CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Striverdi Respimat 2.5 micrograms, solution for inhalation Boehringer Ingelheim International GmbH, Germany

olodaterol

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2498/001/DC
Registration number in the Netherlands: RVG 112058

6 February 2014

Pharmacotherapeutic group:	drugs for obstructive airway diseases; selective beta2-adrenoreceptor agonists
ATC code:	R03AC19
Route of administration:	inhalation
Therapeutic indication:	maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).
Prescription status:	prescription only
Date of authorisation in NL:	23 October 2013
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

A list of abbreviations is given on pages 30-31.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Striverdi Respimat 2.5 micrograms, solution for inhalation from Boehringer Ingelheim International GmbH. The date of authorisation was on 23 October 2013 in the Netherlands.

The product is indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).

A comprehensive description of the indications and posology is given in the SmPC.

Olodaterol has a high affinity and high selectivity to the human beta2-adrenoceptor.
In vitro studies have shown that olodaterol has 241-fold greater agonist activity at beta2-adrenoceptors compared to beta1-adrenoceptors and 2299-fold greater agonist activity compared to beta3-adrenoceptors.
The compound exerts its pharmacological effects by binding and activation of beta2-adrenoceptors after topical administration by inhalation.
Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.
Olodaterol has the pre-clinical profile of a long-acting selective β_2-adrenoceptor agonist (LABA) with a fast onset of action and a duration of action of at least 24 hours.

This decentralised procedure concerns a full application, *i.e.* a dossier with administrative, quality, preclinical and clinical data. Olodaterol is considered a new active substance. The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

The MAH provided sufficient data on pre-clinical studies. The results are summarised in section II.2 of this report (Non-clinical aspects).
The clinical program for olodaterol comprised 12 Phase 1 trials (9 in healthy volunteers, 1 in patients with COPD, 1 in patients with renal impairment and 1 in patients with hepatic impairment), 3 Phase 2 trials in COPD, 4 Phase 2 trials in asthma and 10 Phase 3 trials in COPD.
Overall, 4936 patients with COPD (1095 patients in Phase 1/Phase 2; 3841 patients in Phase 3), 731 patients with asthma (all in Phase 2) and 276 healthy volunteers were included in the olodaterol clinical program (*i.e.* received at least one dose of trial medication). The assessment of the clinical study results is discussed in section II.3 of this report (Clinical aspects).

Paediatric development
A class waiver has been granted for products intended to treat chronic obstructive pulmonary disease (COPD). Accordingly a 'Request for confirmation of the applicability of the agency's decisions on class waivers' has been submitted for olodaterol to the EMA in June 2010. A confirmation of the applicability of the class waiver has been issued by the EMA (EMA/533200/2010) by letter dated 6 August 2010 for olodaterol proposed for maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Scientific Advice
National scientific advice was given twice by the Medicines Evaluation Board of the Netherlands on 16 October 2008 (meeting on clinical aspects) and 28 October 2009 (written advice on a non-clinical question).

CHMP guidelines
For the development program the following guideline was taken into account: Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) (CPMP/EWP/562/98).

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance, the R-enantiomer of olodaterol hydrochloride anhydrate, is a new active substance, not described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to off-white crystalline non-hygroscopic powder that is sparingly to slightly soluble (> 20 – 1.1 mg/ml) over the entire pH range, soluble in ethanol and freely soluble in methanol. The drug substance is the anhydrous form. Polymorphs have not been observed. The molecule contains one chiral centre; the active substance is the R-enantiomer. The S-enantiomer is controlled as an impurity.

Manufacturing process
Full information on the four-step synthesis of olodaterol hydrochloride has been included in the dossier. Acceptable specifications have been adopted for the starting materials, intermediates and solvents. The drug substance and related impurities have been adequately characterised. A degradation pathway of the drug substance has also been included. The control is suitably established and supported by results of the manufacture of seven batches according to the procedure that is proposed for commercial production.

Quality control of drug substance
The drug substance specification includes tests for appearance, identification, colour and clarity of solution, related substances including the S-enantiomer, solvents, metal catalyst residues, sulphated ash, heavy metals, water content and assay, and is acceptable in view of the route of synthesis, observed impurity profiles, and the various ICH guidelines. Results of batch analysis have been provided for all relevant batches used in clinical, toxicological and stability studies.

Stability of drug substance
Stability data has been obtained during storage at 25ºC/60% RH, 30ºC/75% RH and 40ºC/75% RH. The drug substance was packaged in the commercial package.
The solid drug substance is stable and no trends are observed. The substance is sensitive to light when dissolved in water. No racemisation was observed under any of the stress conditions (in solid state and also in aqueous solution). Based on these results, a re-test period of 48 months with no special storage conditions has been approved.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Striverdi Respimat consists of a specifically designed cartridge containing the aqueous solution of olodaterol CL as drug product and a Respimat inhaler as medical device. The solution in the cartridge is metered and nebulised by the inhaler to give a fine aerosol cloud for inhalation. The Respimat inhaler is a pocket-sized, propellant-free device for the nebulisation of solutions for inhalation that is established with the products Spiriva Respimat and Berodual Respimat on European and worldwide markets. The delivered dose is 2.5 micrograms olodaterol (as hydrochloride) per puff. The delivered dose is the dose which is available for the patient after passing the mouthpiece. Two puffs from the Respimat inhaler comprise one medicinal dose.

The primary packaging of the drug product is a 4.5 ml polyethylene/polypropylene cartridge, closed with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder. The cartridge with the inhalation solution and the Respimat inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the inhaler. The labeled number of actuations per cartridge is 60 actuations (30 doses). Each cartridge (4.5 ml) contains 1.12 mg olodaterol hydrochloride or 1.02 mg olodaterol.

The excipients are: benzalkonium chloride, disodium edetate, purified water, citric acid (anhydrous).

Pharmaceutical development

The development of the formulation is based on the Spiriva formulation (tiotropium bromide, NL/H/0718/001/DC), which is very similar and uses the same EC approved inhalation device Respimat. The development of the product has been satisfactory performed and explained. The excipients used are common in the manufacture of a solution for inhalation. The packaging materials are usual and suitable for the product at issue. The minimum fill volume of 4.0 ml allows the extraction of 30 doses. The overfilling is required to guarantee a high dosing accuracy for the patient.
Several dosage strengths of olodaterol Respimat solution for inhalation and one placebo formulation have been used in clinical studies. These formulations are identical to one another except in regards to their drug substance concentration. Similarly, the placebo formulation is identical to the proposed formulation except that it contains no drug substance.
The pharmaceutical development has been described in sufficient detail.

Manufacturing process

The drug product is prepared by dissolving the various components in purified water or water for injection. The solution is filtered through a bacteria-retentive filter and filled into polyethylene/polypropylene containers. The containers are packaged into aluminium cartridges. The process has been adequately validated.

Container closure system

In view of the Guideline on Plastic immediate packaging materials, the presented information on the plastic packaging materials is sufficient for a Ph.Eur. described material. The silicone of the sealing ring complies with Ph. Eur. 3.1.9.

Microbiological attributes

The microbiological attributes of Striverdi Respimat solution for inhalation are in compliance with the harmonized requirements for preparations for inhalation use (e.g. Ph. Eur. 5.1.4). As shown by the results of the primary stability studies, the microbiological quality of the drug product is ensured after storage under long term stability conditions. Preservation effectiveness studies performed during these stability studies showed that the formulation is sufficiently preserved to prevent microbial growth over the shelf life. This was further confirmed by the results of in-use stability studies which showed that the microbiological quality of the inhalation solution is guaranteed after insertion of the cartridge into the Respimat inhaler over the labelled number of actuations.

Control of excipients

All excipients meet the requirements of the monographs in the Ph. Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, colour and clarity of the solution, pH, volume, identification, degradation products, contents, microbiological purity, uniformity of delivered dose, fine particle dose and number of doses. Specifications have been set based on the results of the phase III clinical batch and three primary stability batches. Batch analysis data have been provided of five production-scale batches. Compliance with the release requirements is demonstrated.

Stability of drug product

Stability data has been obtained at 25ºC/60% RH and 40ºC/75% RH on the solution for inhalation in the cartridge as well as the combination of device and cartridge. The only trend observed is a slight increase in the known degradation product in all tests and a very slight increase in assay during in-use as a result of slight evaporation of water from the drug product. All results amply comply. On the basis of the submitted data, a shelf-life of 36 months can be granted. The product should not be frozen.
Based on the results of in-use stability studies, an in-use storage period of three months was granted. Photostability studies were not conducted as the drug substance is known to be sensitive to light when dissolved in water and the drug product is fully protected from light by the aluminium cylinder used as secondary packaging to encase the cartridge containing the inhalation solution.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

Good Laboratory Practice
The MEB has been assured that the pivotal toxicology and safety pharmacology studies were performed in compliance with GLP.

Pharmacology
The selectivity and potency of olodaterol and several metabolites was tested in a series of *in vitro* assays. The efficacy was investigated in models of acetylcholine (ACh)-induced bronchoconstriction in guinea pigs and dogs. Studies on secondary and safety pharmacology were performed to investigate potential neurological, gastrointestinal, renal, pulmonary and cardiovascular effects of olodaterol. Furthermore, drug-drug interaction studies of olodaterol with tiotropium or of olodaterol with a corticosteroid have been performed.

- Primary pharmacodynamics studies

The *in vitro* pharmacological data show that olodaterol is a ß-adrenoceptor agonist with an affinity and functional activity comparable to formoterol and a nearly full agonistic response at the hß$_2$-AR (EC_{50} = 0.1 nM; intrinsic activity (IA) = 88% compared to isoprenaline) and a significant selectivity profile (241-fold and 2299-fold towards the hß$_1$- and hß$_3$-ARs, respectively).
It appears that phase II metabolites of olodaterol do not show significant pharmacological activity at the human ß$_1$-adrenoceptor or the human ß$_2$-adrenoceptor. The phase I metabolite SOM 1522 showed a pharmacological profile similar to the parent compound olodaterol. However, plasma levels of this metabolite in healthy volunteers or COPD patients were very low or undetectable. Moreover, in an *in vitro* study with human lung microsomes no formation of metabolites could be detected, suggesting that in the target organ no relevant oxidative metabolism of olodaterol occurs. Furthermore, subsequent glucuronidation and sulfation of SOM 1522 diminishes the pharmacological activity to a large extent. Thus it may be concluded that olodaterol metabolites do not contribute significantly to the pharmacological activity of olodaterol.

Olodaterol exerts bronchoprotection with a dose-dependent onset of action against acetylcholine-induced bronchospasm in anaesthetized guinea pigs. When olodaterol is administered at the fully effective dose (3 µg/kg inhaled), the onset of action is 10 minutes. Onset of action of olodaterol is comparable to that of formoterol and faster than onset of action of salmeterol.
After intratracheal instillation of 3 µg/kg (olodaterol hydrochloride), olodaterol exerts its bronchoprotective effect against acetylcholine-induced bronchospasm in anaesthetized guinea pigs for 24 h duration. Its duration of action is longer than the duration of action elicited by formoterol.
The studies in dogs show that in this species olodaterol also shows a protective effect against acetylcholine-induced bronchoconstriction. As in the guinea pig, the effect is of a longer duration than the one produced by formoterol. In contrast to the effect in guinea pigs, the maximal protective effect in dogs is only 64%, which diminishes to 19% after 24 hours, which demonstrates that the potency and duration of the bronchoprotective effect of olodaterol depend on the model used.

In the acetylcholine-induced bronchoconstriction model in anaesthetised dogs a bell-shaped dose response curve was observed for olodaterol as well as for the reference compounds formoterol and carmoterol, which is unexpected and hasn't been described for ß2-adrenoceptor agonists before. The discussion in the study report offers a partial explanation for the observed phenomenon. In the study report it is hypothesized that vasodilation of lung vessels may increase local clearance. Yet a flattening of the curve might be expected in that case, and not a lower effect at higher doses. Also receptor kinetics are not taken into account in this hypothesis. Although the explanation given is hypothetical, it appears that the clinical relevance of the finding is remote. The same dose-response was seen for two other ß2-adrenoceptor agonists that were used in the same study (formoterol and carmoterol), suggesting that the effect is model-specific rather than substance-specific. Furthermore, reverse effects at higher doses are not known for formoterol in humans.

- Secondary pharmacodynamics studies

When tested on a panel of cell lines harbouring specific receptors (75 different targets tested) olodaterol's receptor selectivity was further confirmed. At 1 µM (1428-fold of K_i for β_2), olodaterol inhibited specific binding at the following receptors (percentage inhibition is given between brackets): α_1-adrenoreceptor (87%); $ß_1$-adrenoreceptor (96%); $ß_2$-adrenoreceptor (97%); serotonin receptor 5-HT_{2A} (59%).
The effects of olodaterol at the α_1-adrenoreceptor and $5HT_{2A}$ receptors were further investigated in an *in vitro* model (isometric tension recordings in rabbit thoracic aorta rings). Olodaterol did not show any agonistic activity at either α_1-adrenoreceptor or $5HT_{2A}$ receptors at a concentration of 3 µM. To monitor its ability to function as an antagonist, olodaterol was tested at different concentrations for its ability to block phenylephrine-(for the α_1-adrenoreceptor) or 5-HT-(for the 5-HT_{2A}) induced contraction. At 1 µM olodaterol showed 48% and 85% inhibition at α_1-adrenoreceptor and 5-HT_{2A} receptors, respectively. Taken together, these results indicate that olodaterol exerts no agonistic and only weak antagonistic effect at α_1-adrenoreceptor or $5HT_{2A}$ receptors.

- Safety pharmacology programme

Olodaterol produced no behavioral changes or effects on physiological parameters in rats treated with single inhalatory dose levels up to 483 µg/kg. In mice, only at the highest dosage tested, 0.01 mg/kg subcutaneously, olodaterol showed a transient reduction of motility and slightly impaired motor coordination.
Cardiovascular safety was investigated in rats and dogs. The effects were compared with those of formoterol. In rats, inhalatory administration caused a decrease of blood pressure and tachycardia. In dogs various routes of administration were used. Hemodynamic effects observed consisted of a decrease of systolic and diastolic blood pressure and an increase of heart rate. These ß-adrenergic effects occurred after administration of a dose equivalent to two- to several-fold a dose shown to be effective in a bronchoconstriction model when using the inhalatory, intratracheal or intraduodenal route. The effects were long-lasting, usually until the end of the observation period (in most experiments 3 hours), but when 24 hour measurements were made, only the highest dose caused effects for that period. The more persistent effects on HR, LV dP/dt and CO in dogs after intraduodenal administration even after a return of the blood pressure to almost control level may suggest ß-adrenergic cardiac stimulation in addition to an initial baroreflex mechanism.

In vitro, olodaterol had no relevant effect on hERG-mediated K^+ current in HEK293 cells in concentrations up to 30 µM. The only olodaterol-mediated effect on ECG observed was in the oral study where dose-dependent shortening of the PR- and QT-intervals coincided with increases in HR. Shortening of QTcR (QT corrected for HR) was observed between 0.5 and 6 h following 16 and 50 µg/kg olodaterol only, with approximate group mean shortening of 10% 3 h post-dose. Supratherapeutic doses in the inhalatory, intracheal and intraduodenal studies in dogs did not show an effect on ECG. In contrast, in clinical studies, an increase in QTcF was observed at dose levels of 15 µg olodaterol (3-fold recommended therapeutic dose) in female subjects and from 30 µg olodaterol in male subjects. Thus, humans appear to be more susceptible to ECG effects than would be predicted from the dog studies and the effect on QTc is in the opposite direction.

Formoterol showed similar hemodynamic effects in both species, but was more potent, showing effects at a dose equivalent to one shown to be fully effective in a bronchoconstriction model, with a greater

amplitude of the effects and the effects lasting longer. Administration of formoterol also induced a significant prolongation of the corrected QT-interval (SARMA correction formula) at the highest dose (2.08 µg/kg) given inhalatory to conscious Labrador dogs.
Mild increases in respiratory rate (up to 42%) were seen in rats exposed to olodaterol hydrochloride nebulized (up to 3 mg/mL) but no respiratory effects were observed when animals were exposed up to 483 µg/kg by the snout-only inhalatory route.
Other functional changes were an antidiuretic effect seen as a transient reduced urine volume as well as reduced electrolyte excretion and dose-dependently reduced gastric secretion and increased gastric pH, whereas formoterol showed similar effects on gastric secretion but not on pH-value. Gastric emptying was decreased by olodaterol dose-dependently up to 27%. Effects of formoterol given at equipotent bronchodilatory concentrations similarly decreased gastric emptying up to 30%. Olodaterol dose-dependently decreased gastrointestinal transit up to 35% and formoterol up to 46%.

- Pharmacodynamic drug interactions

Pharmacodynamic drug-drug interaction studies of olodaterol with tiotropium or of olodaterol with Ciclesonide, a corticosteroid, have been performed. In both guinea pigs and dogs, the bronchoprotective effect increased more than additive when olodaterol was combined with tiotropium or clicesonide or both compounds. Combination of the compounds had no effect on the (mild) olodaterol-induced increase of heart rate, or on plasma potassium, lactate or glucose levels.

Pharmacokinetics

- Absorption

In vitro studies showed that olodaterol was a weak P-gp substrate. However, inhibition of P-gp in rats significantly increases oral absorption and oral bioavailability of olodaterol. Bioavailability was moderate to high in mice (~55%), rather low in rats (15-29%) and low in dogs (5-11%) after inhalation, the clinical route of administration. Absorption after single inhalation of olodaterol was rapid, in most cases t_{max} was reached at the first sampling point, directly after the end of inhalation. Exposure to olodaterol increased dose proportional in mice, rats and dogs following inhalation. Half-lives following inhalation were between 3 and 10 hours in mice, rats and dogs. The apparent volume of distribution of olodaterol at steady state is high in rats and dogs after inhalation (57-324 L/kg), which suggests extensive tissue distribution. The oral, intratracheal and intravenous pharmacokinetics of drug-related radioactivity are characterized by a high AUC and longer plasma half-life, indicating circulating metabolite(s) with longer elimination rates than olodaterol. In rats and dogs following administration by inhalation, clearance was 173 – 484 mL/min/kg. Following repeated doses, the exposure increased proportionally with dose in most studies. Some toxicity studies in dogs showed a tendency of a slightly lower exposure of males. No consistent accumulative effect was observed after repeated dosing; in most studies no change after repeated dose was observed.

Although the plasma protein binding was moderate for all species, some small differences were observed with rats showing the lowest binding (47-56%) followed by dogs (56-65%), rabbits (59-60%) and humans (56-69%), and the highest protein binding was seen in mice (65-78%). Within blood, olodaterol was distributed preferably into blood cells. Highest tissue concentrations (after intratracheal and intravenous administration) were measured in kidney, pituitary, salivary gland, pancreas and adrenal gland. Olodaterol-related radioactivity also distributed into the brain, to a minimal extent. After 72 hours, drug-related radioactivity was still observed in plexus choroideus, pancreas, adrenal gland, accessory genital glands, pituitary and Harder's gland, suggesting accumulation in these organs. Olodaterol-related material crosses the placenta barrier in rats.

Non-extractable radioactivity was observed in plasma and is an indication for the formation of reactive metabolite intermediates in the metabolism of olodaterol. Olodaterol is metabolized by Phase I and Phase II enzymes. Olodaterol and CD 992 (glucuronide metabolite of olodaterol) are the major compounds present in plasma. Two glucuronides of SOM 1522 (CD 11249 and CD 10915) were identified in rabbit and human plasma, but in the plasma of mouse, rat, and dog only CD 11249 was observed. CD 12656 (a sulfate conjugate of SOM 1522) was only found in humans and accounted for ~5% of the sample radioactivity after intravenous and oral dosing. SOM 1522 was present to a minor extent in plasma of mouse, dog and human. Interspecies differences in metabolism were observed between the non-clinical species and humans. The major human conjugates are Phase II enzymes of olodaterol or of SOM 1522.

They were adequately investigated in the non-clinical species. After inhalation of olodaterol the contribution of the lung to the oxidative demethylation of olodaterol to SOM 1522 and the subsequent formation of SOM 1522-phase II conjugates is negligible.

- Excretion

The predominant route of elimination of drug-related radioactivity was via bile and feces in all animals studied independent of the route of administration. One exception was observed in rabbits following intravenous administration, where more radioactivity was excreted via urine. Most of the radioactivity was recovered in excreta within 3 days in rats and dogs, but a residual amount was excreted very slowly. Drug-related radioactivity was excreted into milk in rats. Interspecies differences in metabolite pattern in the excreta were observed between the non-clinical species and humans. In all species the major component in feces is the parent compound. CD 12656 was the only metabolite present solely in human excreta.

- Drug interaction

At clinically relevant concentrations, olodaterol was neither an inhibitor of drug transporters and CYPs nor an inducer of CYP. Clinical interactions between olodaterol and tiotropium or Ciclesonide are not expected. About 70% increased steady state $C_{max,ss}$ and $AUC_{0-1,ss}$ were observed in a clinical study where olodaterol was combined with ketoconazole (CYP3A4 and P-glycoprotein inhibitor). OAT1 and OAT3 are involved in renal excretion. Since only 15% of olodaterol is excreted via renal transporters, inhibition of these transporters would lead to only a limited increase of olodaterol exposure. A significant increase of olodaterol exposure is not expected due to inhibition of UGTs. As direct sulfation of olodaterol does not occur, inhibition of this pathway is not expected to affect the exposure of olodaterol. The potential of olodaterol to influence the pharmacokinetic profile of co-administered drugs that are substrates of OAT1, OAT3, OCT1, SULT1, or UGT enzymes is expected to be negligible, because of the low plasma concentrations of olodaterol following therapeutic doses.

Toxicology

- Single dose toxicity

Single-dose toxicity studies were performed in mice and rats with inhalational, oral and intravenous administration. Olodaterol was lethal following intravenous administration to mice and rats at 40 and 80 mg/kg respectively and following oral administration to mice and rats at 2000 and 1000 mg/kg respectively. These doses are extremely high compared to the intended human dose of 5 µg daily. Following administration by inhalation, olodaterol was not lethal up to 51.7 mg/kg in mice and 26.6 mg/kg in rats. Reduced motor activity and increased breathing rate were observed in both species. In the inhalation study in mice, also ataxia and tremor were observed.

- Repeat-dose toxicity

Repeat-dose toxicity studies were performed in mice (13 weeks), rats (up to 26 weeks) and beagle dogs (up to 52 weeks); most of these studies were inhalation studies in which animals were exposed to olodaterol through aerosols. Rodents were exposed using snout-only flow past systems and dogs were exposed using a face mask with a mouth tube. Beta-adrenergic effects were observed, such as increased heart rate and decreased blood pressure in dogs and an anabolic effect in mice, rats and dogs. In dogs, at high doses, irreversible focal fibrosis was observed in the myocardium, in the papillary muscle of the left ventricle. An increase in cardiac troponin I which was observed early time points in the study indicated that damage to the myocardium likely occurred in the first part of the studies. This cardiotoxicity is considered due to an exaggerated pharmacological response leading to increased myocardial oxygen demand and poor blood circulation. The safety margin for this effect was at least 8. If olodaterol is used by inhalation as indicated, the systemic exposure will be so low that this cardiotoxicity is not expected to be clinically relevant. Squamous metaplasia and degeneration of the U-shaped cartilage in the larynx were observed at high doses in inhalation studies in rodents. These are considered to be irritation effects due to inhalation of olodaterol at high doses during a fairly long exposure period each day. Squamous metaplasia was minimal or mild and no mention was made of dysplasia or atypia, nor was there an increased number of tumours in the respiratory tract in the carcinogenicity studies. It is considered not clinically relevant because these effects occurred at high exposures and rodents were exposed for at least half an hour

each day, whereas patients will take two short puffs only. Moreover, rodents are more sensitive to the laryngeal effects of inhaled substances than humans. Exophthalmos and corneal epithelial atrophy and focal opacities were observed in the 26-week rat study only. No eye effects were observed in other rat studies nor in any other species. In this study it was likely a consequence of a severe anabolic effect in rats causing difficulties in closing the eyelids in combination with constant pressure against the inhalation tube. It is not expected to be clinically relevant. Prostate atrophy was observed in the 52-week dog study only. The safety margin for this effect was at least 8. This effect is therefore not expected to be clinically relevant. Effects on the female reproductive organs (myometrial hypertrophy and cystic glands in the uterus and the presence of numerous corpora lutea in the ovary) were observed only in mice and only at extremely high dose (safety margin 465 based on AUC). It is therefore not expected to be clinically relevant. In one dog study, the 2-week oral study, a slightly prolonged QT-interval was observed. In all other dog studies, no relevant effect on QT was observed up to high exposures. Also in the safety pharmacology studies, no evidence of QT-prolongation was observed. In patients however, QT prolongation was observed (see 'clinical aspects' below). Humans seem to be more sensitive to ECG effects caused by olodaterol than dogs.

- Genotoxicity

Olodaterol was not genotoxic in the Ames test, a mouse lymphoma assay and two *in vivo* rat micronucleus tests. In a third micronucleus test in rats in which olodaterol was administered intravenously at very high doses, a slight increase in micronucleated erythrocytes was observed. This can be explained by an increased erythropoiesis which was shown to occur at extremely high exposures due to extreme pharmacological effects. Overall, it is concluded that olodaterol is not genotoxic.

- Carcinogenicity

Two-year carcinogenicity studies were performed in rats and mice. Mice and rats were exposed to aerosols for 40 and 35 minutes per day respectively. In these carcinogenicity studies, mesovarian leiomyoma were observed in rats and uterus leiomyoma and leiomyosarcoma in mice. Leiomyoma in mesovarium and uterus of rodents are class effects of β_2-agonists. Up to now, β_2-agonists have not been associated with cancer in humans. These tumours are therefore most likely not clinically relevant. Also in the carcinogenicity studies, ovary cysts were observed in mice and rats. This can be considered a class effect of β_2-agonists, as ovarian cysts in rats were also induced by formoterol and salmeterol. Considering the fact that it is not mentioned as side effect in humans in the SmPCs of formoterol and salmeterol containing products, it is likely that this effect is not considered to be relevant for humans.

- Reproduction toxicity

No effect was observed on reproductive performance or fertility in rats. In the dams, increased food consumption and body weight were observed, which were in accordance with the pharmacological effect. At the highest dose, subdued behaviour was observed and mortality of 2 animals. In an embryofoetal development study in rats, increased post-implantation loss was observed at the highest dose, at very high exposure (safety margin 375 based on AUC). At the mid dose, incomplete ossification of the sternebrae was increased; there were no other skeletal effects. In rabbits, teratogenicity was observed at the highest dose. The exposure at this dose was extremely high (safety margin is 677 based on AUC) and this is therefore not expected to be clinically relevant. In a pre-/postnatal toxicity study in rats, effects on pups were observed only at the highest dose: decreased viability in the first 4 days and a slightly decreased body weight gain in male pups at 3 – 13 weeks of age. This occurred at high exposure (safety margin will be approximately 80 based on exposure data from another rat inhalation study) and is thus not expected to be clinically relevant. In juvenile toxicity studies in beagle dogs, no clinically relevant increased toxicity compared to adult animals was observed. Compared to adult dogs, a much higher dose was needed to induce increased heart rate and the duration of increased heart rate was shorter, which could possibly indicate that olodaterol is less active in juvenile animals than in adult animals. The indicated pharmacological effect (bronchodilation) was however not investigated in juvenile animals. For the current indication, this issue is not relevant. In one juvenile toxicity study in dogs, minimally to mildly increased periportal cellularity was observed at all doses. This finding was characterized by the presence of cells with bile duct epithelial-like morphology arranged in cell clusters or duct-like structures with poorly defined lumen and immature appearance within and adjacent to the periportal areas. Its significance is not clear. The cells were clearly differentiated but the tissue structure was deviant. However, the effect was

minimal to mild and it occurred at high exposures (exposure multiple compared to adult human AUC at least 22). It is agreed that it most likely does not represent a clinically relevant effect. Moreover, for this application children are not the targeted population.

- Local tolerance

Olodaterol was not irritating to rabbit skin and mildly to moderately irritating to rabbit eye. Intramuscular administration to rabbits and paravenous administration to rats were well tolerated. Intravenous and intra-arterial administration of olodaterol to rabbits at the concentration used in clinical trials (0.004 mg/ml) was well tolerated. Intravenous administration of 0.010 mg/ml olodaterol to rabbits caused slight local irritation. Intra-arterial administration of 0.010 mg/ml olodaterol to rabbits caused signs of pain in all rabbits.

- Other toxicity studies

Metabolites were either sufficiently tested in animal studies or present in human plasma only at very low concentrations. Separate studies to investigate the metabolites are not necessary. However, non-extractable radioactivity was observed in plasma, which is an indication for the presence of compounds which are covalently bound to plasma proteins and thus indicative for the formation of reactive metabolite intermediates. However, the percentage non-extractable radioactivity is lower in humans than in animals. Considering the very low clinical dose of olodaterol (5 µg/day), absolute levels of potentially covalently bound compounds will be extremely low. Systemic idiosyncratic reactions are therefore considered very unlikely. Exposure in the lung will be higher but absolutely it will be still very low, considering the low clinical dose. Moreover, it seems that olodaterol is not metabolized in the lung. For this reason, the formation of reactive metabolites in the lung is considered unlikely. Animals were exposed to sufficiently high levels of any reactive intermediates.

Drug substance impurities are specified at ≤ 0.15% and do not need to be toxicologically qualified according to ICH guideline Q3A(R2). The S-enantiomer is specified at ≤ 1.0% and does not need to be toxicologically qualified according to ICH guideline Q3B(R2). Excipients are inhaled in low amounts (benzalkonium chloride 2.21 µg/day, disodium edetate 2.21 µg/day and citric acid 0.66 µg/day). Patients are exposed to these excipients in very low amounts and for a very short duration only (two short puffs daily), and no safety issues are expected from these excipients. Furthermore, benzalkonium chloride and disodium edetate are also used in other products intended for inhalation. Potentially toxic leachables were not found.

0.01 mg/ml olodaterol did not cause significant hemolysis in human blood.

Phototoxicity is not expected because olodaterol absorbs light above 290 nm only to a minor extent and because systemic exposure levels to olodaterol are very low.

Environmental Risk Assessment (ERA)
The MAH submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006). Based on the data provided, olodaterol is not considered Persistent, Bioaccumulative, Toxic (PBT) or very Persistent, very Bioaccumulative (vPvB). A phase II environmental risk assessment is not deemed necessary.

Conclusion on non-clinical aspects
The overall non-clinical development was considered adequate to support the marketing authorisation for olodaterol and the concerns identified by the MEB and the concerned member states during the evaluation are considered resolved.

II.3 Clinical aspects

Clinical studies, compliance with GCP
The clinical program for olodaterol comprised 12 Phase 1 trials (9 in healthy volunteers, 1 in patients with COPD, 1 in patients with renal impairment and 1 in patients with hepatic impairment), three dose finding studies in COPD were submitted (1222.3, 1222.5, and 1222.26) and ten phase III trials in patients with COPD were conducted.

Long-term efficacy and safety were evaluated in two sets of replicate, 48-week clinical trials: the pivotal trial 1222.13 and 1222.14 with designs based on European Union regulatory requirements, including a symptomatic endpoint. Trial 1222.11 and 1222.12 are twin trials based on regulatory requirements of the United States (US) and will be regarded as supportive trials.

Six supportive phase II trials were submitted: two sets of replicate clinical trials to evaluate the bronchodilating profile (FEV1) of once daily olodaterol over a continuous 24 hour dosing interval: 1222.24, 1222.25 with twice daily formoterol 12 µg as an active comparator, 1222.39, 1222.40 with once daily tiotropium HandiHaler® 18 µg as an active comparator, and one set of duplicate trials (1222.37, 1222.38) to evaluate the effect of olodaterol on endurance time during constant work rate cycle ergometry to symptom limitation.

Table 1 Overview of Phase I, II and III olodaterol studies

Study no.	Subjects	Type of study	Dose	No. subjects	
1222.1 Phase I	HV	safety, tolerability, and pharmacokinetics rising single dose	0.5, 1, 2.5, 5, 10, 15, 20, 30, 40, 50, 60 and 70 µg	102 PK: 65	PK plasma, urine, PD safety
1222.2 Phase I	HV	safety, tolerability, and pharmacokinetics 14 day rising multiple dose	2.5, 10, and 30 µg	47 PK: 36	PK plasma, urine, PD safety
1222.7 Phase I	HV	safety, tolerability, and pharmacokinetics single rising dose trial with *i.v.* dosing	0,5 µg, 2.5 µg, 5 µg, 10 µg, 15 µg, 25 µg i.v.	64 PK:48	PK plasma, urine, PD safety
1222.8 Phase I	HV	thorough QT/QTc PD safety study	10, 20, 30, 50 µg	24 PK:24	PK plasma, urine, PD safety
1222.9 Phase I	HV	ADME Mass balance *i.v.* and *oral* single dose	20 µg *i.v.* 40 µg *p.o.*	i.v.: 5 p.o.: 6	Plasma, metabolite profile, excretion
1222.19 Phase I	HV	safety, tolerability, and pharmacokinetics single rising *oral* dosing	15, 30, 40 µg *p.o.*	24 PK:18	PK, Plasma, urine, PD safety
1222.20 phase I	HV	Hepatic impairment single dose PK	20 µg hepatic impaired subjects 30 µg HV	8 mild; 8 moderate hepatic; 16 normal	Plasma, urine protein binding
1222.21 phase I	HV	safety, tolerability, and pharmacokinetics Japanese: 14 day multiple rising dose study	5 µg, 10 µg, 20 µg qd	36 PK: 27	PK plasma, urine, PD safety
1222.35 phase I	HV	Renal impairment single dose	30 µg qd	8 renal, 14 HV	PK plasma, urine, protein binding

1222.47 phase I	HV	PK interaction of olodaterol and ketoconazole at steady-state, cross-over	10 µg qd olodaterol, 400 mg qd ketoconazole	32	PK plasma, urine
1222.48 phase I	HV	PK interaction of olodaterol and fluconazole at steady-state, cross-over	10 µg qd olodaterol, 400 mg qd fluconazole	35	PK plasma, urine
1237.3 phase I	COPD	PK interaction of olodaterol and tiotropium at steady-state, cross-over	10 µg qd olodaterol, 5 µg qd tiotropium, 10/5 FDC qd olodaterol/tiotropium	47	PK plasma, urine
1222.3 Phase II	COPD	Efficacy, dose response single dose, PK	2 µg, 5 µg, 10 µg, 20 µg, 40 qd, placebo	2 µg: 35 5 µg: 35 10 µg: 34 20 µg: 35 40 µg: 14 Placebo: 35	FEV1, PK plasma, urine, PD safety
1222.4 phase II	asthma	Efficacy, dose response single dose, PK	2 µg, 5 µg, 10 µg, 20 µg qd, placebo	2 µg: 28 5 µg: 28 10 µg: 30 20 µg: 29 Placebo: 29	FEV1, PK plasma, urine, PD safety
1222.5 Phase II	COPD	Efficacy, dose response, PK 4 weeks once daily dosing	2 µg, 5 µg, 10 µg, 20 µg qd, placebo	2 µg: 81 5 µg: 80 10 µg: 86 20 µg: 79 Placebo: 79	FEV1, PK plasma, urine, PD safety
1222.6 phase II	asthma	Efficacy, dose response 4 weeks once daily dosing	2 µg, 5 µg, 10 µg, 20 µg qd, placebo	2 µg: 61 5 µg: 60 10 µg: 60 20 µg: 61 Placebo: 54	FEV1, PK plasma, urine, PD safety
1222.22 phase II	COPD	Efficacy Japanese: 4 weeks once daily dosing	2 µg, 5 µg, 10 µg qd	2 µg: 84 5 µg: 79 10 µg: 86	FEV1, PK plasma, urine, PD safety
1222.26 phase II	COPD	Efficacy, 3 weeks once daily vs. twice daily dosing	2 µg bid, 5 µg qd, 5 µg bid, 10 µg qd	2 µg:47 5 µg: 46 5 µg: 47 10 µg: 46	FEV1, PK plasma (sparse), urine
1222.27 phase II	asthma	Efficacy 4 weeks once daily dosing	2 µg, 5 µg, 10 µg, 20 µg qd, 12 µg formoterol bid, placebo	2 µg:121 5 µg: 130 10 µg: 127 20 µg: 124 form: 125 Placebo 125	PK plasma (sparse)
1222.24 Phase III	COPD	Efficacy, 24H broncholidation effect vs formoterol vs placebo	5 µg qd, 10 µg qd, 12 µg formoterol bid, placebo	5 µg : 95 10 µg:92 12 µg 93	FEV1AUC0-12H ;FEV1AUC 12-24H

				Placebo: 96	
1222.25 Phase III	COPD	Efficacy, 24H broncholidation effect vs formoterol vs placebo	5 µg qd, 10 µg qd, 12 µg formoterol bid, placebo	5 µg : 93 10 µg: 95 12 µg: 93 Placebo: 94	FEV1AUC0-12H FEV1AUC 12-24H
1222.39 Phase III	COPD	Efficacy, 24H broncholidation effect vs tiotropium vs placebo	5 µg qd, 10 µg qd, 18 µg tiotropium, placebo	5 µg : 101 10 µg:101 18 µg: 101 Placebo: 102	FEV1 AUC0-12H FEV1 AUC12-24H
1222.40 Phase III	COPD	Efficacy, 24H broncholidation effect vs tiotropium vs placebo	5 µg qd, 10 µg qd, 18 µg tiotropium, placebo	5 µg : 116 10 µg:113 18 µg:113 Placebo: 110	FEV1AUC0-12H FEV1AUC 12-24H
1222.37 Phase III	COPD	Efficacy, endurance time vs. placebo	5 µg qd, 10 µg qd, placebo	5 µg : 147 10 µg: 143 Placebo: 143	Geometric mean endurance time during constant work rate
1222.38 Phase III	COPD	Efficacy, endurance time vs. placebo	5 µg qd, 10 µg qd, placebo	5 µg : 150 10 µg: 147 Placebo: 143	Geometric mean endurance time during constant work rate
1222.11 phase III	COPD	Efficacy/Safety 12 weeks once daily dosing vs. placebo	5 µg qd, 10 µg qd, placebo	5 µg : 208 10 µg: 207 Placebo: 209	Efficacy/Safety FEV1 AUC0-3h, trough FEV1 PK (sparse)
1222.12 phase III		Efficacy/Safety 12 weeks once daily vs. placebo	5 µg qd, 10 µg qd	5 µg : 209 10 µg:217 Placebo :216	Efficacy/Safety FEV1 AUC0-3h, trough FEV1 PK (sparse)
1222.13 phase III	COPD	Efficacy/Safety 48 weeks once daily dosing vs. placebo vs. formoterol	5 µg qd, 10 µg qd, 12 µg formoterol bid, placebo	5 µg : 227 10 µg: 225 form: 227 Placebo:225	Efficacy/Safety FEV1 AUC0-3h, trough FEV1 Transitional Dyspnea Index focal score

					(TDI). PK (sparse)
1222.14 phase III	COPD	Efficacy/Safety 48 weeks once daily dosing vs. placebo vs. formoterol	5 µg qd, 10 µg qd, 12 µg formoterol bid, placebo	5 µg : 232 10µg: 234 form: 233 Placebo: 235	Efficacy/Safety FEV1 AUC0-3h, trough FEV1 and the Transitional Dyspnea Index score (TDI). PK (sparse)

Overall, 4936 patients with COPD (1095 patients in Phase 1/Phase 2; 3841 patients in Phase 3), 731 patients with asthma (all in Phase 2) and 276 healthy volunteers were included in the olodaterol clinical program (*i.e.* received at least one dose of trial medication).

All trials were approved by institutional review boards or independent ethics committees, and regulatory authorities; all trials followed the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

II.3.1 Clinical pharmacology

Pharmacokinetics
Pharmacokinetics of olodaterol has been evaluated following oral, i.v. and inhalation route in healthy subjects and following inhalation in asthma and COPD patients (see Table 1).

- Methods

Plasma and urine samples were analysed for olodaterol and olodaterol-glucuronide by HPLC-MS/MS. All analytical procedures are appropriately validated. LLOQ of olodaterol in plasma is 2 pg/ml. Mean Cmax,ss following inhalation of 5 µg qd is 3.2 - 5.9 pg/ml, only 2-3-fold higher than the LLOQ. Consequently, AUC and elimination half-life cannot be determined accurately in most of the studies. Elimination half-life was determined following inhalation of higher doses at steady-state or following i.v. administration. Urinary excretion was often determined as secondary endpoint. Provided that renal clearance is comparable between groups, renal excretion is a measure for olodaterol systemic exposure at clinical doses.

- Absorption

Following inhalation, peak plasma concentrations of olodaterol were observed within 10 to 20 minutes, indicating rapid initial absorption of olodaterol deposited in the lungs. For olodaterol 5 µg qd, Cmax,ss was ~4.0 pg/ml. Pharmacokinetics of olodaterol were dose proportional over the dose range of 5-70 µg following single dose administration or over the tested dose range 5-20 µg following multiple dosing.

- Bioavailability

Based on the fraction olodaterol excreted in urine during the first 24h after olodaterol administration, an absolute bioavailability 20-25% was estimated for olodaterol inhalation. Oral bioavailability is 1%-2.5% due to moderate absorption (estimated ~30-35%) and extensive first-pass metabolism. Therefore, it is estimated that oral absorption contributes ~10% to the systemic exposure of olodaterol after inhalation of olodaterol.

- Bioequivalence

Since olodaterol is an aqueous solution and the to be market inhaler has been used in the clinical studies, no bioequivalence studies are necessary.

- Distribution

Following i.v. olodaterol infusion, the volume of distribution was high: 1100 L (CV 30%), indicating extensive distribution of olodaterol into tissues.
Tissue distribution in animals demonstrated that olodaterol-related material was poorly distributed to the brain.
In vitro protein binding of olodaterol is moderate ~60% and not different in plasma from subjects with severe renal impairment or mild/moderate hepatic impairment compared to plasma of healty volunteers.

In vitro studies showed that olodaterol is a substrate of the membrane transporters OAT1, OAT3, OCT1 and P-gp. Olodaterol was not a substrate for BCRP, MRP2, OATP2, OATP8, OATP-B, OCT2 and OCT3.

- Elimination

Plasma concentrations declined multi-exponentially with a terminal half-life of 22 h. Total clearance was 872 mL/min, and renal clearance was 173 mL/min indicating active tubular excretion.

Renal clearance following inhalation was comparable to renal clearance following i.v. administration in healthy subjects (163-248 ml/min) and somewhat lower in COPD and asthma patients 92-132 ml/min.

- Excretion

Following 20 µg ^{14}C-olodaterol administration as a 3 h i.v. infusion, 42.5% of the radioactive dose was recovered in the urine (18.9% as olodaterol) and 53% was recovered in faeces (24% unchanged olodaterol), the latter indicating considerable biliary and/or intestinal excretion of olodaterol and its metabolites. Recovery was >90% and excretion was complete 6 days after i.v. administration or oral ingestion.
Olodaterol excretion in urine the first 24 h after inhalation amounted approximately 2.5-4% of the dose after single inhalation and 5-7% at steady state. Urinary excretion of olodaterol was independent of the inhaled dose in the range of 5-70 µg.

- Metabolism

Based on *in vitro* data, cytochrome P450 isozyme CYP2C9 (and to minor extent CYP2C8) is involved in the O-demethylation of olodaterol to SOM 1522, while uridine diphosphate-glucuronosyltransferase isoforms UGT1A1, 1A7, 1A9 and UGT2B7 are involved in the formation of olodaterol glucuronides.

The active metabolite SOM 1522 is the major metabolite excreted in the faeces (28%), but is a minor metabolite in plasma (<10% of olodaterol in plasma). The major plasma metabolite olodaterol glucuronide is not active.

- Enantiomers

The product consists of the R-enantiomer of the two possible stereoisomers. Chiral inversion in humans is negligible.

- Polymorphism

Potential effect of polyphorphism of the 4 UGTs involved in glucuronidation of olodaterol, was analysed by multivariate analyses. There was no pronounced effect of UGT1A1, 1A7, 1A9 or 2B7 gene polymorphisms on the systemic exposure to olodaterol and olodaterol glucuronide. As more UGTs are involved in glucuronidation of olodaterol, lower activity of one UGT may be compensated by another UGT.
As inhibition of CYP2C9 and Pgp affected pharmacokinetics of olodaterol only to a small extent, a clinically relevant increase of olodaterol plasma concentrations due to CYP2C9 and P-gp polymorphisms appears unlikely.

- Dose and time dependency

Pharmacokinetics of olodaterol was dose proportional over the tested dose range of 5-70 µg following single dose administration and 5-20 µg following multiple dose administration. Accumulation ratios observed after repeated doses between 5 and 30 µg olodaterol were in the range of 1.1 to 1.6 for Cmax and 1.3 to 1.8 for AUC values and 1.3-1.9 for urinary excretion. Such an accumulation factor is in line with the estimated terminal elimination half-life 22-38h.

- Intra- and inter-individual variability

In COPD patients, olodaterol pharmacokinetics exhibited a high *intraindividual* coefficient of variation (CV) of ~30% for Cmax,ss and AUC(0-24)ss. Intrasubject variability was lower in healthy volunteers ~15%.

- COPD patients

Pharmacokinetic parameters following single dose and multiple dose administration in COPD patients are summarised in Table 2 for the dose finding study 1222.5. Systemic exposure of olodaterol was usually 30-80% higher in COPD patients than in healthy volunteers. Based on urinary excretion, an accumulation factor for olodaterol exposure of 1.57 is estimated. This is in line with the estimated terminal elimination half-life 32-35h. Pharmacokinetics of olodaterol has been investigated sufficiently in the target population.

Table 2 Single-dose and steady state pharmacokinetic parameters of olodaterol in COPD patients after once daily inhalation of 5 µg olodaterol

Day 1	**N**	**5 µg**	**gCV (%)**	**10 µg**	**gCV (%)**	**20 µg**	**gCV (%)**
C_{max} (pg/ml)	40/71/69	3.58	51	5.45	64	12.2	76
t_{max} (h)	40/71/69	0.167	0.08-1.0	0.183	0.05-1.58	0.20	0.03-1.27
AUC_{0-3} (pg.h/ml)	--/29/58	--	--	13.3	38	20.3	56
fe_{0-3} (%)	66/71/68	0.49	114	0.45	134	0.51	102
Day 29	**N**	**5 µg**	**gCV (%)**	**10 µg**	**gCV (%)**	**20 µg**	**gCV (%)**
$C_{max,ss}$ (pg/ml)	46/72/72	4.02	47	7.13	64	14.4	83
$t_{max,ss}$ (h)	46/72/72	0.19	0.08-1.0	0.20	0.05-1.0	0.20	0.08-1.0
$AUC_{0-6,ss}$ (pg.h/ml)	--/55/69	--	--	29.7	43	46.4	57
$t_{1/2}$ (h)	--/31/52	--	--	34.9	60	31.7	68
fe_{0-3} (%)	66/78/66	0.72	95	0.74	122	0.81	102
R_A, Cmax	28/63/64	1.12	55	1.34	50	1.16	85
R_A, AUC_{0-3}	--/--/54	--	--	--	--	1.37	68

- Special populations

Renal impairment. Univariate analysis of olodaterol Cmax values in the phase III studies at steady state confirm the single dose results of the dedicated renal impairment study that increases of olodaterol plasma concentrations due to renal impairment are modest as can be expected for a compound which is mainly cleared by other pathways. No dose modifications are necessary for patients with renal impairment.

Hepatic impairment. Based on the dedicated single dose inhalation of olodaterol in subjects with mild and moderate hepatic impairment, it can be concluded that a large effect of hepatic impairment on the elimination of olodaterol is unlikely. No patients with hepatic impairment were included in the Phase 3 studies.

Systemic exposure of olodaterol is 30–80% higher in Japanese subjects compared to Caucasian subjects. There were no notable differences in incidence of AEs between Asian and Caucasian subjects in the pivotal studies. No dose modification is necessary.

Multivariate analysis indicated that age, weight, height and lung function (pre-treatment baseline FEV1) were found to be statistically significant covariates for olodaterol plasma concentrations (1222.9956). The effects of the individual covariates however were moderate (15–42% increase of Cmax,ss), and in combination resulted in a no more than 2-fold increase of olodaterol maximum plasma concentrations in exceptionally young, lightweight, and tall COPD patients with low FEV1 (43 years, 42 kg/163 cm or 64 kg/200 cm and 0.46 L FEV1) as compared to average COPD patients (64 years, 78 kg, 170 cm and 1.12 L FEV1). No dose modifications are necessary.

- Interactions

Olodaterol did not inhibit nor induce CYP enzymes or inhibit transporters at clinical concentrations. Therefore, the potential of olodaterol to affect the pharmacokinetics of other co-medicated medicines is considered low.

In vitro investigations identified CYP2C9 as the CYP mostly involved, however, steady state exposure to olodaterol was not relevantly affected by coadministration of 400 mg fluconazole qd in a drug-drug interaction study.

A drug-drug interaction study using ketoconazole (400 mg q.d.) as a potent P-gp inhibitor was conducted. Steady state $C_{max,ss}$ and $AUC_{0-1,ss}$ of olodaterol were ~70% increased in the presence of ketoconazole. In phase II and Phase III studies with or without Pgp inhibitors, there was no increase in frequency of AEs apparent in presence of Pgp inhibitors at the recommended dose of 5 µg olodaterol.

A drug-drug interaction study with tiotropium was performed within BIs development program for the tiotropium+olodaterol fixed dose combination. Pharmacokinetics of olodaterol and tiotropium were not clinically relevant affected by co-administration.

Conclusion on pharmacokinetics
In conclusion, pharmacokinetics of olodaterol have been investigated sufficiently *in vitro* and *in vivo* in healthy volunteers and COPD patients.

Pharmacodynamics

- Mechanism of action

Olodaterol has a high affinity and high selectivity to the human β_2-adrenoceptor. *In vitro* studies have shown that olodaterol has more than 241-fold greater agonist activity at β_2-adrenoceptors compared to β_1-adrenoceptors and 2299-fold greater agonist activity compared to β_3-adrenoceptors.
Olodaterol exerts its pharmacological effects by binding and activation of β_2-adrenoceptors after inhalation. Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP).

- Primary pharmacology

Effects of olodaterol on systemic pharmacodynamic parameters that are known to be sensitive to β_2-agonists cAMP, decrease in serum potassium, increase in plasma glucose were determined in the phase 1/2 dose escalating studies in order to support an appropriate dose selection for Phase 3 (*i.e.* by identifying the threshold for the onset of systemic pharmacodynamic activity).
Most pronounced effects of olodaterol were observed for cAMP and potassium. Statistically significant increases of plasma cAMP concentrations as compared to the placebo group were observed in the dose groups of 10 µg olodaterol and above. The cAMP concentrations in these groups reached their maximum between 1 and 3 hours (median time), and had returned to baseline at 24 hours after the inhalation of olodaterol. It should be noted that the olodaterol Cmax concentration at 10 µg dose in human volunteers following single-dose administration were in the range of Cmax,ss olodaterol concentrations in COPD patients following 5 µg qd inhalation. As there are no known clinical implications of increased plasma cAMP concentrations, measurement of cAMP was not further pursued in Phase 2 and Phase 3 trials.
Statistically significant decreases of serum potassium concentrations as compared to the placebo group were observed in the dose groups 20 µg olodaterol and above in healthy volunteers. Potassium concentrations in these groups reached their minimum between 2 and 3 hours (median time), and had returned to baseline at 24 hours after dosing. Also in COPD patients, a decrease in potassium concentrations was only observed at the highest dose of 20 µg: from a baseline value of 4.40 mmol/L to 4.16 and 4.29 mmol/L at 3 hours post dosing on treatment Days 1 and 8. No effect of 5 µg and 10 µg qd olodaterol on serum potassium concentrations was apparent in COPD patients in the 4 phase 3 studies.

- Secondary pharmacology

A significant increase of glucose compared to placebo could only be observed after treatment with 60 µg and 70 µg olodaterol following single dose administration.
Like other ß$_2$-adrenergic agonists, olodaterol produces a clinically significant cardiovascular effect as measured by increases in pulse rate, blood pressure, changes in electrocardiogram (ECG). In the phase

1/2 dose escalating studies and in a thorough QTc trial 1222.8, treshold for effect of olodaterol inhalation on heart rate increase and QTc prolongation was 20 µg. Similarly, in the 4-week inhalation Study 1222.5 with COPD patients increases in heart rate became apparent only at the highest dose of 20 µg: mean increases from baseline by maximally 6.2 bpm were observed in the 20 µg olodaterol group, while mean increases by maximally 3.6 bpm were observed in the placebo group. The QTc observations are further discussed in the safety sections below. Cardiovascular parameters were monitored in the phase 3 studies.

Patients in the 4 phase 3 studies were characterised for β_2-receptor gene polymorphisms. Patients were divided into subgroups for Group 2 haplotype 2/2, 2/4, 2/6, 4/4 and 4/6 and the common haplotypes 1/1, 1/2, 1/3, 2/2, 2/3, 3/3. AE incidences were comparable across different haplotype groups with no obvious differences across treatments. The effect of these polymorphisms on responses to β_2-agonists in patients with COPD is not known.

Conclusion on clinical pharmacology
The clinical pharmacology of olodaterol is as can be expected for a ß$_2$-adrenoceptor agonist. Statistically significant effects of olodaterol on systemic pharmacodynamic parameters potassium, glucose, heart rate, blood pressure and QTc become apparent at supratherapeutic doses of ≥ 20 µg olodaterol.

II.3.2 Clinical Efficacy

Dose finding studies
Three dose finding randomized (RD), double-blinded (DB). studies in COPD are submitted.

- BI Trial No.: 1222.3: olodaterol was administered to patients with COPD to provide clinical evidence that the bronchodilating effect of olodaterol was maintained up to 24 hours post-dose.
- BI Trial No.: 1222.5 was designed to confirm the 24-hour duration of action of olodaterol after chronic dosing. The inclusion of several doses provided important further information on the effective dose range after chronic dosing.
- BI Trial No.: 1222.26 was designed as an initial exploration of alternative dosing frequencies, by comparing the 24 hour FEV1-time profile of olodaterol when administered once daily or twice daily.

Results
Trial BI: 1222.3
The 36 patients in the safety set were predominantly male (69.4%) and ≥ 50 years of age (88.9%), and white. The majority were ex-smokers (61.1%).

Before bronchodilation, the mean FEV1 (Force expiratory volume in 1 second) of patients was 1.005 L, or 37.44% of predicted normal FEV1, with a mean reversibility of 0.206 L, an improvement of 21.15% over pre-bronchodilator FEV1.

Inhalation of olodaterol resulted in treatment differences from placebo in the primary endpoint, FEV1 at 24 hours, of 0.070 L at 2 µg, 0.099 L at 5 µg, 0.113 L at 10 µg, and 0.119 L at 20 µg.
Differences from placebo were statistically significant (p≤0.0005) at all doses (Table 3).

Table 3: Primary endpoint: adjusted mean FEV1 at 24 hours and treatment differences – Full analyses stet (FAS)

Treatment	FEV_1 [L] Mean (SE)	Difference from Placebo [L]		
		Mean (SE)	P-value	95% CI
Placebo	0.916 (0.014)	—	—	—
BI 1744 CL 2 µg	0.986 (0.014)	0.070 (0.020)	0.0005	(0.031, 0.109)
BI 1744 CL 5 µg	1.015 (0.014)	0.099 (0.020)	<.0001	(0.060, 0.138)
BI 1744 CL 10 µg	1.029 (0.014)	0.113 (0.020)	<.0001	(0.074, 0.152)
BI 1744 CL 20 µg	1.035 (0.014)	0.119 (0.020)	<.0001	(0.080, 0.158)

Trial BI: 1222.5

In general, demographic characteristics across treatment groups were comparable. 244 (60%) of patients were classified as GOLD II (moderate pulmonary impairment), and 157 (39%) patients classified as GOLD III (severe pulmonary impairment).

Trough FEV1 response [L] after four weeks of treatment

Differences in trough FEV1 (primary endpoint) compared with placebo after four weeks of treatment were: 0.061 L for 2 µg olodaterol (p=0.02), 0.097 L for 5 µg olodaterol (p=0.0003), 0.123 L for 10 µg olodaterol (p<0.0001), and 0.132 L for 20 µg olodaterol (p<0.0001) demonstrating a clear dose response (Table 4).

Table 4: Adjusted mean* (SE) FEV1 trough response [L] and comparison to placebo over 4 weeks – analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo		
			Mean (SE)	p-value	95% C.I.
29	R Placebo	-0.014 (0.021)			
	BI 1744 R2	0.046 (0.021)	0.061 (0.027)	0.0233	(0.008, 0.113)
	BI 1744 R5	0.082 (0.021)	0.097 (0.027)	0.0003	(0.044, 0.149)
	BI 1744 R10	0.109 (0.021)	0.123 (0.026)	<.0001	(0.072, 0.175)
	BI 1744 R20	0.118 (0.021)	0.132 (0.027)	<.0001	(0.080, 0.185)

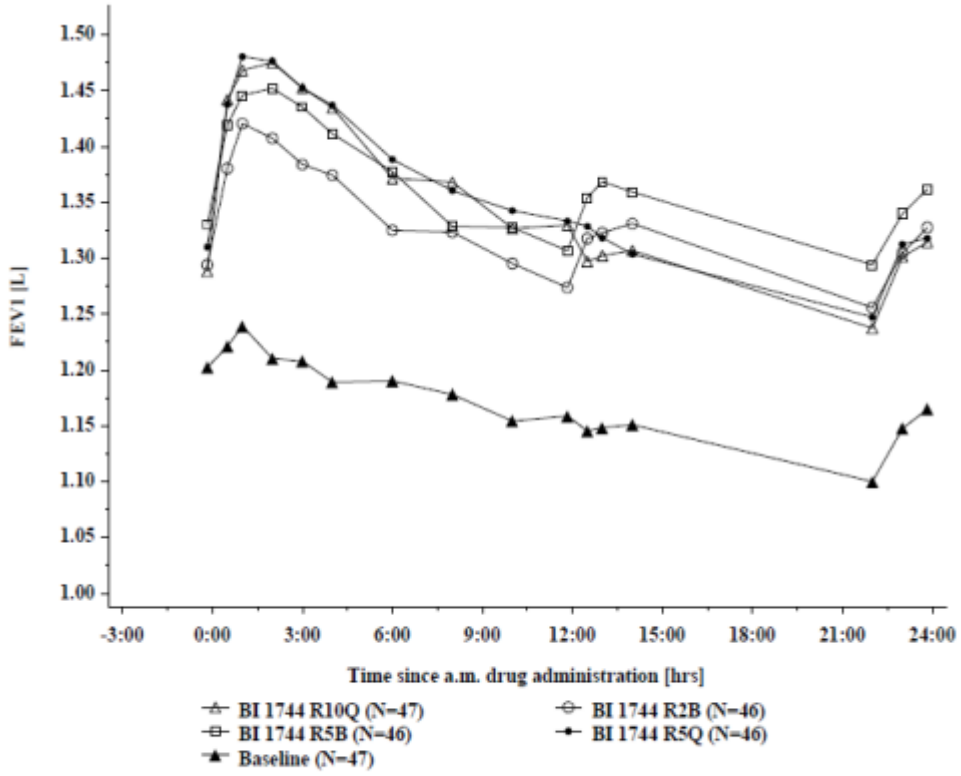
Differences in FEV1 peak 0-3h compared with placebo after four weeks of treatment were: 0.164 L for 2 µg olodaterol, 0.169 L for 5 µg olodaterol, 0.218 L for 10 µg olodaterol, and 0.225 L for 20 µg olodaterol (p<0.0001 for all doses).

A clear dose-response relationship was observed; the 2 µg dose of olodaterol was clearly on the steep part of the dose-response curve, while the similarity in effect of the 10 µg and 20 µg doses suggests that the plateau of the dose-response curve is reached at 10 µg olodaterol.

Trial BI: 1222.26

The course of FEV1 during 24 hours after 3 weeks treatment is displayed in the figure below.

Figure 1: Adjusted mean* FEV1 [L] over time after 3 weeks - analysis with imputation (FAS)



Co-primary endpoints
All olodaterol dose regimens showed a significant increase in FEV1AUC0-12 and FEV1AUC12-24 compared with baseline ($p < 0.001$).

The FEV1-time profiles were almost identical for olodaterol 10 µg qd and olodaterol 5 µg qd with no differences in FEV1 AUC0-12 and FEV1 AUC12-24 response.
Olodaterol 10 µg qd did not show any increased efficacy compared to 5 µg once daily; however, a second dose of 5 µg in the evening provided additional bronchodilation: FEV1 AUC12-24 response for olodaterol 5 µg bid significantly increased compared with olodaterol 10 µg qd: 0.052 (0.015) L, $p = 0.0006$.

In conclusion, in this study, 10 µg once daily did not show any increased efficacy compared to 5 µg once daily.

Main clinical phase III studies
In the two pivotal phase III studies according to the EU requirements (study 1222.13/14), three co-primary endpoints were used: FEV1 AUC0-3h response (change from pre-treatment baseline), trough FEV1 response and the Transitional Dyspnea Index focal score (TDI). The Saint George Respiratory Questionnaire (SGRQ) was used as a key secondary endpoint.
The FEV1AUC0-3 h is the area under the FEV1 time curve, from 0 to 3 h post dosing.
The trough FEV1 is the FEV1 at the end of the dosing interval, measured 24 h after the last drug administration. The trough FEV1 is the preferred measure for determining the efficacy of maintenance treatment in COPD (EMA/CHMP/483572/2012).
The TDI measures the dyspnea in activity of daily living in symptomatic individuals. The TDI is an interviewer administered rating of severity of dyspnea at a single state. The disadvantage of this measurement is that the interpretation of the interviewer may drive the results.
The SGRQ is a self-administered test of 50 items. It is a validated disease-specific instrument designed to measure impact on overall health, daily life and perceived wellbeing in patients with obstructive airways

disease. Compared with the TDI, it does not only measure the dyspnea, and is less vulnerable to bias. The RMS considers that it could also be used as alternative parameter for assessing symptomatic benefit by demonstrating an improvement in quality of life.

Primary analyses Study 1222.13/14
In these studies 1838 patients were included. The mean (SD) age was 63.9 (8.5) years, the mean (SD) post bronchodilator FEV1 at baseline was 1.40 (0.49) L. 53% of patients were classified as COPD GOLD II, 39% patients as COPD GOLD III, and 8% of patients as COPD GOLD IV.

In the clinical trials, in the primary analysis the lung function (FEV1AUC0-3h and trough FEV1) improvements and symptoms derived outcomes were statistically significant for the active treatments compared to placebo. Comparable improvements were observed for olodaterol and formoterol, demonstrating the clinical relevance of the findings.

In support of the efficacy of olodaterol, a higher responder rate in the SGRQ (*i.e.* proportion of patients achieving a clinically significant improvement in SGRQ score) for olodaterol compared to both placebo and formoterol was observed. This substantiates the clinical relevance of the findings.

Additional sub analyses according to tiotropium strata, COPD severity and reversibility were performed to demonstrate efficacy.

Sub analyses
Sub analysis: by tiotropium strata
In previous published clinical studies performed in COPD, the concomitant use of tiotropium was not allowed. About 25% of the included patients used concomitantly tiotropium. A sub analysis according to tiotropium state was performed. The results obtained in the non-tiotropium strata could be most comparable to previous studies in patients with COPD.
In the non-tiotropium stratum the improvement between olodaterol 5 µg and formoterol is comparable, but only for olodaterol accompanied with a significant improvement of symptoms according to the SGRQ measurement.
About 25% of patients of the included patients used concomitantly tiotropium. In the tiotropium stratum the improvement in trough FEV1 was numerically favourable for olodaterol compared to formoterol. The improvement in symptoms as performed with the SGRQ was also numerically in favour of olodaterol.

Sub analysis: COPD severity
Subpopulations of the pivotal studies were defined according to their severity according to the COPD GOLD guidelines. As observed with other β_2-mimetics, the improvements are not consistent among all GOLD classes: the largest improvements were observed in the patients groups with less severe disease.

Sub analysis: Reversibility
The responses were also analysed by reversibility. In the lung function, the best responses were observed in patients with reversible broncho-obstruction.

Exacerbations
Exacerbations were used as secondary outcome measurement to demonstrate a clinical benefit, although the studies were not specifically designed to measure this effect. For example, patients were not selected for having an exacerbation in the previous years.
Neither olodaterol nor formoterol reduced the number of exacerbations or prolonged the time to the first exacerbation significantly compared to placebo. The effect of olodaterol appeared to be different across the tiotropium strata: numerically best improvements were observed in the non-tiotropium strata.

As requested, additional analyses comparing the time to the first exacerbation for formoterol and olodaterol were made. Also the number of moderate and severe exacerbations was compared. No statistical differences between both treatments were observed.

Exercise

The MAH also submitted two studies to support the improvement in exercise tolerance.

In the exercise tests the additional exercise time was 37-42 seconds which is below the Minimally Clinically Important Difference (MCID) of 46 seconds as mentioned by the ATS/ERS task force.

Trials 1222.11 and 1222.12
These studies were placebo controlled, parallel studies of 48 week duration, with a primary evaluation after 12 weeks. Both studies demonstrated statistically significant improvements in the co-primary endpoints FEV1 AUC0-3 and trough FEV1. No symptomatic endpoint was included as a secondary endpoint.

Supportive studies (Phase II)

Trials 1222.24/1222.25 and trials 1222.39/1222.40 are trials determining the 24-hour FEV1-time profiles of olodaterol (10 and 5 µg).
The trials were randomised, double-blind, double-dummy, placebo-controlled, 4-way cross-over studies. The 24-hour FEV1-time profiles of olodaterol 5 µg and 10 µg were compared with either Foradil® 12 µg (studies 1222,24/25) or tiotropium bromide 18 µg (studies 1222.39/40) after 6 weeks.

The bronchodilatory effect throughout the day was displayed by the two co-primary efficacy variable FEV1AUC0-12h and FEV1AUC0-24h. All active treatments demonstrated a statistically significant improvement with placebo. The improvements were comparable for olodaterol and tiotropium. In the combined analyses, a statistically significant difference between olodaterol and formoterol was observed for the FEV_1AUC_{12-24h}, demonstrating a better bronchodilatory effect of formoterol during the night.

II.3.3 Clinical Safety

A total of 4312 subjects have been treated with olodaterol monotherapy. A total of 3152 patients have been exposed to olodaterol in the phase III studies. Long-term safety data have been provided for both olodaterol 5 µg and olodaterol 10 µg. 44% of the patients had study drug exposure between 282 and 337 days and 23.5% of patients were exposed greater than or equal to 338 days. 492 patients treated with olodaterol 5 µg and 496 patients treated with olodaterol 10 µg have been exposed for 282-337 days. An additional 265 patients have been exposed for > 338 days to olodaterol 5 µg and 258 patients to olodaterol 10 µg. The dose submitted for registration with this application is only the lower strength. The provided safety data can therefore be considered sufficient because also data of a higher dosage is included.

Table 5: Exposure to study medication, all patients included Phase II/III studies (1222.11, 1222.12, 1222.13, 1222.14, 1222.24, 1222.25, 1222.39, 1222.40, 1222.37, 1222.38)

	Placebo	Olo 5 µg	Olo 10 µg	Tio 18 µg	Form 12 µg	Total
Number of patients	1579	1578	1574	214	646	3841
Extent of exposure [N (%)]						
<= 15 days	40 (2.5)	11 (0.7)	19 (1.2)	1 (0.5)	11 (1.7)	72 (1.9)
16 – 43 days	557 (35.3)	539 (34.2)	554 (35.2)	187 (87.4)	188 (29.1)	96 (2.5)
44 – 85 days	190 (12.0)	197 (12.5)	175 (11.1)	26 (12.1)	30 (4.6)	110 (2.9)
86 – 127 days	30 (1.9)	23 (1.5)	14 (0.9)	0 (0.0)	5 (0.8)	99 (2.6)
128 – 169 days	16 (1.0)	18 (1.1)	15 (1.0)	0 (0.0)	9 (1.4)	265 (6.9)
170 – 225 days	25 (1.6)	17 (1.1)	27 (1.7)	0 (0.0)	6 (0.9)	338 (8.8)
226 – 281 days	22 (1.4)	16 (1.0)	16 (1.0)	0 (0.0)	12 (1.9)	266 (6.9)
282 – 337 days	457 (28.9)	492 (31.2)	496 (31.5)	0 (0.0)	248 (38.4)	1693 (44.1)
>= 338 days	242 (15.3)	265 (16.8)	258 (16.4)	0 (0.0)	137 (21.2)	902 (23.5)

- Adverse events

In general, the frequency of adverse events (AEs) experienced with olodaterol 5 µg or olodaterol 10 µg was comparable to both placebo and the active comparator formoterol 12 µg. Accordingly, severe AEs were balanced across all treatment groups in the four main trials. There were a higher percentage of investigator-defined related AEs and more AEs leading to discontinuation in the placebo or formoterol treated patients compared to olodaterol treated patients.

Of the AEs that occurred, indicated by preferred terms (PT), the following were reported with an incidence greater than 5% in olodaterol treated patients: nasopharyngitis, upper respiratory tract infection and COPD (exacerbation). Nasopharyngitis was the only PT with a higher incidence in both olodaterol treatment groups compared to placebo. Pneumonia and COPD were also more frequently observed with olodaterol 10 µg than with placebo, while the incidence was lower for olodaterol 5 µg compared with placebo.

The highest frequency of AEs occurred in the Pharmacovigilance (PV) endpoints associated with COPD exacerbation. The PT Chronic obstructive pulmonary disease was reported in a total of 879 patients (28.3%). The most frequent preferred terms with a frequency greater than 2% in these PV endpoints were COPD, bronchitis and pneumonia. A higher incidence in the olodaterol 5 µg group compared to placebo was seen for COPD exacerbation (broad) with pneumonia [RR 1.04 (95% CI 0.91, 1.18)], COPD exacerbation (broad) [RR 1.03 (95% CI 0.91, 1.18)] and COPD exacerbation [RR 1.03 (95% CI 0.89, 1.18)]. Comparable relative risks were observed when comparing formoterol with placebo.

In conclusion, when considering respiratory events for safety only minor differences are observed between olodaterol 5 µg and placebo as between olodaterol 5 µg and formoterol.

- Serious adverse events

The number of patients experiencing at least one SAE was balanced across treatment groups in the 48-week parallel group trials (16.4% for placebo, 15.8% for olodaterol 5 µg, 16.6% for olodaterol 10 µg and 15% for formoterol 12 µg).
The most frequent PT was COPD which is expected for this patient population: olodaterol 5 µg (4.7%), olodaterol 10 µg (6.8%), formoterol 12 µg (5.9%), and placebo (6.0%). The second most frequent PT was Pneumonia; this PT showed a notable increase for olodaterol 10 µg (n=22, 2.5%) compared to placebo (n=13; 1.5%). The observed incidence for olodaterol 5 µg was comparable to placebo (n=14; 1.6%).

- Deaths

There were 81 deaths of which 58 occurred on a treatment. The majority of deaths occurred in the Phase 3 48-week studies (n=76). An additional 5 deaths occurred in the Phase III 6-week trials and the Phase 2 COPD trials. Most frequently deaths were seen in the infections and infestations system-organ class (SOC): 3 (0.3%) fatalities in the olodaterol 5 µg group and 4 (0.5%) in the olodaterol 10 µg group versus 1 (0.1%) each in the placebo and formoterol groups. Within this SOC, pneumonia (overall 7 cases; 0.2%) was most frequent with olodaterol 5 µg (2 cases; 0.2%), olodaterol 10 µg (3 cases; 0.3%), formoterol 12 µg (1 case; 0.2%) and placebo (1 case; 0.1%). The frequency of deaths was comparable between treatment groups.

An imbalance of deaths due to ‘neoplasms benign, malignant and unspecified’ was observed for olodaterol: placebo n=0, olodaterol 5 µg n=2 (0.2%) (one hepatic cancer and one lung cancer), olodaterol 10 µg n=7 (0.8%) (4 lung cancers, one metastases to lung case, one laryngeal, and one oesophageal cancer), formoterol n=1 (0.2%) (lung cancer).
There was no particular pattern of an increase in a particular cancer apparent. In absence of indications from the animal studies, malignancies in the respiratory tract are considered due to coincidence as the observed incidence is below the background incidence as in this study.

- Cardiac events (including SAE)

Frequencies of cardiac arrhythmias ranged from 4.2% to 5.6% across treatment groups. In the SMQ Cardiac arrhythmias, serious AEs occurred more frequently in the olodaterol 5 µg group versus placebo. An analysis of major cardiac adverse events (MACE) was undertaken using the pooled 48-week data. No differences were seen in MACE between olodaterol and placebo or formoterol. Although the results of the MACE might give some assurance, based on the higher frequency of serious AEs in the SMQ Cardiac arrhythmias with olodaterol 5 µg, cardiac arrhythmias is included as an important potential risk in the RMP.

QTc prolongation is a known side effect of β_2-agonists. In a thorough QTc study, olodaterol 10 µg did not exceed 10 ms prolongation by the upper limit of the 90% CI for QTcI and time-matched QTcI. The effect in QTc prolongation was larger in females than in males in the dosing group of 30 µg and 50 µg olodaterol. In the clinical trials no increase in numbers of patients with QTc prolongation were seen. Altogether, knowing the potential risk of QTc prolongation of this medication class, this is included in the SmPC.

- Laboratory findings

No specific findings were seen in laboratory findings, vital signs and physical findings and immunologic events besides rash occurring with an incidence of 2.2% in the olodaterol 5 µg group in the main trials. Specific attention was given to both glucose and potassium as changes in these parameters are known to correlate with β-adrenergic agonist class properties.
A slightly higher percentage of patients with possible clinically significant increases in plasma glucose occurred in the olodaterol 5 µg group (3.7%) compared with placebo (2.6%) while this was not observed in the olodaterol 10 µg group (2.8%) or formoterol (1.7%). The proportion of patients with maximum glucose values shifting outside the normal range during treatment was comparable between treatment groups.

CPK increases which have been observed in some studies in the olodaterol program are believed to be based on a β-agonist mechanism. Increases in CPK have been reported with short-acting inhaled β_2-adrenergic receptor agonists to cause intermittent CPK increases, generally associated with mild or no symptoms.
There were slightly more patients with possible clinically significant increases in GGT in both the olodaterol 10 µg (2.9%) and formoterol 12 µg (2.8%) group compared to the other treatment groups (1.2% for olodaterol 5 µg and 2.2% for placebo). However, the increase of GGT is an isolated increase of hepatic enzymes. Therefore it is considered that no further action is required.

- Data with respect to age group

AE frequency data from the pooled dataset from the 48-week were stratified for age groups 65-74 years, 75-84 years, and 85 years and above. There were a total of 1232 patients within the age group 65-74 years and 352 patients within the age group 75-84 years. Only 8 patients were 85 years of age or older. In the elderly (patients > 65 years) comparable numbers of fatal adverse events, serious adverse events and AE leading to discontinuation were observed between groups.
Adverse events of interest for the elderly (>65) are in the system-organ classes cardiac, vascular, infections and infestations, nervous system disorders, ischemic cerebrovascular disorders SMQ, stroke PV and fall PV. The incidence is comparable between placebo and olodaterol, but compared with formoterol the incidence is consistently higher. Nevertheless, in the pivotal studies 1222.13/14, where a head to head comparison between olodaterol and formoterol was performed, comparable incidences were observed.

Pharmacovigilance System Master File Summary
An adequate Pharmacovigilance System Master File Summary has been submitted. The risk management activities are summarised below.

Risk Management Plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
-	Not applicable	Not applicable
Important potential risks		

Cardiac arrhythmia	Routine + PASS	Routine
Myocardial ischaemia	Routine + PASS	Routine
Off-label use in asthma	Routine + DUS	Routine
Hypokalaemia	Routine	Routine
Important missing information		
Long-term data beyond 1 year of use (adverse cardiovascular outcome)	Routine + PASS	Routine
Patients with a recent history of: -myocardial infarction -unstable or life-threatening cardiac arrhythmia -paroxysmal tachycardia -decompensated heart failure	Routine	Routine
Patients with hepatic impairment	Routine	Routine
Patients with severe renal impairment	Routine	Routine
Safety in pregnant or breast-feeding women	Routine	Routine

The MAH will include more than two EU countries in the Drug Utilisation Study (DUS). The MAH committed to submit the protocols for the DUS and Post Authorisation Safety Study (PASS) within 6 months after closure of the registration procedure.

The PSUR submission scheme will start with 6-monthly PSURs, which is in accordance with the applicable standard.

II.3.4 Discussion on clinical aspects – benefit/risk assessment

Olodaterol is a long acting β_2-agonist with a duration of bronchodilation of ≥24 h, and developed for administration by inhalation using the Respimat inhaler.
The indication applied for is 'maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)'.

The recommended dose for adults is 5 µg olodaterol given as two puffs from the Respimat inhaler once daily.

The MAH performed two pivotal studies with active comparator (formoterol) according the EU requirements. The twin studies according to the US requirements are regarded supportive.

Benefits
Olodaterol provides a bronchodilation lasting at least ≥24 h. Its 24 h bronchodilatory duration profile is comparable to tiotropium. At day 169, in the pivotal trials the $FEV_1AUC_{0\text{-}3\ h}$ and trough FEV_1 demonstrated a consistent statistically significant improvement compared with placebo. The response was comparable to the established therapy formoterol.
Tiotropium was used by 25% of the patients included. A comparable beneficial effect on top of tiotropium was observed for both olodaterol and formoterol.

Symptomatic benefits were demonstrated by the improvement in the SGRQ score.
Statistically significant improvements were observed in the SGRQ total score, while this was not achieved with formoterol. A responder was defined as a patient with an improvement in the SGRQ ≥ 4 points from baseline. A higher responder rate was observed for olodaterol than for formoterol. Statistically significant differences in the responder rate were observed between olodaterol and placebo, as well as olodaterol and formoterol.

Uncertainties in the knowledge about the beneficial effects

General

The observed improvements in the trough FEV_1 and the symptomatic improvements for both olodaterol and formoterol were below the MCID as defined by the ATS/ERS task force. However, Donohue et al.[1] demonstrated that the currently approved salmeterol and formoterol did not provide consistently an improvement in trough FEV1 ≥ 100 mL, as in the submitted studies, although their clinical benefit is acknowledged in the symptomatic treatment of COPD.

Additionally it is acknowledged that a MCID might not be static, and might be dependent on the patient population studied, by the severity of the disease (Cazzola 2008[2], Donohue 2011), or use of concomitant medication like tiotropium, ipratropium, inhaled steroids and xanthines like in the current trials.

Exacerbations

In the clinical studies no statistically significant improvement was observed with either active treatment including formoterol, regarding an exacerbation outcome parameter. However, these studies were not specifically designed to measure an effect on exacerbations, *e.g.* patients were not selected on having an exacerbation in the previous year.

Exercise performance

Two studies were submitted to support the improvement in exercise tolerance. A statistically significant improvement in duration of exercise was observed, which was smaller than the minimal clinically relevant improvement.

Risks

4312 subjects have been treated with olodaterol monotherapy. 3152 patients have been exposed to olodaterol in the phase III studies. 492 patients were treated with olodaterol 5 µg and 496 patients have been treated with olodaterol 10 µg for 282-337 days.

265 patients were treated with olodaterol 5 µg and 258 patients with olodaterol 10 µg for > 338 days (>48 weeks). The clinical pharmacology of olodaterol is as can be expected for a β_2-adrenoceptor agonist including effects on systemic pharmacodynamic parameters such as potassium, glucose, heart rate, blood pressure, and QTc prolongation at supratherapeutic doses. The QTc prolongation becomes apparent at higher doses, ≥ 20 µg olodaterol.

The frequencies of adverse events were comparable between oldaterol 5 µg, olodaterol 10 µg, placebo and the active comparator formoterol.

Nasopharyngitis was reported with a 5% higher frequency with olodaterol 5 µg than placebo. Olodaterol 5 µg demonstrated a lower incidence than placebo for pneumonia and COPD, in contrast to olodaterol 10 µg.

Olodaterol Respimat contains EDTA and benzalkonium chloride, which on high doses are known to induce bronchospasm. Within the olodaterol program there was no evidence of administration related bronchoconstriction associated with olodaterol Respimat.

The number of patients experiencing at least one SAE was balanced across treatment groups in the 48-week parallel group trials: placebo (16.4%), olodaterol 5 µg (15.8%), olodaterol 10 µg (16.6%) and formoterol 12 µg (15%). However, for the SAE pneumonia there was an imbalance for olodaterol 10 µg (2.5%) versus the other treatments (placebo 1.5%; olodaterol 5 µg 1.6%, formoterol 12 µg 1.5%).

The frequencies of deaths were comparable between the groups: placebo (1.5%), olodaterol 5 µg (1.5%), olodaterol 10 µg (1.9%) and formoterol (2.2%).

[1] Donohue JF, Jones PW. Changing patterns in long acting bronchodilator trials in chronic obstructive pulmonary disease. Int J of COPD 2011; 6: 35-45

[2] Cazzola et all. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008: 31:416-68

Adverse events of interest for the elder population (>65) are cardiac SOC, vascular SOC, infections and infestations, nervous system disorders, ischemic cerebrovascular disorders SMQ, stroke and fall. The incidence is comparable between placebo and olodaterol. The incidence was also comparable when formoterol was head to head compared to olodaterol.

Uncertainty in the knowledge about the unfavourable effects
In the animal studies no signals were noted regarding the oncogenicity of olodaterol. In the clinical studies an imbalance of malignancies was observed for olodaterol compared to placebo, although the numbers are small: placebo (n=9; 1.0%), olodaterol 5 µg (n=14; 1.6%), olodaterol 10 µg (n=19; 2.2%), formoterol (n=8; 1.7%).
The events were distributed over the various PTs, no pattern of an increase of a particular cancer was apparent. The malignancies in the respiratory tract (placebo 0.1%; olodaterol 5 µg 0.5%; olodaterol 10 µg 1.4%, formoterol 0.8%) can be regarded as coincidental in the absence of animal studies and a lower incidence as the background incidence in patients with airflow obstruction (11-16,7/1000 patient years).

Balance of favourable and unfavourable effects
In the clinical studies formoterol was included as an active comparator providing assay sensitivity for *demonstrating* the clinical relevance of the findings. The observed improvements in lung function and symptoms were statistically significant from placebo and comparable to formoterol. In contrast to formoterol, statistically significant improvements were observed with the SGRQ. Additionally, a higher responder rate in the SGRQ was observed, which was statistically significantly different from formoterol.
Exacerbations were included as a secondary parameter. No statistically significant improvement was observed, however the studies were not designed and powered to measure this effect.

A total of 3152 patients have been exposed to olodaterol in the phase III studies. Sufficient safety data has been provided by 265 patients over one year (48 weeks) for the registered dose, as well as 258 patients for the higher dose. This complies with the requirement of at least 100 patients.

The adverse events were as expected from a β_2-adrenoceptor agonist The effect in patients with significant cardiac comorbidity is limited, and is mentioned in the SmPC. The adverse events of interest for elderly patients were comparable to placebo.

A numerically small imbalance in disfavor for olodaterol regarding malignancies was observed, with a higher incidence for olodaterol 10 µg. The incidence between olodaterol 5 µg and placebo was comparable. No pattern of an increase of a particular cancer was apparent. The incidence of malignancies of the respiratory tract was highest for olodaterol 10 µg, but lower than the background incidence in patients with airflow obstruction. In absence of indications from the animal studies, these malignancies are considered due to coincidence.

Benefit–risk balance
Olodaterol 5 µg o.i.d is a long acting β_2-agonist indicated for the maintenance treatment in COPD. In the clinical trials assay sensitivity was provided by the long acting β_2-agonist formoterol, and clinically relevant improvements were observed in both the lung function and symptomatic improvements, hereby fulfilling the requirements as requested by the COPD guideline (CHMP/EWP/562/98)

Exacerbations were included as a secondary endpoint. In the pivotal studies, both olodaterol and formoterol did not reduce the exacerbation rate ratio for moderate and severe exacerbations. The effect of formoterol and olodaterol 5 µg was comparable regarding the effect on the time to the first moderate/severe COPD exacerbation and the number of moderate/severe exacerbations, demonstrating a comparable effect between formoterol and olodaterol in the observed patient population.

The adverse events were as expected for a β_2-adrenoceptor agonist. The data of effects in patients with cardiac comorbidity is limited, but is monitored as part of the RMP. A small numerically higher incidence of malignancies was observed for the high dose of olodaterol, but comparable incidences were observed between olodaterol 5 µg and placebo. The number of respiratory malignancies was below the background

incidence. No signals in animal data or a specific pattern of malignancies was observed and therefore this is regarded as a coincidence. The number and patterns of adverse events are considered acceptable.

In conclusion, based on the overall benefits and risks, the member states consider Striverdi Respimat 2.5 micrograms, solution for inhalation approvable for the indication 'maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)'. The approved dose for adults is 5 micrograms olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure covers appropriate information on the use and safety of Striverdi Respimat, and has been adapted in accordance with the comments raised by the member states.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
From the results of the readability test, it can be concluded that most patients who are prescribed this product will be able to find and understand the sought information in the PIL. As a whole, the PIL is intelligibly written. Both the writing style and the clear presentation contribute to this assessment. This is primarily reflected by the fact that information can be found quickly.
The PIL is a useful information source for patients and as such contributes towards preventing unintentional misuse of the medicinal product. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The chemical-pharmaceutical information about the manufacturing, the quality requirements with regard to the substance and the finished product Striverdi Respimat 2.5 micrograms, solution for inhalation are sufficient within the framework of the European registration requirements.

The non-clinical data documentation provided did not give rise to specific concerns for humans that would preclude a recommendation for marketing authorisation.

The results of the clinical studies show that olodaterol provides a bronchodilation lasting at least ≥24 h. Its 24 h bronchodilatory duration profile is comparable to tiotropium. The effects regarding the lung function (trough FEV1) and symptomatic improvement (TDI, SGRQ) were statistically significant and numerically favourable compared to placebo. Statistically more responders with olodaterol than with formoterol were observed in the SGRQ score. This supports the fact that a clinically relevant improvement has been achieved, with a once daily dosing of 5 micrograms.
The adverse events were as expected from a β_2-adrenoceptor agonist. An appropriate Risk Management Plan has been laid down. The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and cover appropriate information to enable safe and effective use of Striverdi Respimat.

In the Board meetings of 30 August 2012 and 8 May 2013 this application was discussed. With regard to the clinical data, the Board concluded that the lung function improvement with olodaterol was demonstrated to be comparable to the comparator formoterol, which is considered clinically relevant. The Board expressed its positive opinion on the application for Striverdi Respimat 2.5 micrograms.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The member states, on the basis of the data submitted, considered that Striverdi Respimat 2.5 micrograms, solution for inhalation demonstrated adequate evidence of efficacy for the approved indication ‘maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)’. The member states considered the benefit/risk profile satisfactory and therefore granted a marketing authorisation. The decentralised procedure was finished on 4 September 2013. Striverdi Respimat 2.5 micrograms, solution for inhalation was authorised in the Netherlands on 23 October 2013.

The PSUR submission cycle is 6-monthly.
The date for the first renewal will be: 4 September 2018.

The following post-approval commitments have been made during the procedure:

Clinical aspects
- The MAH committed to submit protocols for the Drug Utilisation Study (DUS) and Post Authorisation Safety Study (PASS) within 6 months after closure of the registration procedure.
- The MAH committed to submit the results of the DUS not later than 3 years following the end of the registration procedure.
- The MAH committed to submit the results of the PASS not later than 5 years following the end of the registration procedure.

List of abbreviations

ACh	Acetylcholine
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AR	Adrenergic Receptor (adrenoceptor)
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
ATS	American Thoracic Society
AUC	Area Under the Curve
bid	Twice daily
BP	British Pharmacopoeia
Bpm	Beats per minute
cAMP	Cyclic-3',5' Adenosine Monophosphate
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CV	Coefficient of Variation
CYP	Cytochrome P450
DUS	Drug Utilisation Study
EC_{50}	Concentration to induce 50% efficacy
EDTA	Disodium edetate
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EDTA	Disodium edetate
ERS	European Respiratory Society
EU	European Union
FAS	Full Analyses Set
FEV1	Forced expiratory volume during one second
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOLD	Global initiative for chronic Obstructive Lung Disease
HEK293	Human Embryonic Kidney
hERG	Human Ether-a-go-go Related Gene
HR	Heart Rate
IA	Intrinsic Activity
IC	Inspiratory capacity
ICH	International Conference of Harmonisation
ICS	Inhaled Corticosteroids
Ki	Dissociation constant of enzyme inhibitor complex for competitive inhibition
LABA	Long-acting Beta2-adrenoceptor Agonist
LAMA	Long-acting Muscarinic Antagonist
MACE	Major Cardiac Adverse Events
MAH	Marketing Authorisation Holder
MCID	Minimal Clinically Interesting Difference
MEB	Medicines Evaluation Board in the Netherlands
MedDRA	Medical dictionary for regulatory activities
mL	Milliliter

N	Number of patients
OAT	Organic Anion Transporter
OTC	Over The Counter (to be supplied without prescription)
qd	Once daily
QTcI	ECG measurement: QT corrected interval
QTcF	ECG measurement: QT corrected using Fredericia method
QTcB	ECG measurement: QT corrected using Bazette method
PAR	Public Assessment Report
PASS	Post Authorisation Safety Study
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PMM	Pattern Mixture Models
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard error (of the mean)
SGRQ	Saint George Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System-organ Class
Sub-SMQ	Subordinate SMQ
SULT	Sulfotransferase
TDI	Transient Dyspnea Index
t½	Half-life
tmax	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
UGT	UDP-glucuronosyltransferase
US	United States
USP	Pharmacopoeia in the United States
µg	microgram

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached