
Short-term safety population	Adult/adolescent healthy volunteer, COPD and asthma studies of <50 days ‡ treatment and with at least one inhaled indacaterol monotherapy arm: B2305, B2307, B2340, B2201, B2205, B2212, B1202, A2201, A2205, A2208, A2210, A2216, A2218, A2228, A1202, A2105, B2202, B2211, B2217, B2318, A2101, A2103, A2211, A2217, A2219, A1101, A2215, A2311, B2103, B2216, B2220, A2221, A2307, B2339, QMF149B2201, QMF149A2201, QMF149A2206, QVA149A2101	3313 on indacaterol	**Main safety topics:** exposure, disposition, demographics, deaths, SAEs, all AEs, liver chemistries
All treated subjects population	All adult/adolescent healthy volunteer, COPD and asthma studies of any duration with an inhaled indacaterol monotherapy arm: as for Short-term safety population plus studies B2334, B2335S, B2346, B2338	9057 (6003 on indacaterol)	**Main safety topics:** exposure, deaths, SAEs

† Safety population including all treatment groups, unless otherwise stated.
‡ <50 days total exposure (excluding washout)
CCV = cardio- and cerebrovascular, APTC = Anti-platelet Trialists' Collaboration, DM = diabetes mellitus, BP = blood pressure, HT = hypertension, PI = post-inhalation, BMI = body mass index

Safety in the 3-month and 6-month COPD patient populations

The 3-month and 6-month COPD safety populations differ only in that study B2346 is included in the 3-month but not in the 6-month population. Study B2346 was relatively small and had only indacaterol 150 µg od and placebo treatment groups. Hence the safety results in these 2 safety datasets are discussed together in the following sections.

Exposure and baseline patient characteristics

The COPD 3-month dataset included 4180 patients, 2154 of whom received indacaterol treatment at doses of 75 µg od (N=127), 150 µg od (N=627), 300 µg od (N=853) or 600 µg od (N=547) inhaled via the Concept1 device. The COPD 6-month dataset included 3764 patients, 1943 of whom received indacaterol treatment at doses of 75 µg od (N=127), 150 µg od (N=416), 300 µg od (N=853) or 600 µg od (N=547) inhaled via the Concept1 device. The number of patient years of exposure to indacaterol 75 µg od was markedly lower than those for 150, 300 and 600 µg od dose groups (low dose group was included only in Stage 1 of study B2335S). Mean exposure to active comparators, formoterol and tiotropium, was comparable to indacaterol 150 µg, 300 µg and 600 µg od. The majority of the patients in the 3-month and 6-month COPD safety populations were male (75-80%), Caucasians (≥83%) with approximately equal proportion of patients aged < and >65 years. The majority of the patients had moderate to severe COPD (>93%) which is the target patient population for indacaterol with mean COPD duration of 5-7 years. In the 3-month safety dataset, the proportions of patients using ICS were around 10% lower in the indacaterol 150 µg od (35%) and tiotropium (34%) groups compared with the other active treatments (47-50%) and placebo (44%). In all treatment groups, less than half the patients were current smokers with a median usage of >40 pack years. In the 6-month COPD safety dataset, the baseline demographics and disease characteristics for the indacaterol 300 µg od, 600 µg od, formoterol and tiotropium groups were similar.

In the COPD 3-month safety population, 49 to 58% of patients were taking COPD-related concomitant medications (51.7%, 55.1%, 55.0% 57.9%, 49.4% and 58.3% in the indacaterol 150 µg od, 300 µg od, 600 µg od, formoterol, tiotropium, and placebo groups, respectively).

Corticosteroids were the most commonly used medications (37.5%, 48.8%, 50.8%, 52.5%, 38.3% and 48.2%, respectively); inhaled corticosteroids were used by 34.8%, 46.1% and 47.7% of patients in the indacaterol 150, 300 and 600 µg od groups, 49.1% on formoterol, 33.5% on tiotropium and 43.6% on placebo (budesonide and fluticasone propionate were taken most frequently). Oral corticosteroids were taken by 6 to 10% of patients, prednisolone and prednisone being the most widely used. Antibiotics were taken by 6.4%, 7.9%, 7.7%, 9.5%, 8.9% and 9.5% of patients in the indacaterol 150 µg od, 300 µg od, 600 µg od, formoterol, tiotropium, and placebo groups, respectively. The 6-month COPD dataset showed similar concomitant medications although the intake of oral corticosteroids (taken by 12 to 16% of patients, prednisolone and prednisone being the most widely used) and antibiotics (12.5%, 12.5%, 13.2%, 14.8%, 14.0%, 15.2%, respectively) was slightly higher than that observed in the 3-month dataset.

AEs

Incidence, severity, time to onset of AEs

The overall incidence of AEs was slightly higher in the indacaterol, tiotropium and placebo groups compared with the formoterol group (51.7%, 49.1%, 46.1%, 44.2%, 55.2% and 46.3% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively); this was mainly driven by slightly lower incidence of cough and upper respiratory tract infection (URTI) in the formoterol group compared with the other treatment groups. The most common AE in all treatment groups was COPD (includes disease progression and exacerbations) experienced by 10-13% of patients taking indacaterol, formoterol or tiotropium and 15.1% of patients on placebo.

Muscle spasms were experienced by a higher proportion of patients in the indacaterol groups (2.9%, 2.8%, 4.0%, 2.5%, 1.4% and 1.1% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively). Dry mouth occurred notably more often with tiotropium (4.1%) than with any other treatment (0.2-0.8% in the other active treatment groups and placebo) (Table 8). For all individual events, the rate, when corrected for exposure, was less than 1 event per patient year. The AE of highest incidence was COPD (which includes both disease progression and exacerbations). The event rates were lowest in the four indacaterol groups, which may indicate a possible beneficial effect of indacaterol on this condition. The exposure-corrected event rate for cough was higher in the four indacaterol groups compared to the control groups.

Table 8: Common AEs (≥2.0% of patients in any group) by Preferred Term

	Ind 150 µg N=627 n (%)	Ind 300 µg N=853 n (%)	Ind 600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
Patients with ≥1 AE	324 (51.7)	419 (49.1)	252 (46.1)	246 (44.2)	229 (55.2)	488 (46.3)
Preferred term						
COPD †	64 (10.2)	101 (11.8)	56 (10.2)	71 (12.8)	54 (13.0)	159 (15.1)
Cough	33 (5.3)	43 (5.0)	27 (4.9)	15 (2.7)	16 (3.9)	45 (4.3)
Upper RTI	33 (5.3)	30 (3.5)	17 (3.1)	8 (1.4)	22 (5.3)	27 (2.6)
Nasopharyngitis	30 (4.8)	49 (5.7)	43 (7.9)	31 (5.6)	30 (7.2)	61 (5.8)
Headache	28 (4.5)	24 (2.8)	16 (2.9)	16 (2.9)	18 (4.3)	27 (2.6)
Muscle spasms	18 (2.9)	24 (2.8)	22 (4.0)	14 (2.5)	6 (1.5)	12 (1.1)
Diarrhea	15 (2.4)	12 (1.4)	5 (0.9)	8 (1.4)	5 (1.2)	16 (1.5)
Dyspnea	14 (2.2)	19 (2.2)	13 (2.4)	7 (1.3)	11 (2.7)	28 (2.7)
Back pain	13 (2.1)	11 (1.3)	8 (1.5)	9 (1.6)	6 (1.5)	18 (1.7)
Bronchitis	13 (2.1)	11 (1.3)	7 (1.3)	7 (1.3)	5 (1.2)	25 (2.4)
Dizziness	12 (1.9)	14 (1.6)	5 (0.9)	3 (0.5)	2 (0.5)	17 (1.6)
Nausea	12 (1.9)	6 (0.7)	4 (0.7)	5 (0.9)	2 (0.5)	15 (1.4)
Lower RTI	11 (1.8)	19 (2.2)	5 (0.9)	8 (1.4)	11 (2.7)	23 (2.2)
Sinusitis	11 (1.8)	15 (1.8)	2 (0.4)	4 (0.7)	9 (2.2)	8 (0.8)
Urinary tract infection	11 (1.8)	9 (1.1)	1 (0.2)	5 (0.9)	10 (2.4)	13 (1.2)
Dry mouth	5 (0.8)	4 (0.5)	1 (0.2)	1 (0.2)	17 (4.1)	8 (0.8)
Nasal congestion	4 (0.6)	4 (0.5)	3 (0.6)	1 (0.2)	9 (2.2)	7 (0.7)
Upper RTI bacterial	3 (0.5)	16 (1.9)	10 (1.8)	14 (2.5)	9 (2.2)	19 (1.8)
Abdominal pain	2 (0.3)	6 (0.7)	2 (0.4)	4 (0.7)	2 (0.5)	5 (0.5)

Includes studies B2334 up to 3 months, B2335S up to 3 months and B2346.
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg treatment group
† Includes COPD exacerbations. RTI = respiratory tract infection
Selected frequency cut-off of ≥2.0% of patients in any group includes the indacaterol 75 µg od group which is shown in the source post-text table.

Suspected drug-related AEs were reported more frequently in the indacaterol 150 µg od, 300 µg od and 600 µg od groups compared with formoterol, tiotropium and placebo (9.3%, 10.3%, 10.6%, 7.0%, 8.4% and 6.8% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively, respectively). Suspected drug-related cough accounted for some of this difference (3.3%, 2.8%, 3.3%, 0.9%, 0.7% and 1.4%, respectively). The incidence of study drug-related headache was higher in all three indacaterol dose groups compared to formoterol, tiotropium or placebo but did not appear to be dose-related. However, the rate of study drug-related muscle spasm increased with indacaterol dose and was highest with indacaterol 600 µg od (2.0%) compared to 300 µg od (1.1%) or 150 µg od (1.0%); the rate for indacaterol 300 µg od (1.1%) was

similar to formoterol (1.3%) with a 0.1% incidence rate for placebo (there were no reports with tiotropium). In the 150 µg od indacaterol group, there were 5 patients (0.8%) with study drug-related ventricular tachycardia (all asymptomatic); no such events were seen in either of the two higher indacaterol dose groups nor in the formoterol, tiotropium and placebo groups.

An adverse drug reaction (ADR) is an undesirable effect in a patient that is reasonably associated with the use of a drug. It only includes adverse events for which there is some medical basis to suspect a causal relationship between the drug and the event. The 3 most frequent ADRs in the indacaterol 150 µg od group were URTI, nasopharyngitis and headache. Statistically significant treatment differences compared to placebo were seen for URTI and headache at 150 µg od, for rhinorrhoea at 300 µg od, and for muscle spasms at 150, 300 and 600 µg od. The frequency of muscle spasms was dose dependent (linear trend p <0.001).

The majority of AEs in all treatment groups were mild or moderate in severity. Only 3-4% of patients in the indacaterol 300 µg od (3.8%), 600 µg od (4.0%) and formoterol (3.4%) groups had severe AEs compared with 6% of patients in the other groups. COPD (includes disease progression and exacerbations) was the most frequent severe AE and the incidence of severe COPD in the indacaterol groups tended to decrease with increasing indacaterol dose (0.5% with 300 µg od compared with 2.4% with indacaterol 75 µg od and 1.6% with placebo). The majority of cough, nasopharyngitis and muscle spasm AEs were mild in severity. Severe cough was experienced by a higher proportion of placebo patients (0.6%) compared with all other treatments (0-0.2%). Severe muscle spasms affected 0-0.8% of patients and was most frequent with indacaterol 150 µg od (0.8%). Severe nasopharyngitis was reported by 0-0.3% of patients across the groups.

The incidence of adverse events with onset in the first 4 weeks of treatment was lower than the incidence for those with onset >4 weeks after the first dose of study drug. The frequently reported AEs of COPD, URTI, nasopharyngitis and muscle spasms had a greater incidence in the >4 weeks period. However, cough was reported more frequently in the indacaterol groups during the first 4 weeks of treatment. Ventricular tachycardia also occurred more often in the first 4 weeks of treatment (indacaterol 75 µg 1.57% - 2 patients, indacaterol 150 µg 0.64% - 4 patients, no events in the other groups) compared with the >4 week period [1 patient (0.17%) with ventricular tachycardia in the indacaterol 150 µg group and 2 patients (0.51%) on tiotropium].

When compared with the 3-month data, the overall AE rates were higher for each treatment group in the 6-month COPD dataset (66.6%, 60.6%, 56.7%, 55.8%, 67.2% and 56.8% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively). The most common AE in all treatment groups was COPD (includes disease progression and exacerbations) experienced by 17-20% of patients taking indacaterol, formoterol or tiotropium and 22.0% of patients on placebo. Cough and muscle spasms were more common in the indacaterol groups and dry mouth was more common in the tiotropium group (Table 9). The exposure-corrected event rate in the 6-month patient population showed similar results to those observed for the 3-month data.

Suspected drug-related AEs were reported more frequently in the indacaterol 150 µg od, 300 µg od and 600 µg od groups compared with formoterol, tiotropium and placebo (12.3%, 11.8%, 12.2%, 8.3%, 10.4% and 7.9%, respectively). The incidence of cough and muscle spasms appeared to be related to indacaterol dose, while headache was not dose-related; these results were similar to those observed in the 3-month dataset. In the 6-month dataset, statistically significant treatment differences compared to placebo were seen for the ADRs of URTI, headache, myalgia, neck pain, paraesthesia and ventricular tachycardia at 150 µg od, for rhinorrhoea and pneumonia at 300 µg od, for nasopharyngitis and tremor at 600 µg od, and for muscle spasms at 150, 300 and 600 µg od. The frequencies of muscle spasms, nasopharyngitis and tremor were dose dependent (linear trend p <0.001, p = 0.009 and p = 0.031, respectively).

Table 9: Common AEs (≥2.0% of patients in any group) by Preferred Term

Table 2-3 Common AEs (>=2.0% of patients in any group) by preferred term in COPD 6-month safety population

	Ind 150 µg N=416 n (%)	Ind 300 µg N=853 n (%)	Ind 600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=850 n (%)
Patients with ≥1 AE	277 (66.6)	517 (60.6)	310 (56.7)	310 (55.8)	279 (67.2)	483 (56.8)
Preferred term						
COPD †	73 (17.5)	157 (18.4)	95 (17.4)	106 (19.1)	81 (19.5)	187 (22.0)
Upper RTI	35 (8.4)	44 (5.2)	21 (3.8)	16 (2.9)	31 (7.5)	38 (4.5)
Nasopharyngitis	33 (7.9)	82 (9.6)	68 (12.4)	45 (8.1)	36 (8.7)	69 (8.1)
Cough	30 (7.2)	56 (6.6)	29 (5.3)	20 (3.6)	26 (6.3)	40 (4.7)
Headache	28 (6.7)	33 (3.9)	21 (3.8)	17 (3.1)	19 (4.6)	29 (3.4)
Viral upper RTI	16 (3.9)	25 (2.9)	2 (0.4)	8 (1.4)	7 (1.7)	21 (2.5)
Lower RTI	14 (3.4)	27 (3.2)	13 (2.4)	10 (1.8)	14 (3.4)	27 (3.2)
Muscle spasms	13 (3.1)	32 (3.8)	32 (5.9)	17 (3.1)	7 (1.7)	10 (1.2)
Diarrhea	13 (3.1)	17 (2.0)	8 (1.5)	11 (2.0)	8 (1.9)	15 (1.8)
Sinusitis	12 (2.9)	23 (2.7)	3 (0.6)	8 (1.4)	12 (2.9)	12 (1.4)
Dyspnea	12 (2.9)	21 (2.5)	16 (2.9)	10 (1.8)	11 (2.7)	27 (3.2)
Back pain	12 (2.9)	16 (1.9)	12 (2.2)	15 (2.7)	8 (1.9)	24 (2.8)
Pharyngolaryngeal pain	12 (2.9)	15 (1.8)	7 (1.3)	5 (0.9)	10 (2.4)	11 (1.3)
Influenza	11 (2.6)	22 (2.6)	12 (2.2)	7 (1.3)	4 (1.0)	12 (1.4)
Urinary tract infection	11 (2.6)	17 (2.0)	1 (0.2)	7 (1.3)	10 (2.4)	12 (1.4)
Nausea	11 (2.6)	7 (0.8)	4 (0.7)	6 (1.1)	4 (1.0)	19 (2.2)
Dizziness	9 (2.2)	20 (2.3)	8 (1.5)	5 (0.9)	2 (0.5)	19 (2.2)
Arthralgia	9 (2.2)	13 (1.5)	8 (1.5)	3 (0.5)	4 (1.0)	12 (1.4)
Bronchitis	7 (1.7)	25 (2.9)	13 (2.4)	12 (2.2)	13 (3.1)	34 (4.0)
Nasal congestion	6 (1.4)	5 (0.6)	3 (0.6)	2 (0.4)	9 (2.2)	10 (1.2)
Upper RTI bacterial	5 (1.2)	25 (2.9)	19 (3.5)	18 (3.2)	11 (2.7)	33 (3.9)
Hypertension	5 (1.2)	13 (1.5)	6 (1.1)	5 (0.9)	8 (1.9)	21 (2.5)
Dry mouth	5 (1.2)	5 (0.6)	1 (0.2)	1 (0.2)	19 (4.6)	4 (0.5)
Abdominal pain	1 (0.2)	9 (1.1)	2 (0.4)	5 (0.9)	3 (0.7)	7 (0.8)

Includes studies B2334 up to 6 months and B2335S
Preferred terms are sorted in descending order of frequency in the indacaterol 150 µg treatment group
Selected frequency cut-off of ≥2.0% of patients in any group includes the indacaterol 75 µg od group which is shown in the source post-text table.
† Includes COPD exacerbations. RTI = respiratory tract infection

Severity of AEs in the 6-month dataset were similar to those observed in the 3-month data; 6-7% of patients had severe AEs in the indacaterol 75 µg od, 300 µg od, 600 µg od and formoterol groups, 9% in the placebo group and 10% in the indacaterol 150 µg od and tiotropium groups with COPD being the most common severe AE in all treatment groups.

Overall, the incidence of adverse events with onset in the first 13 weeks of treatment was greater than the incidence for those with onset >13 weeks after the first dose for all treatment groups. The most frequently reported adverse events, COPD, URTI and nasopharyngitis occurred with comparable frequencies in the two treatment periods. The frequency of cough and muscle spasm in the indacaterol groups was higher in the first 13 weeks of treatment, and the time of onset was predominantly in the first 4 weeks of treatment.

All ventricular tachycardia events occurred in the first 13 weeks (indacaterol 75 µg 1.57%, indacaterol 150 µg 1.20%, tiotropium 0.48%) compared to only one event in the >13 week period

(placebo 0.15%). In fact, all the ventricular tachycardia events in the indacaterol groups occurred in the first 4 weeks of treatment except for one case in the 150 µg group that occurred in the 4 to 13 week period.

AE incidence in subgroups

The frequencies of AEs were summarized in subgroups by age, sex, race, COPD severity, smoking history and use of ICS. In the 3-month COPD safety dataset, the incidence of adverse events was higher in female patients in all treatment groups and patients with ≤moderate COPD had higher AE rates for all treatment groups, except tiotropium. There were no discernable trends detected for AE patterns in the subgroups by smoking status and ICS use, nor when AE preferred terms were sorted by age**.**

In the 6-month safety dataset, the incidence rates of adverse events were higher for patients ≥ 65 years of age in five of the six treatment groups, with the exception being the formoterol group. The incidence of adverse events was higher in female patients in all treatment groups, as was the incidence of AEs in ex-smokers versus current smokers. Use of ICS was associated with an increased incidence of AEs in all active treatment groups. There were no discernable trends detected for AE patterns in indacaterol-treated patients by COPD severity, baseline ICS use or when AE preferred terms were sorted by age**.**

SAEs, deaths and withdrawals due to AEs

In the COPD 3-month safety population, there were 6 deaths in the 3-month COPD database. The overall frequency of SAEs was similar across the 6 treatment groups (3.1 to 5.1%) and there was no dose-response relationship between the indacaterol doses The most frequent SAE reported in the COPD 3-month safety population was COPD (including disease progression and exacerbations). Overall, there were 9 patients on indacaterol with SAEs suspected by the investigator to be related to the study medication. All these events (up to Day 91) were reported in studies B2334 and B2335S and there were no suspected SAEs in study B2346. These suspected SAEs related mainly to cardiovascular events and occurred between Day 1 and 88. In one patient (68 year old female), with a normal baseline ECG and no cardiac history, atrial fibrillation was reported 1 hour after the first dose of indacaterol 150 µg. In the COPD 3-month safety population, age and sex did not have an effect on the overall frequency of patients with SAEs, nor on the frequency of those with SAEs related to *Respiratory, Thoracic and Mediastinal Disorders* or *Cardiac Disorders*. However, the number of patients with SAEs in these primary System Organ Classes (SOCs) was small and do not allow a definite conclusion. The number of non-Caucasian patients was small and did not allow an analysis by race. COPD severity and smoking status did not have an effect on the overall frequency of patients with SAEs, nor on those with cardiac disorders. Patients with SAEs related to *Respiratory, Thoracic and Mediastinal Disorders* were more frequent in those with severe COPD than those with moderate COPD in the 3 indacaterol and placebo groups. Also ex-smokers in the placebo group had more frequent respiratory disorder SAEs compared to current smokers, but this was not the case across the 3 indacaterol groups The proportion of patients with SAEs over all SOCs in non-ICS users was lower than in ICS users across all treatment groups including placebo, but this consistent pattern was not seen for the SAEs related to *Respiratory, Thoracic and Mediastinal Disorders*, *Infections and Infestations*, or *Cardiac Disorders* by ICS use. However, the number of patients with SAEs in these SOCs was small and does not allow a definite conclusion. Overall, the frequency of SAEs with onset in the first 4 weeks of treatment with study drug was lower than those with onset in the period >4 weeks after the first dose of study drug. However, *Cardiac Disorders* were more frequent in the first 4 weeks, while respiratory disorders had a similar frequency in the two observation periods.

The proportion of patients with any AE leading to discontinuation was lowest with indacaterol 600 µg od (4.9%, 4.9%, 2.7%, 4%, 3.4% and 5.6% in indacaterol 150 µg, 300 µg, 600 µg, formoterol,

tiotropium and placebo groups, respectively). The most frequently reported AE leading to discontinuation was COPD (including disease progression and exacerbations) which was highest in the placebo group (1.1%, 0.9%, 0.4%, 1.6%, 0.2% and 1.7%, respectively). Dyspnoea was the second most frequent AE leading to discontinuation occurring at higher rates with indacaterol 300 µg od and placebo (0.3%, 0.9%, 0.2%, 0%, 0% and 0.8%, respectively). Two of the three most frequent AEs leading to discontinuation in the indacaterol 150 µg od group were related to *Cardiac Disorders* (ventricular tachycardia and atrial fibrillation). Ventricular tachycardia was reported at a frequency of 0.6% with indacaterol 150 µg od compared to not being reported in the other groups except for tiotropium (0.2%) and indacaterol 75 µg od (1.6%, 2 patients). Atrial fibrillation occurred with a comparable frequency in all groups (0.1-0.3%) except for formoterol (0) and indacaterol 75 µg od (0). The frequency of AEs leading to discontinuation with onset in the first 4 weeks was similar to the incidence with onset in the period >4 weeks after the first dose of study drug for all treatment groups. In general, discontinuations due to ventricular tachycardia in the indacaterol groups occurred more frequently in the first 4 weeks of treatment.

In the COPD 6-month safety population, there were 7 deaths in the 6-month database. The overall frequency of SAEs was similar across the 6 treatment groups (6.2 to 8.4%, there was no positive dose-response relationship between the indacaterol doses). The most frequent SAEs reported in the indacaterol groups in the COPD 6-month safety population were COPD (including disease progression and exacerbations) and pneumonia. These SAEs however had a similar frequency in the placebo group. In the 6-month safety population, there were three additional SAE cases of atrial fibrillation suspected to be related to study medication in 1 patient on indacaterol 75 µg and 2 patients on indacaterol 150 µg occurring on Days 101, Day 115 and Day 184. Age, sex and race did not appear to have significant impact on incidence of SAEs, although numbers involved were small and precluded definitive conclusions. COPD severity and smoking status did not have an effect on the overall frequency of patients with SAEs (including respiratory SAEs); ICS users tended to have more SAEs than non-ICS users. The frequencies of SAEs overall, serious cardiac disorders and serious respiratory disorders were independent of the time of onset and were similar in the $\leq$13 weeks or >13 weeks after the start of study drug as the incidence was similar in the two observation periods.

The proportion of patients with any AE leading to discontinuation was higher with placebo (8.5%), indacaterol 75 µg od (7.9%) and 150 µg od (7.2%) compared to the other groups (4.1% to 5.9%). The most frequently reported AE leading to discontinuation was COPD (including disease progression and exacerbations) which occurred at a higher rate in the placebo and formoterol groups compared to the other groups (1.7%, 1.1%, 0.9%, 2.2%, 0.5% and 2.6% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively). Dyspnoea was the second most frequent AE leading to higher rates of discontinuation in the indacaterol (300 µg) and placebo groups compared with other treatment groups (0.2%, 0.9%, 0.4%, 0%, 0.2% and 0.9% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively). Two of the three most frequent AEs leading to discontinuation in the indacaterol 150 µg od were related to *Cardiac Disorders* (ventricular tachycardia and atrial fibrillation). Ventricular tachycardia was reported at a frequency of 1.0% (4 patients) with indacaterol 150 µg od and 1.6% (2 patients) with 75 µg od compared to tiotropium (0.2%, 1 patient), placebo (0.1%, 1 patient) and no reports in the remaining groups. Atrial fibrillation leading to discontinuation occurred most frequently with indacaterol 75 µg od (0.8%) and 150 µg od (0.7%) compared to placebo (0.4%) and 0 to 0.2% in the remaining groups. The frequency of AEs leading to discontinuation with onset in the first 13 weeks was approximately 3-5% greater than the incidence with onset in the period >13 weeks after the first dose of study drug for all treatment groups except indacaterol 600 µg for which the rates were similar. Discontinuations due to *Cardiac Disorders* were greater in the first 13 weeks for all treatment groups.

Long-term safety results from the 12-month COPD population

Exposure and baseline patient characteristics

The COPD 12-month dataset included 1728 patients, 862 of whom received indacaterol treatment at doses of 300 or 600 µg od inhaled via the Concept1 device. A slightly higher proportion of patients in the indacaterol groups completed >44 weeks of treatment (79.4% and 79.1%) compared with formoterol (75.6%) and placebo (71.8%). Total exposure to indacaterol 300 µg od was 372.2 patient-years (N = 437); 364 patients were exposed for >26 weeks and, of these, 172 patients were exposed for >52 weeks. Total exposure to indacaterol 600 µg od was 361.6 patient-years (N = 425); 355 patients were exposed for >26 weeks and, of these, 167 patients were exposed for >52 weeks.

In the 12-month safety dataset, the majority of patients were males (80%), Caucasians (93%) with mean COPD duration of 7 years; baseline demographics were similar in treatment groups. There was a slightly higher percentage of ex-smokers (58.7%) compared to current smokers (41.3%), and total mean number of pack years was 51.1 (range 20 to 900). Approximately half the patients were taking ICS at baseline (ICS users 52.9% versus 47.1% non-ICS users) with a slightly higher percentage of ICS users in the indacaterol 300 µg od group (55.6%) compared with the other groups. The mean percentage of predicted FEV_1 after inhalation of short-acting β-agonist (salbutamol/albuterol) relative to the predicted normal value was 52.5%, and the total mean FEV_1 reversibility after SABA was 12.5%. Patients with other co-morbid conditions were well-represented in this long-term dataset. Overall, 860 (49.8%) patients had hypertension, 547 (31.7%) patients had hyperlipidaemia, 343 (19.8%) patients had cardio or cerebrovascular conditions, and 159 (9.2%) diabetes mellitus. The majority of patients (92.6%) had at least one cardiovascular (CV) risk factor, and 38.0% of patients had ≥3 CV risk factors.

A majority of patients were taking COPD-related concomitant medications (67.3%, 63.5%, 63.6%, 68.3% in the indacaterol 300 µg od, 600 µg od, formoterol and placebo groups, respectively). Corticosteroids were the most commonly used medications (61.6%, 58.6%, 55.8% and 60.6%, respectively). Inhaled corticosteroids were used by 50 to 56% of patients and, of these medications, budesonide and fluticasone were taken most frequently. Oral corticosteroids were taken by 16 to 19% of patients, prednisolone and prednisone being the most widely used. Antibiotics were taken by 25.4%, 21.6%, 23.3%, 25.2% of patients in the indacaterol 300 µg od, 600 µg od, formoterol, and placebo groups, respectively. Oral antibiotics were taken by 20 to 25% of patients, most frequently amoxicillin.

AEs

The incidence of any AE was higher in the indacaterol 300 µg od group (70.9%) compared with indacaterol 600 µg od (64.9%) and formoterol (65.2%) and lowest in the placebo group (61.8%). The most common AE in all treatment groups was COPD (includes disease progression and exacerbations) experienced by about 30% of patients taking indacaterol or formoterol and about 35% of patients on placebo (indacaterol 300 µg od 32.0%, indacaterol 600 µg od 27.5%, formoterol 30.9%, placebo 34.7%). URTIs were common and comparable between the groups when like terms were considered (nasopharyngitis, URTI bacterial, URTI and URTI viral). Cough and muscle spasms were more common in the indacaterol groups (Table 10). No patient had ventricular tachycardia reported as an AE during treatment in 12-month study B2334. However, one patient (66 year old male, indacaterol 600 µg od) had ventricular tachycardia reported on day 176. This event was not included in the AE summaries because it occurred 12 days after the patient discontinued from the study due to a gastric ulcer haemorrhage. The number of AE episodes/patient year varied from 2.814 (formoterol) to 3.369 (indacaterol 300 µg od). These overall rates were quite comparable and were lower for each treatment group than those seen in the 3-month and 6-month data. Hence, the incidence of AEs did not appear to increase following long-term exposure to indacaterol.

Table 10: Common AEs (≥1.5.0% of patients in any group) by preferred term

	Ind 300 µg N=437 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=432 n (%)
Patients with ≥1 AE	310 (70.9)	276 (64.9)	283 (65.2)	267 (61.8)
Preferred term:				
Chronic obstructive pulmonary disease †	140 (32.0)	117 (27.5)	134 (30.9)	150 (34.7)
Nasopharyngitis	73 (16.7)	80 (18.8)	62 (14.3)	56 (13.0)
Cough	32 (7.3)	27 (6.4)	17 (3.9)	19 (4.4)
Upper respiratory tract infection bacterial	29 (6.6)	25 (5.9)	23 (5.3)	36 (8.3)
Lower respiratory tract infection	27 (6.2)	23 (5.4)	22 (5.1)	22 (5.1)
Muscle spasms	23 (5.3)	25 (5.9)	12 (2.8)	6 (1.4)
Upper respiratory tract infection	21 (4.8)	20 (4.7)	18 (4.1)	11 (2.5)
Headache	18 (4.1)	21 (4.9)	15 (3.5)	19 (4.4)
Influenza	18 (4.1)	19 (4.5)	13 (3.0)	13 (3.0)
Viral upper respiratory tract infection	18 (4.1)	8 (1.9)	12 (2.8)	9 (2.1)
Dyspnea	17 (3.9)	19 (4.5)	12 (2.8)	12 (2.8)
Back pain	15 (3.4)	15 (3.5)	13 (3.0)	19 (4.4)
Bronchitis	14 (3.2)	16 (3.8)	11 (2.5)	15 (3.5)
Pneumonia	11 (2.5)	6 (1.4)	8 (1.8)	5 (1.2)
Productive cough	10 (2.3)	5 (1.2)	8 (1.8)	7 (1.6)
Arthralgia	9 (2.1)	9 (2.1)	6 (1.4)	8 (1.9)
Dizziness	9 (2.1)	8 (1.9)	3 (0.7)	6 (1.4)
Dyspepsia	9 (2.1)	3 (0.7)	1 (0.2)	3 (0.7)
Urinary tract infection	9 (2.1)	2 (0.5)	5 (1.2)	5 (1.2)
Diarrhea	8 (1.8)	11 (2.6)	14 (3.2)	8 (1.9)
Hypertension	8 (1.8)	9 (2.1)	7 (1.6)	12 (2.8)
Pharyngolaryngeal pain	8 (1.8)	4 (0.9)	5 (1.2)	10 (2.3)
Pyrexia	8 (1.8)	3 (0.7)	7 (1.6)	7 (1.6)
Chest pain	7 (1.6)	6 (1.4)	4 (0.9)	7 (1.6)
Sinusitis	7 (1.6)	5 (1.2)	6 (1.4)	5 (1.2)
Abdominal pain	7 (1.6)	5 (1.2)	4 (0.9)	6 (1.4)
Pain in extremity	7 (1.6)	2 (0.5)	3 (0.7)	3 (0.7)
Rhinitis	7 (1.6)	2 (0.5)	0	3 (0.7)
Edema peripheral	5 (1.1)	9 (2.1)	6 (1.4)	1 (0.2)
Tremor	1 (0.2)	8 (1.9)	5 (1.2)	2 (0.5)
Nausea	1 (0.2)	4 (0.9)	4 (0.9)	8 (1.9)

Includes study B2334.
Preferred terms are sorted in descending order of frequency in the indacaterol 300 µg group.
† Includes COPD exacerbations

Suspected drug-related AEs were reported more frequently in the indacaterol 300 µg od and 600 µg od groups compared with formoterol and placebo (11.2%, 12.2%, 8.3% and 7.4% in indacaterol 300 µg, 600 µg, formoterol and placebo groups, respectively) and suspected drug-related cough accounted for some of this difference (3.0%, 3.8%, 1.4% and 0.7%, respectively). The incidence of treatment-related muscle spasm and tremor was also higher in the indacaterol groups. The 3 most frequent ADRs in the indacaterol 300 µg od group were nasopharyngitis, cough and muscle spasms. Statistically significant treatment differences compared to placebo were seen for cough at 300 µg od, for nasopharyngitis and peripheral oedema at 600 µg od, and for muscle spasms at 300 and 600 µg od. The frequencies of muscle spasms, nasopharyngitis and peripheral oedema were all dose dependent (linear trend $p < 0.05$).

The majority of AEs were mild or moderate in severity with only 10-12% of severe AEs in all treatment groups. The most frequent severe AE was COPD (includes disease progression and exacerbations), however this occurred less often with both doses of indacaterol (2.5-2.6%) compared with formoterol (5.1%) and placebo (4.4%). Other severe AEs were reported in <1% of patients in any treatment group. There were no severe muscle spasms and incidence of severe cough and nasopharyngitis was also very low.

The incidence rates of AEs starting in the first and second 26 week treatment periods were similar in the placebo and indacaterol 300 µg od groups; however, there were approximately 10% more patients with an AE during the first 26 weeks of treatment in the indacaterol 600 µg od and formoterol groups. The greatest differences between onset times were for *Gastrointestinal Disorders*, *General Disorders and Administration Site Conditions*, *Musculoskeletal and Connective Tissue Disorders* (especially muscle spasms) and *Nervous System Disorders* (notably headache). All were reported by approximately 1-5% more patients in the first 26 week treatment period. There was no relevant difference between the two onset periods for *Infections and Infestations* or *Respiratory, Thoracic and Mediastinal Disorders*, the two most frequently affected SOCs. Cough, muscle spasms and headache occurred more frequently in the first 26 weeks than in the subsequent 26 weeks of treatment in all groups (except for cough in the placebo group), and mostly in the first 13 weeks of treatment, as seen in the 6-month population. The incidence rates of nasopharyngitis and URTIs were not consistently related to time of onset.

In all treatment groups, the incidence of AEs was distinctly higher in female patients and ICS users. The incidence of AEs was slightly higher in patients aged ≥65 years and ex-smokers. The incidence of AEs by COPD severity was comparable in the indacaterol 600 µg group, whereas in the indacaterol 300 µg, formoterol and placebo groups the incidence of AEs was slightly higher for patients with ≤moderate COPD severity compared to those with ≥severe COPD, especially in the placebo group, which was unexpected. Meaningful comparisons of AE incidence by race and treatment were not possible due to the small sample sizes of all races other than Caucasians. There were no discernable trends detected in the incidence rates when AEs were sorted by preferred terms and age.

Deaths, SAEs and discontinuations due to AEs

There were 12 deaths in the 12-month COPD safety population; however, 3 of these deaths were not evaluated further as 2 occurred in patients not exposed to study drug and another patient in the formoterol group died 31 days after last intake of study drug and was therefore not counted in this population. The incidence of deaths was slightly higher in the placebo and formoterol groups.

In the COPD 12-month safety population, the overall incidence of SAEs was similar between the indacaterol 600 µg and the placebo groups, while the 300 µg and the formoterol groups had a higher incidence. There was no positive dose-response relationship between the indacaterol doses. The five most frequent SAEs in the indacaterol 300 µg od group were related to the respiratory tract (COPD-including exacerbations, URTI bacterial, pneumonia, respiratory failure, and dyspnoea), however

all of them were less frequent in the 600 µg od group and only two SAEs (respiratory failure and dyspnoea) had a numerically higher incidence rate with indacaterol than placebo. Other SAEs with a higher incidence rate in at least one of the indacaterol groups included atrial fibrillation (indacaterol 300 µg versus placebo: 0.7% versus 0.2%) and coronary artery disease (0.7% versus 0%). In the COPD 12-month safety population, there was one additional patient on indacaterol 300 µg with a SAE of atrial fibrillation suspected to be related to study medication occurring on Day 197 (the patient had a medical history of occlusive arterial disease and myocardial infarction). Age, sex and race did not appear to have significant impact on incidence of SAEs and trends between demographic subgroups seen on indacaterol were similar to those in the placebo group, reflecting the different risk of certain subgroups. Smoking status did not impact the SAE frequency or pattern. Patients with severe COPD and concurrent use of inhaled corticosteroids were associated with a numerically higher rate of SAEs related to cardiac disorders and those related to infections and infestations, but this trend was seen in both indacaterol groups and in the placebo group. The frequency of SAEs occurring in the first 26 weeks was similar to the frequency of those occurring after 26 weeks. The SAEs related to the respiratory SOC tended to be higher in the second observation period.

The proportion of patients with any AE leading to discontinuation was lowest with indacaterol 600 µg od (5.6%) compared to 300 µg od (8.2%), formoterol (9.7%) and placebo (9.3%). The highest rates involved respiratory disorders which led to discontinuation more frequently with formoterol (4.6%) and placebo (5.8%) than with both indacaterol doses (2.5% and 1.9%). Four of the five most frequent AEs leading to discontinuation in the indacaterol 300 µg od group were related to the respiratory tract (COPD, dyspnoea, lower RTI and URTI bacterial), but all of them were less frequent in the 600 µg od group. Other AE discontinuations with a higher incidence rate in at least one of the indacaterol groups versus placebo included asthenia (indacaterol 300 µg versus placebo: 0.7% vs 0%), vertigo (0.5% vs 0.2%) and rib fracture (0.5% vs 0%), muscle spasms and prostate cancer (0.5% vs 0%); no cases of discontinuations due ventricular tachycardia were reported in the COPD 12-month safety population. Adverse events leading to discontinuation were reported by approximately 2.5% more patients during the initial 26 weeks of the study than after the first 26 weeks. A greater frequency of events occurred in the cardiac and respiratory SOCs in the first 26 weeks than in the later time period for all treatment groups.

AEs of special interest

Cardiovascular AEs

In the COPD 3-month safety population, the overall incidence of cardio-cerebrovascular (CCV) AEs ranged from 1.98 to 4.34%; it was numerically higher than placebo for the 150 and 300 µg od indacaterol groups, but was lower than placebo in the 600 µg od group. The frequency of ventricular tachycardia was higher in the 150 µg od group compared with placebo; the frequencies of angina pectoris, atrial fibrillation, and ventricular extrasystoles were higher in the indacaterol 300 µg group compared with placebo. There was no evidence of a dose-response relationship between 150 and 600 µg od overall nor for any specific CCV Preferred Term. In comparison to the active controls, the overall frequency of CCV AEs for patients on indacaterol was higher than on formoterol but lower than on tiotropium. The five reports of ventricular tachycardia (VT) on indacaterol 150 µg od were asymptomatic findings based on a Holter ECG monitoring conducted at baseline and Days 14 and 84 as part of the protocol for study B2335S. All five cases were suspected to be related to the study medication by the investigators, one was reported as serious; 4 of the 5 patients' ages ranged from 49 to 80 years and 4 out of the 5 patients had pre-existing cardiovascular (CV) risk factors. On indacaterol 150 and 300 µg od, CCV AEs were only reported in patients with at least one CV risk factor, while patients without CV risk factors did not report any CCV events on those doses. The frequency of CCV events was independent of the number of pre-existing CV risk factors in the indacaterol 600 µg od and placebo groups. In the indacaterol 150 µg od dose group, a

positive history of a CCV condition was the CV risk factor associated with the highest frequency of CCV events, that is, 7/125 (5.6%).

In the COPD 3-month safety population the overall frequency of patients with CCV SAEs ranged between 0.55 and 1.45%; it was numerically higher than placebo for the 150 and the 300 µg od groups, while in the 600 µg od group it was lower than on placebo. Each of the individual SAEs occurred in single patients in the indacaterol groups. Coronary events were more frequent than cerebrovascular events in all treatment groups. The number of events was too small for valid assessment of a dose-response relationship. On indacaterol, CCV SAEs were only reported in patients with at least one CV risk factor.

The incidence of CCV AEs and SAEs showed a similar pattern in the 6-month COPD safety dataset. In the 12-month COPD dataset, the overall number of CCV events tended to be 1.5 to 2 times higher on all active treatments compared to placebo, but these were not dose dependent. The two most frequent events, atrial fibrillation and myocardial ischemia were numerically higher on indacaterol 300 µg od than on placebo, but again without a positive dose response relationship. Since most individual CCV events were rare (2 or less per treatment group) an interpretation of the data is difficult. The overall number of serious CCV events was approximately 3 times higher in the indacaterol groups than in the placebo group, without a dose dependency. The most frequent events in the indacaterol 300 µg od group were atrial fibrillation, heart failure and myocardial ischaemia (given incidences have been 0.7%, 0.5%, and 0.5% respectively); coronary artery disease and myocardial infarction were most common in the 600 µg od group. In the indacaterol treatment groups, serious CCV events were only reported in patients with at least one CV risk factor. The rate of serious CCV events generally increased with the number of CV risk factors.

The Phase III databases were explored for APTC (Antiplatelet Trialists' Collaboration 1994) type of events.[14] The overall frequency and the pattern of APTC type of CV events in the indacaterol groups were similar to those on placebo in the 3-month, 6-month and 12-month COPD datasets. The most frequent events were myocardial infarctions and these did not appear to be dose-related.

Diabetes-related AEs

In all treatment groups including placebo, the frequency of diabetes-related events was numerically higher among patients with a history of diabetes mellitus than in those without such a history. In the COPD 3-month safety population, the overall frequency of patients with diabetes-related events was numerically higher on indacaterol than on placebo. In the COPD 6-month safety population, the overall frequency of diabetes-related events was approximately twice as high in the indacaterol groups compared to the placebo group.

In the 12-month COPD population, the overall frequency of diabetes-related events was numerically higher in each of the active treatment groups than in the placebo group without a dose-response relationship for indacaterol. This pattern was mainly due to reports of (newly occurring/worsening) diabetes mellitus or Type 2 diabetes mellitus which were seen in approximately 1% of patients in the active treatment groups. With the exception of one patient with hyperglycaemia on indacaterol 600 µg od (decompensation of pre-existing diabetes, blood glucose 24 mmol/L that is, 432 mg/dL), none of these events were classified as serious.

[14] APTC events are recognized "hard" endpoints (e.g. myocardial infarction, stroke, and/or CV-related deaths) excluding "softer" or less well defined endpoints (e.g. angina pectoris). Overall 48 Preferred Terms were defined prospectively, 6 related to coronary ischemic events, 39 to cerebrovascular events, and 3 Preferred Terms related to death (sudden death, cardiac death, and sudden cardiac death).

Hypertension-related AEs

In the indacaterol and placebo groups, the frequency of hypertension-related events was higher among patients who had a positive history of hypertension. In the COPD 3-month and 6-month safety populations, the frequency of hypertension-related events in the indacaterol groups were low, and numerically lower than in the placebo group. In the 12-month COPD population, the frequency of hypertension-related events was similar across all treatment groups ranging from 2.1 to 2.8%. Among the indacaterol cases, all except one were non-serious events (a patient was hospitalized on Day 241 for cerebral ischemia and worsening of hypertension; the case was not suspected to be related to study medication).

Bronchospasm and hypersensitivity reactions

In the overall COPD population, there were 5 AEs of bronchospasm (2 in formoterol group and 1 each in the indacaterol 300 µg, 600 µg and placebo groups). For the 2 indacaterol-treated patients, the bronchospasm episodes were mild to moderate in severity, not considered by the investigators to be related to study drug and did not lead to discontinuation from the study. With few exceptions, the percentages of patients with FEV_1 reductions of ≥20% (at 5 to 30 minutes post inhalation relative to pre-dose value) were highest in the placebo group at the various visits. At those time points where indacaterol did have a higher percentage of FEV_1 decreases of ≥20% compared to the other groups, the numbers of patients were small and not clinically significant.

In the COPD 3-month safety population, most hypersensitivity events occurred in the placebo group (8 patients, 0.76%) compared with 2 patients (0.23%) in the indacaterol 300 µg od group, and 1 patient in each of the indacaterol 150 µg od (0.16%) and 600 µg od (0.18%) groups. The incidence of hypersensitivity events in the COPD 6-month safety population was also highest in the placebo group (7 patients, 0.82%, eyelid oedema, urticaria, swelling face) compared with 3 patients (0.72%, eye swelling, pharyngeal oedema, swelling face) in the tiotropium group, 2 patients in each of the indacaterol 150 µg od (0.48%, eye swelling and urticaria), 300 µg od (0.23%, urticaria and urticaria papular) and formoterol (0.36%, urticaria and shock) groups, and 1 patient (0.18%, eye swelling) on indacaterol 600 µg od. In the 12-month COPD population, no patient in either of the indacaterol 300 or 600 µg od groups experienced a hypersensitivity AE. Two patients (0.5%) on formoterol and 4 (0.9%) on placebo had a single hypersensitivity episode during the LT study.

No AEs of photosensitivity were reported for any patient in the COPD safety population.

Post-inhalation cough

In the Phase III program, the pivotal studies B2334, B2335S, and B2346 were designed to proactively solicit information about any post-inhalation (PI) events that occurred at the clinic visits after dosing, as observed by the study staff.

In the COPD 3-month safety population, the mean percentages of attended visits at which patients experienced PI cough were 16.7%, 19.2% and 16.6% in the indacaterol 150, 300 and 600 µg groups, respectively, and were statistically significantly ($p<0.001$) greater than in the placebo (2.1%), formoterol (0.9%) and tiotropium (0.9%) groups. There was no significant difference between the indacaterol 300 and 600 µg od groups in the percentage of attended visits at which patients had PI cough, but the percentage was significantly lower in the 150 µg od group compared with the 2 higher dose groups [indacaterol 300 µg versus 150 µg: odds ratio 1.68, 95% CI 1.36 - 2.08 ($p<0.001$); 600 µg od versus 150 µg od: odds ratio 1.50, 95% CI 1.16 - 1.94 ($p=0.002$)]. Similar results were observed in the COPD 6-month safety population and the 12-month COPD population. In the COPD safety population, the mean percentages of attended visits at which patients experienced PI cough ranged from 17.0% to 19.9% across the 3 indacaterol groups, and were statistically significantly greater than in the formoterol (0.9%), tiotropium (0.8%) and placebo (2.2%) groups; there was no significant difference between the indacaterol 300 and 600 µg od

groups in the percentage of attended visits at which patients had PI cough, but the percentage was significantly lower in the 150 μg od group compared with the 2 higher dose groups.

Overall, the percentage of PI coughers in each indacaterol treatment group was similar in the COPD 3 month, 6 month, and 12 month safety populations ranging from 27% to 31% across the 150, 300 and 600 μg od groups.

For the majority of patients, the PI cough started within 15 seconds of inhalation and lasted for ≤15 seconds. The frequency of PI coughers was numerically lower in elderly patients (≥65 years old) than in those <65 years old in the indacaterol 300 and 600 μg od groups, and lower in patients with severe COPD than those with moderate COPD only in the indacaterol 600 μg od group. However, the frequency of PI coughers was greater in women than men across all the treatment groups. While the frequency of PI coughers was numerically higher in smokers versus ex-smokers with all treatments, there were no relevant differences noted with ICS use, or duration of COPD. In general the trends between demographic subgroups seen on indacaterol were similar to those in the placebo group.

In general, the incidence of 'FEV_1 decrease of ≥20%' following inhalation of study medication was low (<3%) and did not show any association with PI cough throughout the 12 months of treatment.

The incidence of COPD exacerbations was numerically higher in the PI cougher subgroup versus the non-PI cougher subgroup in the indacaterol 150 and 300 μg od groups but similar to the non-PI coughers in the indacaterol 600 μg od group and in the placebo group. No dose response was noted. Only 5 patients reported bronchospasm as an AE in the 3 pivotal phase III studies, 2 of these were in the PI cougher subgroup: 1 in the indacaterol 300 μg group and 1 in the 600 μg group. The other 3 patients were in the non-PI cougher subgroup: 1 in the formoterol group and 2 on placebo.

The proportion of PI coughers in the subgroup of ACE inhibitor users was higher in the indacaterol 300 μg od group (33.6%) than in the 150 μg od (25.5%) and 600 μg od (26.0%) groups, whereas there was little difference across the 3 indacaterol dose groups in the ACE inhibitor non-users (29-30% of PI coughers in each indacaterol group). There was no marked or consistent difference in the frequencies of PI coughers by ACE inhibitor user or non-user and treatment. Only a small number of patients in each treatment group were users of anti-cough medication, therefore no firm conclusions about the frequencies of PI coughers by use or non-use of antitussives can be drawn.

There was no apparent association of PI coughers with the overall rates of patient participation or with any specific reasons for withdrawal from the studies in the indacaterol groups. There was no association of PI coughers with AEs leading to discontinuation in the indacaterol groups.

Laboratory parameters

The incidence of clinically relevant abnormalities in haematology parameters was low with no differences between treatment groups in the overall COPD population.

For most chemistry parameters, post-baseline and change from baseline results were not clinically significant. Mean changes from baseline were small and for the most part comparable among the treatment groups at the different time points. The percentages of patients with shifts from normal were low and comparable among treatment groups at the various time points. No trends indicative of clinical significance were noted.

Glucose and potassium were measured at pre-dose (25 minutes) and post-dose (30 minutes, 1 hour) time points at each visit to evaluate acute changes. Glucose mean changes from 25 minutes pre-dose to 1 hour post-dose for all visits were small and comparable among treatment groups, although there was a trend towards higher mean changes from baseline with increasing dose of indacaterol. The greatest mean change from 25 minutes pre-dose at any visit was seen in the indacaterol 600 μg od group at Day 1, 1 hour post-dose (0.35 mmol/L = 6.3 mg/dL). The overall incidence of newly occurring or worsening notably high glucose values (>9.99 mmol/L) in the indacaterol treatment

groups was about 5% in the COPD 3-month safety population**,** about 7% in the COPD 6-month safety population, and approximately 8% in the COPD 12-month and the whole COPD safety population. Among the various safety populations analysed, the incidence of high notable glucose values was greatest for the indacaterol 600 μg od group in the COPD 3-month, 12- month, and whole COPD safety populations. In the COPD 6-month safety population, the greatest incidence of high notable glucose values was in the indacaterol 150 μg od group. The differences in incidence rates between the indacaterol groups and placebo were small and not clinically significant.

In all the assessments and safety populations, there was no indication of a clinically relevant effect of indacaterol on potassium values. Potassium mean changes from 25 minutes pre-dose to 1 hour post-dose for all visits were small and comparable among treatment groups, although the mean changes in the indacaterol groups did show a trend towards mean decreases with increasing indacaterol dose. The greatest mean change from 25 minutes pre-dose at any visit (-0.11 mmol/L) was seen in the indacaterol 600 μg od group at Day 1, 1 hour post-dose.

Analyses of the liver chemistry data collected in the pivotal phase III studies in COPD patients did not show any indication of a hepatic safety signal during treatment with indacaterol at doses from 75 to 600 μg od**.**

Vital signs, ECG

BP, pulse rate

In the phase III, pivotal studies B2334, B2335S and B2346, sitting systolic and diastolic blood pressure and radial pulse rate were recorded at each visit before inhalation of study drug (25 minutes pre-dose), at 30 minutes (except study B2346) and 1 hour post-dose, as well as at screening and at the last visit. All blood pressure measurements were to be taken after the patient had rested in the sitting position for at least 10 min and clinically notable values were pre-defined.[15]

One-hour post-dose mean changes in systolic blood pressure were small among all treatment groups with mean decreases seen in the indacaterol 300 and 600 μg od groups at all visits.

Slightly greater mean decreases occurred with indacaterol 600 μg od compared to 300 μg od at all but the month 9, 1 hour post-dose time point, although the differences were small. One hour post-dose mean changes in diastolic blood pressure were small with mean decreases seen for most of the visits with the exception of month 3 (0.27 mmHg) in the indacaterol 150 μg group. Mean changes for pulse rate at 1 hour post-dose were small, with decreases in pulse rate seen for all treatment groups at all visits; these changes were not clinically significant.

The percentage of patients with low clinically notable systolic blood pressure (SBP) values was similar and about 2% in all treatment groups except indacaterol 150 μg od in which it was lower (0.5%) and formoterol where it was slightly higher (2.7%). The largest percentage of high clinically notable SBP values occurred in the indacaterol 600 μg od group (3.3%) and the lowest was in the indacaterol 150 μg od group (0.8%). The largest percentage of patients with low clinically notable diastolic blood pressure (DBP) occurred in the indacaterol 600 μg od group (2.0%) where the largest frequency of high clinically notable DBP was also seen along with placebo (1.8%). There

[15] Systolic blood pressure- Low criterion: < 75 mmHg (considering newly occurring or worsening cases) and/or ≤ 90 mmHg and decrease from baseline by ≥ 20 mmHg; -High criterion: ≥ 180 mmHg and increase from baseline by ≥ 20 mmHg and/or > 200 mmHg (considering newly occurring or worsening cases); Diastolic blood pressure- Low criterion: < 40 mmHg (considering newly occurring or worsening cases) and/or ≤ 50 mmHg and decrease from baseline by ≥ 15 mmHg; -High criterion: ≥ 105 mmHg and increase from baseline by ≥ 15 mmHg and/or > 115 mmHg (considering newly occurring or worsening cases); Pulse rate- Low criterion: < 40 bpm (considering newly occurring or worsening cases) and/or ≤ 50 bpm and decrease from baseline by ≥ 15 bpm; -High criterion: ≥ 120 bpm and increase from baseline by ≥ 15 bpm and/or > 130 bpm (considering newly occurring or worsening cases).

was some indication of dose dependency in the indacaterol groups in terms of the incidence of notably high or low SBP and DBP values with the lowest rates for any of these criteria being seen in the indacaterol 150 µg od dose group. The most frequent clinically notable low pulse rates occurred in the tiotropium group (1.9% of patients) while the largest percentage of patients with high clinically notable pulse rate occurred in the formoterol group (0.9%).

ECG

In the phase III, pivotal studies B2334, B2335S and B2346, ECGs were performed 25 minutes pre-dose, 30 minutes post-dose and 1 hour post-dose at each visit as well as at screening and at the end of the study. ECGs were to include all 12 standard leads and a Lead II rhythm strip of at least 10-second duration. ECGs were centrally reviewed by a cardiologist.

In the COPD safety population, baseline pulse rate (PR) intervals at corresponding time points were similar between treatment groups with mean values between 159.0 and 161.5 ms. There was an increase from baseline by approx. 1.5 ms over time irrespective of the dose. In addition there was a dose dependent decrease in the mean differences from baseline for several time points; e.g. at 6 months the differences were: +2.1 ms (150 µg), +1.0 ms (300 µg), and -1.8 ms (600 µg), versus +0.3 ms on placebo.

In the COPD safety population, the duration of the baseline QRS interval at corresponding time points was similar between treatment groups with mean values between 90.6 and 91.9 ms. Post-baseline, there was an increase over time irrespective of the dose. In addition there was a dose dependent increase in the mean differences for several time points; e.g. at 6 months the differences were: +1.4 ms (150 µg), +1.4 ms (300 µg), and +1.9 ms (600 µg), versus +1.1 ms on placebo. The maximum mean increase (of 2.8ms) in the QRS duration was at Month 12 on indacaterol 600 µg.

In the COPD safety population, the baseline ventricular rate at corresponding time points was similar between treatment groups with mean values of between 71.0 and 73.2 bpm. Post-baseline, there was a decrease in the ventricular rate of up to 2 bpm for all treatments, which generally increased over time. At 6 months, the difference from baseline was -2.4 bpm (150 µg), -1.9 bpm (300 µg), and -1.4 bpm (600 µg) versus -2.5 bpm on placebo.

There were no clinically relevant changes in the QTcF interval. In the COPD safety population, acute notable increases in the QTcF interval from pre-dose to 1 hour after inhalation were rare. There were no QTcF increases by >60 ms on indacaterol while there were 3 cases in the other treatment groups. Acute prolongations by 30-60 ms were seen in 0.1 to 1.5% of patients on indacaterol, and in 0.4 to 0.8% on placebo. Indacaterol data for QTcF increases of 30-60 ms pre-dose to 1 hour post-dose at Day 1 and Month 3 suggested a positive dose-response relationship although the absolute numbers were small. The frequencies of notable QTcF increases of 30-60 ms were similar for the active control groups as for indacaterol. The central ECG interpretation showed a higher proportion of patients with abnormal ECGs post-baseline than at baseline, across all treatment groups including placebo. The overall percentage of patients with abnormal ECGs increased from 30.4 - 32.0% at baseline to 47.5 - 53.1% post-baseline, without relevant differences between the indacaterol doses or between indacaterol and placebo. The 3 most frequent newly occurring individual ECG diagnoses on indacaterol 150 µg od were atrial/ ventricular premature contractions (APCs/ VPCs) and QTc prolongation. APCs ranged from 14.4% to 23.7% among the treatment groups. VPCs were reported in 13.1%, 18.3%, 19.6% and 16.1% in the indacaterol 150 µg, 300 µg, 600 µg and placebo groups, respectively and the frequency of QTc prolongations reflected a negative dose-response relationship (9.2%, 7.9%, 3.4% and 6.3%, respectively).

Continuous 24 hour ECG recordings (Holter monitoring) were performed in a subset of patients in COPD study B2335S and asthma safety study B2338. The Holter monitoring data were read centrally. In COPD study B2335S, Holter monitoring was undertaken at screening and after 2, 12 and 26 weeks of treatment in a subset of patients (n=522) randomized to one of two indacaterol

dose groups or placebo. The rates of specific arrhythmias were very similar in the indacaterol and tiotropium groups and slightly lower in the placebo group for non-sustained VT. There was no evidence for a pro-arrhythmic potential with indacaterol.

Safety results in other safety datasets

In 38 short-term studies of up to 50 days treatment duration including 11 studies in healthy subjects, 13 studies in patients with COPD and 14 studies in asthmatics, 3313 subjects were treated with indacaterol at daily (in multiple dose studies) or single doses ranging from 25 μg to 3000 μg. It is not possible to draw meaningful conclusions from the frequencies of AEs found in the short-term safety population as it contains a wide variety of study types including healthy subjects, COPD and asthma patients, single dose and multiple dose, crossover and parallel group, controlled and uncontrolled study designs, and treatment duration and size of the pooled treatment groups differ greatly. Cough was the most frequent AE in the all indacaterol group (all doses and all devices), particularly in the group of controlled asthma studies. Headache was the next most frequent AE occurring at a similar rate in the all indacaterol and placebo groups. In the healthy volunteer studies, cough was a common AE in the indacaterol groups. Also, a large proportion of patients in the indacaterol, moxifloxacin and placebo groups in the healthy volunteer controlled studies had contact dermatitis. These patients were all in the Thorough QTc study [B2339] in which repeated application and removal of adhesive electrodes used for the multiple ECG evaluations caused the generally mild contact dermatitis. In the Short-term safety population there were overall 28 patients with a total of 30 SAEs, 18 patients were on indacaterol (doses 50 – 800 μg), 2 on formoterol, and 8 on placebo. In the indacaterol patients the time to the event ranged between 0 and 35 days; 2 of the events were suspected to be related to the study medication (bronchospasm in 2 asthmatic patients). The most frequent SAEs reported were chronic obstructive pulmonary disease. Due to the small numbers and the different types of studies (controlled, uncontrolled) and subjects (asthma, COPD, healthy subjects) an assessment of the comparative frequency of these events is not feasible.

There were two deaths in ongoing studies of use for COPD reported to Novartis as of 1 October 2008, both in study B2336 (a 53 year old male due to COPD exacerbation, status asthmaticus and a 68year old male from death of unknown cause before administration of study drug).

Special safety studies

Asthma study B2338

B2338 was a 26-week treatment, randomized, multicentre, double blind, double dummy, parallel group study to assess the safety of indacaterol (300 and 600 μg od) in 536 patients with moderate to severe persistent asthma, using salmeterol (50 μg bd) as an active control. Patients were randomised (randomisation ratio 1:1:1, indacaterol 300 μg: indacaterol 600 μg: salmeterol 50 μg) with stratification for asthma severity, with a 2 week run-in period, and a 26 week treatment period. The assessment of safety included AEs and asthma exacerbations and the key safety variables for this class of drug namely serum potassium and glucose, heart rate, blood pressure, and QTc. The secondary objectives of this study were to evaluate the effect of indacaterol (300 and 600 μg od) on pulmonary function assessments (trough FEV_1 and FVC) and asthma exacerbation rates over 26 weeks. The exploratory objectives of this study were: to evaluate the effect of indacaterol (300 and 600 μg od) on asthma control over 26 weeks (percentage of days with 'no daytime symptoms'; the percentage of nights with 'no night-time awakenings'; total symptom scores over 26 weeks; the percentage of mornings with 'no symptoms on rising'; morning and evening PEF); to evaluate the effect of indacaterol (300 and 600 μg od) on the mean daily number of puffs of rescue medication used over 26 weeks; to evaluate the performance and properties of the ALIS (Asthma Life Impact Scale) patient reported outcomes measure over 12 and 26 weeks in patients ≥ 18 years of age and to evaluate the effect of indacaterol (300 and 600 μg od) on quality of life measurements (EQ-5D and

AQLQ) over 12 and 26 weeks. This study was conducted to evaluate safety of indacaterol during possible off-label use of indacaterol for asthma.

Safety results

The overall rate of AEs was lower in the indacaterol 300 µg group compared with the indacaterol 600 µg and salmeterol groups (54.9%, 66.4% and 67.3% in indacaterol 300 µg, 600 µg and salmeterol groups, respectively). The most frequently reported AE overall was asthma and occurred at a lower rate in the indacaterol 300 µg group (11.6%, 15.7% and 14.9%, respectively). Cough was the second most frequent AE in the indacaterol 300 µg and indacaterol 600 µg group and was reported for twice the proportion of patients compared with the salmeterol group. Nasopharyngitis was the second most frequent AE in the salmeterol group. Upper respiratory tract infection was reported more frequently in the indacaterol 600 µg group compared with the indacaterol 300 µg group and salmeterol group.

There were two deaths during the study and both were in the indacaterol 300 µg group. Sudden death was reported for one patient (60 year old male) who had previously been treated for an asthmatic crisis in the emergency room and discharged. The cause of death was determined as asthmatic crisis. The event (sudden death) was suspected to be related to study medication. The other patient (75 year old female) died as a result of cardiac arrest that was not suspected to be related to study medication. It is not possible to draw conclusions regarding the risk profile from a single asthma death.

The incidence of SAEs was low (1.9%, 4.1% and 3% in indacaterol 300 µg, 600 µg and salmeterol groups, respectively). A similar proportion of patients in each treatment group discontinued due to SAEs (1.5%, 1.5% and 1.1%, respectively). The incidence of discontinuations due to AEs was low (5.2%, 6.3% and 3.0%, respectively).

The number of clinically significant asthma exacerbation events was 25 in the indacaterol 300 µg group, compared with 29 in the indacaterol 600 µg group and 31 in the salmeterol group. The number of asthma exacerbation SAEs was low and occurred for 2 patients in the indacaterol 300 µg group, 3 patients in the indacaterol 600 µg group and 1 patient in the salmeterol group.

A post-inhalation (PI) cough event was an event that occurred within 5 minutes following inhalation of study medication at any study visit. Indacaterol treatment caused a PI cough that for the majority of patients was characterized by an onset within 15 seconds. Generally, PI cough was a brief event lasting 15 seconds or less and did not interfere with patient participation or completion of the study. The majority of PI coughers (85.0% of indacaterol 300 µg patients, 86.8% of indacaterol 600 µg patients, and 92.3% of salmeterol patients) completed the study and these rates are in line with the overall rates of study completion for each treatment group. PI cough was not a frequent occurrence for most indacaterol treated patients: for those who attended all 8 visits about 45% did not cough at any visit and around 40% coughed at more than two visits. The average percentage of patients with PI cough per visit was 34.4% in the indacaterol 300 µg group, 29.8% in the indacaterol 600 µg group and 2.2% in the salmeterol group. The incidence of patients with at least one PI cough during the study was 53.7% in the indacaterol 300 µg group, 45.1% in the indacaterol 600 µg group and 4.8% in the salmeterol group. The proportion of patients with an asthma exacerbation was higher in PI coughers compared with non PI coughers for indacaterol 300 µg patients (PI cougher versus non-PI cougher: 16.5% versus 7.1%) and indacaterol 600 µg patients (22.3% versus 10.2%). There was no notable difference in the proportion of PI coughers and non PI coughers with asthma exacerbations in the salmeterol group (15.4% versus 15.2%). The most common AE leading to discontinuation for PI coughers was asthma (2.4%, 4.1% and 0% in indacaterol 300 µg, 600 µg and salmeterol groups, respectively). The comparisons between PI coughers on indacaterol and those on salmeterol should be judged in the context of the very low rate of PI cough in patients receiving salmeterol.

Changes in laboratory values were generally small with few meaningful differences between treatment groups. There was little difference between treatment groups for liver function tests.

Serum potassium was statistically significantly lower in the indacaterol 600 μg group compared with salmeterol and indacaterol 300 μg at 1 hour post-dose on Day 1, but by Week 12 there were no significant differences between treatment groups. Blood glucose was statistically significantly higher in the indacaterol 600 μg group compared with salmeterol and indacaterol 300 μg 1 hour post-dose on Day 1 and with salmeterol 1 hour post-dose at Week 12. The effects of the higher dose of indacaterol on serum potassium and blood glucose are as expected for a β2-agonist and were not clinically significant.

Overall changes in pulse rate and blood pressure were small and differences between treatment groups were not clinically meaningful. The effect of indacaterol on the QTc interval was similar to the effect seen with salmeterol and differences between treatment groups were small. No patients had QTcF prolongation >500 ms. Heart rate, determined from ECG Holter monitoring, was not significantly different between treatment groups

Cough study

A2222 was a randomized, exploratory, multicentre, open-label, single dose, crossover study to assess the safety and tolerability of 200 μg indacaterol, delivered via MDDPI, with or without co-administration of water, with inhalation of 50 μg salmeterol, as an active comparator, in adult and adolescent patients with stable persistent asthma, or patients with COPD, **who had reported cough after indacaterol** in previous Phase II trials (studies A2208, A2210, A2216, A2218, B2201 or B2205). The primary objective was to explore whether the co-administration of a glass of water, either immediately prior to or after inhalation compared with inhalation without water, had any influence on the incidence of cough.

The incidence of cough in the five minutes following inhalation was 81.6% for indacaterol without water, 71.3% for indacaterol with water before inhalation, 82.8% for indacaterol with water after inhalation, and 8.0% for salmeterol. When it occurred, cough started immediately after inhalation (within 15 seconds of inhalation), was short in duration and, in the doctors' opinion, was mild or moderate in severity. Drinking water before inhalation reduced the incidence of cough within 5 minutes after inhalation by 10% compared with indacaterol without water, but 71% of patients still coughed. Overall, there was no evidence that drinking water after indacaterol inhalation had a clinically relevant effect on the incidence of cough. Most patients who had experienced cough when taking indacaterol in previous asthma or COPD studies did so again after indacaterol, but did not cough after salmeterol treatment. FEV_1 measurements before and after inhalation of indacaterol indicated that the cough did not have a detrimental effect on the patient's bronchodilation.

Safety in special patient populations

The incidence of diabetes-related AEs was higher in patients with diabetes in both indacaterol and placebo groups. Similarly, the incidence of cardiovascular and hypertension-related AEs was higher in patients with these disorders at baseline. The safety of indacaterol was not evaluated in patients with severe hepatic impairment or any form of renal impairment. There were no pregnancies reported in COPD patients in the indacaterol studies, therefore no clinical data on exposed pregnancies in COPD patients are available. Seven pregnancies have been reported during the indacaterol studies in asthmatics.

Overdose, drug abuse, withdrawal/ rebound effects

In COPD patients, single doses of 3000 μg were associated with a moderate increase in pulse rate and systolic blood pressure and prolonged QTc interval (Study B2202). An overdose of indacaterol is likely to lead to exaggerated effects typical of β2-adrenergic stimulants, that is, tachycardia,

tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

Indacaterol has no abuse potential. No specific studies of the withdrawal and rebound effects of indacaterol have been performed. Indacaterol at proposed doses has no or negligible influence on the ability to drive and use machinery.

Summary of safety

Overall, safety was evaluated in 363, 756 and 445 patients treated with indacaterol 150, 300 and 600 μg od, respectively for ≥3 months; the corresponding numbers exposed for ≥6 months were 243, 628 and 358, respectively. The number of patients exposed to indacaterol 300 and 600 μg od for ≥12 months was 172 and 167, respectively. However, the proposed doses for which approval is being sought are only 150 μg and 300 μg and there is no long-term safety data beyond 6 months for the 150 μg indacaterol dose.

The AEs observed in the indacaterol registration program were generally those that would be expected in the target patient population (COPD) and those commonly associated with the β2-agonist class of drugs.

The most frequent AEs in the 6-month pooled population were COPD, URTI, nasopharyngitis, cough, and headache. The most frequent treatment-related AEs included cough, headache, atrial fibrillation, ventricular tachycardia, and muscle spasms.

The incidence of cardiac arrhythmias was low. Atrial fibrillation showed a low incidence with no dose response seen for indacaterol; this event also occurred in placebo patients with the highest incidence in the tiotropium control group. The few cases of ventricular tachycardia seen at the indacaterol 150 μg dose were all asymptomatic findings noted on Holter monitoring where the investigator chose to report this as an adverse event.

SAEs and patient deaths would be expected in the patient populations studied. These events occurred during the registration program; review of death narratives did not show any patterns suggestive of a unique effect of indacaterol on these serious events.

In summary, at the indacaterol doses of 150 and 300 μg recommended for COPD, the adverse events for this once daily β2-agonist were comparable to those observed for the active control groups, and to the prescribing information for drugs of similar class.

Clinical Summary and Conclusions

Indacaterol is an ultra long-acting beta2-adrenergic agonist for once-daily administration in patients with moderate to severe COPD. The full bronchodilator effect of indacaterol is almost completely achieved within 30 min of inhalation with clinically relevant bronchodilator effects within 5 minutes after inhalation. There was no difference in bronchodilator effect after morning or evening administration of indacaterol. The treatment effects compared to placebo (baseline-adjusted) for indacaterol delivered via the Concept1 device ranged from 120 ml up to 250 ml for inhaled doses of 150 μg to 800 μg. Doses below 150 μg appeared not to provide clinically meaningful single dose bronchodilation over 24 hours. There was only a small or no incremental effect for peak FEV_1 in studies comparing different doses versus placebo above the dose level of 300 μg. Studies in asthma patients also support the consistency of the bronchodilator responses obtained with indacaterol in COPD.

The pharmacokinetics of indacaterol was well-characterised in studies in healthy subjects and in COPD patients and justified once daily administration.

There were 3 pivotal Phase III studies which evaluated efficacy of indacaterol in over 4000 patients with moderate to severe COPD. The proposed doses of indacaterol 150 μg and 300 μg were statistically significantly superior to placebo and non-inferior to tiotropium (18 μg od) in the

primary efficacy endpoint of trough FEV_1 after 12 weeks. These effects were maintained for 26 weeks in study B2335 and up to 52 weeks in study B2334. The improvements in FEV_1 were supported by significant improvements in 'days of poor control', quantitative quality of life measures SGRQ, TDI and BODE, use of rescue medication. Symptom scores also supported the spirometry and QoL results, but to a lesser degree.

The number of patients exposed to indacaterol 150, 300 and 600 μg od for ≥3 months was 363, 756 and 445, respectively, and the corresponding numbers exposed for ≥6 months were 243, 628 and 358. The number of patients exposed to indacaterol 300 and 600 μg od for ≥12 months was 172 and 167, respectively. Safety was adequately assessed and majority of the AEs were similar to those expected with a long-acting beta2-adrenergic agonist.

Some of the limitations of this submission were:-

- In the pivotal Phase III studies, although patients were randomised according to smoking status in all 3 pivotal studies, tobacco exposure during the study was not monitored and any changes in smoking status were not reported or considered in the analysis. In all 3 pivotal Phase III studies, treatment groups were not stratified according to baseline severity of COPD or prior use of ICS, but these were similar in the different treatment groups. However the sponsor highlighted that the baseline severity was accounted for in the statistical model.

- A difference of 120 mL in trough FEV_1 between indacaterol and placebo was considered a clinically important difference for COPD patients by the sponsors, although this is not explicitly defined in the current CPMP guidelines.

- The sponsors claim that when bd LABAs, formoterol or salmeterol were used as active controls, the bronchodilator effects of indacaterol were at least as large, and in some studies better than those of the other two LABA compounds. However, these studies were not powered to detect significant changes between indacaterol and formoterol/ salmeterol and the results can only be considered exploratory. Hence, non-inferiority of indacaterol compared to other established LABAs has not been established.

- Long-term efficacy and safety of proposed dose of 150 μg indacaterol was not established beyond 6 months.

Despite the above limitations, the submitted data suggests that indacaterol provides a safe alternative for 24-hour bronchodilator effect with rapid onset of action for the treatment of patients with COPD. Overall, the risk-benefit profile of indacaterol appears to be favourable for the treatment of adult patients with moderate to severe COPD.

Recommendation

The evaluator recommended that Onbrez (indacaterol 150 μg and 300 μg) oral inhalation be approved for the long-term, once daily, maintenance bronchodilator treatment of airflow limitation in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

V. Pharmacovigilance Findings

The Risk Management Plan submitted with this application was not evaluated since it was not a TGA requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Indacaterol has one chiral centre and the pure R enantiomer is used. Further, indacaterol is crystalline: only one polymorphic form of indacaterol maleate has been identified ("Form A") after crystallisation experiments. Indacaterol maleate is very slightly soluble in water.

The evaluator noted that the product is presented as encapsulated dry powder, the excipient is lactose and the presentation is as a hard gelatin capsule. The capsules are punctured to allow for inhalation via a dedicated device ("Breezhaler").

The evaluation report notes that "When used with the inhalation device provided, under controlled conditions the capsules allow delivery of a dose of 120 µg or 240 µg (expressed as indacaterol base). The dose delivered to the lung as an aerosol powder is estimated in product testing as the 'fine particle dose', showing slight non-linearity. "

The device is described as follows: "The inhaler uses two manually pushed needles to puncture the capsule when it is inside the device. The capsule fits only loosely into the chamber, and on inhalation it moves."

The 'specific resistance' of a dry powder inhaler device determines the flow rate at which the patient can inhale through it. Devices with low specific resistance (such as the Rotahaler, Spinhaler and proposed Breezhaler) allow high flow rates and vice versa.

The Breezhaler device was developed from the Novartis Aeroliser (used with eformoterol capsules). One model (RS01) was used in phase II studies. The Concept1 device was used throughout Phase III studies, including pivotal clinical studies and the dose finding part of the study B2335S. The RS01 and the Concept1 device are stated to have equivalent operating parts (for example, piercing the capsule, and dimensions of device parts which are relevant for dose delivery).

The Concept1 device was used in the pivotal Phase III clinical studies; the device proposed for registration is the same, but the manufacturing process has changed. Equivalence between devices used in Phase III and for commercial use is claimed based on *in vitro* data (delivered dose and cascade impactor profiles). This is considered acceptable.

The inhaler will be separately entered on the Australian Register of Therapeutic Goods (ARTG) as a medical device (allowing separate supply). The effect of variations in device dimensions on drug delivery has not been directly investigated. Data were provided on the effects of cleaning, dropping and the orientation of the device upon its performance.

The evaluator added that "Novartis has provided *in vitro* data on the effect of changes in flow rate on delivered dose and fine particle mass. Increasing the flow rate from 30 to 90 L/min markedly increases the fine particle mass. Novartis claims COPD patients can achieve 50 L/min and greater flows with this device."

Study B2103 was a pharmacokinetic study that compared morning versus evening dosing, using the presentation that is proposed for marketing, but it also included an absolute bioavailability substudy that the evaluator has briefly considered. Part 1 (16 subjects) compared the 300 µg product given in the morning without food to the 300 µg product given in the evening with food.

Part 2 (4 subjects) compared a 300 µg inhalation given in the morning and a 400 µg IV injection. Following intravenous infusion of 236 to 336 µg indacaterol doses, serum levels could be measured up to the last sampling point (168 hours) in all four subjects. Based on the individual dose normalised $AUC_{0\text{-tlast}}$ values, the inhaled bioavailability of indacaterol was 43.2%. The disposition of indacaterol after intravenous administration to 4 subjects in Part 2 was characterized by an extensive distribution (mean Vz: 2557 L), a moderate systemic clearance (mean CL: 23.3 L/h) and a long terminal elimination phase (mean $t_{1/2}$: 76 hours). The sponsor concluded that "The absolute bioavailability of an inhaled indacaterol dose was moderate (42%), suggesting that intestinal

absorption of the swallowed fraction of the dose contributes to the systemic exposure following inhalation."

The Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) reviewed this application at its 131st meeting in March 2010. The PSC was satisfied with questions asked by the TGA of the sponsor but had some suggestions concerning the Product Information document,

The quality evaluator concluded that registration was supported on chemistry and quality control grounds. A shortened shelf-life will be needed.

Nonclinical

The evaluator found the nonclinical submission was adequate and GLP compliant. The following was also noted:

1. Indacaterol is a ß2-adrenoceptor agonist, displaying nanomolar potency and high intrinsic activity. Long-lasting inhibition of bronchoconstriction following intratracheal administration in guinea pigs and inhalation in monkeys was shown *in vivo*. Selectivity for the human ß2 adrenoceptor over the ß1- and ß3- subtypes was high (24- and 20-fold in functional assays).

2. Safety pharmacology studies suggested an adequate safety margin by reference to the proposed clinical dose in regard to CNS effects and in terms of tachycardia in dogs and monkeys after a single inhalational dose. This was said to be consistent with excessive ß-adrenoceptor stimulation from high systemic exposure. Acute toxicity was low in the species examined.

3. Pivotal repeat-dose toxicity studies were conducted in rats (6 months) and dogs (9 months) using the inhalational route. Toxicities were found in the heart, lungs and the rest of the respiratory tract (including squamous metaplasia and hyperplasia of the upper respiratory tract), liver and kidney. When given orally, gastrointestinal tract toxicity was also seen. These effects are considered to be representative of class effects.

4. Indacaterol was not mutagenic in a standard set of assays but it was associated with ovarian leiomyomas in rats.

There were no nonclinical objections to the registration of Onbrez Breezhaler for the proposed indication. Various significant amendments to the product information document were sought.

The Delegate noted combination carcinogenicity studies with cigarette smoke would have been of interest but have not been done.

Clinical

Pharmacokinetics

Pharmacokinetic information has been collected from healthy volunteers, patients with COPD and asthma patients in 36 clinical studies.

The TGA evaluator summarised the pharmacokinetic data as follows:

1. After oral inhalation from an SDDPI device such as the proposed marketing device for administering indacaterol, indacaterol was rapidly absorbed and achieved peak serum levels (C_{max}) in the majority of subjects within the first 30 minutes. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 hours. Data from the multiple dose inhalation studies (A2221 and B2339) suggested that the effective half-life for accumulation was in the range of 40 to 52 hours which was consistent with the observation that steady state was achieved between 12 and 14 days of od dosing. Indacaterol is highly bound to plasma and serum proteins. The in vitro human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively.

2. Indacaterol showed dose proportional pharmacokinetics over a dose range of 150 μg to 600 μg; evening or morning dosing had no significant pharmacokinetic/dynamic effects at a dose of 300 μg; the hydroxylated metabolites P26.9 and P30.3 were found to have similar *in vitro* affinity to human beta-2-receptors. However the hydroxylated metabolites could not compete with indacaterol's duration of action in functional assays and are not expected to contribute significantly to pharmacological activity of indacaterol.

3. Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. The key enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. Mild and moderate hepatic impairment did not alter indacaterol pharmacokinetics or protein binding significantly. The effect of severe hepatic impairment on indacaterol pharmacokinetics was not evaluated. Since renal clearance plays a very minor role in elimination of indacaterol, a study in renally impaired subjects was not conducted.

4. Given the safety data of study B2339 and of the pivotal studies (which both confirmed safe use of a 600 μg dosage regimen), the magnitude of exposure increases due to drug-interactions do not raise any safety concerns for therapeutic doses of 150 μg or 300 μg [as far as inhibitors of the principal metabolic pathways of indacaterol are concerned].

Pharmacodynamics

The pharmacodynamic studies included dose ranging up to 3000μg indacaterol in single dose and from 50 μg to 800 μg in repeat dosing studies; FEV_1 was used to characterise the bronchodilator effect of indacaterol at the end of the 24 hour dosing interval and peak FEV_1.

No safety signals were noted at the higher than recommended doses but dose dependent effects on heart rate are of note. The TGA evaluator noted that "In study B2202, single doses of indacaterol in COPD patients produced a dose-dependent increase in heart rate up to 3000 μg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm. In the double-blind, placebo-controlled study B2201, repeat doses of 400 and 800 μg indacaterol for 28 days produced a maximum heart rate change versus placebo of 2.9 bpm one hour post-dose with the 800 μg dose". Dose dependent changes in the QTc interval were not found after four weeks of treatment.

In regard to the four dose-ranging studies, the TGA evaluator comments, "... clinically meaningful bronchodilator effects of >120 mL have been observed consistently with inhaled indacaterol doses of 150 μg and higher (irrespective of the device used). The trough bronchodilator effect after 24 hours appears to be more pronounced after repeated dosing."

Efficacy

The six Phase III efficacy studies used the device that is proposed for marketing. Three double blind, randomised studies were considered to be pivotal: B2335S included both the proposed indacaterol doses (150 μg and 300 μg) over 26 weeks, B2346 provided efficacy data for up to 6 months for the 150 μg dose and a 52 week long trial, B2334, included data on the 300 μg and 600 μg doses. All studies enrolled patients with moderate or severe COPD (respectively, FEV_1 <80% predicted normal values; <30% predicted normal values) and with non-reversible or partly reversible airway function. B2335S was well-designed with a placebo control and an active control (tiotropium bromide 18 μg daily and formoterol inhaler), necessitating a double-dummy design for the latter and openness in respect of the former. At twelve weeks, all three active treatments were superior to placebo in terms of the primary endpoint and both doses of indacaterol maleate were similarly effective. Both doses of indacaterol maleate were non-inferior to tiotropium bromide; the sponsor tested for superiority which was then claimed. Of the numerous secondary endpoints, the higher dose showed some advantage in terms of time to onset but this was lost some time after 2 days. The proportion of patients who experienced at least one COPD exacerbation was similar

across treatments. Rescue medication use favoured indacaterol maleate over tiotropium bromide and placebo.

B2346 was a 12 week placebo controlled study that used indacaterol maleate 150 µg od as the active treatment. The primary objective was to demonstrate superiority of indacaterol (150 µg) versus placebo with respect to 24 hour post-dose (trough) FEV_1 after 12 weeks of treatment. The least squares mean (LSM) estimate of the trough FEV_1 at Week 12 was statistically and clinically significantly greater for indacaterol 150 µg compared with placebo (1.49 L versus 1.35 L, respectively, $p < 0.001$; difference=0.13 L, 95% CI: 0.09 to 0.18). The numerous secondary endpoints favoured active treatment, including use of rescue treatment. Discontinuation due to lack of efficacy was less common with indacaterol maleate than placebo (0.5% versus 2.9% respectively).

B2334 was a 52-week, multicentric, randomised, double-blind, double dummy, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of indacaterol (300 & 600 µg daily) in patients with moderate/ severe COPD, using formoterol (12 µg bd) as an active control. The primary objective was to assess indacaterol (300 and 600 µg od via SDDPI) superiority in patients with COPD compared to placebo with respect to 24 hour post dose (trough) FEV_1 after 12 weeks of treatment. The key secondary efficacy endpoint was the percentage of 'days of poor control' reported over the 52 week randomized treatment period. The evaluator was of the view that the study was adequately powered to test both doses of indacaterol maleate against placebo with respect to the primary outcome; the study was not powered to detect differences between formoterol and indacaterol. The LS mean of trough FEV_1 at Week 12 was the same for both doses of indacaterol (0.17 L) and both were significantly greater than placebo (hierarchical testing tested 600 µg only if 300 µg versus placebo was significant). Both doses of indacaterol had significantly greater LS mean trough values than formoterol (which had a significantly higher LS mean trough level compared to placebo).

Amongst secondary analyses, the reduction in trough FEV_1 was maintained over 52 weeks of treatment for all indacaterol and formoterol groups and was consistently greater than placebo (Figure 3). Indacaterol maleate was superior to placebo, as was formoterol, in numerous other secondary analyses, including rescue medication use.

Supportive Studies

As noted by the evaluator, the 3 short-term, profiling, crossover, Phase III studies provide information on specific aspects of indacaterol therapy, such as efficacy following evening versus morning dosing (B2305), its lung function profile throughout 24 hours (B2340) and fast onset of effect (B2307). That is, they contributed additional pharmacodynamic data.

Study B2305, a two week long trial, suggested that time of administration of indacaterol (evening or morning) was not likely to affect its efficacy in moderate to severe COPD.

B2340 was a 3-period, 14-day crossover study to determine the 24 hour lung function profile of indacaterol (300 µg daily) in 68 patients with moderate-to-severe COPD, using open-label salmeterol (50 µg bd) as active control: the study was powered for the primary endpoint (trough FEV_1) and the key secondary endpoint (FEV_1 at each time point). However, comparisons between indacaterol and salmeterol were not pre-defined and were thus considered exploratory only. At Day 14, 24 hour serial spirometry was performed. Individual time point analyses of FEV_1 showed that the LS mean treatment difference for indacaterol minus placebo was statistically significant at all post-dose time points evaluated after 14 days of treatment. The difference for indacaterol minus salmeterol was generally statistically significant up to and including 11 hours 45 minutes, with later time points also favouring indacaterol but usually not reaching statistical significance.

Study B2307 suggested a rapid onset of action, similar to salbutamol but the evaluator considered that the study was exploratory only.

Safety

As noted by the evaluator, safety was assessable in six study populations: (1) COPD 3-month safety populations (n=4180), (2) COPD 6-month population (n=3764), (3) COPD 12-month population (n=1728), (4) COPD safety population (n=4180), (5) asthma safety population (n=805), (6) Short-term safety population (n=3313) and (7) 'all-treated' subjects population (n=6003).

In the COPD 3-month population, the overall incidence of AEs was slightly higher in the indacaterol, tiotropium and placebo groups compared with the formoterol group (51.7%, 49.1%, 46.1%, 44.2%, 55.2% and 46.3% in indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo groups, respectively); this was mainly driven by slightly lower incidence of cough and upper RTI in the formoterol group compared with the other treatment groups (Table 8).

Regarding dose dependent adverse effects, the rate of study drug-related muscle spasm increased with indacaterol dose and was highest with indacaterol 600 µg od (2.0%) compared to 300 µg od (1.1%) or 150 µg od (1.0%); the rate for indacaterol 300 µg od (1.1%) was similar to formoterol (1.3%) with a 0.1% incidence rate for placebo (there were no reports with tiotropium). In the 150 µg od indacaterol group, there were 5 patients (0.8%) with study drug-related ventricular tachycardia (all asymptomatic); no such events were seen in either of the 2 higher indacaterol dose groups nor in the formoterol, tiotropium and placebo groups. Overall, the incidence of adverse events with onset in the first 13 weeks of treatment was greater than the incidence for those with onset >13 weeks after the first dose for all treatment groups. The evaluator concluded that the most frequently reported adverse events - COPD, URTI and nasopharyngitis - occurred with comparable frequencies in the two treatment periods. Serious adverse events were evenly distributed across treatment groups. In the COPD 6-month safety population, there were seven deaths in the 6-month database but the evaluator did not perceive dose-related or treatment-related signals.

The COPD 12-month data set included 1728 patients, 862 of whom received indacaterol treatment at doses of 300 or 600 µg daily inhaled via the Concept1 device. Of these patients, 364 patients were exposed to indacaterol for >26 weeks and, of these, 172 patients were exposed to indacaterol for >52 weeks. As noted by the evaluator, suspected drug-related AEs were reported more frequently in the indacaterol 300 µg od and 600 µg daily groups compared with formoterol and placebo (11.2%, 12.2%, 8.3% and 7.4% in indacaterol 300 µg, 600 µg, formoterol and placebo groups, respectively) and suspected drug-related cough accounted for some of this difference (3.0%, 3.8%, 1.4% and 0.7%, respectively). The incidence of treatment-related muscle spasm and tremor was also higher in the indacaterol groups. The frequencies of muscle spasms, nasopharyngitis and peripheral oedema were all dose dependent (linear trend $p < 0.05$) [to the 600µg dose]. The frequency of serious adverse events occurring in the first 26 weeks was similar to the frequency of those occurring after 26 weeks. The proportion of patients with any AE leading to discontinuation was lowest with indacaterol 600µg od (5.6%) compared to 300µg od (8.2%), formoterol (9.7%) and placebo (9.3%).

Overall, the evaluator concluded that "The AEs observed in the indacaterol registration program were generally those that would be expected in the target patient population (COPD) and those commonly associated with the β2-agonist class of drugs... In summary, at the indacaterol doses of 150 and 300 µg recommended for COPD, the adverse events for this once daily β2-agonist were comparable to those observed for the active control groups, and to the prescribing information for drugs of similar class."

Summary of Deficiencies Identified in the Clinical Evaluation Report

The evaluator noted that "some of the limitations of this submission were:-

- In the pivotal Phase III studies, although patients were randomised according to smoking status in all 3 pivotal studies, tobacco exposure during the study was not monitored and any changes in smoking status were not reported or considered in the analysis. In all 3 pivotal Phase III studies,

treatment groups were not stratified according to baseline severity of COPD or prior use of ICS, but these were similar in the different treatment groups. However the sponsor highlighted that the baseline severity was accounted for in the statistical model.

- A difference of 120 mL in trough FEV_1 between indacaterol and placebo was considered a clinically important difference for COPD patients by the sponsors, although this is not explicitly defined in the current CPMP guidelines (dated Jan 22, 2009). Furthermore, the sponsor had not provided any other literature based clinical trials results or consensus guidelines to support their cut-off of 120 mL as being clinically relevant. Novartis provided literature based clinical trials results in response to the TGA request. The sponsor claimed that when bid LABAs, formoterol or salmeterol were used as active controls, the bronchodilator effects of indacaterol were at least as large, and in some studies better than those of the other two LABA compounds. However, these studies were not powered to detect significant changes between indacaterol and formoterol/ salmeterol and the results can only be considered exploratory. Hence, non-inferiority of indacaterol compared to other established LABAs has not been established.

- Long-term efficacy and safety of proposed dose of 150 µg indacaterol was not established beyond 6 months. "

The evaluator has recommended a more precise indication that removes the suggestion that this LABA can "treat" COPD, "It is recommended that Onbrez (indacaterol 150 µg and 300 µg) oral inhalation be approved for the long-term, once daily, maintenance bronchodilator treatment of airflow limitation in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD). The approval is subject to incorporation of the suggested changes to the proposed product information. "

Sponsor's reply to Clinical Evaluation Report:

The sponsor identified three errors in the evaluation report which have been corrected in this AusPAR. The Delegate noted that these minor differences do not affect the security of the evaluator's overall conclusions.

The sponsor had a number of disagreements with findings of fact:

1.1 Lack of stratification of Phase 3 study results according to ICS use and baseline COPD severity.

The sponsor pointed out that there was a pre-planned analysis by severity and smoking history. Smoking status was included in the randomisation. An analysis (Table 1.1) was provided which suggest similar benefit regardless of whether current or ex-smoker.

Table 1-1 Least square means of trough FEV_1 (L) at Week 12 (LOCF), by smoking history (COPD 3 month efficacy population)

		---Treatment ---			---- Treatment difference --------			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Ex-smoker								
Ind 150 ug	315	1.46	0.016	Ind 150 ug – Pbo	0.15	0.016	(0.11, 0.18)	<.001
				Ind 150 ug – For	0.07	0.020	(0.03, 0.11)	<.001
				Ind 150 ug - Tio	0.04	0.020	(0.00, 0.08)	0.059
Ind 300 ug	440	1.49	0.015	Ind 300 ug – Pbo	0.18	0.015	(0.15, 0.21)	<.001
				Ind 300 ug – For	0.10	0.017	(0.07, 0.14)	<.001
				Ind 300 ug – Tio	0.07	0.019	(0.03, 0.11)	<.001
				Ind 300 ug – Ind 150 ug	0.03	0.017	(0.00, 0.06)	0.080
For	293	1.39	0.018	For – Pbo	0.08	0.017	(0.04, 0.11)	<.001
				For - Tio	-0.03	0.021	(-0.08, 0.01)	0.112
Tio	220	1.42	0.019	Tio- Pbo	0.11	0.019	(0.07, 0.15)	<.001
Pbo	515	1.31	0.014					
Smoker								
Ind 150 ug	275	1.48	0.017	Ind 150 ug – Pbo	0.18	0.018	(0.15, 0.21)	<.001
				Ind 150 ug – For	0.09	0.022	(0.04, 0.13)	<.001
				Ind 150 ug - Tio	0.03	0.022	(-0.01, 0.08)	0.116
Ind 300 ug	338	1.46	0.017	Ind 300 ug – Pbo	0.15	0.016	(0.12, 0.19)	<.001
				Ind 300 ug – For	0.06	0.020	(0.02, 0.10)	0.002
				Ind 300 ug – Tio	0.01	0.021	(-0.03, 0.05)	0.659
				Ind 300 ug – Ind 150 ug	-0.03	0.019	(-0.06, 0.01)	0.184
For	202	1.40	0.020	For – Pbo	0.09	0.020	(0.05, 0.13)	<.001
				For - Tio	-0.05	0.024	(-0.10, 0.00)	0.033
Tio	173	1.45	0.021	Tio – Pbo	0.15	0.021	(0.10, 0.19)	<.001
Pbo	422	1.30	0.015					

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

ANCOVA model: Trough FEV_1 = treatment + smoker + treatment *smoker + baseline FEV_1 + FEV_1 reversibility components + study + country + center (country).

Center was included as a random effect nested within country.

Baseline was defined as the average of the -50 min and -15 min FEV_1 values taken at Visit 3 prior to first dose.

Trough FEV_1 was defined as the average of the 23 h 10 min and the 23 h 45 min FEV_1 values.

FEV_1 data taken within 6h of rescue medication was excluded from this analysis, as done for trough data outside 22-25 h.

Source: [SCE Appendix 1, Table 2.2f]

Table 1-2 of the response shows analyses which suggest greater benefit for "moderate or less severe COPD" versus "Severe or worse COPD" but which is characterised in the response as "… there was no effect of disease severity on the efficacy of the indacaterol 150 µg and 300 µg doses".

Table 1-2 Least squares mean of trough FEV_1 (L) at Week 12 (LOCF), by severity of disease (COPD 3 month efficacy population)

		---Treatment ---			------- Treatment difference ---------			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Moderate or less COPD								
Ind 150 ug	359	1.46	0.016	Ind 150 ug – Pbo	0.18	0.015	(0.14, 0.21)	<.001
				Ind 150 ug – For	0.08	0.019	(0.04, 0.12)	<.001
				Ind 150 ug - Tio	0.03	0.019	(-0.01, 0.06)	0.187
Ind 300 ug	458	1.49	0.016	Ind 300 ug – Pbo	0.20	0.014	(0.17, 0.22)	<.001
				Ind 300 ug – For	0.10	0.017	(0.06, 0.13)	<.001
				Ind 300 ug – Tio	0.05	0.019	(0.01, 0.08)	0.013
				Ind 300 ug – Ind 150 ug	0.02	0.017	(-0.01, 0.05)	0.215
For	291	1.39	0.018	For – Pbo	0.10	0.017	(0.07, 0.13)	<.001
				For - Tio	-0.05	0.021	(-0.09, -0.01)	0.015
Tio	223	1.44	0.019	Tio – Pbo	0.15	0.018	(0.11, 0.19)	<.001
Pbo	565	1.29	0.014					
Severe or worse COPD								
Ind 150 ug	231	1.48	0.019	Ind 150 ug – Pbo	0.14	0.019	(0.11, 0.18)	<.001
				Ind 150 ug – For	0.08	0.023	(0.04, 0.13)	<.001
				Ind 150 ug - Tio	0.05	0.023	(0.01, 0.10)	0.027
Ind 300 ug	320	1.46	0.017	Ind 300 ug – Pbo	0.13	0.017	(0.09,. 0.16)	<.001
				Ind 300 ug – For	0.07	0.020	(0.03, 0.11)	0.001
				Ind 300 ug – Tio	0.03	0.022	(-0.01, 0.08)	0.119
				Ind 300 ug – Ind 150 ug	-0.02	0.020	(-0.06, 0.02)	0.412
For	203	1.40	0.020	For – Pbo	0.06	0.020	(0.02, 0.10)	0.002
				For - Tio	-0.03	0.024	(-0.08, 0.02)	0.197
Tio	170	1.43	0.021	Tio – Pbo	0.09	0.021	(0.05, 0.13)	<.001
Pbo	372	1.34	0.016					

LS mean= least squares mean, SE = standard error of the mean, CI = confidence interval.

ANCOVA model: Trough FEV_1 = treatment + COPD sev. + treatment*COPD sev. + baseline FEV_1 + FEV_1 reversibility components + study + smoking status + country + center (country).

Center was included as a random effect nested within country.

Baseline was defined as the average of the -50 min and -15 min FEV_1 values taken at Visit 3 prior to first dose.

Trough FEV_1 was defined as the average of the 23 h 10 min and the 23 h 45 min FEV_1 values.

FEV_1 data taken within 6h of rescue medication was excluded from this analysis, as done for trough data outside 22-25 h.

Source: [SCE-Appendix 1-Table 2.2c]

Patients with ICS use had lower baseline FEV_1 values. Table 1-3 shows the difference between the two doses was 40 mL for those on ICS whereas it was -10mL for non-ICS patients. Both were non-significant; differences versus formoterol are reported [but are clinically small].

Table 1-3 Least squares mean of trough FEV_1 (L) at Week 12 (LOCF), by ICS use (COPD 3 month efficacy population)

Treatment	n	---Treatment --- LS mean	SE	Comparison	-------- Treatment difference --------- LS mean	SE	95% CI	p-value
Non ICS								
Ind 150 ug	384	1.49	0.016	Ind 150 ug – Pbo	0.18	0.015	(0.15, 0.21)	<.001
				Ind 150 ug – For	0.08	0.020	(0.04, 0.12)	<.001
				Ind 150 ug - Tio	0.05	0.019	(0.01, 0.08)	0.013
Ind 300 ug	406	1.47	0.016	Ind 300 ug – Pbo	0.17	0.015	(0.14, 0.20)	<.001
				Ind 300 ug – For	0.07	0.018	(0.03, 0.10)	<.001
				Ind 300 ug – Tio	0.03	0.018	(0.00, 0.07)	0.069
				Ind 300 ug – Ind 150 ug	-0.01	0.017	(-0.05, 0.02)	0.430
For	240	1.41	0.019	For – Pbo	0.10	0.018	(0.07, 0.14)	<.001
				For – Tio	-0.03	0.022	(-0.08, 0.01)	0.126
Tio	252	1.44	0.019	Tio – Pbo	0.14	0.018	(0.10, 0.17)	<.001
Pbo	532	1.30	0.014					
ICS use								
Ind 150 ug	206	1.44	0.019	Ind 150 ug – Pbo	0.13	0.020	(0.09, 0.16)	<.001
				Ind 150 ug – For	0.06	0.022	(0.02, 0.11)	0.004
				Ind 150 ug - Tio	0.02	0.025	(-0.03, 0.07)	0.440
Ind 300 ug	372	1.48	0.016	Ind 300 ug – Pbo	0.16	0.016	(0.13, 0.19)	<.001
				Ind 300 ug – For	0.10	0.018	(0.07, 0.14)	<.001
				Ind 300 ug – Tio	0.06	0.023	(0.01, 0.10)	0.013
				Ind 300 ug – Ind 150 ug	0.04	0.020	(0.00, 0.08)	0.065
For	255	1.38	0.018	For – Pbo	0.06	0.018	(0.03, 0.10)	<.001
				For - Tio	-0.05	0.025	(-0.09, 0.00)	0.067
Tio	141	1.43	0.022	Tio – Pho	0.11	0.022	(0.06, 0.15)	<.001
Pbo	405	1.32	0.015					

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

ANCOVE model: Trough FEV_1 = treatment + ICS use + treatment*ICS use + baseline FEV_1 + FEV_1 reversibility components + study + smoking status + country + center (country).

Center was included as a random effect nested within country.

Baseline was defined as the average of the -50 min and -15 min FEV_1 values taken at Visit 3 prior to first dose.

Trough FEV_1 was defined as the average of the 23 h 10 min and the 23 h 45 min FEV_1 values.

FEV_1 data taken within 6h of rescue medication was excluded from this analysis, as done for trough data outside 22-25 h.

Source: [SCE-Appendix 1-Table 2.2.g]

1.2 Lack of monitoring for tobacco use.

This was agreed by the sponsor.

1.3 Comparative Pharmacokinetics in Smokers versus Non-Smokers

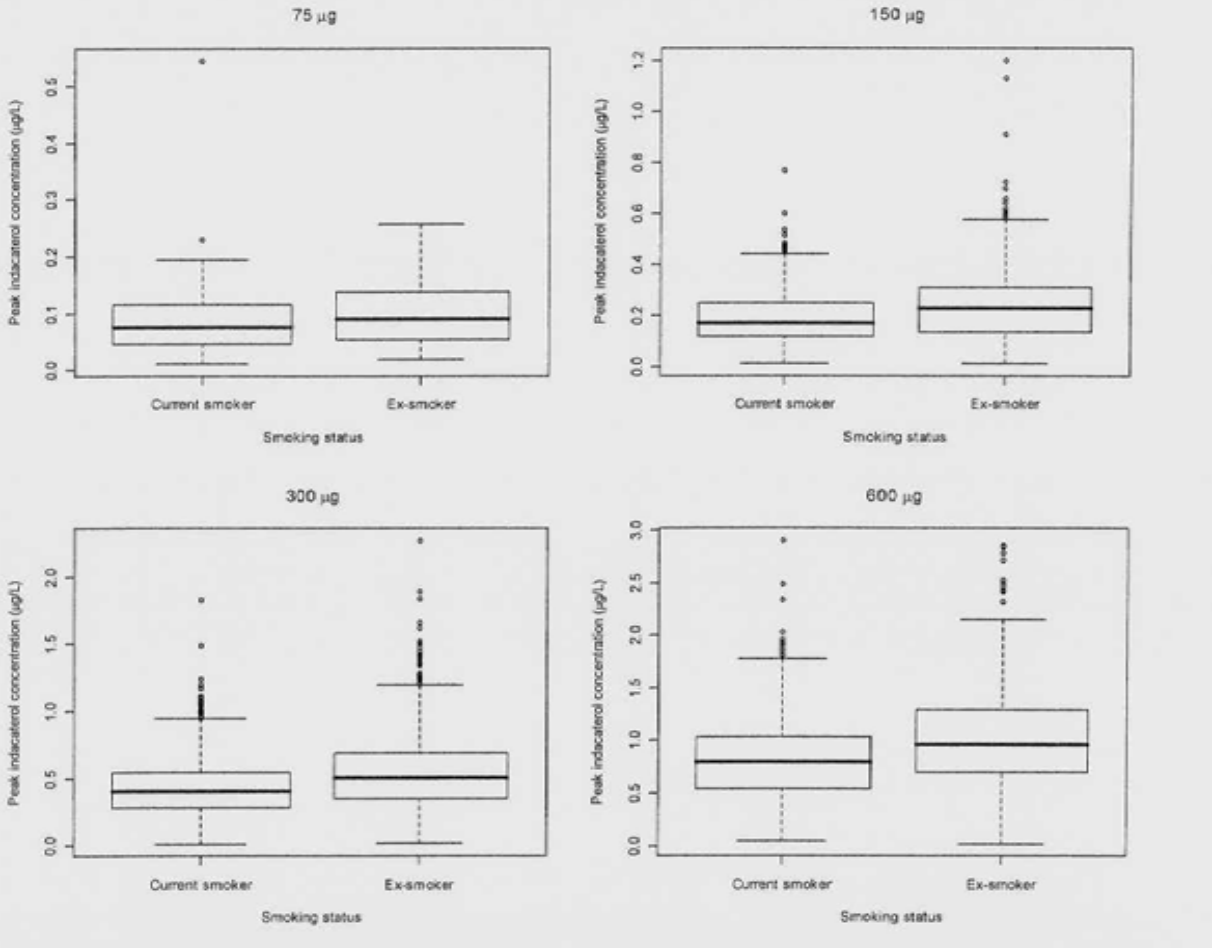
The sponsor responded that nicotine can be derived from smoking or from replacement therapies [the number in this category was small – see Table 1-5].

Table 1-5 Number of patients taking concomitant nicotine replacement therapy (COPD safety database)

	Number of patients						
Drug	Ind 75 µg	Ind 150 µg	Ind 300 µg	Ind 600 µg	For	Tio	Plac
Nicotine	1	3	7	1	4	5	7
Nicotine polacrilex	0	0	2	0	1	0	1
Nicotine resine	0	0	2	0	0	0	2
Total	1	3	11	1	5	5	10
Ind=indacaterol; For=Foradile; Tio= tiotropium; Plac=placebo; Source: Listing 1.3-2							

Indacaterol is not metabolised in the lungs. Nicotine *per se* should not show interactions with indacaterol as it is metabolised by CYP2A6 and maybe 2B1/2 and 2E1. Polyaromatic hydrocarbons induce CYPA1/2 and UGT. Carbon monoxide does not inhibit CYP3A4, the principal cytochrome involved in indacaterol metabolism. The available data support broadly similar pharmacokinetic results for smokers and ex-smokers (see Figure 1-1) (but it is assumed that the data are not sufficient for further analysis).

Figure 1-1 Comparison of peak serum concentrations of indacaterol between ex-smokers and current smokers in the first 15 days of treatment, stratified by dose for Studies CQAB149B2234 and CQAB149B2335S



2. Lack of justification by the sponsor for the choice of 120 mL in trough FEV_1.

There is no general consensus on the minimal clinically important difference. Opinion cited suggests a range for this value in the range 100-140 mL.

3. Indacaterol maleate has not been formally shown to be non-inferior to the active comparators

The sponsor conceded that, in study B2334, the comparison with formoterol with respect to trough FEV_1 was an exploratory objective and a Type 1 error was not controlled. In retrospect, the margin of difference against formoterol (~ 100 mL for the 300 µg and 600 µg doses – see Table 3-1) is arguably clinically significant. It is also argued that the strong post hoc statistical significance is "unlikely to have occurred by chance".

Table 3-1 Trough FEV_1 (L) at Week 12: treatment comparisons (Modified ITT and per protocol populations, LOCF) - Study B2334

		---- Treatment -----			---------- Treatment difference ----------			
Treatment	N	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Modified ITT population								
Ind 300 ug	391	1.48	0.012	Ind 300 ug – Pbo	0.17	0.016	(0.13, 0.20)	<.001 *
				Ind 300 ug – For	0.10	0.016	(0.07, 0.13)	<.001
Ind 600 ug	374	1.48	0.013	Ind 600 ug – Pbo	0.17	0.016	(0.13, 0.20)	<.001 *
				Ind 600 ug – For	0.10	0.016	(0.07, 0.13)	<.001
				Ind 600 ug - Ind 300 ug	0.00	0.016	(-0.03, 0.03)	0.963
For	381	1.38	0.013	For – Pbo	0.07	0.016	(0.03, 0.10)	<.001
Pbo	373	1.31	0.013					
Per protocol population								
Ind 300 ug	353	1.48	0.013	Ind 300 ug – Pbo	0.17	0.017	(0.13, 0.20)	<.001
				Ind 300 ug – For	0.10	0.017	(0.07, 0.14)	<.001
Ind 600 ug	339	1.48	0.013	Ind 600 ug – Pbo	0.17	0.017	(0.14, 0.20)	<.001
				Ind 600 ug – For	0.10	0.017	(0.07, 0.14)	<.001
				Ind 600 ug - Ind 300 ug	0.00	0.017	(-0.03, 0.04)	0.912
For	347	1.38	0.013	For – Pbo	0.07	0.017	(0.03, 0.10)	<.001
Pbo	344	1.31	0.013					

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 + country + center(country), with center(country) as a random effect.
* denotes a statistically significant comparison according to the hierarchical testing procedure.
Source: [B2334 Clinical Study Report, Tables 14.2-1.1, 14.2-1.1a]

The sponsor also conceded that, in study B2340, the comparison with salmeterol with respect to trough FEV_1 was an exploratory objective and a type 1 error was not controlled. Indacaterol maleate 300 µg exceeded salmeterol by 90 mL with respect to trough FEV_1. An argument is made to claim superiority. Despite this result of <100 mL difference, similar arguments to the above are made for significance.

4. No long term efficacy and safety data to support a dose of 150µg indacaterol maleate beyond 6 months.

That is, "The number of patients exposed to indacaterol 150, 300 and 600 µg od for ≥3 months was 363, 756 and 445, respectively, and the corresponding numbers exposed for ≥6 months were 243, 628 and 358. The number of patients exposed to indacaterol 300 and 600 µg od for ≥12 months was 172 and 167, respectively."

This point was agreed by the sponsor – no such data were submitted. The submitted data do demonstrate efficacy and safety to 6 months and there are longer term data on higher doses (Study B2334). There have been other data generated since the application was submitted on the 150 µg dose.

The Delegate noted that the sponsor summarised the two new studies but consideration of them was inappropriate. Supplementary data should have been submitted but the sponsor chose not to do so. It remains the case that no data are available on the efficacy of indacaterol maleate 150 µg /day

beyond 6 months in the treatment of COPD even if it is accepted that safety data on higher doses provide some reassurance regarding safety.

5. The indication should be clarified: The efficacy of indacaterol was evaluated only in patients with moderate to severe COPD (FEV1 ≥30% and <80% of predicted normal) and it was not evaluated in patients with very severe (FEV1<30% of predicted normal) or mild COPD. This fact should be clarified in the indications section of the PI.

That is, the evaluator wrote that "It is recommended that Onbrez (indacaterol 150 µg and 300 µg) oral inhalation be approved for the long-term, once daily, maintenance bronchodilator treatment of airflow limitation in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD)."

The sponsor conceded that the evaluator's recommendation is consistent with GOLD stages II & III (FEV_1 30~80% of predicted normal) but the Australian COPD-X guidelines allow treatment at 60-80% of predicted normal[16] (mild COPD patients according to COPD-X guidelines).

The sponsor argues that the restriction is not justified by reason of the inclusion of patients with mild disease in the studies.

6. Drug interactions with commonly used medications in the COPD patient group were not studied.

The sponsor stated that pharmacokinetic interactions were canvassed. They were considered by reference to what is know with respect to other LABAs and shorter acting agents.

The Delegate noted that this answer is the minimum that might be expected but use with add-on ICS such as ciclesonide or mometasone – if once daily dosing were important for blinding - should have been undertaken in this drug development program and the Delegate considered this to be a major deficiency that will have to be disclosed in the product information document.

Risk-Benefit Analysis

Delegate Considerations

Nonclinical Issues

Combination therapy has been indirectly explored in the Phase III study program. Squamous metaplasia was dose dependent and was detected at several upper respiratory tract sites, consistent with the inhalation of high doses. This will have to be disclosed in the PI.

Clinical Issues

The once daily dosing of indacaterol maleate and its basis in a prolonged duration of action versus eformoterol or salbutamol that are given twice daily would suggest that patient convenience will be somewhat attenuated where inhaled corticosteroids are used twice daily.

Questions asked of the Advisory Committee on Prescription Medicines (ACPM)

1. The action of this LABA in COPD is likely to be symptomatic and it is definitely not a disease modifying agent. Besides, no long term data, over some years, were provided on the rate of decline of lung function. Therefore, is it preferable to use the clinical evaluator's reference to bronchodilation or perhaps symptomatic relief rather than the sponsor's suggestion of "treatment"?

---

[16] "**C2.3 Spirometry**
The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible[28] [evidence level II]. Because COPD is defined by a post-bronchodilator FEV1/FVC ratio < 0.7, spirometry is essential for its diagnosis. Most spirometers provide predicted ("normal") values obtained from healthy population studies, and derived from formulas based on height, age, sex and ethnicity. Airflow limitation is not fully-reversible when, after administration of bronchodilator medication, the ratio of FEV1 to forced vital capacity (FVC) is <70% and the FEV1 is <80% of the predicted value. The ratio of FEV1 to vital capacity (VC) is a sensitive indicator for mild COPD."

2. Is it reasonable to include numerous secondary analyses in the clinical trials section rather than report them in narrative terms as favourable trends?

Proposed Actions

The application to register Onbrez Breezhaler should be approved for the indication:

Onbrez Breezhaler is a once daily, maintenance bronchodilator for long-term use to improve airflow limitation in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Approval is to be subject to clearance of the product information documents and to review of the device by the TGA. The Risk Management Plan (RMP) will have to address inappropriate prescribing in asthma.

Advisory Committee Considerations

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

For a once daily, maintenance bronchodilator for long-term use to improve airflow limitation in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

In making this recommendation, the ACPM considered that the safety concerns required the development of a robust RMP to manage inappropriate prescribing outside of the recommended indication.

The ACPM recommended that the specific conditions of registration should include:

- review of the dosing device to the satisfaction of the TGA;
- development of a full RMP inclusive of an appropriate independently devised and evaluated communication plan; and
- the provision of responses to questions asked by specific foreign regulatory agencies.

The ACPM also recommended a number of changes to the Product Information and Consumer Product Information which should be made prior to approval.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Onbrez Breezhaler indacaterol maleate 150 and 300 microgram hard capsules for inhalation and Arbeela Breezhaler indacaterol maleate 150 and 300 micrograms hard capsules for inhalation, containing the new chemical entity, indacaterol maleate, indicated for:

Onbrez Breezhaler/Arbeela Breezhaler is a long-acting β_2-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease. (See "Clinical Trials").

Specific conditions of registration include:

- Review of the dosing device to the satisfaction of the TGA.
- Development of a full Risk Management Plan (RMP) to manage inappropriate prescribing outside the recommended indication.
- The provision of responses to the TGA to questions asked by specific foreign regulatory agencies as soon as they become available.

Attachment 1. Product Information

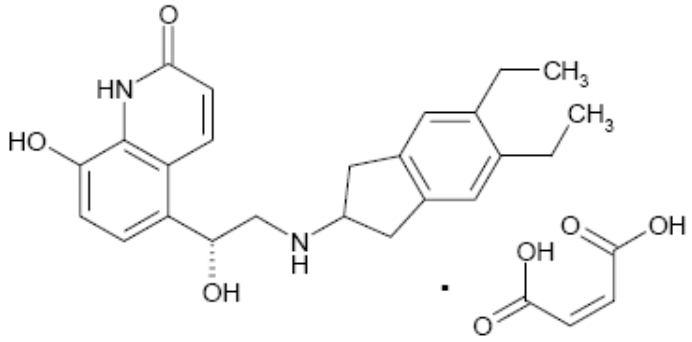
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

ONBREZ® BREEZHALER®

indacaterol maleate

NAME OF THE DRUG

Structural formula:



Chemical name (IUPAC):	(R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H quinolin-2-one maleate
INN:	indacaterol maleate
CAS name:	5-[(1R)-2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl]-8-hydroxy-2(1H)-quinolinone,(2Z)-2-butenedioate (salt) (9CI)
CAS no.:	753498-25-8
Molecular formula:	Free base anhydrous: $C_{24}H_{28}N_2O_3$
	Maleate salt: $C_{24}H_{28}N_2O_3$ $C_4H_4O_4$
Molecular weight:	Free base: 392.49
	Maleate salt: 508.56 (maleate salt)
Stereochemistry:	(R) enantiomer

DESCRIPTION

ONBREZ® hard capsules are for oral inhalation only. ONBREZ® is also supplied with an BREEZHALER® inhalation device to permit oral inhalation of the contents of the capsule shell.

150 μg inhalation powder hard capsules

Black product code "IDL 150" printed above and black company logo printed under black bar on clear colourless hard capsule.

Each capsule contains 194 μg indacaterol maleate equivalent to 150 μg indacaterol.

The delivered dose (the dose that leaves the mouthpiece of the BREEZHALER® device) is 120 μg indacaterol.

300 μg inhalation powder hard capsules

Blue product code "IDL 300" printed above and blue company logo printed under blue bar on clear colourless hard capsule.

Each capsule contains 389 μg indacaterol maleate equivalent to 300 μg indacaterol.

The delivered dose (the dose that leaves the mouthpiece of the BREEZHALER® device) is 240 μg indacaterol.

Excipients: lactose monohydrate and gelatin.

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Indacaterol is an 'ultra' long-acting β_2-adrenergic agonist for once-daily administration. The pharmacological effects of β_2-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol has more than 24-fold greater agonist activity at β_2-receptors compared to β_1-receptors and 20-fold greater agonist activity compared to β_3-receptors. This selectivity profile is similar to eformoterol.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human β_2-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although β_2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1-receptors are the predominant receptors in the human heart, there are also β_2-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of β_2-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective β_2-adrenergic agonists may have cardiac effects.

Long-acting β_2-adrenergic agonists are not a disease modifying agents. There are no data available on the long term morbidity and mortality benefits of indacaterol in patients with COPD.

Primary Pharmacodynamic Effects

Indacaterol provided consistently significant improvement in lung function (FEV_1) over 24 hours in a number of clinical pharmacodynamic and efficacy trials. There was a rapid onset of action within 5 minutes after inhalation of indacaterol comparable to the effect of the fast-acting β_2-agonist salbutamol and a peak effect occurring between 2-4 hours following the dose. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks. The bronchodilator effect did not depend on the time of dosing (morning or evening).

Indacaterol reduced both dynamic and resting hyperinflation in patients with moderate to severe COPD. Peak inspiratory capacity during constant, sub-maximal exercise increased by 317 mL compared to placebo after administration of 300 μg once-daily over 14 days. A statistically significant increase in resting inspiratory capacity, exercise endurance and FEV_1 were also demonstrated as well as a significant improvement in measures of dyspnoea.

Secondary Pharmacodynamic Effects

The characteristic adverse effects of inhaled β_2-adrenergic agonists occur as a result of activation of systemic β-adrenergic receptors. The most common adverse effects include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium and increases in plasma glucose.

Effects on cardiac electrophysiology

The effect of indacaterol on the QT interval was evaluated in a double-blind, placebo- and active (moxifloxacin)-controlled study following multiple doses of indacaterol 150 μg, 300 μg or 600 μg once-daily for 2 weeks in 404 healthy volunteers. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QT_cF). Maximum mean prolongation of QT_cF intervals were <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time-matched comparisons versus placebo. This shows that there is no concern for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses. There was no evidence of a concentration-delta QTc relationship in the range of doses evaluated.

Electrocardiographic monitoring in patients with COPD

The effect of indacaterol on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 605 patients with COPD from a 26-week, double-blind, placebo-controlled Phase III study (see Clinical Trials). Holter monitoring occurred once at baseline and up to 3 times during the 26-week treatment period (at weeks 2, 12 and 26).

A comparison of the mean heart rate over 24 hours showed no increase from baseline for both doses evaluated, 150 μg once-daily and 300 μg once-daily. The hourly heart rate

analysis was similar for both doses compared to placebo and tiotropium. The pattern of diurnal variation over 24 hours was maintained and was similar to placebo.

No difference from placebo or tiotropium was seen in the rates of atrial fibrillation, time spent in atrial fibrillation and also the maximum ventricular rate of atrial fibrillation.

No clear patterns in the rates of single ectopic beats, couplets or runs were seen across visits.

Because the summary data on rates of ventricular ectopic beats can be difficult to interpret, specific pro-arrhythmic criteria were analyzed. In this analysis, baseline occurrence of ventricular ectopic beats was compared to change from baseline, setting certain parameters for the change to describe the pro-arrhythmic response. The number of patients with a documented pro-arrhythmic response was very similar across both indacaterol doses compared to placebo and tiotropium.

Overall, there was no clinically relevant difference in the development of arrhythmic events in patients receiving indacaterol treatment over those patients who received placebo or treatment with tiotropium.

Effects on serum potassium and plasma glucose

Changes in serum potassium and plasma glucose were evaluated in a 26-week, double-blind, placebo-controlled Phase III study (see Clinical Trials). At 1 hour post-dose at week 12, mean changes compared to placebo in serum potassium ranging from 0.03 to 0.05 mmol/L and in mean plasma glucose ranging from 0.25 to 0.31 mmol/L were observed.

Pharmacokinetics

Absorption

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 μg to 600 μg) in a dose proportional manner. Absolute bioavailability of indacaterol after an inhaled dose was on average 43%. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 14 days. The mean accumulation ratio of indacaterol, *i.e.*, AUC over the 24-h dosing interval on Day 14 compared to Day 1, was in the range of 2.9 to 3.5 for once-daily inhaled doses between 150 μg and 600 μg.

Distribution

After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,557 L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Biotransformation/Metabolism

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in

serum, accounting for about one third of total drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. A phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, a carboxylic acid and a N-dealkylated product were further metabolites identified.

In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

Elimination

In clinical studies which included urine collection, the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 L/h. When compared with the serum clearance of indacaterol of 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the faecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human faeces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 52 hours which is consistent with the observed time-to-steady state of approximately 12 to 14 days.

Pharmacokinetics in special patient groups

A population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that indacaterol can be used safely in all age and weight groups and regardless of gender. It did not suggest any difference between ethnic subgroups in this population.

The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [$(TA)_6$, $(TA)_6$] genotype and the low activity [$(TA)_7$, $(TA)_7$] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and C_{max} of indacaterol were 1.2-fold higher in the [$(TA)_7$, $(TA)_7$] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.

CLINICAL TRIALS

The ONBREZ® BREEZHALER® Phase III clinical development program consisted of 6 key studies and enrolled 4,460 patients with a clinical diagnosis of COPD, who were 40 years old or older, had a smoking history of at least 20 pack years, had a post-bronchodilator FEV_1 <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio of less than 70%. The Phase III program includes 3 large, pivotal efficacy and safety studies of up to 52 weeks duration (B2334, B2335 and B2336) and 3 small, short-term profiling crossover studies (B2305, B2307, B2340) in patients with COPD.

The three pivotal studies, (B2334, B2335 and B2336), used the trough 24 hour FEV1 was the primary efficacy endpoint as the primary endpoint to reflect the efficacy of study drug in COPD over 24 hours. A difference of 120 mL in trough FEV1 between indacaterol and placebo was considered to be a clinically important difference for COPD patients. Numerous secondary endpoints were reported. These included the St. Georges' Respiratory Questionnaire, the transitional dyspnoea index, COPD exacerbations, use of rescue medication, days of poor control and daytime and night-time symptoms. These were tested according to a complex series of statistical analyses – the reporting of statistical significance may not relate to predefined clinical significance, unlike the primary endpoint.

The clinical trial program enrolled a diverse patient group. The mean age in the clinical trial program was 63 years. Of the total number of patients who received indacaterol in the clinical studies from the pooled 6-month database, 1,014 were <65 years, 710 were 65–74 years and 219 were ≥75 years of age. The estimated median number of smoking pack-years was around 42 pack years. Approximately 40% of patients had severe COPD and 40% of patients had three or more CV risk factors at enrolment. ICS use occurred in 35% of patients treated with the 150 μg and 47% of patients treated with the 300 μg. Exclusion criteria included asthma, use of anticholinergics or long acting LABAs during the study, other excluded medications were non-potassium sparing diuretics, non-selective beta-blockers, quinidine-like medications, tricyclic antidepressants, monoamino-oxidase inhibitors, terfenadine, astemizole and any other drugs contraindicated for QT prolongation.; concomitant pulmonary disease including lung cancer, active pulmonary tuberculosis, bronchiectasis, hospitalization for an exacerbation of airway disease in the prior 6 weeks, type I or uncontrolled type II diabetes (consistent HbA1c >8%), history or family history of long QT syndrome, other clinically relevant laboratory abnormality or clinical condition which might compromise the patient's safety.

In the 3 smaller, crossover Phase III studies, indacaterol, administered once-daily at the same time each day, either in the morning or evening, provided significant improvement in lung function (FEV_1 over 24 hours, had an onset of action within 5 minutes similar to that of salbutamol 200 μg and statistically significantly faster compared to salmeterol/fluticasone 50/500 μg, and a peak effect occurring between 2-4 hours following the dose. In a 26-week,

placebo- and active (open label tiotropium)-controlled study in 2,059 patients, the mean improvement relative to baseline in FEV_1 at 5 minutes was 0.12 L and 0.13 L for indacaterol 150 µg and 300 µg once-daily, respectively, and the mean peak improvement, relative to baseline, after the first dose (Day 1) was 0.19 L and 0.24 L, respectively, and improved to 0.23 L and 0.26 L, respectively, when pharmacodynamic steady-state was reached (Day 14) . At the primary end point (Week 12), both indacaterol 150 µg and 300 µg once-daily treatment groups showed a significantly higher trough FEV_1 value compared to placebo (both 0.18 L, $p<0.001$). The non-inferiority of indacaterol (150 µg and 300 µg) to tiotropium (18 µg od) was also established in this study.

In this study, 12-hour serial spirometric measurements were performed in a subset of patients throughout daytime hours (12 hours). Serial FEV1 values over 12 hours at Day 1 and trough FEV_1 values at Day 2 are shown in Figure 1, and at Day 182/183 in Figure 2, respectively. Improvement of lung function was maintained for 24 hours after the first dose and consistently maintained over the 26-week treatment period with no evidence of tolerance.

Figure 1 Serial least square mean FEV_1 over 12 h at Day 1 and trough FEV_1 at Day 2 (ITT subset with 12 hour serial spirometry)

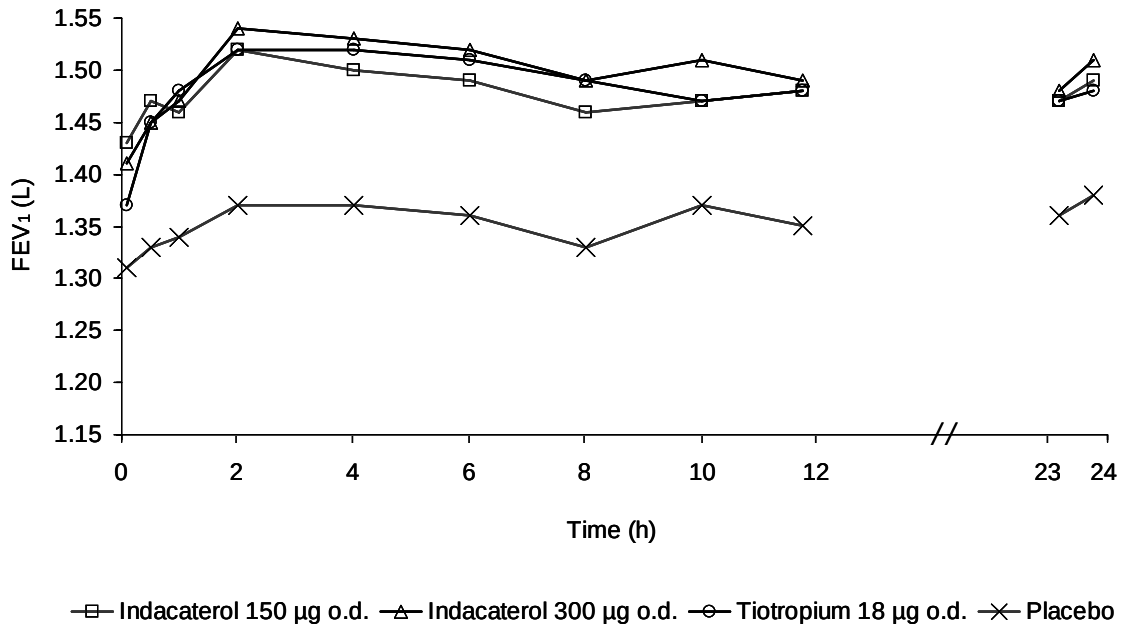
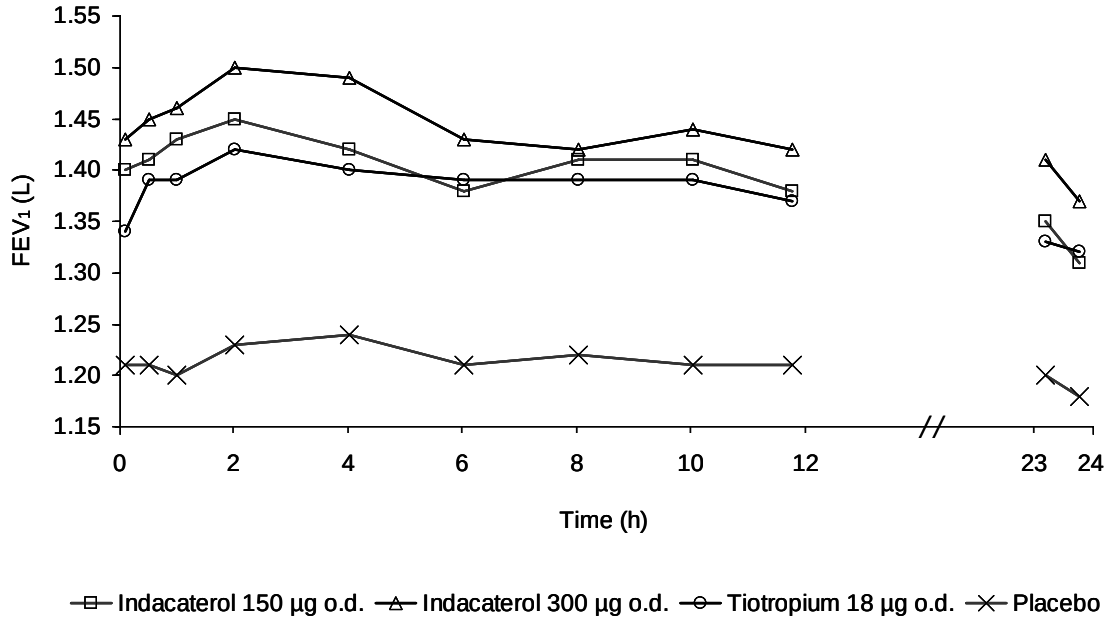


Figure 2 Serial least square mean FEV_1 over 12 h at Day 182 and trough FEV_1 at Day 183 (ITT subset with 12 hour serial spirometry)

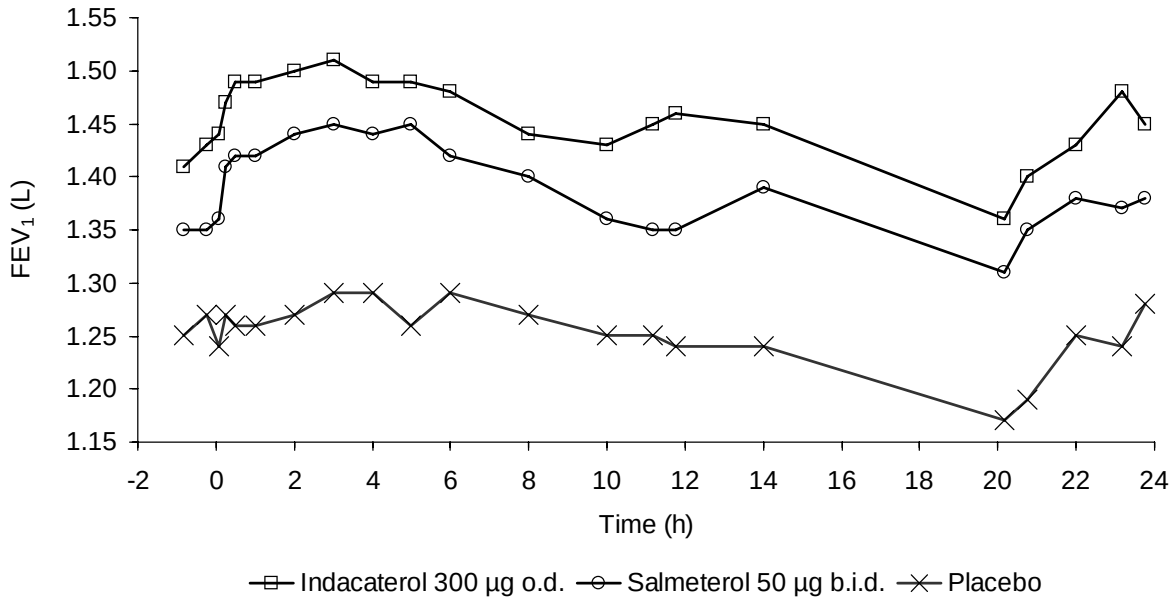


Results of a 12-week, placebo-controlled study in 416 patients which evaluated the 150 µg once-daily dose, were similar to the results for this dose in the 26-week study. The mean peak improvement in FEV_1, relative to baseline, was 0.23 L after 1 day of once-daily treatment At the primary end point (Week 12), treatment with indacaterol 150 µg once-daily resulted in a significantly higher trough FEV_1 value compared to placebo (0.13 L, $p<0.001$).

In a 52-week, placebo- and active (eformoterol)-controlled study in 1,732 patients which evaluated the indacaterol 300 µg once-daily dose and a higher dose, the mean improvement in FEV_1, relative to baseline, at 5 minutes was 0.14 L with a peak improvement of 0.20 L relative to baseline after the first dose (Day 1). At the primary end point (Week 12), treatment with indacaterol 300 µg once-daily resulted in a significantly higher trough FEV_1 value compared to placebo (0.17 L, $p<0.001$) This improvement of lung function was maintained over the 52-week treatment period with no evidence of loss of efficacy over this period.

In a 2-week, placebo- and active (open label salmeterol)-controlled crossover study, 24-hour spirometry was assessed in 68 patients. Serial spirometry values over 24 hours are displayed in Figure 3. After 14 days of once-daily treatment, improvement of lung function compared to placebo was maintained for 24 hours. Similar results from 24-hour serial spirometry were observed after 26 weeks in a subset of patients (n=236) from the 26-week study. Both studies further support the improvement in FEV_1 over placebo with indacaterol administered once-daily, and that bronchodilatation was maintained throughout the 24-hour dosing interval, in comparison to placebo.

Figure 3 24 h profile of least squares means of FEV1 (L) after 14 days treatment (Modified ITT population)



In terms of the evaluation of indacaterol 300 µg was compared to eformoterol in the 52 week study and indacaterol was significantly better than eformoterol on 24 hour trough FEV1 at week 12 (0.10 mL, $p<0.01$), though this was not the primary endpoint of the study. Efficacy and safety data to support a dose of 150µg indacaterol maleate are limited to 6 months' experience in the Phase 3 studies.

The following health outcome effects were demonstrated in the long-term studies of 12-, 26- and 52-week treatment duration. These health outcomes were multiple measured secondary endpoints and the type 1 error were not formally controlled a priori for these comparisons.

Symptomatic benefits

Both doses demonstartaed statistically significant improvements in symptom relief over placebo for dyspnoea and health status (as evaluated by Transitional Dyspnoea Index [TDI] and St. George's Respiratory Questionnaire [SGRQ], respectively). The magnitude of response was generally greater than seen with active comparators (Table 1). In addition, patients treated with Onbrez Breezhaler required significantly less rescue medication, had more days when no rescue medication was need compared to placebo and had a significantly improved percentage of days with no daytime symptoms.

Pooled efficacy analysis over 6 months' treatment demonstrated that the rate of COPD exacerbations was statistically significantly lower than the placebo rate. Treatment comparison compared to placebo show a ratio of rates of 0.68 (95% CI [0.56, 0.96]; p-value 0.026) for 150 µg and 300 µg, respectively.

Limited treatment experience is available in individuals of African descent.

Table 1 Symptom relief at 6 months treatment duration

Treatment Dose (microgram)	Indacaterol 150 once a day	Indacaterol 300 once a day	Tiotropium 18 once a day	Salmeterol 50 twice a day	Formoterol 12 twice a day	Placebo
Percentage of patients who achieved MCID TDI†	57 [a] 62 [b]	71 [b] 59 [c]	57 [b]	54 [a]	54 [c]	45 [a] 47 [b] 41 [c]
Percentage of patients who achieved MCID SGRQ†	53 [a] 58 [b]	53 [b] 55 [c]	47 [b]	49 [a]	51 [c]	38 [a] 46 [b] 40 [c]
Reduction in puffs/day of rescue medication use vs. baseline	1.3 [a] 1.5 [b]	1.6 [b]	1.0 [b]	1.2 [a]	n/e	0.3 [a] 0.4 [b]
Percentage of days with no rescue medication use	60 [a] 57 [b]	58 [b]	46 [b]	55 [a]	n/e	42 [a] 42 [b]

Study design with [a]: indacaterol 150 microgram, salmeterol and placebo; [b]: indacaterol 150 and 300 microgram, tiotropium and placebo; [c]: indacaterol 300 microgram, formoterol and placebo
† MCID = minimal clinically important difference (≥1 point change in TDI, ≥4 point change in SGRQ)
n/e= not evaluated at six months

INDICATIONS

ONBREZ® BREEZHALER® is a long-acting β_2-agonist indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease. (See "Clinical Trials")

CONTRAINDICATIONS

Hypersensitivity to any ingredients of the preparation.

ONBREZ® capsules contain lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PRECAUTIONS

Asthma and mixed airways disease

In the absence of long-term outcome data in asthma with indacaterol, ONBREZ® should not be used in asthma. Indacaterol, the active ingredient of ONBREZ®, belongs to the class of long-acting β2-adrenoceptor agonists. In a study with salmeterol, a different long-acting β2-agonist, a higher rate of severe asthma episodes and death due to asthma was observed in the patients treated with salmeterol than in the placebo group. A differential diagnosis should be

made to exclude asthma or mixed airways disease before initiating ONBREZ®. See Clinical Trials section for clinical experience to date.

Patients who require corticosteroids

COPD patients being treated with long-term inhaled glucocorticoids therapy should continue this therapy when initiating ONBREZ®.

Paradoxical bronchospasm

As with other inhalation therapy, administration of ONBREZ® may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ONBREZ® should be discontinued immediately and alternative therapy instituted.

Deterioration of disease

ONBREZ® is not indicated for the initial treatment of acute episodes of symptomatic exacerbations, *i.e.,* as a rescue therapy. In case of deterioration of COPD whilst on treatment with ONBREZ®, a re-evaluation of the patient and the COPD treatment regimen should be undertaken. An increase in the daily dose of ONBREZ® beyond the maximum dose is not appropriate. The patient's COPD management plan should make this clear.

Systemic effects

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of ONBREZ® at the recommended doses, as with other β_2-adrenergic agonists, ONBREZ®, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to β_2-adrenergic agonists.

ONBREZ®, like other β_2-adrenergic agonists, may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, the drug may need to be discontinued. In addition, β-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT interval, and ST segment depression. The clinical significance of these findings is unknown.

β_2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see Interactions) which may increase the susceptibility to cardiac arrhythmias.

Clinically notable changes in blood glucose and/or serum potassium were infrequent during clinical studies with ONBREZ® at the recommended doses.

As with other inhaled β_2-adrenergic drugs, ONBREZ® should not be used more often or at higher doses than recommended.

ONBREZ® should not be used in conjunction with other long-acting β_2-adrenergic agonists or medications containing long-acting β_2-adrenergic agonists.

Use in Patients with Renal Impairment

No dosage adjustment is required for renally impaired patients.

Use in Patients with Hepatic Impairment

No dosage adjustment is required for patients with mild and moderate hepatic impairment. There is no data available for subjects with severe hepatic impairment (see Pharmacology).

Effects on Fertility

No adverse effects on fertility were observed in male and female rats given indacaterol by subcutaneous injection at doses up to 2 mg/kg/day (yielding approximately 114-times [males] and 86-times [females] the serum AUC in humans at the maximum recommended dose of 300 µg/day). .

Use in Pregnancy (Category B3)

No clinical data on exposed pregnancies in COPD patients are available. Indacaterol was not teratogenic at subcutaneous doses up to 1 mg/kg/day in rats and 3 mg/kg/day in rabbits (up to 43- and 248-times, respectively, the AUC in humans at 300 µg/day). An increase in the incidence of a rib skeletal variation and retarded ossification were observed in the rabbit at 3 mg/kg/day, possibly secondary to maternal toxicity; embryofetal development was unaffected in the species at 1 mg/kg/day (relative exposure, 98). Impaired learning and decreased fertility were observed in the pups of rats given indacaterol at a subcutaneous dose of 1mg/kg/day during pregnancy and lactation (relative exposure, 37; unaffected at 0.3 mg/kg/day, associated with a relative exposure level of 15). The potential risk for humans is unknown. Because there are no adequate and well-controlled studies in pregnant women, indacaterol should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Labour and delivery

Like other β_2-adrenergic agonists, ONBREZ® may inhibit labour due to a relaxant effect on uterine smooth muscle.

Use in Lactation

It is not known whether indacaterol passes into human breast milk. Indacaterol and several of its metabolites have been detected in the milk of lactating rats, and reduced body weight gain, impaired learning and decreased fertility were observed in pups of rats treated with indacaterol during pregnancy and lactation. Because many drugs are excreted in human milk, as with other inhaled β_2-adrenergic drugs, the use of ONBREZ® by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Pediatric Use

ONBREZ® should not be used in patients under 18 years of age.

Use in the Elderly

No dosage adjustment is required for elderly patients.

Carcinogenicity

The carcinogenic potential of indacaterol has been evaluated in a 26-week oral gavage study in transgenic mice (CB6F1/TgrasH2) and a 2-year inhalation study in rats. No carcinogenicity was observed in mice at doses up to 600mg/kg/day (49-times in males and 106-times in females the AUC in humans at the maximum recommended clinical dose of 300 µg/day). Lifetime treatment of rats at 2.1 mg/kg/day (relative exposure, 14) resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β_2-adrenergic agonist drugs. Their development is consistent with proliferation in response to prolonged relaxation of the smooth muscle (pharmacologically mediated), and the finding is not considered to indicate a carcinogenic hazard to patients. Squamous metaplasia was observed in the upper respiratory tract tissues of mice, rats and dogs following inhalation administration of indacaterol. This finding is consistent with an adaptive response to irritation and occurred at large multiples of the human dose. It is not considered to indicate a carcinogenic hazard to humans with the therapeutic use of indacaterol. No data are available to determine whether exposure to tobacco smoke enhances the respiratory tract toxicity of indacaterol.

Genotoxicity

Indacaterol was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosomal aberrations in Chinese hamster V79 cells and the rat bone marrow micronucleus test.

Interactions with Other Medicines

Drugs known to prolong QTc interval

ONBREZ®, as other β_2-adrenergic agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs that are known to prolong the QTc-interval may have an increased the risk of ventricular arrhythmia (see Precautions).

Sympathomimetic agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of ONBREZ® (see Precautions).

Hypokalaemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium- sparing diuretics may potentiate the possible hypokalaemic effect of β_2-adrenergic agonists (see Precautions).

β-adrenergic blockers

β-adrenergic blockers may weaken or antagonise the effect of β_2-adrenergic agonists ONBREZ®. Therefore ONBREZ® should not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective β-adrenergic blockers should be preferred, although they should be administered with caution.

Metabolic and transporter based drug interaction

Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of ONBREZ®. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (*i.e.*, ketoconazole, erythromycin and verapamil). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in C_{max}. Co-administration of erythromycin with ONBREZ® resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C_{max}. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and C_{max}, respectively. Taken together, the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Given the safety data of [D] and of the pivotal studies (which both confirmed safe use of a 600 µg dosage regimen). The magnitude of exposure increases due to drug- interactions does not raise any safety concerns for therapeutic doses of 150 µg or 300 µg. given the safety experience of treatment with ONBREZ® in clinical trials of up to one year at doses two- to four-fold the recommended therapeutic doses.

Indacaterol has not been shown to cause drug interactions with co-medications. *In vitro* investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medications at the systemic exposure levels achieved in clinical practice.

Effects on Ability to Drive and Use Machines

There are no data to suggest that indacaterol affects the ability to drive or use machines.

ADVERSE REACTIONS

Summary of safety profile

The safety experience with ONBREZ® BREEZHALER® comprises exposure of up to one year at doses two- to four-fold the recommended therapeutic doses.

The most common adverse drug reactions at the recommended doses were nasopharyngitis, upper respiratory tract infection, cough and headache. These were in the vast majority mild or moderate.

At the recommended doses, the adverse drug reaction profile of indacaterol in patients with COPD shows clinically insignificant systemic effects of β_2-adrenergic stimulation. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a similar rate as under placebo treatment. Relevant prolongations of QT_cF Relevant prolongations of QT_{cF} were not detectable in comparison to placebo. The frequency of notable QT_cF intervals [*i.e.*, >450 ms (males) and >470 ms (females)] and reports of hypokalaemia were similar to placebo. The mean of the maximum changes in blood glucose were similar on indacaterol and on placebo.

Description of population

The ONBREZ® BREEZHALER® Phase III clinical development program consisted of 6 key studies and enrolled 4,460 patients with a clinical diagnosis of moderate to severe COPD. Safety data from these studies were pooled from 2,154 exposed to indacaterol up to 600 µg once-daily, of which 627 were on treatment with 150 µg once-daily (for up to six months) and 853 on treatment with 300 µg once-daily. Approximately 40% of patients had severe COPD. The mean age of patients was 63 years, with Treatment durations in the three trials were 3, 6 and 12 months, respectively. 47% of patients were aged 65 years of older, and the majority (89%) was Caucasian. [See Clinical Trials for further information.]

Adverse drug reactions from clinical trials

Adverse drug reactions in Table 2 are listed according to MedDRA system organ class. The safety profiles in the 3-, 6- and 12-month COPD safety databases were similar. System organ classes are sorted in descending order of frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Table 2 Adverse Drug Reactions

Adverse Drug Reactions	**Indacaterol 150 µg o.d. n (%)**	**Indacaterol 300 µg o.d. n (%)**	**Placebo n (%)**	**Frequency category**	**Data-base***
Infections and infestations					
- Nasopharyngitis	NA**	73 (16.7)	56 (13.0)	Very common	3
- Upper respiratory tract infection	35 (8.4)	44 (5.2)	38 (4.5)	Common	1
- Sinusitis	12 (2.9)	23 (2.7)	12 (1.4)	Common	1
- Pneumonia	2 (0.5)	16 (1.9)	6 (0.7)	Common	1

Respiratory, thoracic and mediastinal disorders					
- Cough	30 (7.2)	56 (6.6)	40 (4.7)	Common	1
- Pharyngolaryngeal pain	12 (2.9)	12 (2.9)	4 (1.4)	Common	2
- Rhinorrhoea	4 (1.0)	13 (1.5)	1 (0.1)	Common	1
Nervous system disorders					
- Headache	28 (6.7)	33 (3.9)	29 (3.4)	Common	1
- Paresthesia	5 (1.2)	1 (0.1)	2 (0.2)	Common	1
Musculoskeletal and connective tissue disorders					
- Muscle spasm	13 (3.1)	32 (3.8)	10 (1.2)	Common	1
- Myalgia	8 (1.9)	5 (0.6)	5 (0.6)	Common	1
- Neck pain	5 (1.2)	4 (0.5)	2 (0.2)	Common	1
Cardiac disorders					
- Atrial fibrillation	5 (1.2)	5 (0.6)	5 (0.2)	Common	1
- Angina pectoris	3 (0.7)	6 (0.7)	2 (0.2)	Uncommon	1
General disorders and administration site conditions					
- Chest discomfort	4 (1.0)	1 (0.1)	1 (0.1)	Common	1
Metabolism and nutrition disorders					
- Diabetes mellitus	NA**	5 (1.1)	1 (0.2)	Common	3

* Database 1: 6-month COPD safety database. Includes all ADRs of study B2335S and those occurring within the first 6 months of B2334. Number of patients on Indacaterol 150 µg once-daily, 300 µg once-daily and on placebo: n=416, 853, and 850, respectively. Database 2: ADRs of study B2335S. Number of patients on Indacaterol 150 µg once-daily, 300 µg once-daily and on placebo: n=416, 416, and 418, respectively. Database 3: ADRs of study B2334. Number of patients on Indacaterol 300 µg once-daily and on placebo: n=437 and 432, respectively.

** Dose not evaluated in database 3. Number of patients and frequency in database 1 for nasopharyngitis was 33 (7.9%) and 69 (8.1%) on Indacaterol 150 µg once-daily and on placebo, respectively. Number of patients and frequency in database 1 for diabetes mellitus was 0 (0%) and 1 (0.1%) on indacaterol 150 µg once-daily and on placebo, respectively.

At a higher dose, *i.e.*, 600 µg once-daily, the safety profile of indacaterol was overall similar to that of recommended doses. Additional adverse drug reactions were peripheral edema and tremor. Nasopharyngitis and muscle spasm occurred more frequently than at the recommended doses.

Selected adverse drug reactions

In Phase III clinical studies, health care providers observed that at clinic visits on average 17-20% of patients experienced sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds. This cough experienced post inhalation was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses Phase III studies did not demonstrate an association between cough experienced post inhalation and bronchospasm, exacerbations, deteriorations of disease, or loss of efficacy.

DOSAGE AND ADMINISTRATION

Adults with COPD

The recommended and usual dosage of ONBREZ® BREEZHALER® is the once-daily inhalation of the content of one 150 µg ONBREZ® capsule using the BREEZHALER® inhaler. The dosage should only be increased on medical advice.

Once-daily inhalation of the content of one 300 µg ONBREZ® capsule, using the BREEZHALER® inhaler, has been shown to provide additional clinical benefit to some patients. The maximum dose is 300 µg once-daily. This dose should not be exceeded.

Patients with COPD who require corticosteroids should retain this treatment. (See Precautions - Patients who require corticosteroids.)

Other patient populations

ONBREZ® BREEZHALER® should not be used in patients under 18 years of age or in patients with asthma or with mixed airways disease.

Method of Administration

ONBREZ® capsules must be administered only by the oral inhalation route and only using the BREEZHALER® inhaler. ONBREZ® capsules must not be swallowed. ONBREZ® capsules must always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

Patients with Renal Impairment

No dosage adjustment is required for renally impaired patients.

Patients with Hepatic Impairment

No dosage adjustment is required for patients with mild and moderate hepatic impairment. There is no data available for subjects with severe hepatic impairment (see Clinical Pharmacology).

Elderly Patients

No dosage adjustment is required for elderly patients.

OVERDOSAGE

In COPD patients single doses of 10 times the maximum recommended therapeutic dose were associated with a moderate increase in pulse rate, systolic blood pressure increase and QT_c interval.

An overdose of indacaterol is likely to lead to exaggerated effects typical of β_2-adrenergic stimulants *i.e.*, tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalaemia and hyperglycaemia.

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective β-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of β-adrenergic blockers may provoke bronchospasm.

PRESENTATION

ONBREZ® (indacaterol maleate) hard capsules are supplied in blister packs of 30 with a BREEZHALER® inhalation device to allow oral inhalation of the content of the capsule shell.

Pack sizes: Pack of 10 capsules and a Breezhaler device, Pack of 30 capsules and a Breezhaler device, and pack of 60 capsules and two Breezhaler devices. Not all pack sizes may be marketed.

Storage: Store below 30°C. Protect from moisture. Keep out of the reach and sight of children.

Poison schedule: Schedule 4.

SPONSOR

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Approved by the Therapeutic Goods Administration: 2 July 2010