European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Hirobriz Breezhaler

International Nonproprietary Name: indacaterol

Procedure No. EMEA/H/C/001211

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 24 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Hirobriz Breezhaler, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 29 September 2008.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

The applicant applied for the following indication: maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) 1901/2006, the application included an EMEA Decision (EMEA-000043-PIP01-07) for the following condition:

- *Chronic obstructive pulmonary disease.*

on the granting of a product-specific waiver.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 28 April 2006. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Steffen Thirstrup Co-Rapporteur: David Lyons

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 24 July 2009.
- The procedure started on 26 July 2009.
- This application forms part of a multiple application for amlodipine indacaterol maleate. The initial application was submitted by Novartis Europharm Limited (EMEA/H/C/1114) on 18 December 2008. The review process for both applications has been integrated at the time of the Responses to the List of Questions, allowing the CHMP opinion to be adopted in the same timeframe as EMEA/H/C/1114.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 04 September 2009.
- During the meeting on 21-24 September 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Hirobriz Breezhaler on 24 September 2009. The

applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 September 2009.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Chronic obstructive pulmonary disease (COPD) has been described as a "preventable and treatable disease state characterised by airflow limitation that is not fully reversible". However, in reality the disease is not limited to the airway and treating physicians are faced with a multi-component disease that is characterised by a range of pathological changes, which include mucous hypersecretion, airway narrowing, loss of alveoli in the lungs, and loss of lean body mass and cardiovascular effects at a systemic level. COPD patients are heterogeneous in terms of their clinical presentation, disease severity and rate of disease progression. Their degree of airflow limitation, as measured by FEV_1, is also known to be poorly correlated to the severity of their symptoms. The most widely accepted classification of the severity of COPD is according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) which is a highly respected partnership between the pharmaceutical industry and academia. The GOLD classification is based on the degree of impairment of lung function; four categories are recognised; mild, moderate, severe, very severe (Stages I – IV). The most important aspect of management of the condition is educational and social: the avoidance and cessation of tobacco smoking. However, once it is established the recommendations for the pharmacological treatment of COPD are based on the severity of the condition. In outline, treatment should be started with one or more short acting bronchodilators at Stage I, a long acting bronchodilator should be added at Stage II together with rehabilitation, with inhaled steroid at Stage III and domiciliary oxygen at Stage IV. These treatments are additive i.e. treatments started in Phase I are maintained during the later phases. The prevalence of COPD is difficult to estimate, but it is a major public health problem, and is currently the fourth leading cause of chronic morbidity and mortality in the USA. Mortality due to COPD appears to be increasing.

Indacaterol maleate (IND) is a novel, long-acting inhaled β_2-agonist. The claimed indication for this product is: long term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease. The granted indication is: maintenance of bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease. The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using indacaterol inhaler. The dose should only be increased on medical advice. The inhalation of the content of one 300 microgram capsule once a day, using the indacaterol inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once daily. Indacaterol should be administered at the same time of the day each day. If a dose is missed the next dose should be taken at the usual time the next day.

Inhaled β_2-agonists were first developed fifty years ago. Early β_2-agonists, acted over short periods of time and required frequent dosing to maintain a bronchodilator effect. Long-acting inhaled β_2-agonists (LABAs) such as formoterol and salmeterol have been available for approximately 12 years, and are recommended for twice daily use for maintenance treatment in COPD.

This application was submitted according to article 8(3) of Directive 2001/83/EC via the optional scope of the centralised procedure in accordance with article 3(2) of Regulation (EC) no 726/2004. Conditional approval or approval under exceptional circumstances was not requested. A Paediatric Product Specific Waiver was granted on the grounds that the disease or condition for which the product is intended occurs only in the adult population. CHMP Scientific Advice was given in the context of paediatric asthma only. A number of member states have given national scientific advice. The clinical issues addressed in these advices related to the QTc study, and COPD pivotal study design and doses (as well as design of asthma studies - an indication not pursued).

2.2. Quality aspects

Introduction

Hirobriz Breezhaler contains indacaterol maleate as active substance, a novel long-acting β_2-adrenergic agonist which causes bronchodilation and is intended for long-term maintenance treatment of COPD.

Hirobriz Breezhaler is presented in hard gelatin capsules containing inhalation powder intended for oral inhalation via the Hirobriz Breezhaler single dose dry powder inhaler.

Capsules contain either 150 µg or 300 µg (the maximum daily dose) of indacaterol as the maleate. The capsules are taken once daily using an inhalation device. The capsules are commercially supplied in blister packaging.

Active Substance

The recommended INN name of the active substance is indacaterol, which is present in the product in the form of the maleate salt. The chemical name is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one corresponding to the molecular formula $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$ and molecular mass of 508.56 (392.49 free base)

Indacaterol appears as a white to very slightly greyish or very slightly yellowish not hygroscopic powder. It is very slightly soluble in water, insoluble in 0.9% NaCl and insoluble in buffer solutions from pH 1 to pH 10, though a slightly greater solubility is observed in the range pH 1-5. The pH of a 0.1% aqueous suspension is 4.9. Its pKa has been found 7.3 and 8.0 in water at room temperature and K_{ow} has been found 212.6 in n-octanol / buffer pH 7.4 at 37 °C and 10.0 in n-octanol/hydrochloric acid 0.1N. It contains one chiral centre and the drug substance is the R-isomer. Polymorphic form A has been defined as crystal form of indacaterol maleate.

- Manufacture

The synthesis of indacaterol maleate is performed in a multi-step sequence. The various steps in the synthesis and post-synthetic processing of indacaterol maleate drug substance are performed at different manufacturing sites. When needed and if possible, reprocessing might take place according to the described procedures, starting at an appropriate stage. The manufacturing process and process parameters have been adequately described and characterised.

- Specification

The drug substance specification includes tests for appearance (visual), colour and clarity of solution (Ph.Eur.), identification (IR X-ray diffraction), assay (HPLC, potentiometric titration, maleate content by potentiometric titration), impurities (HPLC), residual solvents (GC), loss on drying (thermogravimetry), amorphous content (microcalorimetry), S-Enantiomer (chiral HPLC), sulphated ash (Ph.Eur.), heavy metals (Ph.Eur.), microbial quality (Ph.Eur.), bacterial endotoxins (Ph.Eur.), and particle size (laser light diffraction).
Results from 23 batches synthesised with the current process were provided, 13 of which using production equipment. In total results of 33 batches were provided. All batches complied with the specification valid at the time of testing.

- Stability

Stability data were provided for five pilot batches of indacaterol maleate manufactured with the current process and stored for up to 24 months under refrigerated, for up to 48 months under long-term, for up to 12 months under intermediate and for up to 6 months under accelerated conditions.

These results were supplemented by a photostability study, stress testing (storage for one month at 50 °C, 60 °C and 80 °C/ 75% RH), and forced decomposition studies (heated in aqueous solution under acidic, alkaline, neutral and oxidising conditions).

The stability data indicate a reasonably stable drug substance with no significant changes observed under ICH conditions when stored in the proposed packaging materials.

Stability results showed the active substance is not hygroscopic and no evidence of instability was observed under long term or accelerated conditions when samples were stored in the proposed container closure system. It was further shown that indacaterol maleate is not photosensitive.

Overall, the results of the stability studies demonstrate that the drug substance is stable when stored in the proposed packaging system at the proposed storage conditions and support the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The drug product is presented as a single-dose inhalation powder in a hard gelatin capsule. Each capsule contains 150 µg or 300 µg of indacaterol.

The inhalation powder contains the drug substance along with lactose monohydrate as a carrier. The capsules are printed with inks of different colours as an aid to strength identification.

As the method of administration is by inhalation, particle size is carefully controlled to achieve the required lung deposition profile. Particle size of representative batches of lactose and particle size distribution of indacaterol maleate have been investigated for potential effects on drug product performance at production scale, but no effect other than on Aerodynamic Particle Size Distribution has been observed.

Because the product is very low dose and requires accurate homogeneity of the active substance in the powder blend, suitable powder blend flowability to ensure accurate capsule filling, and aerolisation of the drug particles during patient use. These are achieved by a combination of particle size of both active substance and lactose monohydrate carrier.

The manufacturing process consists of standard pharmaceutical operations. The filled capsules are then stored under controlled conditions.

Device

The inhalation device for the capsules has been developed from a currently marketed device used for another inhalation powder hard capsules product. A device called "Concept1" has been used throughout Phase III studies including the dose finding part of the adaptive study B2335S. A different model RS01 device has also been used during phase II studies. The RS01 and the Concept1 device are equivalent with regards to the operating principle, e.g. piercing the capsule, and dimensions of device parts which are relevant for dose delivery.

Concept1 is a low resistance device (0.07 cm $H_2O^{½}$ L^{-1} min) and has been clinically shown to enable COPD patients (mild to very severe) achieve peak inspiratory flow rates above 60 L/min, which represents the relevant air flow range in these patients.

A number of different studies have been performed to demonstrate the suitability of the device for this product including DDU and FPM over patient flow rate range, single dose fine particle mass, particle size distribution, actuator deposition, cleaning requirements, environmental moisture effects, robustness and device delivery development.

Development of the device/product has been performed in accordance with the requirements of EMEA/CHMP/QWP/49313/2005. Testing has been performed on commercial scale batches which have also been employed in clinical testing. Device development satisfactorily addressed potential scale-up issues pertaining to moulding tools and critical assembly steps.

Device moulding tools for the commercial device supply is the same as used for phase III though with a higher cavity number. Assembly will be fully automated and critical assembly steps will be run on the same automated assembly equipment as for Phase III clinical supplies. Equivalence between devices used in Phase III and for commercial use has been demonstrated. Devices are produced under clean room conditions.

The inhaler is a Class I medical device and its conformity with directive 93/42/EEC concerning medical devices has been certified by Novartis Pharma AG in a 'declaration of conformity' dated October 2008.

- Adventitious Agents

The supplier of lactose monohydrate certified that it is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

The capsule shells contain gelatine of porcine and/or bovine origin and relevant certificates of suitability have been provided by the suppliers.

- Manufacture of the Product

Manufacture consists of powder blending, capsule filling and equilibration. There are no intermediates apart from the bulk filled capsules.

Five production-scale batches of both capsule strengths, all produced at the intended site of manufacture, were used for process evaluation. It is concluded that all of the process parameters are adequately supported by the data presented and that the manufacturing process is well controlled and capable of producing a product of consistent quality.

- Product Specification

The specifications of the drug product at release and shelf-life include tests for appearance (visual), identity (TLC and HPLC, release only), assay (HPLC), uniformity of delivered dose (HPLC), uniformity of dosage units (HPLC), degradation products (HPLC), S-enantiomer (HPLC), water (Karl Fischer), fine particle mass (Ph.Eur.) and microbial enumeration (Ph. Eur.).

Batch analyses have been provided for nine batches of each capsule strength which were produced at the intended site of manufacture and at the intended production scale. Some changes to the analytical procedures and the product specification were introduced over that period and are described in the dossier. The results comply with the specification and confirm consistency of the product.

- Stability of the Product

Stability studies have been conducted on three batches of each strength, all of which were manufactured at the intended site of manufacture, at the intended production scale and packaged in the proposed container. These batches were stored under long-term (25 °C/60% RH), intermediate (30 °C/75% RH), and accelerated (40 °C /75% RH) conditions. Results were presented for up to 18 months in long-term and intermediate conditions and for at least 6 months in accelerated conditions in as required by relevant ICH guidelines.

All batches complied with the specifications for assay and degradation products under both long-term and intermediate conditions at all time points up to 18 months, and under accelerated conditions for up to 6 months. No significant changes in the assay values were noted. The content of the S-enantiomer was stable under long-term conditions. The results for uniformity of delivered dose showed no trend under long-term or intermediate storage conditions. The fine particle mass showed a slight increase between the initial and the 3 month test points at intermediate and accelerated storage conditions, but remained stable thereafter.

Further stability studies were conducted under other storage conditions: -20 °C (for 6 months), 5 °C (for 6 months), 25°C 75% RH (for 9 months) and 50 °C 75% RH for 1 month. Photostability was investigated by exposing unpacked capsules to light. The drug product was found not to be sensitive to freezing, refrigeration or light.

In conclusion stability studies have been performed in accordance with ICH Q1A guideline, and results support the proposed shelf life and storage conditions.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Hirobriz Breezhaler inhalation powder, hard capsule is adequately established. Information on development, manufacture and control of the drug substance has been presented in a

satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

Introduction

No scientific advice has been given by the CHMP in relation to this application. The non-clinical programme is in agreement with EU/ICH guidelines. The pivotal safety pharmacology and toxicity studies have been conducted in compliance with GLP. No significant deviation of the principles of GLP has been detected.

Pharmacology

- Primary pharmacodynamics

Indacaterol is a long-acting potent partial β_2 adrenergic agonist with nanomolar potency and a rapid onset of action. 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 AMP). Increased cyclic AMP levels result in relaxation of bronchial smooth muscle. Thus, indacaterol acts locally as a bronchodilator when inhaled.

The β adrenoceptor selectivity profile of indacaterol is similar to the long-acting β_2 adrenoceptor agonist formoterol. Indacaterol was a long-acting airway smooth muscle relaxant in human lung tissue with a comparable duration of action as salmeterol. *In vivo* studies have also shown that indacaterol has a significantly longer duration of action than other β_2 adrenoceptor agonists (it is still effective as a bronchodilator at 24 hours compared to formoterol that only demonstrates a 12 hour duration of action) and as such has the potential for a longer duration of action in the clinic than available presently. The long duration of action of indacaterol is hypothesised to correlate with the association of the drug with cell membranes due to its lipophilic nature. Indacaterol had an onset of action comparable to the onset of action of the short-acting (salbutamol) and the long-acting β_2 adrenoceptor agonist (formoterol) but much faster than the long-acting β_2 adrenoceptor agonist salmeterol. In isolated human lung mast cells, indacaterol was shown to be less prone to desensitisation when compared with formoterol and salmeterol. Clinical studies of up to one year duration with indacaterol show no tachyphylaxis. The effect of indacaterol was not investigated in pathophysiological animal models. This is deemed acceptable as 1) it is well-known that β_2 adrenoceptor agonists are effective in treatment of patients with COPD and 2) none of the available models reproduces the exact changes seen in humans.

- Secondary pharmacodynamics

It is very unlikely that systemic exposure to indacaterol will lead to interactions with secondary receptor systems following inhalation at the recommended therapeutic dosages. However, interactions with several receptor systems expressed in lung tissues may be significant. In vitro, indacaterol has a higher binding affinity for several of the secondary receptor targets as compared to formoterol (up to 15-fold). The MAH has provided a sufficient discussion on the potential for secondary pharmacodynamic effects in the lung providing reassurance that this has little relevance for the safety profile of indacaterol.

- Safety pharmacology programme

No unexpected adverse effects were observed in the safety pharmacology studies. Patients experienced post-inhalational cough during clinical trials with indacaterol. Animal models of cough response, both *in vitro* and *in vivo* were carried out in order to investigate the mechanism for this effect. However, no model was shown to be appropriate to mimic the cough observed in humans. The MAH has discussed a potential mechanism for this effect, i.e. that a certain cation channel (TRPA1) is stimulated by many irritant molecules such as mustard oil and cinnamaldehyde and functions as a sensor to damaging chemicals. Indacaterol is active at this receptor whereas salbutamol and formoterol are not. However, salmeterol is a more potent stimulant of this ion channel than indacaterol. Since post inhalation cough is not listed as an adverse reaction for salmeterol, the weak activity of indacaterol at the TRPA1 ion channel is unlikely to be related to the cough observed.

- Pharmacodynamic drug interactions

The lack of pharmacodynamic drug interaction studies is acceptable in the view of the low systemic exposure at therapeutic inhaled dosages.

Pharmacokinetics

Absorption

The absorption of indacaterol was investigated in CD-1 mice, Wistar rats, NZW rabbits and Beagle dogs following PO, IV, SC and intratracheal (IT) dosing. Hence, the clinical route of administration, inhalation, was not applied in the PK studies. Nevertheless, the IT route mimics to some extent the clinical route of administration but was only investigated in the rat. Indacaterol was rapidly absorbed following PO administration with T_{max} ranging from 0.5 to 2.3 hours in the various species. Oral bioavailability was 1%, 0% and 33% in mice, rats and dogs, respectively. Plasma T_{max} was 0.5-3 h and 0.8 h following SC dosing of rats and rabbits, respectively. SC bioavailability was 67-100% in rats and 51% in rabbits. The terminal half-life of indacaterol following IV administration was 5.7 h, 7.9 h, 10.9 h and 20 h in mice, rats, rabbits and dogs, respectively. In humans, the terminal half-life following PO administration varied from 116 to 182 h thus it was significantly longer than in dogs ($T_{½}$=12 h). The volume of distribution following IV dosing was reported to 26 L/kg, 5.3 L/kg, 13 L/kg and 2557 L/kg in rats, rabbits, dogs and humans, respectively. Hence, indacaterol is extensively distributed to the tissues.

Distribution

^{3}H-indacaterol was rapidly distributed following IV administration to Long Evans Hooded rats; it was detected in all tissues and organs within 5 minutes. At 8 hours post dose, radioactivity in most tissues declined but was still higher than the level in blood except for the eye, testis, seminal vesicles, brain, and spinal cord. Following PO administration, peak radioactivity concentrations were reached in most of tissues within 2 hours. Radioactivity was predominantly observed in the GI-tract, bile, kidney, liver, lung, pancreas, spleen, urine, and blood. No remaining radioactivity was observed at 24 h post PO dosing. Moreover, no significant distribution into the bone marrow, seminal vesicles or brain took place following PO administration to rats. ^{3}H-indacaterol did not display particular affinity for pigmented tissues. In rats, dogs and humans, ^{3}H-indacaterol preferably distributed with the red blood cells. In rats, the blood:plasma ratios ranged from 1.8-2.2, while the ratios in dogs and humans ranged from 1.1-1.3 and 1.1-1.4, respectively. These results suggest that the serum drug levels should be monitored during the toxicological studies, especially in rats. The plasma protein binding of the compound, determined by ultracentrifugation, was similar in the rat (90.6-92.0%) and dog (92.5-93.5%) and higher in human (95.1-96.2%). Hence, the free drug concentrations are higher in the toxicological species than in humans. In pregnant rabbits administered ^{14}C-indacaterol on gestational day 14 and 17, the highest levels of radioactivity were observed in the kidney, spleen, liver, lung, heart, and amnion while the lowest levels of radioactivity were observed in the amniotic fluid, brain, white fat, and foetus. On gestational day 17, the drug-related radioactivity moderately distributed to the foetus with a foetus-to-maternal blood C_{max} ratios of 0.24-0.90, and AUC ratios ranging from 0.33-1.2 over a 24 h time period.

Metabolism

MAH has studied the formation of metabolites in the mouse, rat, rabbit and dog following either PO, IV, SC or IT dosing. The major metabolite in mice, rats, rabbits and dogs was O-glucuronidated indacaterol (P37) (23-81% of total AUC), whereas in humans it was the monohydroxylated P26.9 (12% of total AUC). The active metabolite P26.9 was only detected in human plasma. A follow-up metabolism study was performed in order to obtain an estimate of the absolute animal/human serum metabolite exposure multiples for the toxicological species. The analysis was based on samples obtained from toxicokinetic and clinical studies with non-radiolabeled indacaterol administered via the inhalation route. Taking into account that the applied human dose was 2 mg, the metabolite exposures obtained in the rat and dog inhalation toxicity studies are expected to be equivalent to or higher than those observed in humans at the maximal recommended daily dose (0.3 mg). As such the metabolites P19, P26.9, P30.3, P37 and P38.2 are considered qualified. The minor human metabolites P37.7, P38.2 and P39 could not be discriminated chromatographically in human plasma but together they constituted 13% of total AUC. Based on metabolite data from plasma and excreta, it is suggested that the rabbit does not form P37.7 while the mouse does not form P39. The lack of glutathione/cysteine conjugates and the relatively low potential of indacaterol for covalent protein binding suggest that no reactive metabolites are formed. Formation of the active metabolites P26.9 and P30.3 was observed following incubation of 10 µM 3H-indacaterol with recombinant human CYP1A1, CYP2D6 and CYP3A4. Following 3H-indacaterol incubation with recombinant human UGT enzymes, it was concluded that UGT1A1 was responsible for indacaterol glucuronidation. Based on clinical data, UGT1A1 and CYP3A4 are the major enzymes responsible for metabolic clearance of indacaterol. No apparent 3H-indacaterol metabolism was detected in human lung slices and pulmonary microsomes, hence indacaterol does not appear to be metabolised locally in the lung.

Excretion

^{3}H-indacaterol was predominantly excreted via the faeces in mouse, rat, rabbit, dog and human regardless of the route of administration (PO, SC, IV, IT). Hence, the biliary excretion route was the major route of elimination of indacaterol and its metabolites. The recovery across all species ranged from 65-98% of the dose for collection times up to 216 h. Indacaterol and its metabolites is rapidly transferred into rat milk (T_{max} = 1h) following SC administration to lactating rats. The overall milk:plasma concentration ratio of total radioactivity was 1.3, based on $AUC_{0\text{-}24\ h}$ values. Based on the rat data, it is estimated that the maximum amount of indacaterol and/or its metabolites that a breast-fed infant could be exposed to by ingesting 1 L of milk daily is 0.18% of a 300 µg adult dose.

Drug interaction

Indacaterol is a P-glycoprotein (P-gp) substrate and co-administration with P-gp inhibitors increases indacaterol AUC and C_{max} in human subjects. Inhibition of the metabolism of CYP1A1, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 substrates are not likely to occur at clinically relevant doses. The kinetics of ^{3}H-indacaterol glucuronidation by UGT1A1 was examined and the K_m value for formation of P37 was found to be 23 µM, which is similar to the K_m value for bilirubin glucuronidation. However, considering the clinical C_{max} of 2.2 nM, it is unlikely that indacaterol inhalation would affect bilirubin glucuronidation.

Toxicology

- Single dose toxicity

Oral administration of indacaterol to mice and rats did not cause signs of toxicity and therefore SC administration was used to examine systemic toxicity in rodent species. Systemic exposure via the SC route resulted in significant toxicities in rodents, whereas in dogs, oral dosing resulted in significant toxicities especially ECG abnormalities that were consistent with the pharmacological effect (sinus tachycardia). Skin lesions associated only with subcutaneous dosing were evident in all species tested and severity was considered dose related. Indacaterol was considered a slight skin sensitizer in the studies of local tolerance.

- Repeat dose toxicity (with toxicokinetics)

The repeat-dose inhalation studies were conducted in mice, rats and dogs. The majority of studies were conducted with a dry powder formulation consisting of indacaterol and lactose. However, the pivotal studies (26-week in rat and 39-weeks in dog) were conducted with a hydrofluoroalkane (HFA) metered dose inhaler (MDI) formulation. A dry powder formulation is used clinically which consists of indacaterol (approximately 1.6%) and lactose monohydrate. Still, non-clinical bridging studies have demonstrated comparability between the different formulations. Upper respiratory tract irritation, i.e. reversible alterations described as inflammation/irritation of nasal cavity (focal, olfactory epithelial degeneration along roof of dorsal meatus) and larynx (ventral floor at base of epiglottis, focal squamous metaplasia in epithelial lining) in rats and mice were found which were not progressive after long term exposure. Similar findings in rats were also observed for other marketed inhaled drugs including beta-2 adrenoceptor agonists (*e.g.* formoterol, salmeterol) and muscarinic antagonists (*e.g.* tiotropium). These effects may be species specific since they were not observed in the 39-week inhalation dog study with indacaterol. Squamous metaplasia of laryngeal epithelium was observed in mice and rats at doses corresponding to 2.7 and 1.7-fold the maximal human exposure on a mg/m^2 basis. Moreover, minimal squamous hyperplasia of laryngeal and pharyngeal epithelium was observed in rats and male dogs, respectively, at clinically relevant exposure levels (mg/m^2). These findings were reversible since they were not seen following a recovery period. Furthermore, minimal hyperplasia of the olfactory epithelium and at the epithelium near the maxillo-turbinate in the nasal cavity was seen in rats at clinically relevant exposure levels (mg/m^2). Laryngeal metaplasia and hyperplasia are common findings in chronic rodent inhalation toxicity studies in response to repeated irritation. Indeed, similar findings were made in rats with other marketed inhaled drugs including β_2-adrenoceptor agonists. Mild squamous hyperplasia was recorded in the pharynx of two high-dose dogs in the 39-week inhalation toxicity study. However, squamous hyperplasia is very rarely found in non-rodents. Nevertheless, this finding occurred with a NOEL approximately 11-fold higher than the maximum proposed therapeutic dose of 300 µg/day (mg/m^2). Furthermore, a re-review of the slides suggested that the finding could be related to slight variations in the plane of section and did not represent a true hyperplasia. Hence, this issue is not considered a safety concern for humans.

Dose-dependent tachycardia was observed in dogs inhaling ≥0.01 mg/kg. These findings were accompanied by myocardial fibrosis of the ventricular wall and the papillary muscles at doses ≥0.9 mg/kg, which corresponded to plasma exposure (AUC) levels 12 to 42-fold higher than is obtained clinically with the maximal recommended dose (300 µg). Exaggerated pharmacological alterations in the heart of dogs dosed with cardiovascularly active compounds are well documented. Marked tachycardia increases the myocardial oxygen demand. As a result of the high demand and poor capillary perfusion in the subendocardium of the ventricular papillary muscles, focal myocardial necrosis is a common reaction (Turton and Hooson, 1998). Clinical experience in humans shows that multiple doses below 800 µg/day do not affect the heart rate, hence there is a large exposure margin. The QTc (Fridericia's formulae) was increased at doses ≥0.1 mg/kg (3 to 8-fold the clinical plasma AUC). Inhibition of the hERG current was observed at relatively high doses in the safety pharmacology studies, thus suggesting that the effect on QTc is mediated via β-adrenergic receptors. Please refer to the clinical assessment report for a discussion on the risk for QT-prolongation in humans.

Hepatic findings were periportal glycogen vacuolation at all doses studied in dogs. MAH has described the possible reason for this occurrence and considers it to be of no clinical relevance. This effect was not noted in mice or rats. The finding of increased levels of hepatocellular glycogen in the dog liver, but not in the rat liver parallels the distribution of the β-adrenoceptors in these species, indicating a relationship to pharmacology. There was no apparent increase in severity with long term use, nor did it appear that there were any functional consequences to the presence of these glycogen vacuolated hepatocytes in the periportal area. The effect was reversible. The relevance of reversibility is questionable for a product that is to be used on a chronic basis. There is no safety margin for this effect when comparing the exposure multiples in dogs and humans. Nevertheless, the increased hepatocellular glycogen vacuolation was considered a secondary response related to a combination of overnight fasting of the animals (up to 24 hours) and increased lipolysis and glucagon receptor down-regulation as a consequence of chronic beta-adrenoceptor stimulation. As the adaptive response

observed in dog hepatocytes under fasting conditions was mild, it is not considered to have any significant consequences for patients during normal therapeutic use.

An increased skeletal muscle mass accompanied by increased body weight was observed at doses of ≥ 0.31 mg/kg/day in the 26-week rat repeat-dose toxicity study. According to the MAH, it is well-documented that β-adrenoceptor stimulation activates the cAMP-protein kinase A signalling pathway.

In skeletal muscle, activation of this pathway is believed to be, at least in part responsible for the anabolic response of skeletal muscle to β-adrenoceptor stimulation.

- Genotoxicity

Indacaterol was considered negative in the standard battery of in vitro and in vivo genotoxicity tests.

- Carcinogenicity

An increased incidence of ovarian leiomyomas and ovarian smooth muscle hyperplasia was observed in rats inhaling 2.09 mg/kg/day indacaterol for 2 years. Several β-agonists have been shown to induce mesovarian leiomyomas in certain strains of rats (Monro, 1992) and there is evidence from a study with salbutamol that co-administration of a β-antagonist, such as propranolol, abolishes the tumours (Gibson et al., 1987). Thus, the induction of these tumours appears to be the results of adrenergic stimulation. Furthermore, epidemiological data indicate that the incidence of mesovarian leiomyomas is not increased in women following use of adrenergic agents (EMEA/MRL/030/95). A high incidence of squamous cell hyperplasia of the limiting ridge was observed in the stomach of male high-dose rats. Following indacaterol inhalation, the animals may swallow a part of the administrated dose which leads to significant exposure of the stomach epithelium. Moreover, hyperplasia of the limiting ridge epithelium was observed in CB6F1-TgrasH2 mice receiving PO administered indacaterol. These lesions were mild or less in severity and did not progress to neoplasia. Taken into account the considerably longer inhalation procedure in rodents (approximately 30 min per day) as compared to humans, these findings are considered unlikely to be of relevance for human safety following inhalation of the maximum proposed therapeutic dose of 300 µg/day.

Indacaterol was not carcinogenic in a transgenic mice model (CB6F1/TgrasH2) at doses up to 600 mg/kg/day PO (corresponds to a safety margin of more than 50-fold relative to the maximum recommended human dose).

- Reproduction Toxicity

There was no evidence of teratogenicity in the embryo-foetal development studies. However, an increased foetal incidence of full supernumerary ribs was observed in rabbits treated with 0.1 and 3 mg/kg/day indacaterol. The values for incidence of full supernumerary ribs were within the range of the historical control data and therefore not considered relevant for human safety.

A NOAEL of 0.1 mg/kg/day was established in the pre- and postnatal developmental study for the F_0 offspring. At higher dosages (≥0.3 mg/kg/day), an increase in dying, stillborn, missing and/or cannibalised F_0 offspring was observed without significant maternal toxicity. A decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at 1 mg/kg/day. Hence, an effect on fertility cannot be excluded. Using a NOAEL of 0.3 mg/kg/day from the peri- and post-developmental rat study, the safety margin for male and female fertility is approximately 14-fold when compared to human serum exposure following inhalation of the maximum recommended dose (based on AUC data for pregnant rats obtained in the embryo-foetal development study [PCS-R0270037]). Indeed, no findings were made in the adult fertility study but apparently exposure to indacaterol in utero and in juvenile animals may affect fertility. Considering the 14-fold safety margin and that the present application concerns COPD (and not e.g. asthma) which is not a relevant disease in the paediatric population (<18 years), no problems concerning fertility are expected in the treatment population.

Phototoxicity, allergenicity and environmental risk assessment

An in vitro 3T3 phototoxicity assay indicated a probable phototoxic potential for IND. However, as systemic absorption following inhalation is very limited, further non-clinical or clinical evaluations are

not deemed necessary. The risk of allergic potential of indacaterol in humans is considered to be low based on both non-clinical and clinical data. Indacaterol is not considered a risk for the environment.

2.4. Clinical aspects

Introduction

Indacaterol is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease. The recommended dose is the inhalation of the content of one 150 microgram capsule once a day, using indacaterol inhaler. The dose should only be increased on medical advice. The inhalation of the content of one 300 microgram capsule once a day, using the indacaterol inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum dose is 300 microgram once daily. The phase III program includes 3 large, pivotal efficacy and safety studies of up 52 weeks duration, and 3 small, short-tem profiling cross-over studies in patients with COPD.

The pivotal trials are summarised below:

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm	Gender M/F Median Age	Diagnosis Incl. criteria	Primary and Other Endpoints
Pivotal studies:								
B2335S	334 centers	26 weeks multicenter, randomised, double-blind, double-dummy placebo-controlled (adaptive, seamless) parallel group **2 stages**	**Stage 2:** Ind 150 µg Ind 300 µg Tiotropium 18 µg Placebo	Superiority over placebo	416 416 415 418	(F: 37.2 %) Age (median (min-max)): 64.0y (40-88) (>65y: 47.5%) Pack years (median (min-max)): 43 (13-208)	COPD* Mild: 4.4 % Moderate: 55.7% Severe: 39.3% Very severe: 0.4 %	Primary: 24-h (trough) FEV1 after 12 weeks Secondary: Days of poor symptom control. Non inferiority to tiotropium.
B2346	103	12 weeks multicenter, randomised, double-blind, double-dummy placebo-controlled	Ind 150 µg placebo	Superiority over placebo	211 205	F: 47.6% Age (median (min-max)):63.0 y (40-89) (>65y: 43.3%) Pack years (median (min-max)): 49 (20-728)	COPD* Mild: 4.1 % Moderate: 56.7% Severe: 38.5% Very severe: 0.5 %	Primary: 24-h (trough) FEV1 after 12 weeks Secondary: Days of poor symptom control
B2334	240	52 weeks multicenter, randomised, double-blind, double-dummy placebo-controlled	Ind 300 µg Ind 600 µg Formoterol 12 µg Placebo	Superiority over placebo	437 425 434 432	F: 20.3% Age (median (min-max)): 64.0y (41-90) (>65 y: 46.9%) Pack years (median (min-max)): 40 (20-900)	COPD* Mild: 1.4 % Moderate: 50.9% Severe: 43.2% Very severe: 2.5 %	Primary: 24-h (trough) FEV1 after 12 weeks Secondary: Days of poor symptom control. Non inferiority to formoterol.

In response to the LoQ the MAH has submitted the extension to pivotal study B2335SE as well as a new study, B2336.

GCP

The Clinical trials were performed in accordance with GCP. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Pharmacokinetic data were obtained from a number of clinical studies, from healthy volunteers and COPD patients.

- 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 microgram to 600 microgram) 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 microgram and 600 microgram.

- Distribution

After intravenous infusion the volume of distribution of indacaterol was 2557 litres indicating an extensive distribution. The *in vitro* human serum and plasma protein binding was 94.1-95.3% and 95.1-96.2%, respectively.

- Elimination

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 hours. 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, and C- and N-dealkylated products were further metabolites identified. *In vitro* investigations indicated that UGT1A1 is the only UGT isoform that metabolised 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 IND. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp. 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 litres/hour. When compared with the serum clearance of indacaterol of 23.3 litres/hour, it is evident that renal clearance plays a minor role (about 2 to 5% of systemic clearance) in the elimination of systemically available IND. 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 substance (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 12-14 days.

- Dose proportionality and time dependencies

Dose proportionality is demonstrated for AUC and Cmax following repeated administration of therapeutic over 14 days. For single-dose administration a slightly deviation with respect to AUC dose-proportionality was noted. This is not of clinical relevance. The PK of indacaterol is not time

dependent at the three dose levels tested. Intra- and inter-individual variability are modest with CV% for AUC's between 20-48% for inter-individual variability and 14-28% for intra-individual variability.

- Special populations

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 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.

- Pharmacokinetic interaction studies

Three drug-drug interaction studies in healthy volunteers have been performed: (1) a study with the potent CYP3A4 inhibitor ketoconazole and indacaterol at clinically relevant doses demonstrate a 40% and 100% increase in Cmax and AUC, respectively. The MAH made a justifiable argument that since safety data for a 600 µg dose does not suggest clinically relevant concerns, a 2-fold increase in exposure, due to CYP3A4 inhibition, from the proposed maximum dose of 300 µg is not of clinically relevance; (2) a study with indacaterol and the moderate CYP3A4 inhibitor erythromycin at clinically relevant doses demonstrate a 20% and 40 (0-24h) -60 (0-infinite h) % increase in Cmax and AUC, respectively. These changes are unlikely to be of clinical relevance; (3) a study with the specific and potent p-pg inhibitor verapamil and indacaterol at clinically relevant doses demonstrate a 50% and 35 % increase in Cmax and AUC, respectively. The DDI interaction with verapamil is unlikely to be of clinical relevance. In vitro studies suggest that indacaterol is moderate to strong inhibitor of CYP2D6 and CYP1A2, respectively with Ki values below 10 micromolar. Due to low systemic concentrations, clinically relevant inhibition of CYP mediated metabolism by indacaterol is unlikely.

Pharmacodynamics

- Mechanism of action

The pharmacological effects of $beta_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses 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 $beta_2$-receptors compared to $beta_1$-receptors and 20-fold greater agonist activity compared to $beta_3$-receptors. This selectivity profile is similar to formoterol. When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial agonist at the human $beta_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

- Primary and Secondary pharmacology

Indacaterol, administered once daily at the same time each day, either in the morning or evening, provided consistently significant improvement in lung function (FEV_1) over 24 hours in a number of clinical pharmacodynamic and efficacy trials. There was an onset of action within 5 minutes after inhalation of indacaterol, comparable to the effect of the fast-acting $beta_2$-agonist salbutamol 200 microgram and statistically significantly faster compared to salmeterol/fluticasone 50/500 microgram. Indacaterol had a peak effect occurring between 2-4 hours following the dose. There was no evidence of loss of efficacy of 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. Inspiratory capacity during constant, sub-maximal exercise increased by 317 ml compared to placebo after administration of 300 microgram 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.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10-50% of the total adrenergic receptors. The precise function of $beta_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

A double-blind, placebo- and active (moxifloxacin)-controlled study for 2 weeks in 404 healthy volunteers following multiple doses of indacaterol showed no concerns for a pro-arrhythmic potential related to QT-interval prolongations at recommended therapeutic doses or at twice the maximum recommended dose. There was no evidence of a concentration-delta QTc relationship in the range of doses evaluated. As demonstrated in 605 patients with COPD in a 26-week, double-blind, placebo-controlled Phase III study, there was no clinically relevant difference in the development of arrhythmic events monitored over 24 hours, at baseline and up to 3 times during the 26-week treatment period, between patients receiving recommended doses of indacaterol treatment and those patients who received placebo or treatment with tiotropium.

There were no clinically relevant changes in serum potassium and plasma glucose evaluated in a 26-week double-blind, placebo-controlled Phase III study.

Clinical efficacy

- Dose response study

Study B2335S (Stage 1- dose finding part)

It was a multicenter, randomised, double-blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group dose-ranging part of study B2335S in patients with COPD using blinded formoterol (12 µg b.i.d) and open label tiotropium (18 µg o.d.) as active controls. Two out of four indacaterol doses were selected following interim analysis to continue into a second stage for comparisons of efficacy, safety and tolerability for up to 26 weeks total treatment. The primary objective was to investigate four doses of indacaterol (75, 150, 300 & 600 µg o.d. via SDDPI) versus placebo and active controls with respect to 24 h post dose (trough) FEV1 and FEV1 AUC(1h-4h) after 2 weeks of treatment in patients with COPD. The secondary objectives were to investigate the four doses of indacaterol vs. placebo and active controls with respect to cumulative selected safety parameters (AEs, QTc, heart rate, serum potassium and glucose). The patient population consisted of adult males and females (aged 40 years and over) with a clinical diagnosis of moderate to severe COPD and a smoking history of at least 20 pack years (as defined by the GOLD Guidelines, 2005). Spirometric criteria were as follows. Post-bronchodilator FEV1 $< 80\%$ and $\geq 30\%$ of the predicted normal value and post-bronchodilator FEV1/FVC $< 70\%$. Both reversible and non-reversible patients were enrolled. Following the dose selection guidelines the reference value used for trough FEV1 was 140 mL (tiotropium *vs.* placebo difference) and for FEV1 AUC(1h-4h) was 220 mL (formoterol *vs.* placebo). All the indacaterol doses were superior to the reference value for trough FEV1. The indacaterol 150 µg, 300 µg, and 600 µg, doses were superior to the reference value for FEV1 AUC (1h-4h). The lowest dose to surpass these reference values was therefore the indacaterol 150 µg dose, with the next highest dose being 300 µg.

- Main studies

The phase III program included 3 large, pivotal efficacy and safety studies of up to 52 weeks duration (B2335S, B2346 and B2334)
All three pivotal studies had similar in- and exclusion criteria.

Study B2335S (Stage 2 – safety and efficacy)
A 26-week treatment, multicenter, randomised, 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 & 600 µg o.d.) in patients with COPD using blinded formoterol (12 µg b.i.d) and open label tiotropium (18 µg o.d.) as active controls.

METHODS

Study Participants

Inclusion criteria were: (1) Adult males and females (aged 40 years and over) with a clinical diagnosis of moderate to severe COPD and a smoking history of at least 20 pack years (as defined by the GOLD Guidelines, 2005), (2) Both reversible and non-reversible patients were enrolled, (3) Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value, (4) Post-bronchodilator FEV1/FVC < 70%.

Patients with the history of asthma were excluded. For Studies B2335S and B2346 presence of asthma was determined by, but not limited to: (1) blood eosinophil count > 400/mm^3 and; (2) onset of respiratory symptoms prior to age 40 years. COPD patients with and without reversibility to short-acting beta-2-agonist were enrolled in all three pivotal studies. COPD patients may exhibit a degree of reversibility however, the MAH sufficiently justified that the study populations in the pivotal studies comprised COPD patients and not asthma patients.

Treatments

• indacaterol 150 µg o.d delivered via SDDPI or

• indacaterol 300 µg o.d delivered via SDDPI or

• Placebo delivered via SDDPI device or

• Tiotropium (18 µg) dry powder capsules delivered via manufacturer's proprietary inhalation device (Handihaler®)

Stage 2 After completion of Stage 1 an additional 285 patients per treatment group were randomised until the total required number of patients (400 per group) had been included. Each patient in Stage 2 was to receive study drug for a total of 26 weeks. A subset of patients underwent 12 hour serial spirometry assessments, and another subset extended 24 hour serial spirometry assessments. A further subset of patients underwent 24 hour Holter monitoring.

Patients were required to stop the use of any long acting β2-agonist (LABA) prior to Visit 1 (start of the run-in period) until the completion of the study. Patients were switched to the 'as needed' use of the SABA salbutamol at least 48 h prior to Visit 1. Patients taking fixed dose combination treatment with inhaled corticosteroid plus a LABA were taken off the combined medication and given equivalent monotherapy with an inhaled corticosteroid at the same dose and dosage regimen for the duration of the study, plus the inhaled short acting β2-agonist (SABA) salbutamol (as needed), at least 48 h prior to Visit 1. Patients taking a fixed dose combination of an anti-cholinergic plus a SABA must have been taken off the combination at least 8 h prior to Visit 1. Instead, salbutamol only was to be used. Regular dosage regimens of salbutamol and/or use as rescue medication were permitted during the screening period. However, during the treatment period salbutamol was to be taken for rescue purposes only. During the randomised treatment period of the study, all patients were to receive the same ICS treatment regimen as taken during the run-in period.

Objectives

The primary efficacy objective was to demonstrate that at least one of the selected indacaterol doses (150 and 300 µg o.d.) was superior to placebo with respect to 24 hour post dose (trough) FEV1 after 12 weeks of treatment. The key secondary efficacy objective was to show that at least one of the selected indacaterol doses was non-inferior to tiotropium with respect to 24 hour post dose (trough) FEV1 after 12 weeks of treatment. The important secondary objective was to demonstrate superiority

over placebo of the two selected indacaterol doses with respect to the percentage of COPD 'days of poor control' during 26 weeks of treatment.

Outcomes/endpoints

Primary endpoint was 24 hour post dose (trough) FEV1 after 12 weeks of treatment.

Sample size

A total of 4130 patients were screened and 2059 patients were randomised to treatment. For treatments not continued into Stage 2 127 patients received indacaterol 75 µg, 122 patients received indacaterol 600 µg and 122 patients received formoterol.

Randomisation

In Stage 2 sites re-commenced recruitment for the two chosen indacaterol doses, placebo and tiotropium. Randomisation was stratified by smoking status. A randomisation ratio of 1:1:1:1 in each treatment group was maintained for smoking status and 12 h spirometry sub-group. The balance of treatment groups was maintained at the country, not center level.

Patients randomised in Stage 1 or Stage 2 at Visit 3, were given a randomisation number by an interactive voice recognition system (IVRS) that assigned them to one of the treatment groups. In addition, if this patient was not randomised to tiotropium, IVRS specified the unique medication numbers for the packs of study drug to be dispensed to the patient; one medication number for indacaterol/placebo treatment and one number for formoterol/placebo.

Blinding (masking)

Patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock. Treatment was blinded for the indacaterol-, formoterol- (study B2335S Stage 1) doses and for placebo using a double dummy design, whereas tiotropium was open-label (study B2335S Stage 2). The identity of the active and placebo indacaterol treatments was concealed by the use of identical packaging, labeling, schedule of administration and appearance.

Statistical methods

Non-inferiority was defined as a difference in FEV1 not less than 55 mL. A clinically meaningful difference from placebo in trough FEV1 was considered to be 120 mL. The standard deviation of 270 mL for trough FEV1 was based on previous formoterol studies. If the stage 1 sample size was 110 per treatment arm and the stage 2 sample size was 230, then the chosen indacaterol treatment group would have 340 patients. With this number of patients, and the assumed dose response, the power for the primary endpoint was nearly 100%. The power for the primary and key secondary variables was at least 85%.

Three populations were defined for analysis. The intention-to-treat (ITT) population included all randomised patients who received at least one dose of study drug. The per-protocol (PP) population included all patients of the ITT population without any major protocol deviations. The safety population included all patients who received at least one dose of study drug.

The primary variable was analyzed using a mixed model. The model contained treatment as a fixed effect with the baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility at Day -14), FEV1 prior to inhalation and FEV1 one hour post inhalation of ipratropium (components of anti-cholinergic reversibility at Day -13) as covariates. To reflect the randomisation scheme the model included also the smoking status (current/ex-smoker) and country as fixed effects with center nested within country as a random effect.

RESULTS

*Participants flow*For the four treatment groups continued into Stage 2, 76.7% of patients completed the study. Discontinuations occurred more frequently for placebo than for the indacaterol or tiotropium

treatment arms and were 22.6%, 18.4%, 21.2%, and 30.8%, for the indacaterol 150 µg, indacaterol 300 µg, tiotropium, and placebo groups, respectively. The most common reasons for discontinuation were adverse events (6.9%, 6.2%, 4.0%, and 10.8% for indacaterol 150 µg, indacaterol 300 µg, tiotropium, and placebo, respectively), and withdrawal of consent (6.9%, 5.3%, 4.8%, 8.7%, respectively).

Patients' baseline demographics and pulmonary function. Data are mean (s.d.)

	Indacaterol 150 µg	Indacaterol 300 µg	Tiotropium	Placebo
Number treated	416	416	415	418
% completing study	77.4	81.6	78.8	69.2
Age (mean) years	63.4 (9.4)	63.3 (9.3)	64.0 (8.8)	63.6 (8.9)
Male (%)	62.3	63.2	64.8	61.0
COPD Grade moderate (%)	57.5	57.7	51.3	56.5
COPD Grade severe ((%)	37.7	37.5	42.4	39.5
Current smoker (%)	45.0	45.4	44.6	45.7
Estimated pack years	48.3	50.8	50.0	49.7
Pre-bronchodilator FEV1 (L)	1.34 (0.49)	1.36 (0.51)	1.28 (0.50)	1.33 (0.47)
FEV1 predicted normal (%)	56.1 (14.5)	56.3 (14.5)	53.9 (15.6)	56.1 (14.3)
FEV1 reversibility to SABA (% increase)	15.6 (15.4)	15.2 (15.4)	15.6 (17.6)	15.5 (18.0)

The results of the study are presented in the table below.

Outcomes for selected efficacy criteria ITT population LS mean (s.e.)

	indacaterol 150 µg	indacaterol 300 µg	Tiotropium	Placebo
FEV1 at Visit 1* (L)	1.34	1.36	1.28	1.33
Trough FEV1 at Week 12** (L)	1.46 (0.015)	1.46 (0.015)	1.42 (0.015)	1.28 (0.015)
Trough FEV1 at Week 26 (L)	1.41 (0.017)	1.44 (0.017)	1.40 (0.017)	1.26 (0.017)
AUC FEV1 to four hours (L)	1.55 (0.044)	1.55 (0.042)	1.50 (0.043)	1.34 (0.043)
SGRQ at Week 12	38.3 (0.74)	38.6 (0.74)	40.1 (0.74)	42.1 (0.75)
Days of poor control over 26 weeks	31.5 (1.51)	30.8 (1.51)	31.0 (1.50)	34.0 (1.53)
Exacerbation free rate at 26 weeks (% with 95% CI)	80.8 (76.7, 84.8)	80.0 (76.0, 84.1)	79.2 (75.1, 83.3)	74.5 (69.9, 79.1)

For trough FEV1 at Weeks 12 and 26 and AUC FEV1 at week 12 both doses of indacaterol were superior to placebo $p < 0.001$. Advantages for SGRQ were significant $p \sim 0.001$ The proportion of patients exacerbation free at month 6 was significant for indacaterol 150 µg $p = 0.019$ but not for indacaterol 300 µg $p = 0.054$ (Cox regression analysis). The numerical advantage in days of poor control over 26 weeks over placebo was not significant for either indacaterol dose.

* taken from demographics for reference s.d. not s.e. is the scatter presented ** primary efficacy comparison

Study B2335SE

On D150 an extension to study B2335S was submitted. Study B2335SE was a placebo controlled 26 weeks extension study to study B2335S. The primary endpoint was safety.

Study B2346

A 12-week treatment, multi-center, randomised, double-blind, placebo controlled, parallel group study to assess the efficacy and safety of indacaterol (150 µg o.d.) in patients with COPD.

METHODS

Study Participants

Eligible patients were male and female aged 40 years and above. Patients had a clinical diagnosis of COPD according to the GOLD guidance, and additionally met the following criteria: a smoking history of at least 20 pack years. Post-bronchodilator FEV1 less than 80% and at least 30% of the predicted normal value. Post-bronchodilator* FEV1/FVC < 70%. at Visit 1.

Treatments

- indacaterol 150 µg o.d. via SDDPI or
- matched placebo o.d. via SDDPI.

Objectives

The primary objective was to demonstrate superiority of indacaterol (150 µg) versus placebo with respect to 24 h post-dose (trough) forced expiratory volume in 1 second (FEV1) after 12 weeks of treatment in patients with COPD. The secondary objectives were to compare indacaterol (150 µg o.d.) to placebo on spirometry assessments in terms of: (1) trough FEV1 measured on Day 2, (2) FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response, (3) the standardized AUC for FEV1 (5 min – 4 h), (5 min – 1 h) and (1 h – 4 h) on Day 1 and after 12 weeks of treatment, (4) to assess the 12 week safety (particularly with regard to ECG, laboratory tests, blood pressure and adverse events) of indacaterol (150 µg o.d.).

Outcomes/endpoints

Primary endpoint was 24 h post-dose (trough) forced expiratory volume in 1 second (FEV1) after 12 weeks of treatment in patients with COPD.

Sample size

The randomisation scheme did not ensure perfect balance (equal arms or a ratio of 1 for the treatment groups) so to ensure at least 90% power which allows for potential imbalance in the number of patients in each treatment group the sample size calculation assumed a worst case ratio of 0.6. This implied a sample size of 232 evaluable patients will be needed to detect this difference between indacaterol 150 µg and placebo as statistically significant at the 5% significance level (2 sided) with 90% power. Therefore, assuming a drop out rate of 20% over 12 weeks of treatment, a minimum sample size of 290 patients was chosen that provides 90% power for the primary endpoint (trough FEV1).

Randomisation

Randomisation was stratified by smoking status (current or ex-smoker). A randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomisation numbers in the specified 1:1 ratio.

Blinding (masking)

Patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock. The identity of the active and placebo indacaterol treatments was concealed by the use of identical packaging, labeling, schedule of administration and appearance.

Statistical methods

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 lay entirely to the right of (higher than) 0 mL.

RESULTS

Participants flow

A total of 788 patients were screened, and 416 randomised. Almost 90% of patients completed the study as planned. Discontinuations from the study overall 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% vs. 3.3% for placebo vs. indacaterol, respectively), and unsatisfactory therapeutic effect (2.9% vs. 0.5% for placebo vs. indacaterol, respectively).

Table Demographic baseline and principal efficacy data group mean (s.e.)

	indacaterol 150 µg	Placebo
Baseline data		
No. of patients	211	205
Age (years)	62.9 (9.9)	63.2 (9.6)
Male gender (%)	51.2%	53.7%
BMI (kg/m^2)	28.4 (7.1)	27.6 (6.0)
Duration of COPD (years)	6.6 (4.7)	7.3 (5.6)
GOLD severe COPD (%)	39.8%	37.1%
Current smoker (%)	51.2%	52.7%
FEV1 (L)	1.3 (0.5)	1.4 (0.5)
Efficacy variables		
Trough FEV1 at Week 12 (L)	1.49 (0.02)	1.35 (0.02)
Days of poor control (%)	31.19 (1.5)	40.24 (1.6)
SGRQ at Week 12	43.38 (0.9)	48.13 (0.9)
IND was superior to placebo in the above variable with $p < 0.001$ (mixed model analysis).		

Indacaterol 150 µg showed a clinically relevant and statistically significant difference to placebo in post-dose (trough) FEV1 after 12 weeks of treatment, achieving a difference from placebo of 130 mL. The results of this study are summarized in the table below:

Study B2346 Trough FEV_1 (L) at Week 12: treatment comparisons (ITT and per-protocol populations, LOCF)

		Treatment			**Treatment difference**			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
ITT population								
Indacaterol 150 µg	201	1.48	0.018	Ind 150 µg - Placebo	0.13	0.024	(0.09, 0.18)	<0.001
Placebo	189	1.35	0.019					
Per-protocol population								
Ind 150 µg	193	1.49	0.019	Ind 150 µg - Placebo	0.13	0.025	(0.08, 0.18)	<0.001
Placebo	172	1.35	0.020					

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+center, with center as a random effect]

Study B2334

A 52-week treatment, multicenter, randomised, double-blind, double dummy, placebo controlled, parallel-group study to assess the efficacy, safety and tolerability of indacaterol (300 & 600 µg o.d.) in patients with COPD, using formoterol (12 µg b.i.d.) as an active control.

METHODS

Study Participants

The study population consisted of adult male and female outpatients (aged 40 years and over) with a clinical diagnosis of moderate to severe COPD and a smoking history of at least 20 pack years (1 pack/day for one year x 20). Eligible patients had a post-bronchodilator FEV1 less than 80% and at least 30% of the predicted normal value. Post-bronchodilator FEV1/FVC was less than 70%. Principal exclusion criteria were the following: pregnant or lactating women, women of child-bearing potential unless using an approved method of contraception, patients who had been hospitalized for a COPD exacerbation in the 6 weeks prior to Visit 1, patients requiring chronic oxygen therapy, patients who had a respiratory infection within 6 weeks prior to Visit 1, patients with other significant co-morbidity or who had participated in an investigational study in the previous thirty days.

Treatments

- indacaterol 300 µg o.d delivered via SDDPI or
- indacaterol 600 µg o.d delivered via SDDPI or
- Placebo delivered via SDDPI device or
- Formoterol 12 µg b.i.d. via Aerolizer device

Objectives

The primary objective was to demonstrate superiority of indacaterol (300 µg and 600 µg) versus placebo with respect to 24 h post-dose (trough) forced expiratory volume in 1 second (FEV1) after 12 weeks of treatment in patients with COPD.

The key secondary objective was to evaluate the effect of indacaterol (300 and 600 µg o.d.) on the percentage of 'days of poor control' reported over the 52 week randomised treatment period, as compared to placebo. Important secondary objectives were: (1) to evaluate the effect of indacaterol (300 and 600 µg o.d.) on the total score of the St George's Respiratory Questionnaire (SGRQ), as compared with placebo after 12 weeks treatment, (2) to evaluate the effect of indacaterol (300 and 600 µg o.d.) on time to first COPD exacerbation during the 52 week randomised treatment period as compared with placebo, (3) to evaluate the effect of indacaterol (300 µg and 600 µg) versus placebo on COPD exacerbation rates during the 52 treatment period, (TDI) focal score, trough FEV1 after 52 weeks of treatment, other clinical variables such as morning (pre-medication) and evening (pre-medication) PEF, clinical symptoms and use of rescue medication over 52 weeks.

Outcomes/endpoints

The primary efficacy variable was 24 h post dose (trough) FEV1 after 12 weeks of treatment. The principal secondary variable was 'days of poor control' reported over 52 weeks. A day of poor control was defined as any day with a score of at least 2 (i.e. moderate or severe symptoms) for at least two out of five symptoms; cough, wheeze, sputum production, color of sputum, breathlessness. Other secondary objectives were to evaluate the effect on the total score of the St George's Respiratory Questionnaire (SGRQ) after 12 weeks treatment, and on time to first COPD exacerbation during the 52 week randomised treatment period.

Sample size and statistical methods

A treatment difference of 120 mL in trough FEV1 was considered a clinically important benefit. The standard deviation of 270 mL for the trough in FEV1 was based on previous formoterol studies. A sample size of 108 evaluable patients in each treatment group would be needed to detect this difference between indacaterol 300 µg and placebo at $p = 0.05$ with 90% power. The subsequent comparison in the hierarchical testing procedure of indacaterol 600 µg vs. placebo would be powered at a level of 84%. However, in order to meet the regulatory requirement for safety it was proposed to have 300 evaluable patients in each of the indacaterol dose groups which gave a power of 99% for the primary comparison.

For the percentage of COPD days of poor control, a difference of 8% was considered clinically important based upon data from prior studies with formoterol as was the estimate of 28% for the standard deviation. With these parameters, the number of evaluable patients for safety implied for the comparisons of indacaterol 300 µg and 600 µg at the 5% significance level a power of 93% and 89% respectively in the hierarchical testing procedure.

The primary analysis for efficacy was based on the modified ITT population (Patients from centres in Egypt were excluded due to poor GCP compliance and data unreliability). The primary variable was analyzed using a mixed model containing treatment as a fixed effect with baseline FEV1, SABA reversibility, ipratropium reversibility as covariates. The model also included smoking status and country as fixed effects. The percentage of 'days of poor control' was summarized by treatment and analyzed using the same mixed model as specified for the primary analysis using the modified ITT population.

Randomisation

Participants were randomised to one of the four available treatment groups (randomisation ratio 1:1:1:1 with stratification for smoking status) to inhaled indacaterol 300 µg o.d., indacaterol 600 µg o.d., formoterol 12 µg b.i.d. or placebo.

Blinding (masking)

Patients, investigator staff, persons performing the assessments and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock. Treatment was blinded for the indacaterol-, formoterol- doses and for placebo using a double dummy design. The identity of the active and placebo indacaterol treatments was concealed by the use of identical packaging, labeling, schedule of administration and appearance. Individual sets of code breaker scratch cards describing the actual treatment were supplied with each container of medication and distributed to each investigator. One complete set was kept by the Novartis Country Pharma Organization. The scratch cards were only to be opened in an emergency.

RESULTS

*Participants flow*A total of 2446 patients were screened and 1732 were randomised; 74% of patients completed the study. 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 event(s) was the main reason for discontinuation in the formoterol and indacaterol treatment groups. There were 12 deaths during the course of the study. Patients' baseline characteristics are shown in table below.

Table Patients' baseline data mean (s.d.)

	indacaterol 300 µg	indacaterol 600 µg	Formoterol	Placebo
Demographic characteristics				
Age in years	63.9 (8.6)	62.9 (8.7)	63.6 (8.5)	63.2 (8.3)
Male gender (%)	80.3	76.9	80.2	81.5
MBI (kg/m^2)	26.2 (4.9)	26.5 (5.1)	26.3 (4.8)	26.8 (5.1)
Disease characteristics and smoking history				
Duration of COPD	7.4 (7.1)	6.8 (7.8)	7.3 (6.2)	7.0 (6.1)
Proportion with severe COPD (%)	43.5	44.2	41.9	43.1
Smoking history in pack-years	48.6 (41.5)	53.6 (67.2)	49.0 (60.7)	53.3 (69.9)
Proportion of current smokers (%)	41.6	42.1	`41.0	40.3
Pulmonary function				
Pre-bronchodilator FEV1 (L)	1.33 (0.41)	1.32 (0.45)	1.35 (0.43)	1.37 (0.47)
FEV1 reversibility to SABA (%)	11.7 (12.7)	13.7 (14.5)	11.8 (12.7)	12.7 (13.1)
FEV1 reversibility to anti-cholinergic (%)	15.0 (15.7)	14.1 (14.5)	13.6 (14.6)	13.6 (13.4)

The primary efficacy analysis showed that both the 300 and 600 µg indacaterol doses resulted in a significantly superior LS mean trough FEV1 over placebo (treatment-placebo difference of 170 mL for both doses, well in excess of the predefined MCID of 120 mL, table below).

Table: Study B2334 Trough FEV_1 (L) at Week 12: treatment comparisons (mITT and per protocol populations, LOCF)

	---- Treatment ----				---------- Treatment difference ----------			
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Modified ITT population								
Ind 300 µg	389	1.48	0.012	Ind 300 µg - Placebo	0.17	0.016	(0.13, 0.20)	<0.001
				Ind 300 µg - For	0.10	0.016	(0.07, 0.13)	<0.001
Ind 600 µg	374	1.48	0.013	Ind 600 µg - Placebo	0.17	0.016	(0.13, 0.20)	<0.001
				Ind 600 µg - For	0.10	0.016	(0.07, 0.13)	<0.001
				Ind 600 µg - Ind 300 µg	0.00	0.016	(-0.03, 0.03)	0.993
For	379	1.38	0.013	For - Placebo	0.07	0.016	(0.04, 0.10)	<0.001
Placebo	371	1.31	0.013					

B2334 achieved the primary objective of showing superiority of indacaterol 300 µg and 600 µg over placebo. There was no difference between the responses in trough FEV1 to indacaterol 300 µg compared to 600 µg. The LS mean difference in through FEV1 between indacaterol 300µg and 600µg vs. formoterol amounted to 100 ml. The clinical relevance of this can be questioned. In addition the comparison was not a predefined primary or secondary objective but was a predefined exploratory objective of the study.

- Additional studies

Study B2336
On D150 a new study (study B2336) was submitted. Study B2336 was a 26-week treatment, multi center, randomised, double blind, double dummy, placebo controlled, parallel group study to assess the efficacy (primary objective: superiority of Indacaterol 150µg vs. placebo on 24 h post dose trough FEV1 after 12 weeks of treatment) and safety of indacaterol 150µg o.d., N=320) in patients with COPD, using salmeterol (50 µg b.i.d., N=317) as an active control. Inclusion criteria were as for the 3 pivotal studies.

Study B2338 (Asthma study)

Methods

The primary aim of the study was to evaluate the safety of indacaterol 300 and 600 µg o.d over 26 weeks, in patients with moderate to severe persistent asthma who were receiving background therapy with inhaled corticosteroid. The assessment of safety included adverse events, asthma exacerbations, serum potassium and glucose, heart rate, blood pressure. The secondary objectives were to evaluate the effect of indacaterol on pulmonary function (trough FEV1 and FVC) and on asthma exacerbation rates.

Eligible patients were male and female aged at least 12 years with moderate to severe persistent asthma, diagnosed according to GINA guidelines. Patients who had used treatment with a bronchodilator, either regularly or on-demand, and who had used a daily dose of at least 100 µg beclamethasone or equivalent dose of an alternative inhaled corticosteroid. Patients whose FEV1 was at least 50% of the predicted normal value. Patients with documented at least 12% and at least 200 ml increase in FEV1 over their pre-bronchodilator value within.

Key exclusion criteria were patients had used tobacco products within 12 months or who had a smoking history of greater than 10 pack years, were suffering from COPD, had emergency treatment for an acute asthma attack in the previous 6 weeks or who had been hospitalized for an acute asthma attack in the previous six months.

Patients were randomised to one of the following treatment arms; indacaterol 300 µg daily, indacaterol 600 µg daily, salmeterol 50 µg twice daily. It was planned to recruit approximately 750 patients with the intention that at least 200 patients in each of the 3 treatment arms

Results

Of the 1146 patients who were screened, 805 were randomised and treated. Overall 85.5% completed the study. A higher proportion of patients in the indacaterol 300 µg group (16.0%) and the indacaterol 600 µg group (16.0%) discontinued prematurely compared with the salmeterol group (11.5%). The most common reasons for discontinuation were adverse events (AEs) and subject withdrawing consent for the indacaterol 300 µg group, AEs and protocol deviations for the indacaterol 600 µg group, and subject withdrawing consent and AEs for the salmeterol group. A greater proportion of patients in the indacaterol 600 µg group discontinued due to AEs compared to the other two treatment groups. A slightly greater proportion of patients in the indacaterol 300 µg and 600 µg groups discontinued due to protocol deviations compared with the salmeterol group. Two patients died, both in the indacaterol 300 µg group, during the study.

No efficacy data were assessed. Safety data were assessed and are presented in the Safety section.

Overview of results. Data relate to the ITT population and are mean (s.d.) treatment differences are not statistically significant.

	IND 300 µg	IND 600 µg	Salmeterol
Patient disposition			
No. of patients treated	268	268	269
Patients completed	84%	84%	88.5%
Patient demographics			
Age (years)	43.5 (15.8)	44.5 (15.2)	42.5 (15.2)
Male gender	43.7%	34.7%	39.0%
MBI (kg/m^2)	27.8 (6.0)	28.2 (6.0)	28.8 (6.2)
Baseline disease characteristics			
Duration of asthma (years)	19.7 (15.5)	19.8 (15.4)	18.2 (14.0)
GINA severe	34.0%	35.1%	34.2%
FEV1 (L)	2.47 (0.80)	2.38 (0.82)	2.46 (0.74)
FEV1 reversibility (%)	22.5 (10.1)	22.8 (12.1)	21.7 (12.5)
Efficacy variables			
Trough FEV1 at Week 12 (L)	2.61 (0.02)*	2.62 (0.02)	2.54 (0.03)
Trough FEV1 at Week 26 (L)	2.59 (0.03)*	2.60 (0.03)	2.54 (0.03)
No. of exacerbations over 26 weeks	0.17 (0.6)	0.19 (0.5)	0.19 (0.5)
Safety variables			
No. of deaths	2	0	0
Patients with any AE	54.9%	66.4%	67.3%
Patients with serious AE	1.9%	4.1%	3%
No. discontinued due to AE	14	17	8

*(s.e.)

- Analysis performed across trials

Baseline data:

	B2335S (n= 1665)	B2346 (n= 416)	B2334 (n=1728)
Age (median(min-max))	64.0 (40-88)	63.0 (40-89)	64.0 (40-90)
Gender (% females)	37.2	47.6	20.3
Smoking history (%current smokers)	45.2	51.9	41.3
Pack years (median (min-max))	43 (13-208)	48.5 (20-728)	40.0 (20-900)
Severity of COPD n(%):			
At risk	3 (0.2)	1 (0.2)	29 (1.7)
Mild	73 (4.4)	17 (4.1)	25 (1.4)
Moderate	928 (55.7)	236 (56.7)	880 (50.9)
Severe	654 (39.3)	160 (38.5)	746 (43.2)
Very severe	7 (0.4)	2 (0.5)	43 (2.5)

FEV1 % pred V1 (postbronchodilator)			
(mean (SD))	55.6 (14.7)	55.1 (13.7)	52.5 (13.8)
(median (min-max))	54.7 (21.3-132.3)	53.7 (27.6-91.9)	51.8 (17.6-101.4)
FEV1/FVC ratio (postbronchodilator)			
(mean (SD))	52.9 (10.1)	53.5 (10.1)	51.4 (10.59)
(median (min-max))	53.3 (24.0-72.6)	54.8 (28.0-70.0)	51.2 (15.8-96.5)
FEV1 reversibility after SABA at Visit 1 (% increase)			
(mean (SD))	15.5 (16.7)	16.5 (18.4)	12.5 (13.3)
(median (min-max))	13.2 (-45.2-222.7)	13.6 (-46.5-160.1)	10.5 (-34.3-89.6)
Use of ICS (%)	37.5%	31.5%	52.9%

Primary endpoint:

The primary efficacy analysis of the three pivotal trials showed that all three doses of indacaterol (150 µg o.d., 300 µg o.d. and 600 µg o.d.) were associated with a statistically significant and clinically relevant improvement in post-dose (trough) FEV1 relative to placebo after 12 weeks of treatment, supporting the once daily dosing of IND. Furthermore, study B2334 showed that indacaterol 300 µg o.d. and 600 µg o.d were also superior to placebo after 52 weeks of treatment. A remarkable finding was that no difference was observed between the responses in trough FEV1 to indacaterol 150 µg compared to 300 µg. The MAH sufficiently justified that the 300 µg dose may provide better bronchodilation and more importantly symptomatic relief in the most severely affected COPD patients.

Table 4-3 Summary statistics of primary endpoint in the pivotal studies, including changes from baseline

Study	Primary endpoint	Treatment	Baseline (L)	Mean change from baseline (L)
B2335S	Trough FEV_1 at Week 12	Indacaterol 150 µg	1.31	0.16
		Indacaterol 300 µg	1.34	0.17
		Tiotropium	1.24	0.13
		Placebo	1.31	-0.01
B2346	Trough FEV_1 at Week 12	Indacaterol 150 µg	1.34	0.15
		Placebo	1.34	0.01
B2334	Trough FEV_1 at Week 12	Indacaterol 300 µg	1.28	0.19
		Indacaterol 600 µg	1.29	0.18
		Formoterol	1.32	0.08
		Placebo	1.33	0.02

Secondary endpoints:

"Days of poor control"

Secondary efficacy analysis on days of poor control showed inconsistent results with a statistically significant effect in only two out of three studies. A significant effect of indacaterol 150 µg o.d vs placebo was observed in study B2346 after 12 weeks (mean difference: -9; 95% CI: -13.3,-4.8;$p < 0.0001$), and of indacaterol 300 and 600 µg o.d vs placebo in study B2334 after 52 of treatment (mean difference: -4.7; 95% CI: -8.4,-1.0; $p= 0.013$ / -8.3; 95% CI: -12.0,-4.6; $p< 0.0001$), whereas no effect was observed in study B2335S after 12 weeks of treatment (150 µg o.d: -2.5; 95% CI: -7.0,2.1; $p=0.179$. 300 µg o.d: -3.1; 95% CI: -7.7,1.4;, $p=0.086$). The observed difference in efficacy may be due to a higher frequency of "days of poor control" at the time of randomisation in the group treated with indacaterol in Study B2346. The choice of this non-validated endpoint was not supported by CHMP but due to the results of SGRQ and TDI scores (see below) "days of poor control" is considered supportive of the effectiveness of indacaterol in COPD patients for both FEV_1 and symptomatic endpoints.

SGRQ

SGRQ is a validated measure of the impact of COPD on quality of life, and provides a relevant indication of the degree of symptomatic relief. However, also for this secondary endpoint inconsistent efficacy results were observed. Analysis of the SGRQ score showed that the effect of indacaterol reached the minimal clinically important difference (MCID) of > 4 for the 150 doses in study B2346, and for the 600 g dose, but not the 300 g dose in study B2334, or for the 150 and the 300 g doses in study B2335S. In the response to the D120 LoQ the MAH provided a responder analysis of the proportion of patients with a clinically important improvement of ≥4 in the SGRQ total score, after 12 and 26 weeks in study B2335S and 12 and 52 weeks in study B2334 which showed statistically significantly superior effect of indacaterol vs. placebo.

TDI score

In study B2335S, a statistical significant increase in TDI was observed for both the 150 and 300 µg dose of indacaterol vs. placebo (P<0.001 for both). However, only the 300 µg reached the predefined MCID of ≥1 compared to placebo at week 26. Also in study B2334 a statistical significant increase in TDI was observed for both the 300 and 600 µg dose of indacaterol vs. placebo (P<0.001 for both). However, only the 300 µg reached the predefined MCID of ≥1 compared to placebo at week 52. TDI focal score outcomes were not measured in Study B2346. Also for the TDI score in the response to the D120 LoQ the MAH provided a responder analysis of the proportion of patients with a clinically important improvement of ≥1 in the TDI score, after 12 and 26 weeks in study B2335S and 12 and 52 weeks in study B2334. In this responder analysis indacaterol was statistically significantly superior vs. placebo.

Time to first COPD exacerbation

As for the above secondary endpoints the results on the effect on the time to first exacerbation and the number of exacerbations showed inconsistent results. In study B2335S a statistical significant effect on COPD exacerbations vs. placebo was observed for indacaterol 150µg (HR=0.69; 95% CI: 0.5, 0.94; p=0.019) but not for the 300 µg dose (HR=0.74; 95% CI: 0.56, 1.005; p=0.054). In study B2346, there was no effect of the 150µg dose (HR=0.6; 95% CI: 0.31, 1.13 p=0.113) whereas, in study B2334, both the 300 µg and the 600 µg dose had a significant effect on exacerbations (300 µg: HR=0.77; 95% CI: 0.61, 0.98; p=0.03, 600 µg: HR=0.69; 95% CI: 0.54,0.88; p=0.003). 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 showed a ratio of rates of 0.68 (95% CI [0.47, 0.98]; p-value 0.036) and 0.74 (95% CI [0.56, 0.96]; p-value 0.026) for 150 microgram and 300 microgram, respectively.

Subgroup analysis:

The MAH has presented a subgroup analysis for the 3-months efficacy population on 1) trough FEV1 at Day 2 and after 12 weeks of treatment and 2) standardized FEV1 AUC (5 min-4h) at Day 1 and Week 12. The analyses showed no significant impact of age, gender, race, smoking history or use of ICS on the treatment effect of either dose of indacaterol on trough FEV1 and FEV1 AUC5min-4h at day 1 and at 12 weeks. In addition, the subgroup analysis by severity of COPD similarly suggested that there was no effect of severity.

Also a sub-group analysis for the 6-month efficacy population on "days of poor control" was presented. Overall, the result of the subgroup analysis showed that the 300 µg dose of indacaterol reduced the % days of poor control in younger subjects (< 65 y), smokers and males, non ICS user and subjects with less severe COPD (FEV1 > 50% of predicted), whereas no effect of either dose of indacaterol was observed in older subjects, females, ex-smokers, current ICS users and subjects with severe COPD.

However, due to large differences in demographic characteristics in between the 3 pivotal studies, the 'Days of poor control' efficacy results obtained from the overall 3 month- and 6 month efficacy populations were at best considered supportive.

Other factors:

Time to exacerbation and ICS usage
An analysis of the time to first COPD exacerbation over 6 months of treatment by use of ICS, showed that patients using ICS did not appear to be protected, as judged by event free days, as none of the comparisons of time to exacerbation with placebo were statistically significant. However, ICS use has been shown to protect patients from exacerbations and so these findings may present a lack of ability to show an additional effect in a group of this size). In those patients not using ICS, all comparisons vs. placebo were significant, with the exception of formoterol.

Post-inhalation cough
Efficacy, as measured by trough FEV1, health-related quality of life assessed by the SGRQ, cough severity recorded in patient diaries and dyspnoea measured by TDI, was not affected by cough experienced post-inhalation. PI was not associated with any significant impact on treatment effect of either indacaterol, formoterol or tiotropium on spirometric and subjective outcomes.

Clinical safety

- Patient exposure

In the completed clinical studies to date, regardless of duration, delivery device, indication or design 6003 subjects were exposed to IND. The overall exposure to indacaterol was 1555.8 subject-years. The MAH has taken the view that in analyzing the safety data studies of reasonably similar design and duration should be pooled and that it would be inappropriate for example to pool data from asthma and COPD populations. Following this approach the populations were organized into seven datasets, according to the type of clinical trial:

(1) COPD 3-month safety population containing pooled data from studies B2346 (all data), B2334 (up to day 91) and B2335S (up to day 91);

(2) COPD 6-month safety population containing pooled 6-month (26 week) data from studies B2334 (up to day 182) and B2335S (all data);

(3) COPD 12-month safety population containing 52 week, from study B2334;

(4) COPD safety population containing all data from studies B2346, B2334 and B2335S;

(5) Asthma safety population containing 26 week, phase III study B2338;

(6) Short-term safety population containing pooled data from all completed COPD, asthma and healthy volunteer studies of indacaterol with total exposure to study drug (excluding washout periods) of less than 50 days, excluding PI cough study A2222, pediatric study C2101, and 3 ADME studies A2106, A2214 and A2223;

(7) All treated subjects' population containing pooled data from all completed COPD, asthma and healthy volunteer studies of indacaterol regardless of study design, excluding post-inhalation cough study A2222, paediatric study C2101, and 3 ADME studies A2106, A2214 and A2223.

The COPD safety population consisted of 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 (table 1-19 below). The number of patients exposed to indacaterol 150, 300 and 600 µg od for ≥3 months (363, 756 and 445) and for ≥6 months (243, 628 and 358) is sufficient. No patients from the 150 µg indacaterol treatment group (the proposed dosage for indacaterol treatment) were exposed for 1 year. However, this is superseded by a sufficient number of COPD patients exposed for at least 1 year from the 300 µg treatment group (N= 172 (N=167 for indacaterol 600µg)) for which no unsettled clinically relevant findings from a safety perspective have emerged.

- Adverse events

Due to the evaluation of safety for the different COPD populations AEs were difficult to evaluate. The most frequent AEs were: COPD (includes exacerbations), upper respiratory tract infections, nasopharyngitis, cough, headache, and muscle spasms. AEs occurring with higher incidences in the

COPD 6-months safety population in one or more indacaterol treatment groups compared to the comparator and placebo groups are cough, muscle spasms, upper RTI, viral upper RTI, nasopharyngitis as well as headache and diarrhoea. The latter 2 terms only occurred with a higher incidence in the 150 µg indacaterol treatment group. As can be expected, incidences were lower in the in the COPD 3-months population and higher in the COPD 12-month safety population.

In the COPD 12-months safety population higher incidences for indacaterol were seen for the following (IND 300µg - formoterol - placebo): nasopharyngitis (16.7% - 14.3% - 13.0%), cough (7.3% - 3.9% - 4.4%), lower respiratory tract infection (6.2% - 5.1% - 5.1%), muscle spasms (5.3% - 2.8% - 1.4%), upper respiratory tract infection (4.8% - 4.1%- 2.5%) and dyspnoea (3.9%- 2.8% - 2.8%).

The slightly higher incidences for indacaterol for dyspnoea were not observed for the 3-months- and 6-months populations. As dyspnoea is one of the most prominent symptoms in COPD the slightly higher incidence for dyspnoea in the 12-months safety population (also observed when adjusting for exposure (episodes per patient year): indacaterol 300µg = 0.051, formoterol = 0.036, placebo = 0.035) may be of concern. However, the observed excess rate of dyspnoea vs. placebo was small (an excess of 1.6 episodes of dyspnoea per 100 patient years). The new safety data from the in the 26 weeks DB, placebo controlled extension to study B2335S could not reproduce the finding. No further initiatives were deemed necessary.

As regards muscle spasms this AE has been described as AE for formoterol and other drugs of this class. The incidence of muscle spasms with indacaterol is clearly higher (12-months safety population: indacaterol 300µg: 5.3%; formoterol: 2.8%; placebo: 1.4%). The MAH provided evidence that no difference in compliance was observed between patients experiencing muscle spasms vs. those that did not.

In general, a dose-relationship for AEs for indacaterol could not be observed. The majority of AEs were mild or moderate in severity. Six to 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.

During the evaluation the MAH presented the most frequent AEs adjusted for exposure in the COPD safety population. No new safety signals emerged from this new dataset not either when subgroup analyses (age, COPD severity, use of ICS) were performed.

AEs by onset:

The incidence of adverse events with onset in the first 13 weeks after the first dose was greater for all treatment groups than the incidence for those with onset >13 weeks. In general, the three most frequent adverse events (COPD, upper RTI, nasopharyngitis) occurred with comparable frequencies in the two treatment periods. The same pattern was observed for cough. As regards the incidence of muscle spasms this was higher in the first 13 weeks of treatment compared to the >13 week period for all active treatment groups. In general, comparing the incidence in the 3-month and 6-month populations, muscle spasms in the indacaterol groups appeared to occur in the 4-13 week treatment period. Headache was seen at a higher rate for the indacaterol groups in the first 13 weeks of treatment (2.81%-5.53%) compared to the >13 week period (1.32%-1.99%).

Relationship of AEs to study drug:

More AEs were judged to be study drug related with indacaterol (11.8% -12.3%) compared to formoterol (8.3%), tiotropium (10.4%) and placebo (7.9%) (data from the 6-month population).

Post-inhalation cough (PI-cough)

A patient was said to be a PI-cougher if the number of visits with PI cough was at least 1 or R (whichever is greater), where R was defined as 20% of all the attended (post-baseline) visits, rounded to the nearest integer. In the COPD 6-month safety population, the mean percentages of attended visits at which patients experienced PI cough in the 3 indacaterol groups ranged from 16.6 to 19.7% (table 4-39) and were statistically significantly greater than in the placebo (2.0%), formoterol (0.9%) and tiotropium (0.8%) groups ($p<0.001$ for all comparisons vs. placebo). 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 ($p \leq 0.001$ for both comparisons). The same pattern was observed for the COPD 3-month and 12-month safety population.

The vast majority of inhalation induced cough had an on-set after ≤ 15 sec post-inhalation. Median duration ranged from 5-8 sec. for the proposed doses. The frequency of COPD exacerbations in the group of patients with PI-cough seemed higher than in the population without PI-cough (150µg: 17.3% vs. 12.7%; 300µg: 29.6% vs. 23.5%; 600µg: 26.3% vs. 24.4%). As requested the MAH conducted a number of analyses to investigate a potential relationship of PI cough and COPD exacerbations. A clear relationship could not be confirmed. The frequency of PI-cough was clearly higher in female patients than in males (150µg: 39.2% vs. 22.6%; 300µg: 46.4% vs. 23.1%; 600µg: 36.6% vs. 25.7%) as well as in current smokers vs. ex-smokers (150µg: 33.22% vs. 26.2%; 300µg: 33.7% vs. 26.6%; 600µg: 31.0% vs. 26.9%). Likewise was the duration of PI-cough also longer in current smokers vs. ex-smokers. As regards the analysis of post-inhalational cough by degree of reversibility a relationship seemed to exist. PI-cough was more frequent in patients with a baseline reversibility of >12% (i.e. those patients with a possible asthma component) compared to those ≤ 12%. However, SmPC changes were not deemed necessary. There did not seem to be an association between COPD severity/COPD duration/ICS use and frequency/duration of PI-cough. Neither did PI-cough seem related to FEV1 decrease ≥ 20% from pre- to post-dose, bronchospasm, patient participation/withdrawals or use of ACE-Is/anti-cough medication.

Based on the known risks with other LABAs of cardiovascular events (coronary ischemia, arrhythmias, heart failure, and cerebrovascular events), hypertension, metabolic effects (hyperglycemia, hypokalaemia) and paradoxical bronchospasm, these events have been investigated carefully in the indacaterol safety database. Cardiovascular AEs and SAEs were generally slightly lower in the placebo group compared to the active treatment groups. Ventricular tachycardia was highest in the indacaterol 150 µg group but due to the overall low incidence this is difficult to assess. A clear signal of increased incidence of any cardiovascular AEe s and SAEs in the indacaterol groups compared to the active comparators could not be identified. Neither were signs of a dose-response relationship between the indacaterol dosages for the overall cardiovascular AEs nor for any specific cardiovascular preferred term identified. Data on cardio- and cerebrovascular AEs were presented for the COPD safety population adjusted for exposure as well as for the asthma safety population. No new signal emerged.

No safety signals for diabetes, hypertension or paradoxical bronchospasm related AEs were seen. All these potential risks are adequately covered in section 4.4 of the SPC and are as well covered sufficiently in the RMP.

- Serious adverse event/deaths/other significant events

Three patients in the COPD safety population treated with indacaterol died (one case on each dose; 150 µg [sudden death], 300µg [cardiac arrest – suspected to be study drug related] and 600 µg [COPD exacerbation]). In the formoterol treatment arms 4 patients died; the causes of death were multi-organ failure, respiratory failure, and sudden death. Two patients who received tiotropium died; the causes of death were arteriosclerosis and bronchopneumonia. Eight patients who received placebo died; the causes of death were aortic aneurysm rupture, cardiac arrest myocardial infarction, head injury, death and 3 sudden deaths. In the asthma safety study B2338 there were two deaths (2/268, 0.7%: 1 cardiac arrest and 1 sudden death – the latter suspected to be drug related by the investigator) on indacaterol 300 µg od, while no deaths were reported in the 600 µg o.d. and salmeterol groups.

As regards SAEs there did not seem to be any consistent relationship between treatment with indacaterol and SAEs compared to the other COPD treatments, including placebo. In general, the incidence of SAEs by preferred term and adjusted for exposure was comparable between the 3 months, 6 months and 12 months COPD safety populations and without a dose-relation ship for the 3 indacaterol dosages.

Across the safety populations the most frequent SAEs were: COPD, pneumonia, dyspnoea and AF. Fourteen of the 202 SAEs were suspected to be related to indacaterol treatment. Of these 10 were related to the CV system (TIA, AF or MI), 5 of them had no prior cardiac medical history. However, in the overview of cardio- and cerebrovascular SAEs for the COPD safety population, the overall SAE episodes per patient year for indacaterol 150 µg, 300 µg and 600 µg were higher than placebo but

lower than tiotropium. Apart from cardiac disorders which were more frequent in the first 4 weeks of the studies, the onset of SAEs were more frequent in the period >4 weeks after the first dose of study drug. However, onset of SAEs were similar for ≤13 weeks or >13 weeks as well as ≤26 weeks or >26 weeks after the start of study drug.

- Laboratory findings

The MAH has made an evaluation of laboratory abnormalities to be expected with a long acting beta-agonist, it does not bring anything to light of a quantitative or qualitative nature which might give cause for concern about the safety of IND.

ECG and QTc assessment

The thorough QTc study (Study B2339: single-center, randomised, multiple-dose, placebo-controlled and positive-controlled parallel group study) was negative. Daily doses of indacaterol (150, 300 and 600 µg using the concept1 device for 14 days) resulted in mean maximum time matched differences versus placebo that were lower than 5 ms for delta QTcF vs. baseline. The upper limit of the 90% CIs were below 10 ms for all time matched comparisons. In the phase III, pivotal studies B2334, B2335S and B2346, ECGs were performed 25 min pre-dose, 30 min post-dose and 1 h post-dose at each visit as well as at screening and at the end of the study. The ECGs were evaluated with respect to PR intervals, QRS interval and QTcF values. In addition Holter monitoring (study B2335S) was undertaken at screening and after 2, 12 and 26 weeks of treatment in a subset of patients (N=124-150 across the treatment groups). indacaterol treatment did not seem to be associated with QTc prolongation or any other pathological ECG alterations. The pre-cautions related to treatment of patients with known cardiovascular disease (coronary insufficiency and cardiac arrhythmias) with $beta_2$-agonists have been appropriately reflected in section 4.4 of the SmPC.

- Safety in special populations

For all active treatment groups age ≥ 65 years was associated with an increased incidence of AEs. Age did not seem associated with a different pattern in AEs compared to the overall population. For patients with hepatic impairment the MAH was primarily referring to a PK-study in patients with mild and moderate hepatic impairment. The MAH presented safety data for a very limited number of patients with hepatic impairment/elevated bilirubin at baseline. At present no definite conclusions can be drawn due to the very limited treatment experience in patients with hepatic impairment (who were not classified according to Child-Pugh scale) or elevated bilirubin levels. No pharmacokinetic data (study CQAB149B2307) or treatment experience exists for patients with severe hepatic impairment. These issues should be reflected in section 4.2 of the SmPC.

The safety profile of indacaterol is not characterised for patients with impaired renal function. However, as the kidneys play a very low role in the elimination of the drug, this is acceptable.

- Discontinuation due to adverse events

No consistent pattern in any of the safety populations has emerged in indacaterol induced AEs leading to discontinuation compared to the other treatments. Neither was a dose-relation ship observed for indacaterol treatment.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The primary focus of the Risk Management plan is on the monitoring and prevention of off-label use in asthma by use of additional pharmacovigilance and risk minimization activities, i.e. post-

authorisation studies and a targeted education of prescribers. The main objectives are to monitor and prevent the off-label use in asthma, and to further characterise and quantify known class effects of long-acting β_2-agonists and to detect any other important safety signals.

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Important identified risks		
QTc prolongation and pro-arrhythmic effects	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient. Precaution and Warning (CDS Section 6, SmPC Sect 4.4) Overdose (CDS Sect 10, SmPC Sect 4.9). No additional routine risk minimization actions
Cardiovascular events (coronary ischaemia, arrhythmia, heart failure, cerebrovascular events)	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient: Precaution and Warning (CDS Sect 6, SmPC Sect 4.4) Overdose (CDS Sect 10, SmPC Sect 4.9). No additional routine risk minimization actions
Hyperglycaemia	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient: Precaution and Warning (CDS Sect 6, SmPC Sect 4.4). Overdose (CDS Sect 10, SmPC Sect 4.9). Clinical pharmacology (CDS Sect 11) Pharmacodynamic properties (SmPC Sect. 5.1). No additional routine risk minimization actions
Hypokalaemia	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient: Precaution and Warning (CDS Sect 6, SmPC Sect 4.4). Precaution and Warning (CDS Sect 6) Overdose (CDS Sect 11, SmPC Sect 4.9). Clinical pharmacology (CDS Sect 11). Pharmacodynamic properties (SmPC Sect. 5.1). No additional routine risk minimization actions

Important potential risks		
Hospitalization and death due to asthma related events in asthma population (off-label use)	Routine pharmacovigilance activities USA: i3 Drug Safety post-authorization safety study (to track off-label use and identify reasons/ circumstances) UK. THIN post-authorization safety study (only to track off-label use and identify reasons/ circumstances)	Label incl. Patient Information. Precaution and Warning (CDS Sect 6, SmPC Sect 4.4) Educational measures included as part of all launch activities. Escalations in case activities above are insufficient: 1) Dear Doctor Letter, 2) Update salesforce training & revision educational material 3) Restricted distribution/use
Paradoxical bronchospasm	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient. Precaution and Warning (CDS Sect 6, SmPC Sect 4.4) No additional routine risk minimization actions
Identified and potential interactions		
Inhibitors of CYP3A4	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Interactions (CDS Sect 8) Interactions (SmPC Sect 4.5) No additional routine risk minimization actions
Inhibitors of P-glycoprotein	Routine pharmacovigilance activities	Interaction specified in label. See above interaction with CYP3A4 inhibitors. No additional routine risk minimization actions
Subpopulation with uridine-diphosphate glucuronlytransferase (UGT1A1) deficiency	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Clinical pharmacology (CDS Sect 11), PK properties (SmPC Sect 5.2) No additional routine risk minimization actions
Drugs known to prolong QTc interval	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Interactions (CDS Sect 8, SmPC Sect 4.5). No additional routine risk minimization actions
Sympathomimetic agents	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Interactions (CDS Sect 8, SmPC Sect 4.5). No additional routine risk minimization actions
Drugs associated with	Routine pharmacovigilance activities	Label incl. Patient Information

hypokalaemia		sufficient. Interactions (CDS Sect 8, SmPC Sect 4.5). No additional routine risk minimization actions.
Beta-adrenergic blockers	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Interactions (CDS Sect 8, SmPC Sect 4.5). No additional routine risk minimization actions.
Important missing information (list)		
Safety in non-Caucasian with COPD	Routine pharmacovigilance activities i3 Drug Safety post-authorization safety study THIN post-authorization safety study	Label incl. Patient Information sufficient. Pharmacodynamic properties (SmPC Sect 5.1.) Clinical pharmacology (CDS Sect 11), PK properties (SmPC Sect 5.2). No additional routine risk minimization actions.
Safety in COPD with significant CV co-morbidity	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Precaution and Warning (CDS Sect 6, SmPC Sect 4.4). No additional routine risk minimization actions.
Safety in COPD during long-term use of >1 year	Routine pharmacovigilance activities	Label incl. Patient Information sufficient. Adv Drug Reactions (CDS Sect 7). Undesirable effect (SmPC Sect 4.8). No additional routine risk minimization actions.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are a number of quality issues that will be resolved as Follow-up Measures within an agreed timeframe. None of these issues is expected to have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritancy of the nasal cavity and larynx were seen in rodents. All these findings occurred at exposures sufficiently in excess of

those anticipated in humans. Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F_1 offspring was observed in the peri- and post-developmental rat study at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol was not embryotoxic or teratogenic in rats or rabbits. Genotoxicity studies did not reveal any mutagenic or clastogenic potential. Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other $beta_2$-adrenergic agonists. No evidence of carcinogenicity was seen in mice. Systemic exposures (AUC) in rats and mice at the no-observed adverse effect levels in these studies were at least 7- and 49-fold higher, respectively, than in humans treated with indacaterol once a day at a dose of 300 microgram.

Efficacy

The primary endpoint for all three pivotal studies was 24 hour post dose FEV1 after 12 weeks of treatment (defined as a difference in FEV1 not less than 120 ml). Indacaterol treatment was associated with a statistically significant and clinically relevant improvement in post-dose FEV1 relative to placebo after 12 weeks of treatment supporting the once daily dosing of the drug. The effect on trough FEV1 was evident regardless of degree of reversibility at baseline. Thus, the submitted studies showed that indacaterol is an efficacious bronchodilator in COPD patients with moderate to severe COPD. The key secondary endpoint 'days of poor control' showed inconsistent results with a statistically significant effect in two out of three studies. The choice of this endpoint was questioned as it is a non-validated measure, in contrast to the symptomatic endpoints TDI- and SGRQ scores. The effect on the latter two was also inconsistent in the pivotal studies but the responder analyses showed that a statistically significantly higher proportion of patients treated with all three indacaterol doses achieved the minimal clinically important difference for both TDI- and the SGRQ compared to placebo. The CHMP review discussed that the efficacy with respect to symptomatic endpoints was similar to that of currently marketed bronchodilators for COPD with the conclusion that both recommended doses demonstrated statistically significant improvements in symptom relief versus placebo, as evaluated by TDI and SGRQ and that the magnitude of response was generally greater than seen with active comparators.

The CHMP review discussed that individual study results from two doses of indacaterol did not have a consistently statistically significant effect on the number or rate of exacerbations when compared to placebo. No effect was observed when analysed according to COPD severity, reversibility and smoking status. The possibility of a once daily dosing indacaterol has the potential advantage for the patient as presently, no LABAs for o.d. dosing are marketed, and the approval of indacaterol would therefore offer a new treatment option for COPD patients.

Safety

No major safety issues have been identified, and the safety profile of indacaterol is what would be expected of a long acting β-2 agonist. The CHMP review discussed the most notable adverse event which clearly may influence treatment compliance was the observation of post-inhalation cough (PI-cough) in the indacaterol groups. The conclusion of the CHMP is that cough experienced post inhalation was generally mild and did not lead to any patient discontinuing from the studies at the recommended doses. The percentages of PI coughers were 29.5% for indacaterol 150 μg and 29.7% for 300 μg. PI-cough had an onset after ≤ 15 sec post-inhalation. The incidence did not seem to decline over time. A clear relationship between PI-cough and exacerbations could not be defined. There did not seem to be an association between COPD severity/COPD duration/ICS use and frequency/duration of PI-cough. In addition, PI-cough did not seem to be related to FEV1 decrease ≥ 20% from pre- to post-dose, bronchospasm, patient participation/withdrawals or use of ACE-inhibitors/anti-cough medication. A relationship was found between PI-cough and degree of reversibility. PI-cough was more frequent in those patients with a baseline reversibility of >12% compared to those ≤ 12%. An analysis of indacaterol potential to cause cardiac rhythm disturbance based on Holter monitoring was performed in a subset of patients in Study B2335S (about 150 per treatment arm). Review of the analysis and the raw data does not indicate a potential to cause arrhythmias beyond that seen in the placebo group. The between group and within group over time patterns were probably abnormal with

respect to equivalent healthy subjects but did not change in any recognisable pattern. Despite the potential of indacaterol to cause tachycardia at high dose (~ 1,000 µg) in healthy volunteers there was a fall compared to baseline in mean maximum heart rate in all treatment groups in Study B2335S suggesting a non-specific beneficial effect from inclusion in the clinical study. Several potential risks were defined based on the known risks with other LABAs (cardiovascular events, metabolic effects, hypertension and paradoxical bronchospasm). Cerebro- and cardiovascular AEs and SAEs were generally slightly lower in the placebo group compared to the active treatment groups. A clear signal of increased incidence of any cardiovascular AEs and SAEs in the indacaterol groups compared to the active comparators was not identified. No safety signals for diabetes, hypokalemia, hypertension or bronchospasm related AEs were seen. Indacaterol treatment did not seem to be associated with a higher risk of death or SAEs compared to other COPD treatments (formoterol or tiotropium). For the SAEs no dose-relationship or time-dependency was identified.
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these issues.

- User consultation

In order to comply with the requirements of articles 59(3) and 61(1) of Directive 2001/83/EC a consultation with target patient groups was carried out on the indacaterol package leaflet (PL). The testing was carried out by Luto Research Ltd (UK). Twenty eligible participants were recruited in the Leeds area of the United Kingdom and were interviewed during June 2009. The questionnaire was composed of fifteen items considered to be the most important points of information relating to safety, compliance, and general issues for the use of the product. For each of the fifteen questions, at least 95% individuals were able to both locate the relevant information and demonstrate good understanding of the information. At least 95% of the participants were able to both locate and understand the relevant information for each of the fifteen questions over the two stages of the test, which meets the current European Commission benchmark (i.e. 90% of participants should be able to find the information in the leaflet and of those 90% should be able to understand it). In addition, for the majority of the questions the success rate was of 100%. Two patients in the assessed group were aged less than thirty and two were in their 30s. COPD is uncommon under the age of 40 and an older population would have been preferable. In general the patient information was considered clear and relevant.

Risk-benefit assessment

In the submitted studies treatment with indacaterol was associated with a statistically significant and clinically relevant improvement in post-dose FEV1 relative to placebo after 12 weeks of treatment.
The overall efficacy with respect to symptomatic endpoints was inconsistent between studies and doses and on the whole rather modest, albeit it seemed comparable to previously authorised inhalational bronchodilators. However, a higher proportion of the indacaterol treated patients vs. placebo obtained clinically and statistically significantly relevant improvements in TDI- and SGRQ-scores. Thus, it is considered that indacaterol may have beneficial effect in some COPD patients also from the subjective symptomatic point of view. The response whether the once daily dosing schedule of indacaterol represents a true patient benefit will have to wait until the product will be used in clinical practice. Judged by the basic pharmacology of interaction at the β-receptor, ex-vivo inhibition of induced bronchial smooth muscle contraction, and duration of action, indacaterol looks quite similar to other long acting beta agonists. How these modest differences will fulfil the clinical need of "ultra long acting" LABA is difficult to say. It is worth noting that indacaterol has not been compared to other members of the class on alike for like basis i.e. both used once a day or both used twice a day. Major safety issues have not been identified. The cough experienced post inhalation was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses. However, from a treatment compliance perspective and possible also patients' quality of life the 6.8% frequency of PI-cough may be an issue hampering the clinical utility of this product

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- The following additional risk minimisation activities were required: see as detailed in section 2.5

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Hirobriz Breezhaler in the maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD) was favourable and therefore recommended the granting of the marketing authorisation.