Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for olodaterol (as hydrochloride)

Proprietary Product Name: Striverdi Respimat

Sponsor: Boehringer Ingelheim Pty Ltd

Date of first round CER: 7 February 2013
Date of second round CER: 31 May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
[^{14}C]	Drug labelled with radioactive carbon
ADME	Absorption, distribution, metabolism and excretion
Ae	Amount excreted unchanged in urine
$Ae_{t1\text{-}t2(,ss)}$	Amount excreted unchanged in urine within the time interval t1 to t2 (at steady state)
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the analyte plasma concentration time curve
$AUC_{(x\text{-}yh)}$	Area under the time curve from x to y hours after dosing (normalised)
$AUC_{0\text{-}\infty}$	Area under the analyte plasma concentration time curve from time point of administration extrapolated to infinity
$AUC_{0\text{-}tz(,ss)}$	Area under the analyte plasma concentration time curve from time point of administration to the time point of the last quantifiable plasma concentration (at steady state)
$AUC_{t1\text{-}t2(,ss)(,norm)}$	Area under the analyte plasma concentration time curve from the time point t1 to the time point t2 (at steady state) (dose normalized)
bid	Twice daily
BLQ	Below limit of quantification
BP	Blood pressure
bpm	Beats per minute
$C_{0.167(,ss)}$	Plasma concentration 10 minutes after administration (at steady state)
cAMP	Cyclic adenosine monophosphate
Cc/Cp	Concentration ratio of drug related radioactivity between blood cells (CC) and plasma (CP)
CD 10915	Metabolite M551(2) of olodaterol (= isomer 2 of SOM 1522 glucuronide)
CD 11249	Metabolite M551(1) of olodaterol (= isomer 1 of SOM 1522 glucuronide)
CD 12656	Metabolite M455(1) of olodaterol (= SOM 1522 sulphate)

Abbreviation	Meaning
CD 992	Metabolite M565(1) of olodaterol (equals olodaterol glucuronide isomer 1, formed by glucuronidation of the 6-hydroxy-benzoxazine-moiety of olodaterol). MW: 562.57 g/mol
CI	Confidence interval
CL	Total clearance of the analyte in plasma following intravenous single dose administration
CLi	Intrinsic clearance (=Vmax/Km)
$CLR_{,t1-t2}$	Renal clearance of the analyte from the time point t1 until the time point t2
$Cmax_{(,ss)(,norm)}$	Maximum analyte plasma concentration (at steady state) (dose normalized)
COPD	Chronic Obstructive Pulmonary Disease
$C_{pre,ss}$	Predose concentration of the analyte in plasma at steady state immediately before administration of the next dose
CSR	Clinical Study Report
CV	Coefficient of variation
CYP	Cytochrome P450
dBP	Diastolic blood pressure
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
fe	Fraction of the administered dose excreted in urine
$fe_{t1-t2(,ss)}$	Fraction of the administered dose excreted in urine over the time interval t1 to t2 (at steady state)
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HPLC	High performance liquid chromatography
HR	Heart rate

Abbreviation	Meaning
iv or i.v.	Intravenous
IVRS	interactive voice response system
L	Liter(s)
LABA	long acting beta2 adrenergic agonist
LLOQ	Lower limit of quantification
M375(1)	SOM 1522, metabolite of olodaterol (equals desmethyl olodaterol)
M455(1)	CD 12656, metabolite of olodaterol (equals sulphate of SOM 1522)
M551(1)	CD 11249, metabolite of olodaterol (= isomer 1 of SOM 1522 glucuronide)
M551(2)	CD 10915, metabolite of olodaterol (= isomer 2 of SOM 1522 glucuronide)
M565(1)	CD 992, metabolite of olodaterol (=isomer 1 of olodaterol glucuronide)
M565(2)	Metabolite of olodaterol (= isomer 2 of olodaterol glucuronide)
MAP	Mean arterial pressure
mg	Milligram
mL	Millilitre
mmHg	Millimetre of mercury; unit of pressure
mmol	Millimol
ms	Milliseconds
MW	Molecular weight
n.a.	Not applicable
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OCTN	New type organic cation transporter
PD	Pharmacodynamic(s)
PEFR	Peak expiratory flow rate
pg	Picogram(s)

Abbreviation	Meaning
P-gp	P-glycoprotein (synonymous to MDR-1)
PGR	Patient's Global Rating
PK	Pharmacokinetic(s)
qd	Once daily
QT Uncorrected	QT interval
QTc	Umbrella term for QTcI, QTcF, QTcB or QTcN
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericias formula
QTcI	QT interval individually corrected for heart rate according to a factor estimated from the subject
QTcN	QT interval corrected for heart rate according to a factor estimated from the study population
RA,AUC	Accumulation ratio of the analyte in plasma, calculated as ratio of AUCss at steady state after multiple dose administration and AUC after single dose administration
RA,Cmax	Accumulation ratio of the analyte in plasma, calculated as ratio of Cmax,ss at steady state after multiple dose administration and Cmax after single dose administration
sBP	Systolic blood pressure
SD	Standard Deviation
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SOM 1522	M375(1); metabolite of olodaterol obtained by demethylation of the methoxyphenyl-moiety SOM 1522 BS SOM 1522 free base, analyte name in bioanalytical determinations. MW: 372.42 g/mol
ss	steady state
t½(,ss)	Terminal half life of the analyte in plasma (at steady state)
t1/2	Half life associated with the terminal slope
Tmax(,ss)	Time from dosing to the maximum concentration of the analyte in plasma (at steady state)

Abbreviation	Meaning
tz(,ss)	Time point of last measurable concentration of the analyte in plasma (at steady state)
UDP	Uridine diphosphate
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit normal
Vss	Apparent volume of distribution at steady state following intravascular administration
ΔΔHR	Time matched change from baseline and placebo of heart rate
ΔΔQTcI	Difference from placebo of time matched change from baseline in QTcI
µg	Microgram(s)

1. Clinical rationale

The sponsor had stated that chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, and that the prevalence and burden of COPD are projected to increase due to continued exposure to COPD risk factors and the changing age structure of the world's population, with more people living longer and therefore expressing the long term effects of exposure to COPD risk factors.

Two classes of inhaled bronchodilators are currently available: β2 agonists and anticholinergics. The initial β2 agonists (for example salbutamol) and anticholinergics (for example ipratropium) have short duration of action, necessitating multiple daily dosing regimens in order to maintain bronchodilator activity. More recent β2 agonists (for example formoterol, salmeterol), called long acting β2 agonists (LABAs), have longer duration of action, allowing for a twice daily dosing regimen. The sponsor had stated that within the anticholinergic class, a more recent anticholinergic agent, tiotropium (Spiriva; developed by the sponsor), had been found to be able to retain bronchodilator effect for 24 hours, thus allowing for a once daily dosing regimen, and had been established as part of standard treatment regimen in COPD. The sponsor was therefore of the opinion that the development of β2 agonists with a similar duration of action as tiotropium and which can provide 24 hour bronchodilator activity with a once daily dosing regimen will be a valuable addition to the treatment options in COPD.

The sponsor had stated that indacaterol (developed by Novartis) had been recently approved in the European Union (EU) and the United States (US) as a once daily LABA for the maintenance treatment of airflow obstruction in COPD. Infortispir Respimat[1] is intended to be an alternative once daily maintenance bronchodilator treatment in patients with COPD. In addition, the sponsor had stated that Infortispir Respimat had been found to have a rapid onset of action and high β2 selectivity, with almost full intrinsic activity at β2 adrenoceptors and low intrinsic activity at β1 adrenoceptors.

> Comments: The clinical rationale is sound and logical. In Australia, indacaterol (under the proprietary name of Onbrez Breezhaler) was approved by the TGA in 2010, for the indication of long term, once daily, maintenance bronchodilator treatment of airflow limitation in patients with COPD.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 15 clinical pharmacology studies, including 14 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 7 dose finding Phase II studies (3 conducted in COPD patients, and 4 in asthma patients).
- 4 pivotal efficacy/safety studies (Phase III) studies consisting of 2 sets of replicate, randomised, double blind, parallel group studies, each with a 48 week treatment duration. One set of replicate studies (Studies 1222.11 and 1222.12) was placebo controlled, while

[1] Infortispir Respimat was the intended trade name for olodaterol (as hydrochloride) 2.5 micgrogram/actuation inhalation cartridge at the time of preparation of this document. Striverdi Respimat is the Australian Register of Therapeutic Goods trade name however at the time of this report Infortispir Respimat was used. For the purposes of this document the name Infortispir Respimat is used however the AusPAR will refer to Striverdi Respimat.

the other set (Studies 1222.13 and 1222.14) was both placebo and active controlled (active control: formoterol).

- 6 other efficacy/safety studies (Phase III) including 2 sets of replicate, randomised, double blind, placebo and active controlled, cross over studies, each with a 6 week treatment duration, evaluating the lung function profile of olodaterol over 24 hours. In the first set of replicate studies (Studies 1222.24 and 1222.25), formoterol was the active control, and in the second set of replicate studies (Studies 1222.39 and 1222.40), tiotropium was the active control. In addition, there was 1 set of replicate, randomised, double blind, placebo controlled, cross over studies with a 6 week treatment duration to evaluate the effect of olodaterol on symptom limited exercise tolerance (Studies 1222.37 and 1222.38).
- Other reports including 9 combined pooled analyses reports. These consisted of the combined analyses of the respective sets of replicate Phase III studies (Studies 1222.11/1222.12 (report 1222-9992), Studies 1222.13/1222.14 (report 1222-9993), Studies 1222.24/1222.25 (report 1222-9991) and Studies 1222.39/1222.40 (1222-9994)), a Summary of Clinical Efficacy Supplement (report 1222-9995), a Summary of Clinical Safety Supplement (report 1222-9996), a meta analysis of ADRB2 haplotypes across Studies 1222.11, 1222.12, 1222.13 and 1222.14 (report 1222-0050), a combined analysis of two Phase II Studies (1222.5 and 1222.6) evaluating the covariate effects on olodaterol pharmacokinetic (PK) parameters in patients with COPD (Study 1222.5) and those with persistent asthma (Study 1222.6) (report 1222-9956), and an "embellished narrative summary table", which is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 with serious adverse event (SAE) or non SAE leading to discontinuation.

The submission did not contain the following clinical information:

- No population pharmacokinetic analyses were provided.

In this evaluation, the four (2 sets of replicate studies) 48 week Phase III studies (Studies 1222.11/1222.12 and 1222.13/ 1222.14) will be evaluated as pivotal efficacy/safety studies, with the other six (3 sets of replicate studies) Phase III studies (Studies 1222.24/1222.25, 1222.39/1222.40, and 1222.37/1222.38) evaluated as supporting efficacy/safety studies. The 3 Phase II studies in COPD patients will be evaluated with regards to the rationale for the selected dosing regimen in the Phase III studies. As this submission is for the indication for use of olodaterol in COPD patients, and as per instructions in the TGA's "notes to evaluator", the 4 Phase II studies conducted in asthma patients will be evaluated only for safety, and will be described and evaluated in the safety section in this report. With regards to the combined/pooled analyses reports submitted, the Summary of Clinical Safety Supplement and the "embellished narrative summary table" involved only safety data and will be described and evaluated in the safety section in this report. The Summary of Clinical Efficacy Supplement and the Summary of Clinical Safety Supplement consisted of a listing of tables on efficacy and safety data, respectively, from the Phase III efficacy/safety studies, which were referenced in the Summary of Clinical Efficacy and the Summary of Clinical Safety, respectively, but not found in the individual or combined study reports (for example combined dataset from all 4 pivotal Phase III studies). As such, they will not be presented separately, but data drawn from these 2 reports will be incorporated and discussed in the evaluation of efficacy and safety.

In addition, there are additional reports submitted, consisting of 4 Phase II studies, all with treatment duration of 4 weeks (one study was a dose response and PK study in Japanese COPD patients, while the other 3 studies involved the evaluation of a fixed dose combination of tiotropium and olodaterol in COPD patients). As these studies are not relevant to the evaluation of this submission, the sponsor is not proposing a fixed dose combination formulation in this submission, and these studies are not referenced either in the Summary of Clinical Efficacy and

Summary of Clinical Safety or in the TGA's "notes to evaluator", these studies will be evaluated with regards to whether the results has raised concerns relevant to this submission.

2.2. Paediatric data

The submission did not include paediatric data. As COPD is not a disease affecting paediatric patients, the use of olodaterol in the treatment of COPD is not considered relevant in the paediatric population.

2.3. Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.[2]

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic (PK) data

Table 1 below provides a summary of the studies providing PK data.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	U06-1418 U08-1081 U08-1060 U08-2268 U08-3758	* * * *
	- Multi-dose	U07-2062 U08-3758	* *
	Food effect	No studies	
PK in special populations	Target population COPD	U09-1422	
	Hepatic impairment	U10-2864	*
	Renal impairment	U10-2081	*
	Neonates/infants/children/adolescents	No studies	
	Elderly	No studies	
Genetic / gender-related PK	Males versus Females	No specific studies	
PK interactions	Tiotropium	U09-1422	*
	Ketoconazole	U10-3390	*
	Fluconazole	U10-3391	*
Population PK analyses	Healthy subjects	No studies	
	Target population	No studies	

* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

[2] European Medicines Agency, "ICH Topic E 6 (R1) Guideline for Good Clinical Practice Step 5: Note for guidance on good clinical practice (CPMP/ICH/135/95)", July 2002, Web, accessed 6 February 2014 <www.edctp.org/fileadmin/documents/EMEA_ICH-GCP_Guidelines_July_2002.pdf>

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Specific and highly sensitive methods based on HPLC-MS/MS were used to measure olodaterol concentrations in human plasma and urine. Lower limits of quantification were 2.0 pg/mL and 10 pg/mL, respectively. Despite the sensitive bio analytical method, olodaterol was mostly not detectable in plasma after inhaled doses below 5 µg. Following inhalation, peak plasma concentrations of olodaterol were observed within 20 minutes, indicating rapid absorption once deposited in the lungs. A slower absorption process appears to determine the terminal half life of olodaterol in plasma after inhalation (45 hours), which is longer than that after intravenous (IV) administration (22 hours). Oral bioavailability of olodaterol is low, so that the fraction of the drug swallowed does not contribute significantly to the plasma concentration profiles after inhalation. Olodaterol exhibits linear pharmacokinetics with a dose proportional increase of systemic exposure. Steady state is achieved within 8 days upon repeated inhalations, with accumulation factors for both Cmax and AUC in the range of 1.1 to 1.8. The inter individual variability of olodaterol plasma concentrations is moderate (CV% 26 to 57%) based on Cmax and AUC values in COPD patients after inhalation of the planned clinical dose of 5µg. Olodaterol is extensively distributed into the (volume of distribution: 1110 L). There is moderate binding to human plasma proteins (approximately 60%) which is unchanged in renal or hepatic insufficiency.

Olodaterol undergoes substantial metabolism; about half of the drug related material excreted after IV administration is metabolites. The 6 metabolites identified represent 1 Phase I reaction product with binding affinity and agonistic potency on the β2 receptor similar to olodaterol, but negligible plasma concentrations, and 5 Phase II reaction products with insignificant pharmacological activity. Olodaterol is the only compound relevant for pharmacological activity.

The Phase I metabolism of olodaterol is dependent primarily on CYP 2C9, with minor contributions from CYP 2C8 and CYP 3A4. Inhibition of CYP2C9 with fluconazole did not result in a clinically relevant change in the systemic exposure to olodaterol. Olodaterol is a P-gp substrate *in vitro* and in animal studies, a drug-drug interaction study with ketoconazole (an inhibitor of P-gp and CYP isozymes) was performed. Steady state exposure to olodaterol after inhalation was found to be increased by about 70% when co-administered with ketoconazole. The magnitude of the increase was not thought to raise any safety concerns as higher doses of olodaterol are well tolerated. No special precautions are recommended when P-gp and/or CYP inhibiting other medications are co-administered with olodaterol. Although glucuronidation of olodaterol is a major metabolic pathway, genetic polymorphisms known to be associated with altered activity of the involved uridinediphosphate glucuronosyltransferase isoenzymes (UGT 1A1, 1A7, 1A9 and 2B7) had no obvious impact on systemic exposure to olodaterol and olodaterol glucuronide. A clinical drug-drug interaction study with tiotropium showed that concomitantly inhaled tiotropium and olodaterol did not significantly affect each other's pharmacokinetics.

After IV administration of [^{14}C] olodaterol, 53% of the total radioactivity was excreted in faeces and 38% was excreted in the urine. Both hepatic and renal impairment could potentially affect olodaterol systemic exposure. No change in systemic exposure to inhaled olodaterol was observed in subjects with mild and moderate hepatic impairment, and only a modest 40% increase was observed in subjects with severe renal impairment. No special precautions are necessary in patients with hepatic or renal impairment.

Throughout the various inhalation studies performed with olodaterol, systemic exposure in COPD patients was usually higher than in healthy volunteers. A meta analysis of Phase II PK data showed no influence of gender and only moderate influence of age, weight, height and lung function (pre treatment baseline FEV1) on the systemic exposure to olodaterol. Based on

comparisons within and across studies, higher systemic exposure was observed in Asians (especially in Japanese) compared to Caucasians. However, differences in exposure related to these demographic factors did not exceed a factor of 2; the safety experience in the Phase III studies with twice the planned clinical dose does not suggest a need for any special caution.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Absorption

Maximum plasma concentrations of olodaterol after inhalation via the Respimat inhaler were usually observed within 10 to 20 minutes. Concentrations thereafter declined multi exponentially with a terminal half life of about 45 hours (U07-2062). Multi exponential disposition kinetics was also observed after intravenous administration with a shorter terminal half life of about 22 hours (U08-2268). A shorter elimination half life (less than 20 hours) was observed after 30 minutes and 3 hour infusions of olodaterol (U08-1081). Thus, the terminal half life observed after inhalation appears to be determined by continuous absorption via the lung rather than by elimination processes.

3.2.1.1.1. Sites and mechanisms of absorption

Olodaterol is absorbed from the lungs.

3.2.1.2. Bioavailability

3.2.1.2.1. Absolute bioavailability

By comparing dose normalized $AUC_{0-\infty}$ values obtained from healthy volunteers after single inhalation of 30 to 70 µg olodaterol (U06-1418) with those obtained after intravenous infusion of 20µg olodaterol (U08-2268) the absolute bioavailability of olodaterol after inhalation was estimated to be approximately 30%. The absolute bioavailability of olodaterol administered as an oral solution in contrast was found to be below 1% (U08-2268). From these results it is concluded, that systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

3.2.1.2.2. Bioequivalence of clinical trial and market formulations

Clinical studies were conducted with the proposed market formulation.

3.2.1.2.3. Bioequivalence of different dosage forms and strengths

Only one formulation is to be marketed.

3.2.1.2.4. Bioequivalence to relevant registered products

Not applicable.

3.2.1.2.5. Influence of food

A formal study to investigate the influence of food on systemic olodaterol exposure was not conducted.

3.2.1.2.6. Dose proportionality

Systemic exposure after single inhaled doses in the range of 5 to 70 µg (assessed by Cmax and $AUC_{0-\infty}$) and multiple inhaled doses in the range of 2 to 20 µg (assessed by Cmax,ss and $AUC_{0-1,ss}$) overall increased in proportion with the dose (U06-1418; U08-1543; U08-3758; U09-3125; U10-2537; U09-1850). Cmax and $AUC_{0-\infty}$ values observed after single intravenous doses of 0.5 to 25 µg (U08-1081), and Cmax values after single oral administration of 30 and 40 µg olodaterol also gave no evidence for a deviation from dose proportionality (U08-1060).

3.2.1.3. Distribution

3.2.1.3.1. Volume of distribution

The volume of distribution (V_{ss} 1110L) exceeds the total body volume, indicating extensive distribution of olodaterol into tissues.

3.2.1.3.2. Plasma protein binding

Plasma protein binding of olodaterol in humans amounted to about 60%, and was unchanged in patients with renal or hepatic insufficiency (U08-2233, U10-1883). The extent of binding was virtually constant at olodaterol concentrations between 0.01nmol/L and 1.0nmol/L, indicating non saturable binding in this concentration range.

3.2.1.3.3. Erythrocyte distribution

Using [^{14}C] olodaterol, the ratio of radioactivity concentrations in blood cells versus plasma concentrations (Cc/Cp) over a period of 180 minutes on average was found to be 2.97 in males and 2.48 in females, indicating high association of drug related radioactivity with blood cells (U04-1983).

3.2.1.4. Metabolism

The metabolism of olodaterol was investigated following administration of single IV and oral doses of [^{14}C] olodaterol in healthy volunteers. Metabolism occurred via Phase I metabolism by CYP mediated oxidative demethylation of the methoxy moiety of olodaterol leading to the metabolite SOM 1522. Phase II conjugation reactions resulted in the olodaterol glucuronides CD 992 and M565(2), the SOM 1522 glucuronides CD 10915 and CD 11249, and the SOM 1522 sulphate CD 12656.

Following intravenous administration, unchanged olodaterol was the dominant compound in human plasma (41% of total drug related material), followed by CD 992 and CD 10915 (each 22% of total drug related material, metabolite to parent ratio: 0.5). After oral administration, predominantly CD 992 was found in plasma (55% of total drug related material, metabolite to parent ratio: 5.0), followed by CD 10915 (17% of total drug related material, metabolite to parent ratio: 1.5) and unchanged olodaterol (11% of total drug related material).

The metabolites SOM 1522, CD 11249, CD 12656 and M565(2) each were present in amounts below 10% of total drug related material after both administration routes. Non extractable radioactivity, representing drug related material covalently bound to plasma proteins, also accounted for less than 10% of total drug related material. The Phase I product SOM 1522 is the only olodaterol metabolite with pharmacological activity at the human β2 and β1 adrenoceptors comparable to parent compound.

3.2.1.4.1. Interconversion between enantiomers

Olodaterol is formulated as a single enantiomeric form. There do not appear to be any human studies on the potential for inter conversion between isomers.

3.2.1.4.2. Pharmacokinetics of metabolites

Attempts to quantify SOM 1522 after inhaled administration of olodaterol were made in single and multiple dosing studies in healthy volunteers and COPD or asthma patients (U08-1262, U08-3758, U10-2864, U10-2081, U10-3390, U08-1543, U08-1263, U09-3125, and U09-1850). However, even with supra therapeutic single doses of 40 µg or multiple doses of 20 µg SOM-1522 concentrations in plasma, with the exception of few individual samples, were below the lower limit of quantification (10 pg/mL). Maximum plasma concentrations of olodaterol glucuronide were usually observed 2 to 3 hours after the inhalation of olodaterol. The elimination half life of olodaterol glucuronide based on the available data could not be reliably determined; however, accumulation ratios for Cmax, AUC_{0-1} and/or AUC_{0-3} of olodaterol glucuronide observed after repeated inhalations of olodaterol doses up to 30 µg were usually in

the range of 1.0 to 1.8, that is comparable to those of the parent drug. Based on molar AUC ratios ($AUC_{0-6,ss}$ or $AUC_{0-24,ss}$) systemic exposure to olodaterol glucuronide at steady state amounted to approximately 50 to 70% of the olodaterol exposure (U07-2062, U08-3758, U09-3125, U09-1850, U10-3390, U10-3391). Molar ratios between olodaterol glucuronide and unchanged olodaterol excreted in the urine within the 24 hour dosing interval after inhalation varied between 0.2 and 0.9 (U08-1262).

3.2.1.4.3. Consequences of genetic polymorphism

Since glucuronidation is a predominant reaction in the metabolism of olodaterol, altered activity of the relevant uridine diphosphate glucuronosyltransferase isoenzymes (UGT1A1, 1A7, 1A9 and UGT2B7) potentially could affect systemic exposure to olodaterol. Therefore, pharmacogenomic samples obtained from COPD and asthma patients in the Phase II studies (U09-3125) and (U09-1850) were used to analyse polymorphisms in the respective genes. The impact of UGT1A1*28/36/37, *60, *93, UGT1A7*2, *3, *4, *12, UGT1A9*3 and UGT2B7*2 alleles on olodaterol systemic exposure was evaluated (U10-2212). No relationship between systemic exposure to olodaterol or olodaterol glucuronide and UGT genotype became obvious; the UGT genotype does not appear to make any relevant contribution to the inter subject variability of systemic exposure to olodaterol and olodaterol glucuronide.

3.2.1.5. Excretion

3.2.1.5.1. Mass balance studies

After intravenous administration of [^{14}C] olodaterol, 42.5% of the total radioactive dose was recovered in urine and 53.0% in faeces (U08-2268). More than 90% of the administered dose was excreted within the first 6 days. Following oral administration, only 8.90% of the radioactive dose was excreted in urine, while the major portion of total radioactivity was recovered in faeces (84.4%). More than 90% of the dose was excreted within 5 days.

3.2.1.5.2. Renal clearance

Total clearance of olodaterol as determined in healthy volunteers following intravenous infusion was 872 mL/min, and renal clearance was 173 mL/min (U08-2268). As the latter exceeds the glomerular filtration rate, active secretion of olodaterol in the kidney can be concluded. In line with this, olodaterol in *in vitro* experiments was found to be a substrate of the membrane transporters OAT1, OAT3 and P-gp, which are known to be located in the proximal tubule of the kidney. Olodaterol also is a substrate of OCT1, which together with P-gp may be involved in biliary excretion and intestinal efflux of olodaterol.

3.2.1.6. Intra and inter individual variability of pharmacokinetics

The inter individual variability of olodaterol plasma concentrations after inhalation was moderate. After inhalation of the planned therapeutic dose of 5 µg by COPD patients, geometric coefficients of variation for single dose and steady state Cmax and AUC_{0-1} values ranged from 26% to 57%. At the higher dose of 10 µg the inter individual variability was similar.

3.2.2. Pharmacokinetics in the target population

Geometric means and geometric coefficients of variation of single dose and steady state Cmax and AUC_{0-1} values obtained from healthy volunteers, asthma patients and COPD patients following inhalation of the planned therapeutic dose of 5 µg olodaterol are presented in the table below.

Table 2: Geometric means and geometric coefficients of variation (%) of pk parameters of Olodateral after inhalation

Parameter¤	2.5µg¶ (N=4)¶ ¤	5µg¶ (N=6)¶ ¤	10µg¶ (N=6)¶ ¤	15µg· male¶ (N=6)¤	15µg· female¶ (N=6)¤	20µg¶ (N=6)¤	30µg¶ (N=6)¶ ¤	40µg¶ (N=6)¶ ¤	50µg¶ (N=6)¶ ¤	60µg¶ (N=6)¶ ¤	70µg¶ (N=5)¤	¤
AUC0-∞· [pg·h/mL]¤	NR¤	NR¤	NR¤	NR¤	NR¤	NR¤	126¶ (90.0)¤	145¶ (79.9)¤	356¶ (89.8)¤	398¶ (43.8)¤	304¶ (105)¤	¤
AUC0-24· [pg·h/mL]¤	NR¤	NR¤	NR¤	NR¤	NR¤	NR¤	80.6¶ (44.0)¤	96.2¶ (54.9)¤	144¶ (40.1)¤	162¶ (37.0)¤	177¶ (68.2)¤	¤
Cmax· [pg/mL]¤	NR¤	NR¤	3.62¶ (24.0)¤	4.89¶ (52.6)¤	7.89¶ (26.1)¤	5.33¶ (76.2)¤	17.7¶ (57.3)¤	15.4¶ (68.2)¤	26.2¶ (28.3)¤	29.8¶ (71.1)¤	32.7¶ (54.3)¤	¤
Tmax·[h]*¤	NR¤	NR¤	0.333¶ (0.167-¶ 0.500)¤	0.367¶ (0.200-¶ 0.533)¤	0.367¶ (0.217-0.383)¤	0.350¶ (0.183-0.850)¤	0.275¶ (0.167-0.500)¤	0.367¶ (0.117-0.517)¤	0.292¶ (0.200-0.550)¤	0.292¶ (0.217-0.550)¤	0.233¶ (0.217-0.383)¤	¤
t½·[h]¤	NR¤	NR¤	NR¤	NR¤	NR¤	NR¤	16.8¶ (116)¤	16.7¶ (50.8)¤	38.0¶ (91.0)¤	39.5¶ (43.4)¤	21.5¶ (81.0)¤	¤
CL/F· [mL/min]¤	NR¤	NR¤	NR¤	NR¤	NR¤	NR¤	3960¶ (90.0)¤	4610¶ (79.9)¤	2340¶ (89.8)¤	2510¶ (43.8)¤	3830¶ (105)¤	¤
Vz/F·[L]¤	NR¤	NR¤	NR¤	NR¤	NR¤	NR¤	5760¶ (27.0)¤	6680¶ (25.8)¤	7690¶ (33.3)¤	8600¶ (38.7)¤	7140¶ (45.8)¤	¤

*range·of·values¶

Since the largest part of PK information was obtained with the 10 µg dose, the respective data are additionally given in the table below. Beyond inter study differences related to low subject numbers, the data suggest higher exposure in COPD patients than in asthma patients and healthy volunteers. Other studies to be evaluated for efficacy included the 3 Phase II studies conducted in COPD patients, and the combined/pooled analyses reports. In this efficacy section of this evaluation report, the respective sets of replicate studies will be presented in the same sub sections, together with their combined analysis results, for ease of reference.

Table 3. Comparison of olodaterol systemic exposure after inhalation of 10 ug olodaterol by healthy volunteers, asthma patients and COPD patients

	Healthy volunteers			Asthma patients			COPD patients		
Parameter [Unit]	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source	N	gMean (gCV%)	Source
C_{max} [pg/mL]	6	3.62 (24.0)	1222.1	26	4.54 (39.5)	1222.4	16	4.95 (53.8)	1222.3
	16[1]	4.21 (27.1)[1]	1222.2	44	4.63 (59.7)	1222.6	71	5.45 (63.5)	1222.5
	17	3.29 (42.1)	1222.8						
	9[#]	5.44 (29.4)[#]	1222.21[#]				81[#]	8.22 (58.3)[#]	1222.22[#]
AUC_{0-1} [pg·h/mL]	5	2.90 (16.3)	1222.1	21	3.91 (30.9)	1222.4	11	4.22 (39.0)	1222.3
	12[1]	3.36 (23.7)[1]	1222.2	31	3.95 (49.4)	1222.6	48	4.93 (45.7)	1222.5
	---	---	1222.8						
	8[#]	4.21 (26.0)[#]	1222.21[#]				77[#]	6.08 (50.8)[#]	1222.22[#]
$C_{max,ss}$ [pg/mL]	17[1]	5.33 (44.4)[1]	1222.2	45	5.09 (53.0)	1222.6	72	7.13 (63.8)	1222.5
	26[§]	3.32 (24.1)[§]	1222.47[§]				44[§]	5.30 (54.2)[§]	1237.3[§]
	30[§]	5.36 (34.4)[§]	1222.48[§]						
	9[#]	6.80 (53.5)[#]	1222.21[#]				78[#]	13.1 (58.6)[#]	1222.22[#]
$AUC_{0-1,ss}$ [pg·h/mL]	16[1]	4.67 (38.1)[1]	1222.2	43	4.37 (50.3)	1222.6	68	5.76 (55.8)	1222.5
	24[$]	2.78 (23.5)[$]	1222.47[$]				37[§]	4.30 (62.3)[§]	1237.3[§]
	31[$]	4.01 (30.3)[$]	1222.48[$]						
	8[#]	6.17 (35.8)[#]	1222.21[#]				77[#]	10.8 (54.0)[#]	1222.22[#]

--- no descriptive statistics is available, since parameter was available for less than 2/3 of the subjects
1 The given numbers include males and females, hence differ from numbers given in CTR 1222.2 (males and females presented separately).
Japanese study
§ Olodaterol mono arm in the tiotropium+olodaterol FDC Study 1237.3
$ Olodaterol treatment within the DDI studies 1222.47 and 1222.48

3.2.3. Pharmacokinetics in other special populations

3.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

The effect of mild (Child Pugh 5 to 6) and moderate (Child Pugh 7 to 9) hepatic impairment on the PK of olodaterol was investigated in Study U10-2864. Exposure to olodaterol in patients with liver impairment of both degrees was not altered as compared to healthy subjects matched by age, weight and gender.

3.2.3.2. Pharmacokinetics in subjects with impaired renal function

The effect of renal impairment on the pharmacokinetics of olodaterol was investigated in dedicated Study U10-2081. The study included subjects with severe renal impairment (creatinine clearance 18.6 to 29.8 mL/min) and a control group of healthy subjects with normal renal function (creatinine clearance 81.2 to 117 mL/min) matched by age, weight and gender. On average, a 1.4 fold higher systemic exposure to olodaterol was observed in severely renally impaired subjects as compared to the control group.

3.2.3.3. Pharmacokinetics according to age, weight, height and lung function

Based on a multivariate linear regression analysis of Phase II pharmacokinetic data age, weight, height and lung function (pre treatment baseline FEV1) were found to be statistically significant covariates for olodaterol plasma concentrations (U10-2212). The effects of the individual covariates however were moderate (15–42% increase of $C_{max,ss}$), 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). Gender was not found to be a relevant intrinsic factor for systemic exposure to olodaterol.

3.2.3.4. Pharmacokinetics according to race

The pharmacokinetics of olodaterol in Caucasians and Japanese were compared across the Phase I Studies (U06-1418, U07-2062, U08-3758) and across the Phase II Studies (U07-1743, U09-3125, U10-2537). Systemic exposure was about 30 to 50% higher in Japanese healthy subjects and about 30 to 80% higher in Japanese COPD patients than in the corresponding Caucasian population. After 4 weeks once daily inhalation of 5 µg olodaterol steady state exposure in Japanese COPD patients was 40% to 50% higher than in the Caucasian COPD patients (based on $AUC_{0\text{-}1,ss}$ and Cmax,ss ; U07-2062, U09-3125).

Slightly higher systemic exposure was also observed for Asians other than Japanese in the Phase III studies: geometric mean plasma concentrations at 10 minutes after the inhalation of 5 or 10 µg olodaterol were approximately 20% higher in the Asians than in Caucasians (U10-3303, U10-3302).

Due to insufficient numbers of Blacks/African Americans participating in the Phase II and Phase III studies, comparison of geometric mean plasma concentration data between Blacks/African Americans and Caucasians is not reliable. The individual dose normalized Cmax,ss or $C_{0.167,ss}$ values of the Blacks/African Americans however were generally within the range of values observed in the Caucasians (U09-3125, U09-1850, U10-3192, U10-3193, U10-3194). There is no evidence for a pronounced difference in systemic exposure to olodaterol between Blacks/African Americans and Caucasians.

3.2.4. Pharmacokinetic interactions

3.2.4.1. Pharmacokinetic interactions demonstrated in human studies

Based on the results of the human Absorption, distribution, metabolism and excretion (ADME) Study U08-2268 approximately 40% of an intravenous olodaterol dose is eliminated via CYP mediated metabolism. According to *in vitro* investigations CYP2C9 is most prominently involved in this metabolism. Therefore, a possible effect of co medicated drugs with CYP inhibition potential on the systemic exposure to inhaled olodaterol was investigated by a drug-drug interaction study using fluconazole (400 mg q.d.) as model inhibitor of CYP 2C9 (U10-3391). Steady state exposure to olodaterol in this study was found not to be relevantly affected by co administration of fluconazole.

Since *in vitro* and animal studies indicated that olodaterol is substrate of P-gp, an additional drug-drug interaction study using ketoconazole (400 mg q.d.) as potent P-gp inhibitor was conducted (U10-3390). Steady state exposure to olodaterol in the presence of ketoconazole was found to be increased by about 70%. As it is known that besides being a potent inhibitor of P-gp ketoconazole inhibits an array of drug metabolising enzymes the observed effect of ketoconazole on olodaterol plasma concentrations is likely attributed to inhibition of both, P-gp and at the same time inhibition of enzymes involved in the Phase I and or Phase II metabolism of olodaterol. In conclusion, drugs with inhibitory potential on P-gp may lead to increased olodaterol exposure. However, even with a strong inhibitor of both, P-gp and CYP enzymes, olodaterol plasma concentrations were elevated by no more than 1.7 fold.

An additional drug-drug interaction study with tiotropium (U09-1422) was performed for the tiotropium with olodaterol fixed dose combination. Although Cmax,ss of olodaterol was found to be statistically significantly increased when 10 µg olodaterol and 5 µg tiotropium were administered together as a fixed dose combination via an inhaler, the effect was small (11% increase as compared to inhalation of olodaterol alone. Systemic exposure to tiotropium as

assessed by urinary excretion ($Ae_{0\text{-}24,ss}$) was unaffected by the concomitant administration of olodaterol. In conclusion, co administration of olodaterol and tiotropium did not relevantly affect each other's PK.

3.2.4.2. Clinical implications of in vitro findings

In vitro investigations indicated that olodaterol and its major metabolite CD 992 had no potential to inhibit or induce CYP enzymes at the exposure levels expected to be achieved in clinical practice. Likewise, inhibition of P-gp and other transporters based on the results of *in vitro* studies is unlikely. Thus, effects of olodaterol on systemic exposure levels of other medications are not to be expected and were therefore not investigated in clinical studies. This is largely borne out by the studies that were conducted.

3.3. Evaluator's overall conclusions on pharmacokinetics

In general the PK studies presented by the sponsor were well designed and for the most part subject numbers were based on *a priori* power calculations, with the numbers of subjects investigated meeting the requirement for the pre determined power. Dose proportionality of kinetics was demonstrated across a range of doses which exceeded that recommended for therapeutic use. Metabolism of the medication was thoroughly investigated and although there is an active metabolite it is present in concentrations unlikely to contribute to pharmacological activity. The effects of renal and hepatic impairment on single dose PK were investigated in two studies. These were adequately powered and suggested that hepatic impairment does not significantly alter the PK of olodaterol. On the other hand, severe renal impairment increases systemic exposure to olodaterol. There was no specific study examining extremes of age on the PK of olodaterol. The effect of age on PK was inferred from a multivariate analysis. A study in Japanese subjects suggested that systemic exposure after both single and repeated doses (by inhalation) was increased compared to Caucasians. This conclusion relied on a *post hoc* comparison across different studies so was not derived from a simultaneous assessment. Similarly the PK in Black subjects was available from *post hoc* comparisons in limited PK sampling in the clinical trial programme. Numbers of subjects may have been inadequate to draw meaningful conclusions about PK in such populations. There was no population PK analysis performed based on sparse sampling although there appears to be data available to perform such an analysis with standard methods. Such an analysis would allow for further exploration of issues known to influence clearance (such as age, weight, ethnicity) and would further add to the conclusions drawn from multivariate analysis.

Based on the known metabolic profile of olodaterol and the enzymes responsible, some drug-drug interaction studies were performed. These were adequately powered and suggested that olodaterol PK was not affected by fluconazole (CYP2C9 inhibitor) but systemic exposure was increased by ketoconazole (P-gp inhibitor). The lack of specificity of ketoconazole (for P-gp) leaves open the possibility of CYP enzymes being involved in this observation. A study with a selective P-gp inhibitor (for example, quinidine) would have been more informative. Thus questions remain about the PK interaction potential of olodaterol with other commonly prescribed agents. Furthermore neither study had a physiological end point included, such as FEV1, which might have been more relevant to assess interaction potential given the proposed therapeutic indication. An interaction study with tiotropium was also performed with the view that both drugs may be used concomitantly for COPD treatment. While there no interaction on the PK of either drug no physiologically relevant end point was included. Tiotropium was the only medication regularly used in the treatment of COPD for which an interaction with olodaterol was studied. There were no studies which examined the potential interaction with other bronchodilators and inhaled steroids. Similarly, no studies were presented which examined the potential interaction of olodaterol with antibiotics which are often co administered in COPD patients.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

The table below shows the studies relating to each pharmacodynamic topic.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on cyclic AMP	U06-1418 U07-2062 U08-1060 U08-1081	
Secondary Pharmacology	Effect on heart rate	U08-1543 U09-3125	 §
	Effect on blood pressure	U08-1543 U06-1418	
	Effect on potassium concentrations	U06-1418 U07-2062 U07-1743 U07-2062 U08-1060 U08-1081 U09-3125 U10-3192 U10-3193 U10-3194 U10-3195	 § § § § § §
	Effect on QTc interval	U08-1543	*
Gender other genetic and Age Related Differences in PD response	Effect of gender	U08-1543	
	Effect of age	None	
PD Interactions		None	
Population PD and PK-PD Analyses	Healthy subjects	None	
	Target population	None	

* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

A number of PD parameters known to be responsive to β2 agonists were examined and included cardiovascular parameters (blood pressure, heart rate, QT/QTc intervals), and laboratory parameters (cAMP, potassium, glucose, insulin, C peptide, free fatty acids, lactate). Among the laboratory parameters, cAMP and potassium levels were found to be the most sensitive markers of systemic PD activity; their dose response relationship was further evaluated in subsequent studies besides the cardiovascular parameters.

Dose and exposure dependent increases in cAMP concentrations after inhalation of olodaterol in healthy volunteer studies were seen starting with the dose of 10 µg. As there are no known

clinical implications of increased cAMP plasma concentrations, measurement of cAMP was not pursued further in Phase II and Phase III trials.

In healthy volunteer studies, treatment related transient decreases of blood potassium concentrations were observed starting at inhaled doses of 10 to 20 µg which became more pronounced with increasing doses. At the highest tested inhaled dose of 70 µg, the maximum decrease from baseline potassium concentrations amounted to -0.63mmol/L. In Phase II and Phase III studies with COPD patients, treatment related decreases of potassium were noted only at doses of 20 µg or above, while no effects of olodaterol on blood potassium concentrations were apparent at the therapeutic dose (5 µg) or twice the therapeutic dose (10 µg).

The effects of olodaterol on cardiac repolarisation were compared to moxifloxacin as a positive control in healthy male and female volunteers. The study investigated single inhaled doses up to 50 µg of olodaterol. A small but dose and plasma concentration dependent effect of olodaterol on QT intervals was observed. Females appeared to be slightly more sensitive to the effects of olodaterol on QTc than males. Treatment related decreases in diastolic blood pressure and or increases in systolic blood pressure were noted after inhaled doses of 20 µg or greater.

4.2.1. Mechanism of action

Olodaterol exerts its pharmacological effects by binding and activation of β2 adrenoceptors after 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.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects:

In order to investigate the acute response following binding of olodaterol to the β2 adrenoreceptor, plasma concentrations of the second messenger cAMP were measured over a period of 6 hours post inhalation, intravenous and oral dosing for dose escalation trials with healthy volunteers (U06-1418, U07-2062, U08-1081, U08-1060). Dose and exposure dependent increases in plasma cAMP levels were observed. As there are no known clinical implications of increased plasma cAMP concentrations, measurement of cAMP was not pursued further in Phase II and Phase III trials.

4.2.2.2. Secondary pharmacodynamic effects:

4.2.2.2.1. Heart rate

Effects of inhaled olodaterol on the heart rate were investigated in healthy male and female volunteers in the QT/QTc trial (U08-1543). Small, but dose dependent increases in heart rate from baseline exceeding those in the placebo group were observed from the 20 µg olodaterol dose. The mean maximum changes seen within the observation period from 10 minutes to 8 hours after inhalation ranged from 9.3 bpm (placebo) to 14.0 bpm (50 µg olodaterol). Similarly, in a 4 week inhalation study in COPD patients increases in heart rate became apparent only at the 20 µg dose level of olodaterol, which was the highest dose tested. Mean maximum increases from baseline of 6.2 bpm were observed in the 20 µg olodaterol group, while mean maximum increases of 3.6 bpm were observed in the placebo group (U09-3125).

4.2.2.2.2. QTc interval

The effects on cardiac repolarisation after single inhalation of 10, 20, 30, and 50 µg olodaterol by healthy male and female volunteers were investigated in Trial U08-1543. A small but dose and plasma concentration dependent effect of olodaterol on QT intervals was observed. Uncorrected QT intervals shortened; this however did not fully compensate for the increases in heart rate, resulting in small but dose and plasma concentration dependent increases of the individually heart rate corrected QT intervals (QTcI). The upper limit of the two sided 90%

confidence interval of the maximum observed difference to placebo of time matched QTcI changes from baseline was 5.5 ms after the 10 µg olodaterol dose, and slightly exceeded the pre defined 10 ms margin from the 20 µg dose upwards (10.2 ms, 11.8 ms and 12.6 ms). Assay sensitivity in this study was demonstrated by comparing the difference in QTcI intervals of moxifloxacin (400 mg single dose) with that of placebo. Using an ANCOVA model the difference in QTcI intervals between moxifloxacin and placebo yielded a mean of 12.8 ms (90% CI 10.0 to 15.5 ms).

4.2.2.2.3. Blood pressure

Serial measurements of blood pressure up to at least 3 hours after administration were performed in virtually all studies. The majority of the studies employed inhaled doses of olodaterol up to 40 µg. There was no clear association of any observed changes in blood pressure with the active treatment. Higher inhaled doses of up to 50 µg and up to 70 µg were given to healthy volunteers (U08-1543; U06-1418 respectively). There was a trend for treatment related decreases in diastolic blood pressure apparent from doses of 15 µg or 30 µg onwards, and increases in systolic blood pressure were noted starting with the dose of 40 µg and 20 µg. The average changes from baseline even at the highest dose of 70 µg olodaterol did not exceed -13.7 mmHg for diastolic blood pressure and 7.3 mmHg for systolic blood pressure.

Greater and clearly dose dependent changes in blood pressure were observed following intravenous administration of olodaterol in healthy volunteers (U08-1081). Maximum effects were recorded at the end of a 30 minute infusion of 15 µg olodaterol, with a mean decrease in diastolic blood pressure from baseline of 30.7 mmHg and a concomitant mean increase in systolic pressure of 22 mmHg.

4.2.2.2.4. Plasma potassium

Serum potassium concentrations were evaluated over a period of 6 hours post inhalation, intravenous and oral dosing for dose escalation trials with healthy volunteers (U06-1418, U07-2062, U08-1081 and U08-1060). Dose and exposure dependent decreases of potassium were observed.

After inhalation, decreases of potassium related to the active treatment in the healthy volunteers were observed starting at doses of 10 µg for females (U07-2062) or 20 µg for males (U06-1418). The effects were transient, and minimum potassium concentrations in the affected dose groups were usually observed between 1 and 3 hours after the inhalation. At the highest tested dose of 70 µg a decrease of potassium from baseline by 0.63 mmol/L was observed.

Monitoring of potassium was continued throughout Phase II and Phase III studies with COPD patients. In a single dose study, geometric mean potassium concentrations after inhalation of 40 µg olodaterol decreased from a baseline value of 4.65 mmol/L to a minimum value of 4.07 mmol/L at 1 hour post dosing, while overall no statistically significant reduction relative to placebo was noted in the lower dose groups of 2 to 20 µg (U07-1743). In a 4 week inhalation study, potassium concentrations decreased slightly but statistically significantly and exceeded those after treatment with placebo but only in the highest dose group of 20 µg olodaterol (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, respectively; (U09-3125)). There was overall no evidence for treatment related effects on potassium concentrations measured at 1 and 3 hours post dosing on treatment Days 43 and 85 in the Phase III studies with daily inhalations of 5 µg or 10 µg olodaterol (U10-3192, U10-3193, U10-3194, U10-3195).

4.2.3. Time course of pharmacodynamics effects

There were no studies examining the time course of the effects of olodaterol on respiratory function in healthy volunteers.

The effect of olodaterol administered at different doses on the QTcI was studied in healthy volunteers (U08-1543). The mean time matched changes from baseline between 20 minutes

and 2 hours were -7.2 ms in the placebo group and -7.0, -7.3, -11.2 and -12.8 ms after inhalation of 10, 20, 30 and 50 µg olodaterol, respectively. In contrast, individually heart rate corrected QT intervals (QTcI) increased, dose dependently with adjusted mean time matched changes from baseline between 20 minutes and 2 hours of -5.8 ms in the placebo group, and -4.2, -1.7, -0.5 and 0.7 ms after inhalation of 10, 20, 30 and 50 µg olodaterol, respectively. The difference to placebo of the mean QTcI time matched change from baseline between 20 minutes and 2 hours.

4.2.4. Relationship between drug concentration and PD effects

In the QTc investigation the relationship between olodaterol plasma concentrations and change of QTcI (ΔΔQTcI) interval as well as between olodaterol plasma concentrations and change of heart rate was examined using linear regression models. Simulations using a non linear mixed effect modelling approach confirmed that the linear model used to describe the relationship between olodaterol plasma concentration and ΔΔQTcI was adequate, although the effect of olodaterol on QTcI (estimated Tmax: 0.54 hours (33 minutes)) was slightly delayed compared to the reported Tmax of olodaterol plasma concentrations (median Tmax: 0.233 to 0.400 hours (14 to 24 minutes)) (U08-1543).

Throughout all studies performed in the olodaterol development program, highest olodaterol plasma concentrations were achieved in the intravenous infusion Study U08-1081, with up to 8 fold higher Cmax values (133 pg/mL) as compared those observed after inhalation of the 50 µg olodaterol dose in the QT/QTc study (Cmax: 16.2 pg/mL). The highest individual QTcF change from baseline, which was observed during infusion of 25µg olodaterol over 3 hours, was 44 ms. The greatest mean increase in QTcF seen after the 30 minute infusion of 15 µg olodaterol was 16.9 ms, and was associated with a mean decrease of the uncorrected QT interval by 32.6 ms and a mean increase in heart rate by 25.4 bpm.

No relationship was found between olodaterol plasma concentrations (C0.167,ss) and potassium concentrations (1 hour and 3 hours post dose values) in COPD patients based on a statistical analysis using a mixed models repeated measures analysis (U10-3689).

4.2.5. Genetic, gender, age related differences in PD response

Females appeared to be slightly more sensitive to the effects of olodaterol on QTcI than males (U08-1543).

PD responses with respect to age and genetic differences were not presented.

4.2.6. Pharmacodynamic interactions

No studies presented.

4.3. Evaluator's overall conclusions on pharmacodynamics

A thorough QTc study was performed using moxifloxacin as a positive control to investigate the effects of olodaterol on the corrected interval. The effect was less than 10 ms on the QT interval even at doses which exceeded that to be used in clinical practice (5 to 10 µg). Olodaterol had effects on plasma cAMP concentrations and on plasma potassium. The former increased and the latter decreased dose dependently. The consequences of increased cAMP are not known. The decrease in potassium was relatively small and probably not clinically significant. The lack of drug interaction studies evaluating PD based outcomes is surprising given the indication for the medication and the potential for it to be used with other agents in management of COPD.

5. Dosage selection for the pivotal studies

The sponsor had provided the rationale for the dose selection of olodaterol for the Phase III studies (5 µg and 10 µg once daily). The dose selection for the Phase III clinical development

program for olodaterol was based on the safety and tolerability results and the dose response relationship results in 2 Phase II studies, Study 1222.3 (single dose study in COPD patients) and Study 1222.5 (4 week once daily dosing study in COPD patients). These 2 studies showed no safety or tolerability concerns after single dose administration of up to 40 µg (Study 1222.3) and after 4 week once daily dosing of up to 20 µg (Study 1222.5). In addition, in Study 1222.5, the effects of olodaterol on systemic pharmacodynamic (PD) parameters (serum potassium and creatine phosphokinase) were used to identify the threshold for the onset of systemic PD activity, and hence support an appropriate dose selection for the Phase III studies. Results showed that after the first dose, serum potassium levels for olodaterol 2 µg, 5 µg and 10 µg were similar to placebo, while there were small but statistically significant reductions in serum potassium levels for olodaterol 20 µg compared to placebo. After 4 weeks of treatment, there were no statistically significant differences in serum potassium levels at any dose compared to placebo. Evaluations of serum creatine phosphokinase showed a similar pattern, suggesting that the threshold for systemic PD activity for olodaterol was about 20 µg in patients with COPD.

Evaluation of the efficacy dose response relationship of olodaterol in Studies 1222.3 and 1222.5 (doses of 2 µg, 5 µg, 10 µg and 20 µg olodaterol were investigated in both studies) showed no clear evidence of an incremental increase in efficacy for olodaterol 20 µg compared to olodaterol 10 µg based on FEV1 (forced expiratory volume in one second) responses. The efficacy associated with administration of olodaterol 2 µg was consistently lower than that with olodaterol 10 µg or 20 µg, while the relative efficacy of olodaterol 5 µg was more variable than the response with 2 µg and with 10 µg, such that the position of olodaterol 5 µg on the dose response curve could only be characterised as intermediate between suboptimal (2 µg) and plateauing in efficacy (10 or 20 µg). These efficacy results will be described later in this section.

The sponsor had judged that the above results supported the selection of olodaterol 10 µg for further evaluation in the Phase III studies, while olodaterol 5 µg was also included because it was judged that the variability in efficacy observed in the Phase II studies warranted further investigation in larger Phase III studies. Prior to initiation of the Phase III program, the decision to evaluate olodaterol 5 µg and olodaterol 10 µg in the Phase III studies had been accepted by the FDA at the end of Phase II meeting and by the Netherlands Medicines Evaluations Board[3] at the Scientific Advice Meeting.

The efficacy results of Studies 1222.3 and 1222.5 will be described briefly in this section. Studies 1222.3 and 1222.5 were Phase II studies in COPD patients. Study 1222.3 was a single dose, randomised, double blind, placebo controlled, 5 way cross over study evaluating the efficacy and safety of single doses of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) in COPD patients, followed by an optional period of open label olodaterol 40 µg (to assess pharmacokinetics (PK) of 40 µg olodaterol[4]). The primary endpoint was FEV1 at 24 hours post dose (that is, trough FEV1). Results from Study 1222.3 showed that all single doses of olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) had statistically significantly greater FEV1 at 24 hour post dose compared to placebo.

Study 1222.5 was a 4 week, randomised, double blind, placebo controlled parallel group study evaluating the efficacy and safety after 4 weeks of once daily treatment of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) in COPD patients. The primary endpoint was the trough FEV1 response after 4 weeks of treatment. Results showed that after 4 weeks of treatment,

[3] Netherlands is the Reference Member State in EU.

[4] The open-label period of study 1222.3 was conducted to characterise the PK of two metabolites of olodaterol, SOM 1522 BS and BI 1744 BS–glucuronide, following single inhalation of 40 µg of olodaterol in COPD patients. The PK results of this open label period were presented in report 1222.9003. These PK results are not relevant to the evaluation of this submission for registration of olodaterol. They were evaluated for the purpose of this evaluation, and the results did not raise any concerns relevant to this submission, and hence will not be further described in this evaluation. Safety results of subjects on 40 µg of olodaterol was described in the main study report (1222.3), and will be described and evaluated in the Safety section of this report.

there were statistically significantly greater mean trough FEV1 response and FEV1 AUC_{0-6h} response for all olodaterol doses compared to placebo. With regards to dose response relationship, doses of olodaterol 10 µg and olodaterol 20 µg showed increased efficacy (in terms of trough FEV1 response) compared with olodaterol 2 µg, suggesting that olodaterol 2 µg was on the steep portion of the dose response curve. The efficacy of olodaterol 10 µg and olodaterol 20 µg was similar, suggesting that both doses were on, or close to, the plateau of the dose response curve. Over the 4 week study duration, the relative efficacy of olodaterol 5 µg compared with olodaterol 2 µg and olodaterol 10 µg was variable, such that in some cases, similar efficacy was observed between olodaterol 2 µg and olodaterol 5 µg, in some cases, similar efficacy was observed between olodaterol 5 µg and olodaterol 10 µg, and in some cases, the efficacy of olodaterol 5 µg was between those of olodaterol 2 µg and olodaterol 10 µg.

Comments: The evaluator considered the rationale for the dose selection in the Phase III studies is appropriate.

6. Clinical efficacy

Four pivotal Phase III studies were submitted to support clinical efficacy for the proposed indication. These consisted of 2 sets of replicate, randomised, double blind, parallel group studies, each with a 48 week treatment duration, where one set of replicate studies (Studies 1222.11 and 1222.12) was placebo controlled, while the other set (Studies 1222.13 and 1222.14) was both placebo and active controlled (active control: formoterol). All 4 studies evaluated the efficacy of olodaterol with respect to bronchodilatation (peak and trough lung function responses). In addition, the replicate Studies 1222.13 and 1222.14 included endpoints evaluating potential symptomatic benefit by reduction of dyspnoea (assessed via the Mahler Transition Dyspnea Index (TDI) focal score), and by improvement of health related quality of life (assessed via the St. George's Respiratory Questionnaire (SGRQ) total score). The sponsor had stated that Studies 1222.11 and 1222.12 were designed to satisfy the clinical regulatory standards in the US, with primary efficacy evaluation after 12 weeks of treatment, efficacy endpoints based upon lung function assessment, and being placebo controlled. However Studies 1222.13 and 1222.14 were designed to satisfy the clinical regulatory standards in the EU, with primary efficacy evaluation after 24 weeks of treatment, efficacy endpoints based upon assessment of both lung function and symptomatic benefit, and being both placebo and active controlled with an active comparator of known therapeutic benefit.

In addition, 6 supporting Phase III efficacy studies were submitted. These included 2 sets of replicate, randomised, double blind, placebo and active controlled, cross over studies, each with a 6 week treatment duration, evaluating the lung function profile over a 24 hour dosing interval in order to characterise the bronchodilator profile of olodaterol over 24 hours. The first set of replicate studies, Studies 1222.24 and 1222.25, used formoterol as the active control, and the second set of replicate studies, Studies 1222.39 and 1222.40, used tiotropium as the active control. In addition, there is another set of replicate, randomised, double blind, placebo controlled, cross over studies (Studies 1222.37 and 1222.38) with a 6 week treatment duration to evaluate the effect of olodaterol on symptom limited exercise tolerance. An overview of the main efficacy variables in the olodaterol Phase III studies is presented in the table below.

Table 5. Main efficacy variables overview

Variable	Trial				
	1222.11 1222.12	1222.13 1222.14	1222.24 1222.25	1222.39 1222.40	1222.37 1222.38
Pulmonary function					
FEV_1	X	X	X	X	X
FVC	X	X	X	X	X
Morning PEFR	X	X			
Evening PEFR	X	X			
Functional Residual Capacity (FRC)					X
Inspiratory Capacity (IC)					X
Symptomatic benefit					
Mahler Transition Dyspnea Index (TDI)		X			
St. George's Respiratory Questionnaire (SGRQ)		X			
Daily rescue medication (salbutamol/albuterol)	X	X			
Patient's global rating (PGR)	X	X			
Exercise					
Exercise endurance time					X
Inspiratory capacity (IC) during exercise					X
Breathing discomfort during exercise					X
COPD Exacerbations					
Time to first exacerbation	X	X			

Other studies to be evaluated for efficacy included the 3 Phase II studies conducted in COPD patients, and the combined/pooled analyses reports. In this efficacy section of this evaluation report, the respective sets of replicate studies will be presented in the same sub sections, together with their combined analysis results, for ease of reference.

6.1. For the indication of long term, once daily bronchodilator treatment of airflow obstruction in patients with COPD

6.2. Pivotal efficacy studies

6.2.1.1. Studies 1222.11 and 1222.12

6.2.1.1.1. Study design, objectives, locations and dates

Both Studies 1222.11 and 1222.12 are multi centre, randomised, double blind, placebo controlled, parallel group studies evaluating the efficacy and safety of 48 weeks of once daily treatment of orally inhaled olodaterol (5 µg and 10 µg) delivered by the Respimat inhaler, in patients with COPD. The primary objective of both studies was to assess the efficacy and safety of once daily treatment of olodaterol inhalation solution (5 µg and 10 µg) compared to placebo in patients with COPD.

Studies 1222.11 and 1222.12 were multi centre studies where subjects were enrolled in a total of 54 study sites across 6 countries (21 in the US, 11 in China, 8 in Germany, 5 in Australia, 5 in Taiwan, and 4 in New Zealand), and 52 study sites across 4 countries (29 in the US, 11 in China, 7 in Germany, and 5 in Taiwan), respectively. The study start and end dates of Study 1222.11 were 05 November 2008 and 21 September 2010, respectively, and those of Study 1222.12 were 05 February 2009 and 27 September 2010, respectively.

Following the Screening Visit (Visit 1) and a two week baseline period, subjects were to be randomised on Visit 2 into 1 of 3 treatment groups: olodaterol 5 µg, olodaterol 10 µg, or placebo. Additional visits were to be scheduled after 2, 6, 12, 18, 24, 32, 40, and 48 weeks of treatment (Visits 3 to 10). There was one post treatment visit, two weeks after the end of treatment (Visit 11) to ensure stability of patient after wash out of olodaterol and prior to trial completion.

6.2.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in these 2 studies were male or female patients aged 40 years or older with a diagnosis of COPD, who had a smoking history of more than 10 pack years, and had post bronchodilator FEV1 less than 80% predicted normal and post bronchodilator FEV1 forced vital capacity (FVC) less than 70% at the screening visit.[5]

Subjects were excluded if they had a history of asthma, had undergone thoracotomy with pulmonary resection, regularly used daytime oxygen therapy for more than one hour per day and were, in the investigator's opinion, unable to abstain from the use of oxygen therapy during study clinic visits, or had completed a pulmonary rehabilitation program in the six weeks prior to the screening visit (Visit 1) or were currently in a pulmonary rehabilitation program.

> Comments: The inclusion and exclusion criteria were in line with recommendations on study population in the EMA guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease[6] as well as the FDA Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment.[7] The diagnostic criteria for COPD (post bronchodilator FEV1 less than 80% predicted normal and post bronchodilator FEV1 FVC less than 70%) were consistent with those in the above guidelines, as well as with current clinical practice guidelines.[8]

6.2.1.1.3. Study treatments

The study treatment groups were olodaterol 5 µg (2 actuations of 2.5 µg each), olodaterol 10 µg (2 actuations of 5 µg each), and matching placebo, all to be administered once daily[9] with the Respimat inhaler. The treatment duration was 48 weeks.

During the study, a short acting β2 agonist medication (salbutamol) was provided to all subjects for rescue use, and appropriate medications were allowed to control acute exacerbations as medically necessary. In terms of concomitant pulmonary medications, only LABAs were withdrawn prior to study entry, and all subjects treated with other pulmonary medications prior to study enrolment (for example inhaled steroids, short and long acting anticholinergics, xanthines) were eligible for the study and were continued on these medications as concomitant therapy during the treatment period. In particular, with regards to long acting anticholinergics, subjects using long acting anticholinergics such as tiotropium as a maintenance bronchodilator therapy (for at least 6 weeks prior to Visit 1) could continue on this therapy for the duration of the trial. Subjects not on maintenance long acting anticholinergics prior to the trial and who subsequently required a new, chronic maintenance long acting anticholinergic prescription prior to Visit 5 (Week 12; time point for evaluation of primary efficacy endpoint) were discontinued from the trial. Subjects not on maintenance long acting anticholinergics prior to the trial and who subsequently required a new, chronic maintenance long acting anticholinergic after Visit 5 were permitted to continue that treatment during the trial.

[5] At screening, pulmonary function was measured before and after administration of 400 µg of salbutamol to assess study eligibility.

[6] European Medicines Agency, Guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. 21 June 2012. This EMA guideline was adopted by the EU Committee for Medicinal Products for Human Use (CHMP) on 9 July 2012, and was intended to replace the TGA adopted EMA guidelines "Points to consider on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease" (CPMP/EWP/562/98, 19 May 1999).

[7] FDA, Guidance for Industry- Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.

[8] Australian Lung Foundation. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease. 2010.

[9] The first administration of study drug occurred at Visit 2, when it was to be self-administered between 7:00 a.m. and 10:00 a.m. Subsequent study drug administration was to occur within plus or minus 30 minutes of the time of administration at Visit 2.

Comments: The study dose selection is appropriate and has been previously discussed. The study design involving a placebo control is appropriate and consistent with the recommendation of the FDA Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment.[10] The provision of a short acting β2 agonist as rescue medication is in keeping with both FDA and EMA guidelines.

In these studies, LABAs were not permitted as concomitant medications, but subjects were allowed to be on other long acting bronchodilators such as long acting anticholinergics. The sponsor had provided the rationale for this, where the sponsor noted that Phase III pivotal studies for Spiriva (tiotropium) and for indacaterol allowed co administration with inhaled steroids, but did not allow the use of other anticholinergics (for example, ipratropium) or LABAs (for example, formoterol, salmeterol). The sponsor had stated that given that long acting bronchodilators (for example, long acting anticholinergics or LABAs) are currently well established as maintenance treatment of moderate to severe COPD, the sponsor was of the opinion that placebo controlled studies without any allowance for some form of maintenance bronchodilator treatment were no longer justified. Therefore, the Phase III pivotal studies for olodaterol allowed the use of long acting anticholinergics. This rationale appeared sound. In addition, a look through the EMA and FDA guidelines showed that there was no specific recommendation given with regards to concomitant pulmonary medications or specifications that concomitant pulmonary medications should not be permitted. The EMA guidelines on clinical investigation of medicinal products in the treatment of COPD stated simply that

> '*The use of all concomitant therapies should be accurately recorded and balanced across treatment groups at baseline*',

and the FDA guidelines stated that

> *'Patients enrolled in the study should be permitted to use concomitant treatments as needed to manage disease symptoms"*

The evaluator is of the opinion that the presence of concomitant long acting anticholinergics would not introduce a bias into the study results as long as the use of these medications during the treatment period is comparable across treatment groups.

6.2.1.1.4. Efficacy variables and outcomes

There were two co primary endpoints in these studies: FEV1 $AUC_{0\text{-}3h}$ response at Day 85 (that is after 12 weeks of treatment) and trough FEV1 response at Day 85.

Secondary endpoints evaluating FEV1 included FEV1 $AUC_{0\text{-}12h}$ response at Day 85 (in subset of subjects with available data[11]); FEV1 $AUC_{0\text{-}3h}$ response, trough FEV1 response, and FEV1 $peak_{0\text{-}3h}$ response over 48 weeks; FEV1 at individual time points during the 3 hour post dose period over 48 weeks; FEV1 at individual time points during the 12 hour post dose period at Day 85 (in subset of subjects with available data). Secondary endpoints evaluating FVC included FVC $AUC_{0\text{-}12h}$ response at Day 85 (in subset of subjects with available data); FVC $AUC_{0\text{-}3h}$ response, trough FVC response, and FVC $peak_{0\text{-}3h}$ response over 48 weeks; FVC at individual time points during the 3 hour post dose period over 48 weeks; FVC at individual time points during the 12 hour post dose period at Day 85 (subset of subjects with available data). Other

[10] FDA, Guidance for Industry- Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.

[11] At Visit 5 (that is, Week 12 or Day 85), in a sub-set of subjects labelled "*12-hour PFT set*", pulmonary function testing (PFT) were to be performed pre dose (−1 hour and −10 minutes prior to test-drug inhalation) and at 5, 15 and 30 minutes, and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after inhalation of study medication. In subjects not in this sub-set, PFTs were to be performed at Visit 5 at 5, 15 and 30 minutes, and at 1, 2 and 3 hours after inhalation of study medication.

secondary endpoints included weekly mean pre dose morning and evening peak expiratory flow rate (PEFR); weekly mean number of puffs of rescue medication used per day; Patient's Global Rating (PGR)[12] over 48 weeks; time to first COPD exacerbation; time to first moderate COPD exacerbation; time to first COPD exacerbation leading to hospitalisation; number of COPD exacerbations (per patient year); number of moderate COPD exacerbations (per patient year); number of COPD exacerbations leading to hospitalisation (per patient year).

FEV1 AUC and FVC AUC were defined as the area under the respective FEV1 or FVC curve normalised for time. $AUC_{x\text{-}yh}$ was calculated as the area under the curve from x to y hours using the trapezoidal rule, divided by the full duration (that is, y to x hours). Trough FEV1 was defined as the FEV1 value at the end of the dosing interval (that is, 24 hours), performed 10 minutes prior to the next study drug inhalation.[13] FEV1 $peak_{0\text{-}3h}$ or FVC $peak_{0\text{-}3h}$ was calculated as the maximum of the measurements during the first three hours after dosing. "Response" referred to change from pre treatment baseline (for example trough FEV1 response was defined as the change from baseline in trough FEV1).

COPD exacerbation was pre defined as

> *'a complex of lower respiratory events/symptoms (increase or new onset) related to the underlying COPD, with a duration of three days or more, requiring a change in treatment'.*

A "complex of lower respiratory events/symptoms" included at least two of the following symptoms: shortness of breath, sputum production, occurrence of purulent sputum, cough, wheezing, or chest tightness. A "required change in treatment" included prescription of antibiotics and or systemic steroids, and or significant change for prescribed respiratory medication (bronchodilators, including theophyllines). Moderate COPD exacerbations were defined as those which did not lead to hospitalisation, but needed treatment with antibiotics and or systemic steroids. Pulmonary function tests and assessments of endpoints were performed according to a schedule.

The primary and secondary endpoints for the combined analysis of Studies 1222.11 and 1222.12 (Study report 1222-9992) will be described here for ease of reference and for completeness. In the combined dataset analysis, primary endpoints were the same as those in the individual studies (that is FEV1 $AUC_{0\text{-}3h}$ at Day 85, trough FEV1 at Day 85). The key secondary efficacy endpoints were FEV1 at Day 1 over 3 hours post dose, FEV1 pre dose and over the 12 hour post dose period at Day 85, and FEV1 $AUC_{0\text{-}12h}$ response at Day 85, all in the 12 hour PFT set.[14]

> Comments: Overall, the primary and secondary endpoints of this study are appropriate and consistent with the recommendations in the EMA guidelines on clinical investigation of medicinal products[15] in the treatment of chronic obstructive pulmonary disease, as well as the FDA Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment,[16] which recommended endpoints evaluating

[12] Subjects were asked to rate their respiratory condition on a 7-point patient's global rating (PGR) scale (1 equals very much better; 2 equals much better; 3 equals a little better; 4 equals no change; 5 equals a little worse; 6 equals much worse; and 7 equals very much worse).

[13] When FEV1 was available at both 1 hour and 10 minutes prior to study drug inhalation, trough FEV1 was the mean of these two pre-inhalation measurements.

[14] Australian Lung Foundation. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease. 2010.

[15] European Medicines Agency, Guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. 21 June 2012. This EMA guideline was adopted by the EU Committee for Medicinal Products for Human Use (CHMP) on 9 July 2012, and was intended to replace the TGA-adopted EMA guidelines "Points to consider on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease" (CPMP/EWP/562/98, 19 May 1999).

[16] FDA, Guidance for Industry- Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.

FEV1, symptom relief, and effect on exacerbations of COPD. The study primary and secondary endpoints allowed evaluations of the post dose bronchodilatory effect of olodaterol after 12 weeks of treatment (FEV1 AUC_{0-3h} response at Day 85), the bronchodilatory effect of olodaterol at the end of the 24 hour dosing interval after 12 weeks of treatment (trough FEV1 response at Day 85), the bronchodilatory profile of olodaterol over 48 weeks (FEV1 AUC_{0-3h}, trough FEV1 and FEV1 $peak_{0-3h}$ responses over 48 weeks), the bronchodilatory profile of olodaterol over 12 hours post dose period at Day 85 (FEV1 AUC_{0-12h} response at Day 85 in subset of study population), as well as effect on symptom relief (subjective patient rating of improvement or worsening of respiratory condition via the PGR score, use of rescue medications, and COPD exacerbations (number of exacerbations and time to first exacerbations)). The FDA guidelines did not specify recommended instruments for measurement of symptom relief, but the EMA guidelines cited the Chronic Respiratory Questionnaire (CRQ) and the St George's Respiratory Questionnaire (SGRQ). These were not used in Studies 1222.11 and 1222.12, but the SGRQ was used in Studies 1222.13 and 1222.14, which will be described later.

With regards to the subset of study population that had additional serial pulmonary function tests up to 12 hours on Day 85 in both studies ("12 hour PFT set"), it was not clearly explained in the clinical study reports (CSR) or protocols how this subset had been selected. In the CSR, it was stated that

> *'Based on a regulatory authority request to provide a more complete description of the spirometric profile over time from the large parallel Phase III studies, a sub group of subjects performed additional serial PFTs up to 12 hours post dose on Day 85 in both Study 1222.11 and the replicate Study 1222.12, with the pre specified intention of describing the results in a separate report based on the pooled dataset'*

and in the Clinical Overview, it was stated that

> *'following a US FDA recommendation, lung function was measured up to 12 hours post dose at Day 85 in a subset of patients in 1222.11 (N=241) and 1222.12 (N=321)'.*

These statements clarified that the reason for this subset was based on an FDA recommendation, and that the analysis of the 12 hour PFT in this subset was pre specified to be performed on the combined dataset rather than the individual studies. However no explanation or clarification was provided regarding how the selection of subjects into this subset was done. This will be raised as a clinical question.

6.2.1.1.5. Randomisation and blinding methods

In each study, eligible subjects were randomised into one of 3 treatment groups: olodaterol 5 µg once daily, olodaterol 10 µg once daily, or matching placebo once daily. Randomisation was stratified according to the concomitant use of tiotropium. The sponsor had stated that a stratified randomisation was used in order to ensure that the treatment groups were balanced with respect to concomitant use of tiotropium. The inclusion of subjects on tiotropium was also monitored and if the number of subjects treated concomitantly with tiotropium exceeded 30% of the anticipated total number of subjects in any given country, enrolment into the tiotropium stratum of the study was curtailed in that country. An interactive voice response system (IVRS) was used for randomisation to a treatment group within strata and for the appropriate allocation and supply of study drug to subjects throughout the trial.

Both studies had a double blind study design. The sponsor generated the randomisation schedule, prepared and coded the study drug in a blinded fashion, and provided all study drugs. The IVRS was available for unblinding of subjects in an emergency situation.

6.2.1.1.6. Analysis populations

Several analysis data sets were pre defined in the trial statistical analysis plan. The randomised set (RAND) included all randomised subjects, whether treated or not. The treated set (TRT) included all subjects who were dispensed study medication and were documented to have taken at least one dose of study treatment. The full analysis set (FAS) included all subjects in the treated set who had both baseline and at least one post baseline measurement at or before Day 85 (12 weeks) for either co primary efficacy variable. The per protocol set (PPS) included all subjects in the full analysis set except those who had at least one important protocol violation related to efficacy. The 12 hour PFT set (TPS) included all subjects in the full analysis set who had any spirometry data after 3 hours post dose on Visit 5 (Day 85).

Primary efficacy analyses were performed in the FAS. In addition, if the number of subjects in the PPS was less than 90% of the number of subjects in the FAS, the primary analyses were also to be performed using the PPS and these analyses were to be considered as supportive analyses. In both Studies 1222.11 and 1222.12, the number of subjects in the PPS was greater than 90% of the number of subjects in the respective FAS, and hence these analyses were not performed. Safety analyses were performed on the treated set.

> Comments: The definitions of the analysis populations are in keeping with the TGA adopted ICH E 9 Statistical Principles for Clinical Studies.[17] Although the FAS excluded subject who took no study drug, the intent to treat principle would be preserved as the study was double blind, and the initial decision by subjects of whether or not to begin treatment would not be influenced by knowledge of the assigned treatment, and hence the exclusion of these subjects is not deemed to have introduced any potential bias.

6.2.1.1.7. Sample size

Sample size estimation was based on previous studies that gave an estimate of the expected standard deviation for FEV1 $AUC_{0\text{-}3h}$ as 0.226 litres, and for trough FEV1 as 0.225 litres. The sponsor had stated that as patient drop out at Day 85 was expected to be low, and the repeated measures model (this will be described later in this report) to be used accounted for missing values, no additional sample size inflation had been performed to account for patient attrition in the determination of sample size.

The method of the two sample t test with equal sample numbers within the software program nQuery Advisor was used to calculate sample sizes. It was estimated that to detect a difference of 120 mL in FEV1 $AUC_{0\text{-}3h}$ response between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 76 subjects per treatment group were required, while to detect a difference of 80 mL in trough FEV1 between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 168 subjects per treatment group were required. An internal review by the sponsor of published data suggested that the FEV1 response of a LABA when added to a long acting anticholinergic would be less than the FEV1 response of a LABA alone. The sponsor was of the opinion that as a proportion of subjects entering these 2 studies were allowed to take tiotropium, a long acting anticholinergic, as concomitant therapy, it would be appropriate to set a smaller target delta to be detected with 90% power in these 2 studies. The sponsor therefore calculated that to detect a difference of 75 mL in trough FEV1 between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 191 subjects per treatment group were required. Based on these considerations, a sample size of 200 subjects per treatment group was selected.

6.2.1.1.8. Statistical methods

The trial was analysed using a likelihood based mixed effects model with repeated measures (MMRM) terms for treatment, tiotropium use stratum, test day, treatment by test day

[17] European Medicines Agency, "ICH Topic E 9 Step 4: Statistical Principles for Clinical Trials", 5 February 1998, <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf>

interaction, treatment by tiotropium use stratum interaction, tiotropium use stratum by test day interaction, and treatment by tiotropium use stratum by test day interaction as fixed classification effects, and baseline and baseline by test day interaction as covariates.

The primary treatment comparisons were between active treatments and placebo at Day 85. The superiority of olodaterol to placebo was tested by the comparison of the mean FEV1 AUC_{0-3h} response and the mean trough FEV1 response at Day 85. The sponsor had stated that as there were 2 different dose levels of olodaterol (5 µg and 10 µg) and 2 co primary endpoints, the following hypotheses were tested in hierarchical order, each at 2.5% level of significance (one sided) to protect the overall probability of type I error at 0.025 (one sided).

- Superiority in mean FEV1 AUC_{0-3h} response in subjects treated with olodaterol 10 µg compared with those treated with placebo at Day 85
- Superiority in mean trough FEV1 response in subjects treated with olodaterol 10 µg compared with those treated with placebo at Day 85
- Superiority in mean FEV1 AUC_{0-3h} response in subjects treated with olodaterol 5 µg compared with those treated with placebo at Day 85
- Superiority in mean trough FEV1 response in subjects treated with olodaterol 5 µg compared with those treated with placebo at Day 85

Each test was considered confirmatory providing all the previous tests were successful. Otherwise it was considered as descriptive.

For the secondary analyses, spirometry (trough, AUC_{x-yh}, $peak_{0-3h}$ and measurements at individual time points), PEFR and rescue medication use were summarised using the same model as for the primary endpoint. The PGR was analysed using the same model but without the covariates as there was no baseline for this endpoint. As only a single measurement (at Visit 5) was taken to evaluate the secondary efficacy variable of FEV1 AUC_{0-12h} response, the ANCOVA model was used for analysis of this endpoint.

For the analysis of time to COPD exacerbation, Cox regression and log rank tests were used. The Cox regression model was used for parameter estimation and confidence intervals. The log rank test was used for p values. The Cox model contained a stratification term for tiotropium use stratum and a covariate for treatment group. For analyses of exacerbation counts, negative binomial models accounting for exposure were used.

Subgroup analyses were performed on the co primary endpoints of FEV1 AUC_{0-3h} and trough FEV1 on the combined dataset. The subgroups were based on demographic[18] and baseline spirometry[19] parameters.

> Comments: The hierarchical testing of the hypothesis is consistent with the TGA adopted EMA guidelines on Points to consider on multiplicity in clinical trials.[20]

6.2.1.1.9. Participant flow

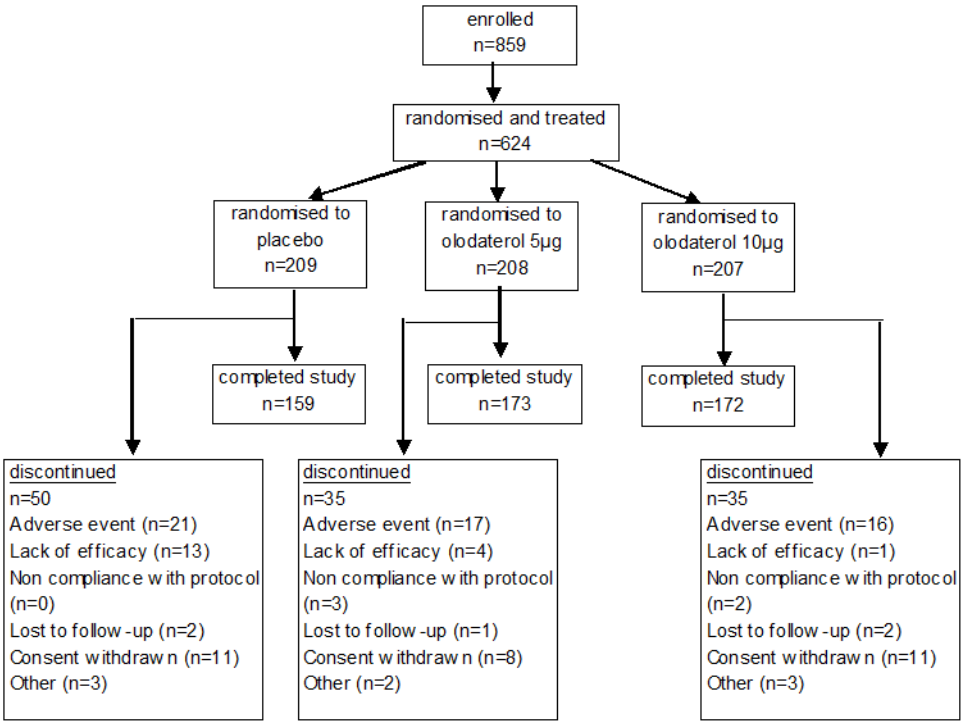
In Study 1222.11, out of a total of 859 subjects enrolled, 624 subjects were randomised and treated: 209 in the placebo group, 208 in the olodaterol 5 µg group, and 207 in the olodaterol 10 µg group (see the figure below).

[18] Gender (male; female), age (less than or equal to 65 years; greater than 65 years), race (white; Asian), xanthine use at baseline (yes; no), inhaled corticosteroid use at baseline (yes; no), short-acting muscarinic antagonist (SAMA) use at baseline (yes; no), LABA use prior to study entry (yes; no), smoking status at baseline (current smoker, ex-smoker), region (US; Asia; other), beta blocker use at baseline (yes; no), tiotropium stratum (non-tiotropium; tiotropium).

[19] Baseline disease severity (GOLD II; GOLD IIII; GOLD IV), FEV1 reversibility (yes; no) FEV1 reversibility (greater than 12% only) (yes; no), pre-bronchodilator baseline FEV1 (less than 35% predicted, 35% to less than 50% predicted, greater than or equal to 50% predicted).

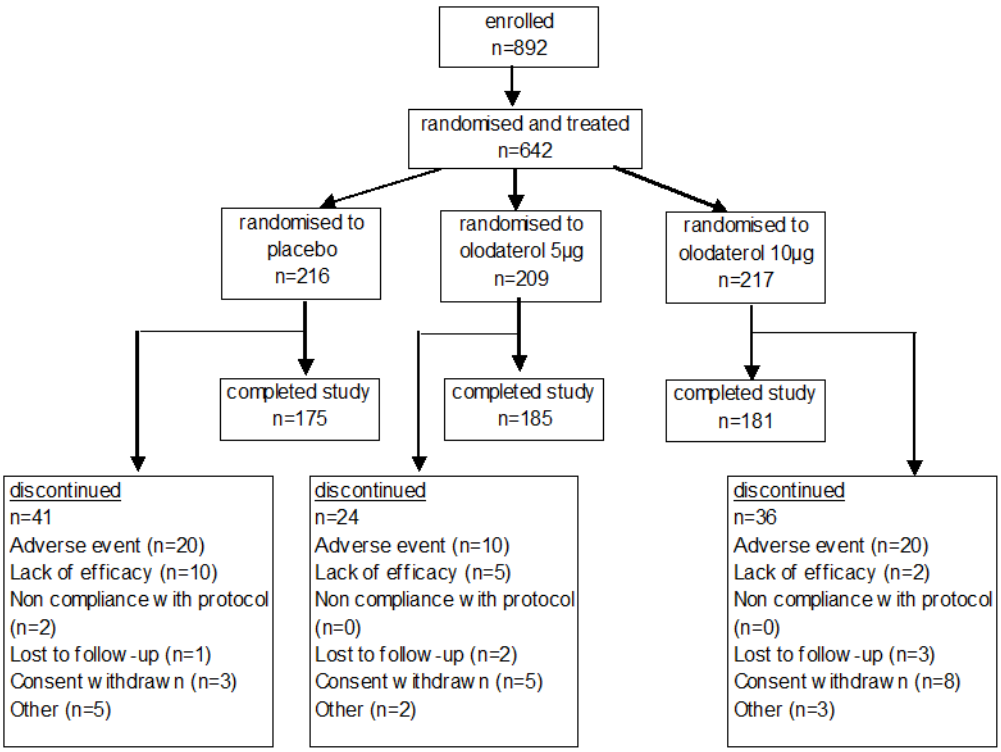
[20] European Medicines Agency, Points to consider on multiplicity in clinical trials. 19th September 2002.

Figure 1. Flow chart of participant flow, Study 1222.1



In Study 1222.12, out of a total of 892 subjects enrolled, 642 subjects were randomised and treated: 216 in the placebo group, 209 in the olodaterol 5 µg group, and 217 in the olodaterol 10 µg group (Figure 2 below).

Figure2. Flow chart of participant flow, Study 1222.12



6.2.1.1.10. Major protocol violations/deviations

In Study 1222.11, the incidence of protocol violations was low. Overall, a total of 27 (4.3%) subjects had an important protocol violation (2.9% (6 out of 209), 4.8% (10 out of 208) and

5.3% (11 out of 207) in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively). The most commonly reported important protocol violations in all 3 treatment groups was

'study medication taken significantly longer than planned treatment duration'

(5 subjects (2.4%) each in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively).

In Study 1222.12, the incidence of protocol violations was also low. Overall a total of 25 (3.9%) subjects had an important protocol violation (6.0% (13 out of 216), 1.9% (4 out of 209) and 3.7% (8 out of 217) in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively).The most commonly reported important protocol violations in all 3 treatment groups was

'study medication taken significantly longer than planned treatment duration'

(4.2% (9 out of 216), 1.4% (3 out of 209) and 1.8% (4 out of 217) in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively).

Treatment compliance was monitored via a patient specific electronic diary, into which subjects recorded whether they took their daily dose of study drug. Treatment compliance was high and comparable across the treatment groups in both Studies 1222.11 (mean (SD) compliance of 96.01% (10.87), 97.00% (8.35) and 96.83% (10.49) in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively) and 1222.12 (mean (SD) compliance of 97.55% (6.36), 97.20% (6.95) and 97.70% (5.13) in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively).

6.2.1.1.11. Baseline data

In Study 1222.11, the baseline demographic characteristics were comparable among treatment groups. The majority of subjects in each treatment group were male (72% to 75%) and White (62% to 63%) The mean age was 64 to 66 years. Baseline mean BMI was similar among treatment groups (mean BMI of 25 to 27). The mean smoking history was also similar among treatment groups (48 to 49 pack years).

The baseline disease characteristics were also comparable among treatment groups. COPD disease history was comparable among treatment groups, with a mean (SD) duration from COPD diagnosis to trial enrolment of 8.6 (6.8), 8.4 (6.5) and 8.4 (6.7) years in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively. Screening pre bronchodilator and post bronchodilator spirometry parameters were comparable among treatment groups, as were concomitant pulmonary medications taken during the treatment period. Randomisation was stratified by concomitant tiotropium use at randomisation, and analyses showed that the proportions of subjects in the tiotropium stratum and the non tiotropium stratum were comparable across treatment groups (placebo group: 160 and 49 subjects in the non tiotropium stratum and tiotropium stratum, respectively; olodaterol 5 µg group: 161 and 47 subjects, respectively; olodaterol 10 µg group: 156 and 51 subjects, respectively).

In Study 1222.12, the baseline demographic characteristics were also comparable among treatment groups. The majority of subjects in each treatment group were male (70% to 73%) and White (63% to 64%). The mean age was 64 to 65 years. Baseline mean BMI was similar among treatment groups (mean BMI of 25 to 26). The mean smoking history was also similar among treatment groups (48 to 52 pack years).

The baseline disease characteristics were also comparable among treatment groups. COPD disease history was comparable among treatment groups, with a mean (SD) duration from COPD diagnosis to trial enrolment of 7.7 (6.4), 7.5 (6.9) and 7.6 (6.5) years in the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively. Screening pre

bronchodilator and post bronchodilator spirometry parameters were comparable among treatment groups. Concomitant pulmonary medications taken during the treatment period were generally comparable among treatment groups. Randomisation was stratified by concomitant tiotropium use at randomisation, and analyses showed that the proportions of subjects in the tiotropium stratum and the non tiotropium stratum were comparable across treatment groups (placebo group: 175 and 41 subjects in the non tiotropium stratum and tiotropium stratum, respectively; olodaterol 5 µg group: 170 and 39 subjects, respectively; olodaterol 10 µg group: 173 and 44 subjects, respectively).

Baseline demographic and disease characteristics were also comparable between Studies 1222.11 and 1222.12, as were concomitant pulmonary medications taken during the treatment period.

> Comments: Overall, the baseline demographic and disease characteristics were comparable among treatment groups in each study. The concomitant pulmonary medications taken during the treatment period were also comparable among treatment groups. The study populations in these studies were reflective of the target patient population, with mean (SD) age of 64.9 (8.5) years and 64.6 (8.8) years in Studies 1222.11 and 1222.12, respectively, mean (SD) duration from COPD diagnosis to trial enrolment of 8.4 (6.7) years and 7.6 (6.6) years, respectively, and with 88.0% and 86.6% of the respective study populations in GOLD grades II and III of COPD (representing moderate and severe COPD, respectively).[21]
>
> The baseline demographic and disease characteristics were comparable between Studies 1222.11 and 1222.12. Given this and the fact that both studies were replicate studies with the same study design, analyses based on pooled datasets of these 2 studies is appropriate.
>
> The baseline demographic and disease characteristics of the 12 hour PFT subset were not provided, and comparability of these baseline characteristics across the treatment groups in this subset of study population could not be ascertained. This will be raised as a clinical question.

6.2.1.1.12. Results for the primary efficacy outcome

The two co primary endpoints in these studies were FEV1 $AUC_{0\text{-}3h}$ response at Day 85 and trough FEV1 response at Day 85. In both studies, there was a statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response at Day 85 compared to placebo for both the olodaterol 5 µg group (Study 1222.11: difference of 172mL over placebo, p<0.0001; Study 1222.12: difference of 151mL over placebo, p<0.0001) and the olodaterol 10 µg group (Study 1222. difference of 176mL over placebo, p<0.0001; Study 1222.12: difference of 143mL over placebo, p<0.0001). There was also statistically significantly greater mean trough FEV1 response at Day 85 compared to placebo for both the olodaterol 5 µg group (Study 1222.11: difference of 91mL over placebo, p<0.0001; Study 1222.12: difference of 47mL over placebo, p=0.0116) and the olodaterol 10 µg group (Study 1222.11: difference of 101mL over placebo, p<0.0001; Study 1222.12: difference of 48mL over placebo, p=0.0095).

Integrated analyses with the combined datasets of Studies 1222.11 and 1222.12 showed similar results, with statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response and mean trough FEV1 response at Day 85 compared to pooled placebo group for both pooled olodaterol 5 µg group and pooled olodaterol 10 µg group (FEV1 $AUC_{0\text{-}3h}$: difference of 161mL for olodaterol 5 µg

[21] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD into 4 grades of severity: Grade I (mild; FEV1 greater than or equal to 80% predicted), Grade II (moderate; FEV1 greater than or equal to 50% and less than 80% predicted), Grade III (severe; FEV1 greater than or equal to 30% and less than 50% predicted), and Grade IV (very severe; FEV1 less than 30% predicted). FEV1 is based on post-bronchodilator FEV1; Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of COPD. 2011.

over placebo, p<0.0001; difference of 159mL for olodaterol 10 µg over placebo, p<0.0001; trough FEV1: difference of 69mL for olodaterol 5 µg over placebo, p<0.0001; difference of 74mL for olodaterol 5 µg over placebo, p<0.0001).

6.2.1.1.13. Results for other efficacy outcomes

6.2.1.1.13.1. Other analyses on the primary endpoints

In both studies, subjects who were taking tiotropium at screening continued with tiotropium as concomitant therapy throughout the studies, and trial randomisation was stratified by concomitant tiotropium use. The sponsor had performed additional analysis with tiotropium use stratum included as a covariate in the model for the primary endpoints analyses.

Results showed that when the analysis of FEV1 AUC_{0-3h} response at Day 85 was performed by tiotropium stratum, both doses of olodaterol (5 µg and 10 µg) had mean FEV1 AUC_{0-3h} responses at Day 85 that were statistically significantly greater than that of placebo in both the tiotropium stratum and the non tiotropium stratum, in both individual studies and in the combined dataset. However, when analysis of trough FEV1 response at Day 85 was performed by tiotropium stratum, the mean trough FEV1 responses at Day 85 were statistically significantly greater than that of placebo for both doses of olodaterol only in the non tiotropium stratum. The differences in mean trough FEV1 response at Day 85 between olodaterol 5 µg and placebo, and between olodaterol 10 µg and placebo, were not statistically significant in the tiotropium stratum in either the individual studies or in the combined dataset.

Subgroup analyses based on demographic subgroups and on baseline spirometry subgroups yielded results consistent with the primary efficacy analysis, showing results in favour of both olodaterol dose groups over placebo across the subgroups. There appeared to be a trend for an increased treatment effect in subjects with lesser baseline disease severity (compared to those with greater baseline disease severity), and in those with higher baseline pre bronchodilator FEV1 (compared to those with lower).

6.2.1.1.13.2. Secondary endpoints evaluating FEV1

Secondary endpoints evaluating FEV1 included FEV1 AUC_{0-12h} response at Day 85 (in the 12 hour PFT analysis set); FEV1 AUC_{0-3h} response, trough FEV1 response, and FEV1 $peak_{0-3h}$ response over 48 weeks; FEV1 at individual time points during the 3 hour post dose period over 48 weeks; and FEV1 at individual time points during the 12 hour post dose period at Day 85 (in the 12 hour PFT analysis set).

Analyses of the FEV1 AUC_{0-12h} response at Day 85 in the 12 hour PFT analysis set showed that for both the olodaterol 5 µg and olodaterol 10 µg groups, there was a statistically significantly greater mean FEV1 AUC_{0-12h} response at Day 85 compared to the placebo group in both individual studies and in the combined dataset.

Analyses on the effects of olodaterol on FEV1 AUC_{0-3h} response over 48 weeks showed that for both olodaterol 5 µg and olodaterol 10 µg groups, there were statistically significantly greater mean FEV1 AUC_{0-3h} responses compared to the placebo group on all test days (Days 1, 15 (Week 2), 43 (Week 6), 85 (Week 12), 169 (Week 24), and 337 (Week 48)), in both individual studies and in the combined dataset).

Analyses on the effects of olodaterol on trough FEV1 response over 48 weeks showed that there were statistically significantly greater mean trough FEV1 responses compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, and 337) for both olodaterol 5 µg and olodaterol 10 µg groups in both individual studies and in the combined dataset, except for olodaterol 10 µg on Day 225 (Week 32) in Study 1222.12 (p=0.1614).

Analyses on the effects of olodaterol on FEV1 $peak_{0-3h}$ response over 48 weeks showed that for both olodaterol 5 µg and olodaterol 10 µg groups, there were statistically significantly greater

mean FEV1 $peak_{0-3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset.

Analyses of FEV1 at individual time points up to 3 hour post dose over 48 weeks (at 5, 15, and 30 minutes, and at 1, 2 and 3 hours after inhalation of study drug, at Day 1 and after 2, 6, 12, 24 and 48 weeks) showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all post dose time points in both individual studies and in the combined dataset, for Studies 1222.11 and 1222.12, respectively.

The FEV1 time profiles in both Studies 1222.11 and 1222.12 showed the mean FEV1 increased within 5 minutes after the administration of both olodaterol dose levels, and these increases were sustained over the 3 hour post dose evaluation period. The sponsor had tabulated the FEV1 by time points up to 30 minutes post dose on Day 1, which showed that in both studies, FEV1 increased within 5 minutes after the first administration (Day 1) of olodaterol 5 µg (increase from pre treatment baseline in mean FEV1 of 0.128 Litres (L)in Study 1222.11 and of 0.135 L in Study 1222.12) and of olodaterol 10 µg (increase from pre treatment baseline in mean FEV1 of 0.129 L in Study 1222.11 and 0.133 L in Study 1222.12), with further increases after 15 minutes (olodaterol 5 µg: 0.168L and 0.169L in Studies 1222.11 and 1222.12, respectively; olodaterol 10 µg: 0.166L and 0.166L, respectively) and 30 minutes (olodaterol 5 µg: 0.183L and 0.187L in Studies 1222.11 and 1222.12, respectively; olodaterol 10 µg: 0.181L and 0.188L, respectively).

Analyses of FEV1 at individual time points up to 12 hours post dose at Day 85 in the 12 hour PFT analysis set showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all post dose time points in both individual studies and in the combined dataset. The FEV1 time profiles up to 12 hours post dose at Day 85 both studies and the combined dataset are presented in. The mean FEV1 increased within 5 minutes after the administration of each olodaterol dose level, peaked at 2 hours post dose and then reduced progressively towards baseline, although at 12 hours post dose, the difference from placebo was still statistically significant in favour of both doses of olodaterol.

6.2.1.1.13.3. Secondary endpoints evaluating FVC

Analyses of the FVC AUC_{0-12h} response at Day 85 in the 12 hour PFT analysis set showed that for both olodaterol 5 µg and olodaterol 10 µg groups, there was a statistically significantly greater mean FVC AUC_{0-12h} response at Day 85 compared to the placebo group in both individual studies and in the combined dataset.

Analyses on the effects of olodaterol on FVC AUC_{0-3h} response over 48 weeks showed that for both olodaterol 5 µg and olodaterol 10 µg groups, there were statistically significantly greater mean FVC AUC_{0-3h} responses compared to the placebo group on all test days (Days 1, 15, 43, 85, 169, and 337), in both individual studies and in the combined dataset.

Analyses on the effects of olodaterol on trough FVC response over 48 weeks showed that there were statistically significantly greater mean trough FVC responses compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, 337) for both olodaterol 5 µg and olodaterol 10 µg groups in Study 1222.11 and in the combined dataset, while in Study 1222.12, the differences from placebo were not statistically significant on most test days.

Analyses on the effects of olodaterol on FVC $peak_{0-3h}$ response over 48 weeks showed that for both olodaterol 5 µg and olodaterol 10 µg groups, there were statistically significantly greater mean FVC $peak_{0-3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset.

Analyses of FVC at individual time points up to 3 hour post dose over 48 weeks (at 5, 15, and 30 minutes, and at 1, 2 and 3 hours after inhalation of study drug, at Day 1 and after 2, 6, 12, 24 and 48 weeks) showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all post dose time points in both individual studies and in

the combined dataset for Studies 1222.11 and 1222.12, respectively. In both studies, the mean FVC increased within 5 minutes after the administration of both olodaterol dose levels on each test day (Day 1 and Weeks 2, 6, 12, 24, and 48), and these increases were sustained over the 3 hour post dose evaluation period and were statistically significantly higher compared to placebo.

Analyses of FVC at individual time points up to 12 hours post dose at Day 85 in the 12 hour PFT analysis set showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all post dose time points in both individual studies and in the combined dataset, except at the 6 hour post dose time point for olodaterol 5 µg in Study 1222.12 (p=0.0544), for Studies 1222.11 and 1222.12, respectively). The mean FVC increased within 5 minutes after the administration of both olodaterol dose levels, peaked at 2 hours post dose (3 hours post dose for olodaterol 5 µg in Study 1222.12) and then reduced progressively towards baseline, although at 12 hours post dose, the difference from placebo was still statistically significant in favour of both doses of olodaterol.

6.2.1.1.13.4. Secondary endpoints evaluating PEFR

Analyses of the weekly mean values for morning (pre dose) PEFR and evening PEFR showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all time points in both individual studies and in the combined dataset.

6.2.1.1.13.5. Other secondary endpoints

Analyses of the weekly mean number of daytime rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in both individual studies and in the combined dataset, except at Week 1 (p=0.0514) and Week 6 (p=0.1886) for olodaterol 5 µg, and at Week 2 for olodaterol 10 µg (p=0.0764) in Study 1222.11, and at Week 1 (p=0.0628) and Week 2 (p=0.4455) for olodaterol 5 µg in Study 1222.12, and at Week 2 (p=0.0513) for the pooled olodaterol 5 µg group in the combined dataset.

Analyses of the weekly mean number of night time rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in both individual studies and in the combined dataset, except at Week 2 (p=0.0676) for olodaterol 5 µg in Study 1222.11.

Analyses of daily (24 hour) rescue medication use (measured weekly) showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in both individual studies and in the combined dataset.

Analyses of the Patient's Global Rating over 48 weeks showed that in Study 1222.11, the mean scores after 6, 12, 24, and 48 weeks ranged from 3.0 to 3.1 in both olodaterol treatment groups and from 3.4 to 3.5 in the placebo treatment group. The lower scores (that is, perceived greater improvement) in the olodaterol treatment groups compared to placebo were statistically significant at all time points. In Study 1222.12, the mean score after 6, 12, 24, and 48 weeks ranged from 2.9 to 3.1 in both olodaterol treatment groups and from 3.2 to 3.3 in the placebo treatment group. The lower scores in the olodaterol treatment groups compared to placebo were statistically significant at all time points except Day 337 (week 48) for olodaterol 5 µg. In the combined analyses, the mean score after 6, 12, 24, and 48 weeks ranged from 3.0 to 3.1 in both pooled olodaterol treatment groups and from 3.3 to 3.4 in the pooled placebo treatment group. The lower scores in the pooled olodaterol treatment groups compared to pooled placebo group were statistically significant at all time points.

Cox proportional hazards regression analysis showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between both olodaterol treatment groups and the placebo treatment group, in both individual studies and in the combined datasets. There were also no statistically significant differences between both olodaterol treatment groups and

the placebo treatment group in the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in both individual studies and in the combined datasets.

Comments on Studies 1222.11 and 1222.12: Overall, efficacy results in these 2 studies supported the efficacy claim for olodaterol over placebo. Results in both studies showed statistically significantly greater mean FEV1 AUC_{0-3h} response and greater mean trough FEV1 response at Day 85 (co primary endpoints) for both the olodaterol 5 µg and 10 µg groups compared to the placebo group. Pooled analyses on the combined dataset of both studies yielded the same results.

Secondary endpoints characterising the FEV1 and FVC profile on Day 85 (that is, after 12 weeks of treatment) showed that in the 12 hour PFT analysis set, there was a statistically significantly greater mean FEV1 AUC_{0-12h} response and mean FVC AUC_{0-12h} response at Day 85 for both olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group, in both individual studies and in the combined dataset. Analyses of FEV1 and FVC at individual time points up to 12 hours post dose at Day 85 in the 12 hour PFT analysis set also showed that there were statistically significant differences from placebo for both olodaterol doses (in favour of olodaterol) at all post dose time points in both individual studies and in the combined dataset, except at the 6 hour post dose time point for the endpoint of FVC in the olodaterol 5 µg group in Study 1222.12. The mean FEV1 and mean FVC increased within 5 minutes after the administration of both olodaterol dose levels, peaked around 2 to 3 hours post dose and then reduced progressively towards baseline, although at 12 hours post dose, the difference from placebo was still statistically significant in favour of both doses of olodaterol.

The FEV1 time profile up to 3 hours post dose on Day 1 in the FAS also showed that FEV1 increased within 5 minutes after the first administration of olodaterol 5 µg and of olodaterol 10 µg, with further increases after 15 and 30 minutes, and was sustained over the 3 hour post dose evaluation period. Evaluation of FEV1 and FVC profile over 48 weeks (that is, duration of treatment in the studies) showed that there were statistically significant differences in FEV1 and FVC at individual time points up to 3 hour post dose over 48 weeks between placebo and both olodaterol doses (in favour of olodaterol) at all post dose time points in both individual studies and in the combined dataset. Analyses on the effects of olodaterol on FEV1 AUC_{0-3h} response, trough FEV1 response, and FEV1 $peak_{0-3h}$ response over 48 weeks showed statistically significantly greater responses for both olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group on all test days in both individual studies and in the combined dataset, except for olodaterol 10 µg on Day 225 (Week 32) in Study 1222.12 for the endpoint of trough FEV1 response. Analyses on the effects of olodaterol on FVC AUC_{0-3h} response and FVC $peak_{0-3h}$ response over 48 weeks also showed statistically significantly greater responses for both olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group on all test days in both individual studies and in the combined dataset. However, analyses on the effects of olodaterol on trough FVC response over 48 weeks showed that there were statistically significantly greater mean trough FVC responses compared to placebo on all test days for both olodaterol 5 µg and olodaterol 10 µg groups only in Study 1222.11 and in the combined dataset, while in Study 1222.12, the differences from placebo were not statistically significant on most test days.

Other secondary endpoints evaluating PEFR, rescue medication use and the Patient's Global Rating supported the efficacy claim for olodaterol over placebo. However, evaluation of the secondary endpoints of exacerbations of COPD showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between both olodaterol treatment groups and the placebo treatment group, in both

individual studies and in the combined datasets. There were also no statistically significant differences between both olodaterol treatment groups and the placebo treatment group in the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in both individual studies and in the combined datasets.

Additional analysis with tiotropium use stratum included as a covariate in the model for the primary endpoints analyses showed that both doses of olodaterol (5 µg and 10 µg) had mean FEV1 $AUC_{0\text{-}3h}$ responses at Day 85 that were statistically significantly greater than that of placebo in both the tiotropium stratum and the non tiotropium stratum, in both individual studies and in the combined dataset, but that the mean trough FEV1 responses at Day 85 were statistically significantly greater than that of placebo for both doses of olodaterol only in the non tiotropium stratum (that is, the differences in mean trough FEV1 response at Day 85 between olodaterol 5 µg and placebo, and between olodaterol 10 µg and placebo, were not statistically significant in the tiotropium stratum in either the individual studies or in the combined dataset). It is noted by the evaluator that taking into account the hierarchical hypothesis testing method described in the study statistical plan, in the tiotropium stratum, only the statistically significantly greater FEV1 $AUC_{0\text{-}3h}$ responses at Day 85 of the olodaterol 10 µg group compared to placebo group can be considered confirmatory. As the difference in mean trough FEV1 response at Day 85 between olodaterol 10 µg and placebo in the tiotropium stratum was not found to be statistically significant, the results of the comparison between olodaterol 5 µg and placebo in the tiotropium stratum for the endpoints of FEV1 $AUC_{0\text{-}3h}$ response and trough FEV1 response at Day 85 can only be considered as descriptive. These results are difficult to interpret due to the small sample size in the tiotropium stratum, in the individual studies and also in the combined dataset.

Subgroup analyses on the co primary endpoints yielded results that were consistent with the primary efficacy analysis. However, it is noted that with regards to interaction between smoking status and efficacy, only the smoking status at baseline was considered. A look through the study protocols of Studies 1222.11 and 1222.12 showed that smoking status of subjects was reviewed at Weeks 24 and 48. However, the potential interaction between smoking status at these time points and efficacy was not explored or presented. This will be raised as a clinical question.

6.2.1.2. Studies 1222.13 and 1222.14

6.2.1.2.1. Study design, objectives, locations and dates

Both Studies 1222.13 and 1222.14 are multi centre, randomised, double blind, double dummy, placebo controlled, parallel group studies evaluating the efficacy and safety of 48 weeks of orally inhaled olodaterol (5 µg once daily and 10 µg once daily) delivered by the Respimat inhaler, and 48 weeks of formoterol (Foradil; 12 µg twice daily) delivered by the Aerolizer Inhaler, in patients with COPD. The primary objective of both studies was to assess the long term efficacy and safety of once daily treatment of olodaterol inhalation solution (5 µg and 10 µg) compared to placebo in patients with COPD. Comparison of efficacy between the 2 olodaterol doses with the active comparator of formoterol had been pre specified to be performed for the primary endpoints only on the combined dataset of Studies 1222.13 and 1222.14.

Both Studies 1222.13 and 1222.14 were multi centre studies where subjects were enrolled in a total of 93 study sites across 20 countries[22] and 99 study sites across 20 countries,[23]

[22] There were 4 study sites in Argentina, 5 in Brazil, 11 in Canada, 4 in Croatia, 3 in Czech Republic, 3 in Denmark, 3 in Finland, 12 in Germany, 1 in Hong Kong, 11 in India, 5 in Italy, 4 in Malaysia, 2 in Norway, 3 in the Philippines, 6 in Republic of Korea, 2 in South Africa, 6 in Spain, 2 in Sweden, 3 in Thailand and 3 in Ukraine.

respectively. The study start and end dates of Study 1222.13 were 05 February 2009 and 02 December 2010, respectively, and those of Study 1222.14 were 27 January 2009 and 08 December 2010, respectively.

Following the Screening Visit (Visit 1) and a two week baseline period, subjects were to be randomised on Visit 2 into 1 of 4 treatment groups: olodaterol 5 µg once daily (qd), olodaterol 10 µg qd, formoterol 12 µg twice daily (bid), or placebo. Additional visits were to be scheduled after 2, 6, 12, 18, 24, 32, 40, and 48 weeks of treatment (Visits 3 to 10). There was one post treatment visit, two weeks after the end of treatment (Visit 11) to ensure stability of patient after wash out of olodaterol and prior to trial completion.

The study design of Studies 1222.13 and 1222.14 were similar to those of Studies 1222.11 and 1222.12, except that evaluation of primary endpoints was performed after 24 weeks of treatment instead of 12 weeks, there was an additional active comparator arm, and there were additional endpoints evaluating potential symptomatic benefit in terms of reduction of dyspnoea (assessed via the Mahler Transition Dyspnea Index (TDI) focal score), and improvement of health related quality of life (assessed via the St. George's Respiratory Questionnaire (SGRQ) total score). In this evaluation report, references will be made to the study design previously described for Studies 1222.11 and 1222.12, and only the differences for Studies 1222.13 and 1222.14 will be elaborated.

6.2.1.2.2. Inclusion and exclusion criteria

The study inclusion and exclusion criteria were the same as those for Studies 1222.11 and 1222.12 (described and commented on later in this report).

6.2.1.2.3. Study treatments

The study treatments are olodaterol 5 µg (2 actuations of 2.5 µg once daily with the Respimat inhaler), olodaterol10 µg (2 actuations of 5 µg once daily with the Respimat inhaler), formoterol 12 µg twice daily with the Aerolizer inhaler, placebo matching olodaterol Respimat, and placebo matching formoterol Aerolizer.[24] The treatment duration was 48 weeks.

As with Studies 1222.11 and 1222.12, during Studies 1222.13 and 1222.14, a short acting β2 agonist medication (salbutamol) was provided to all subjects for rescue use, and appropriate medications (as previously described) were allowed to control acute exacerbations as medically necessary. Permitted and restricted concomitant medications were as described for Studies 1222.11 and 1222.12.

> Comments: The study dose selection for olodaterol is appropriate and has been previously discussed. The study design involving a placebo control and an active control is appropriate and consistent with the recommendation of the EMA guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. The choice of active control of formoterol 12 µg bid was appropriate. Formoterol (International Non proprietary Name (INN)) is a LABA and is registered in Australia as eformoterol (British Approved Name (BAN)), indicated
>
> *'for the prophylaxis and treatment of bronchoconstriction in patients with reversible or irreversible chronic obstructive pulmonary disease (COPD)'.*[25]

[23] There were 5 study sites in Argentina, 6 in Brazil, 14 in Canada, 4 in Czech Republic, 3 in Denmark, 3 in Finland, 13 in Germany, 1 in Hong Kong, 11 in India, 5 in Italy, 3 in Malaysia, 2 in Norway, 3 in the Philippines, 6 in Republic of Korea, 3 in Romania, 3 in Russia, 2 in South Africa, 6 in Spain, 3 in Sweden, and 3 in Thailand.

[24] The first administration of study drug occurred at Visit 2, when it was to be self-administered between 7:00 a.m. and 10:00 a.m. Subsequent study drug administration was to occur within plus or minus 30 minutes of the time of administration at Visit 2. With regards to the evening treatment (for formoterol or matching placebo), administration was to occur 12 hours (plus or minus 15 minutes) after administration of the morning dose of study drug.

[25] Australian Product Information for eformoterol.

It is currently accepted as part of standard treatment regimen for COPD. The dose of formoterol in the study is the recommended therapeutic dose in clinical practice.

6.2.1.2.4. Efficacy variables and outcomes

There were three co primary endpoints in these studies: FEV1 AUC_{0-3h} response at Day 169 (that is, after 24 weeks of treatment), trough FEV1 response at Day 169, and the Mahler TDI focal score[26] at Day 169. Although a co primary endpoint, analysis of the Mahler TDI focal score had been pre specified to be performed only in the combined dataset of Studies 1222.13 and 1222.14.

The key secondary endpoint was the SGRQ[27] total score after 24 weeks of treatment, and had been pre specified to be performed only on the combined dataset of Studies 1222.13 and 1222.14. Other secondary endpoints were the same as those previously described for Studies 1222.11 and 1222.12, except that Studies 1222.13 and 1222.14 did not have a pre defined subset of subjects labelled "12 hour PFT set" (where pulmonary function testing was done up to 12 hours post dose on Day 85) and hence did not have secondary endpoints pertaining to this subset of subjects, and there were additional secondary endpoints involving the SGRQ and the Mahler TDI. The definitions of these endpoints have been previously described. Pulmonary function tests and assessments of endpoints were performed according to a schedule.

The primary and secondary endpoints for the combined analysis of Studies 1222.13 and 1222.14 (Study report 1222-9993) will be described here for ease of reference and for completeness. In the combined dataset analysis, there were 3 co primary endpoints: FEV1 AUC_{0-3h} response at Day 169 (pooled olodaterol versus pooled placebo), trough FEV1 response at Day 169 (pooled olodaterol versus pooled placebo), and the Mahler TDI focal score at Day 169 (pooled olodaterol versus pooled placebo). The key secondary efficacy endpoints were SGRQ total score at Day 169 (pooled olodaterol versus pooled placebo), FEV1 AUC_{0-3h} response at Day 169 (pooled olodaterol versus pooled formoterol), trough FEV1 response at Day 169 (pooled olodaterol versus pooled formoterol), and the Mahler TDI focal score at Day 169 (pooled olodaterol versus pooled formoterol). Other secondary efficacy endpoints were the Mahler TDI component scores at Day 169 (pooled olodaterol versus pooled placebo) and the SGRQ component scores at Day 169 (pooled olodaterol versus pooled placebo).

> Comments: Overall, the primary and secondary endpoints of this study are appropriate and consistent with the recommendations in the EMA guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease,[28] as well as the FDA Guidance for Industry Chronic Obstructive Pulmonary Disease:

[26] The Baseline Dyspnea Index (BDI) was administered at Visit 2 (randomisation visit) and documented the level and extent to which activities caused the patient to feel breathless prior to treatment. When administering the Mahler TDI during treatment (Weeks 6, 12, 18, 24, 32, 40, and 48), the BDI assessment was reviewed prior to selecting a Mahler TDI score. For each of the 3 components of the Mahler TDI (functional impairment, magnitude of task, magnitude of effort), scoring was done as follows: -3 units equals major deterioration, -2 units equals moderate deterioration, -1 unit equals minor deterioration, 0 equals no change, +1 unit equals minor improvement, +2 units equals moderate improvement, + 3 units equals major improvement. The score for each component was added to give an overall score (called the TDI focal score) from -9 to +9.

[27] The SGRQ has 3 components: symptom, activity and impact. Scores range from 0 to 100, with higher scores indicating more limitations. The SGRQ was administered at Visit 2 (randomisation visit) to document health related quality of life at baseline, prior to treatment, and was then administered during treatment, after 12 weeks (Day 85), 24 weeks (Day 169) and 48 weeks (Day 337) to evaluate changes in health related quality of life compared with pre-treatment baseline.

[28] European Medicines Agency, Guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. 21 June 2012. This EMA guideline was adopted by the EU Committee for Medicinal Products for Human Use (CHMP) on 9 July 2012, and was intended to replace the TGA-adopted EMA guidelines "Points to consider on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease" (CPMP/EWP/562/98, 19 May 1999).

Developing Drugs for Treatment,[29] which recommended endpoints evaluating FEV1, symptom relief, and effect on exacerbations of COPD. The study primary and secondary endpoints allowed evaluations of the post dose bronchodilatory effect of olodaterol after 24 weeks of treatment (FEV1 AUC_{0-3h} response at Day 169), the bronchodilatory effect of olodaterol at the end of the 24 hour dosing interval after 24 weeks of treatment (trough FEV1 response at Day 169), the bronchodilatory profile of olodaterol over 48 weeks (FEV1 AUC_{0-3h}, trough FEV1 and FEV1 $peak_{0-3h}$ responses over 48 weeks), as well as effect on symptom relief (Mahler TDI score, PGR score, use of rescue medications, and COPD exacerbations (number of exacerbations and time to first exacerbations)) and on health related quality of life (SGRQ score). The use of the SGRQ is in line with the recommendations of the EMA guidelines, which cited the use of the Chronic Respiratory Questionnaire or the St George's Respiratory Questionnaire.

6.2.1.2.5. Randomisation and blinding methods

Eligible subjects were randomised into one of 4 treatment groups: olodaterol 5 µg qd (named the "olodaterol 5 µg group"), olodaterol 10 µg qd (named the "olodaterol 10 µg group"), formoterol 12 µg bid (named the "formoterol 12 µg group") and placebo. Both studies had a double dummy design, such that subjects in the olodaterol 5 µg or olodaterol 10 µg groups would receive active olodaterol 5 µg qd or olodaterol 10 µg qd, respectively, as well as placebo matching formoterol bid; subjects in the formoterol 12 µg group would receive active formoterol bid as well as placebo matching olodaterol qd; subjects in the placebo group would receive placebo matching formoterol bid as well as placebo matching olodaterol qd.

Randomisation was stratified according to the concomitant use of tiotropium. The sponsor had stated that a stratified randomisation was used in order to ensure that the treatment groups were balanced with respect to concomitant use of tiotropium. The inclusion of subjects on tiotropium was also monitored and if the number of subjects treated concomitantly with tiotropium exceeded 30% of the anticipated total number of subjects in any given region,[30] enrolment into the tiotropium stratum of the study was curtailed in that region. An IVRS was used for randomisation to a treatment group within strata and for the appropriate allocation and supply of study drug to subjects throughout the trial.

Both studies had a double blind study design. The sponsor generated the randomisation schedule, prepared and coded the study drug in a blinded fashion, and provided all study drugs. The IVRS was available for unblinding of subjects in an emergency situation.

6.2.1.2.6. Analysis populations

The analysis populations were the same as those for Studies 1222.11 and 1222.12, except there was no 12 hour PFT set for Studies 1222.13 and 1222.14, and the definition of the FAS took into account that the primary endpoints were evaluated at Day 169 instead of Day 85. The analysis populations for Studies 1222.13 and 1222.14 will be described here for ease of reference.

Several analysis data sets were pre defined in the trial statistical analysis plans for Studies 1222.13 and 1222.14. The randomised set (RAND) included all randomised subjects, whether treated or not. The treated set (TRT) included all subjects who were dispensed study medication and were documented to have taken at least one dose of study treatment. The full analysis set (FAS) included all subjects in the treated set who had both baseline and at least one post baseline measurement at or before Day 169 (24 weeks) for any of the co primary efficacy variable. The per protocol set (PPS) included all subjects in the full analysis set except those who had at least one important protocol violation related to efficacy.

[29] FDA, Guidance for Industry- Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007.

[30] There were four regions defined for Studies 1222.13 and 1222.14: Europe (including Canada and South Africa but excluding Germany), Germany, Asia, and Latin America.

Primary efficacy analyses were performed in the FAS. In addition, if the number of subjects in the PPS was less than 90% of the number of subjects in the FAS, the primary analyses were also to be performed using the PPS and these analyses were to be considered as supportive analyses. The sponsor had stated that in both Studies 1222.13 and 1222.14, the number of subjects in the PPS was greater than 90% of the number of subjects in the respective FAS, and hence these analyses were not performed. Safety analyses were performed on the treated set.

6.2.1.2.7. Sample size

Sample size estimation was based on previous studies that gave an estimate of the expected standard deviation for FEV1 $AUC_{0\text{-}3h}$ as 0.226 litres, and for trough FEV1 as 0.225 litres. The sponsor had stated that as patient drop out at Day 169 was expected to be low, and the repeated measures model (this will be described later in this report) to be used accounted for missing values, no additional sample size inflation had been performed to account for patient attrition in the determination of sample size.

The method of the two sample t test with equal sample numbers within the software program nQuery Advisor was used to calculate sample sizes. It was estimated that to detect a difference of 120 mL in FEV1 $AUC_{0\text{-}3h}$ response between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 76 subjects per treatment group were required, while to detect a difference of 80 mL in trough FEV1 between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 168 subjects per treatment group were required. The sponsor also estimated that to detect a difference of 0.7 units in the Mahler TDI focal score between olodaterol and placebo with 90% power at the 1 sided alpha of 0.025, 338 subjects per treatment group were required (when the data from the 2 studies were combined), and that to detect a difference of 50 mL in trough FEV1 between olodaterol and formoterol with 90% power at the 1 sided alpha of 0.025, 427 subjects per group were required (when the data from the 2 studies were combined). Based on these considerations, a sample size of 215 subjects per treatment group in each study was selected (yielding 430 subjects per pooled treatment group when the data from the 2 studies were combined).

6.2.1.2.8. Statistical methods

The trial was analysed using a likelihood based mixed effects model with repeated measures (MMRM) with terms for treatment, tiotropium use stratum, test day, treatment by test day interaction, treatment by tiotropium use stratum interaction, tiotropium use stratum by test day interaction, and treatment by tiotropium use stratum by test day interaction as fixed classification effects, and baseline and baseline by test day interaction as covariates.

The primary treatment comparisons were between active treatments and placebo at Day 169 (after 24 weeks of treatment). The superiority of olodaterol to placebo was tested by the comparison of the mean FEV1 $AUC_{0\text{-}3h}$ response, the mean trough FEV1 response and the mean Mahler TDI focal score. As there were 2 different dose levels of olodaterol (5 µg and 10 µg) and 3 co primary endpoints, the following hypotheses were tested in hierarchical order, each at 2.5% level of significance (one sided) to protect the overall probability of type I error at 0.025 (one sided).

- Superiority in mean FEV1 $AUC_{0\text{-}3h}$ response in subjects treated with olodaterol 10 µg compared with those treated with placebo after 24 weeks of treatment.
- Superiority in mean trough FEV1 response in subjects treated with olodaterol 10 µg compared with those treated with placebo after 24 weeks of treatment.
- Superiority in mean FEV1 $AUC_{0\text{-}3h}$ response in subjects treated with olodaterol 5 µg compared with those treated with placebo after 24 weeks of treatment.
- Superiority in mean trough FEV1 response in subjects treated with olodaterol 5 µg compared with those treated with placebo after 24 weeks of treatment.

- Superiority in mean TDI focal score in subjects treated with olodaterol 10 µg compared with those treated with placebo, after 24 weeks of treatment.
- Superiority in mean TDI focal score in subjects treated with olodaterol 5 µg compared with those treated with placebo, after 24 weeks of treatment.

Each test was considered confirmatory providing all the previous tests were successful.

Otherwise it was considered as descriptive. The first four hypotheses were tested for each individual study. The last two hypotheses were to be tested only for the combined dataset.

For the secondary analyses, spirometry (trough, $AUC_{x\text{-}yh}$, $peak_{0\text{-}3h}$ and measurements at individual time points), the Mahler TDI focal score, SGRQ total score, individual components of the SGRQ and Mahler TDI, PEFR and rescue medication use were summarised using the same model as for the primary endpoint. The PGR was analysed using the same model but without the covariates as there was no baseline for this endpoint. Responder analyses for SGRQ total score and Mahler TDI focal score at 24 weeks were performed with logistic regression, using terms for treatment, tiotropium use stratum, and treatment by tiotropium use stratum interaction.

For the analysis of time to exacerbation, Cox regression and log rank tests were used. The Cox regression model was used for parameter estimation and confidence intervals. The log rank test was used for p values. The Cox model contained a stratification term for tiotropium use stratum and a covariate for treatment group. For analyses of exacerbation counts, negative binomial models accounting for exposure were used.

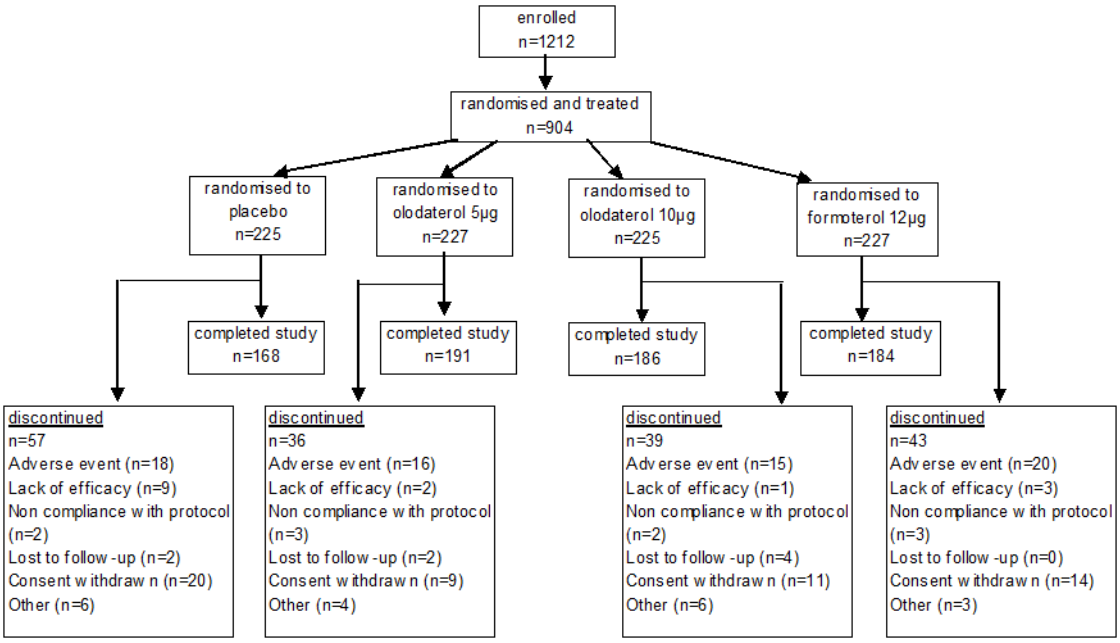
Subgroup analyses were performed on the co primary endpoints of FEV1 $AUC_{0\text{-}3h}$ and trough FEV1 on the combined dataset. The subgroups were based on demographic[31] and baseline spirometry parameters.[32]

6.2.1.2.9. Participant flow

In Study 1222.13, a total of 1212 subjects were enrolled, and 904 subjects were randomised and treated: 225 in the placebo group, 227 in the olodaterol 5 µg group, 225 in the olodaterol 10 µg group, and 227 in the formoterol 12 µg group (Figure 3 below).

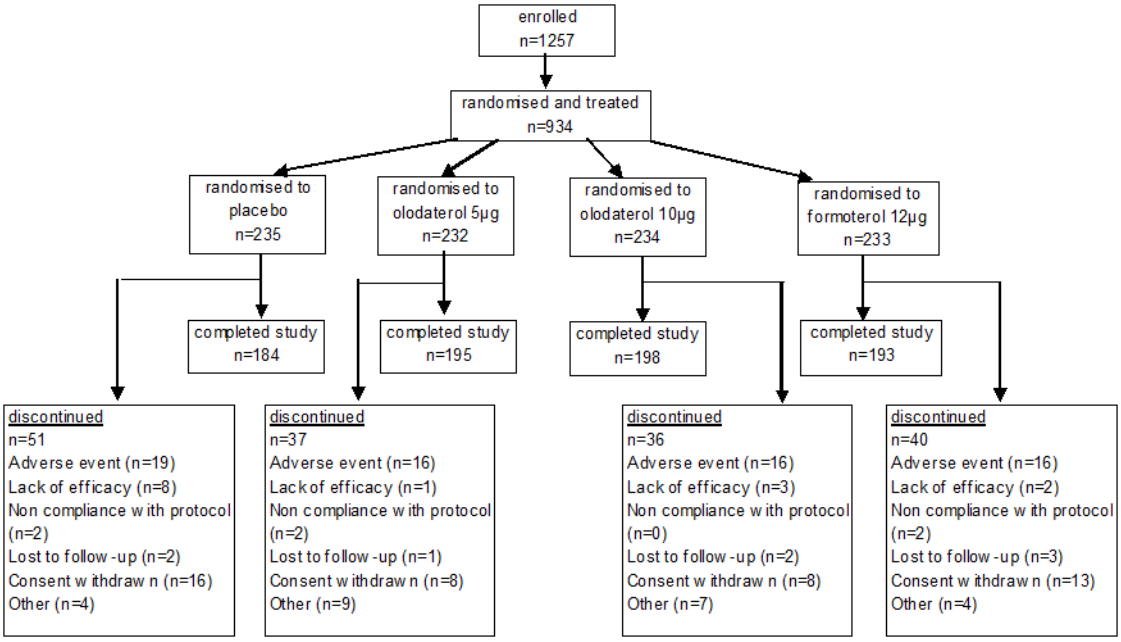
[31] Gender (male; female), age (less than or equal 65 years; greater than 65 years), race (white; Asian), xanthine use at baseline (yes; no), inhaled corticosteroid use at baseline (yes; no), short-acting muscarinic antagonist (SAMA) use at baseline (yes; no), LABA use prior to study entry (yes; no), smoking status at baseline (current smoker, ex-smoker), region (Europe; Asia; other), beta blocker use at baseline (yes; no), tiotropium stratum (non-tiotropium; tiotropium).
[32] Baseline disease severity (GOLD II; GOLD IIII; GOLD IV), FEV1 reversibility (yes; no) FEV1 reversibility (greater than 12% only) (yes; no), pre-bronchodilator baseline FEV1 (less than 35% predicted, 35% to less than 50% predicted, greater than or equal to 50% predicted).

Figure 3. Flow chart of participant flow, Study 1222.13



In Study 1222.14, a total of 1257 subjects were enrolled, and 934 subjects were randomised and treated: 235 in the placebo group, 232 in the olodaterol 5 µg group, 234 in the olodaterol 10 µg group, and 233 in the formoterol 12 µg group (Figure 4 below).

Figure 4. Flow chart of participant flow, Study 1222.14



In Study 1222.13, two study sites were identified (1 site in Argentina and 1 site in India) as having non compliance issues that warranted review of the data by the sponsor to confirm inclusion in the FAS and safety dataset. At the site in Argentina, a non compliance issue relating to medication dispensing and accountability concerning 1 patient was identified during a

routine monitoring visit,[33] but after review by the sponsor, it was decided that the issue did not significantly impact the efficacy or safety of the subjects at the site, and their data were included in the FAS and safety dataset. At the site in India, an audit performed at the site following quality concerns raised by the site monitor, indicated that there were irregularities in the prescription sheets and in the documentation of the time of medication washout for almost all subjects. The eligibility of subjects could not be confirmed and it was questionable whether the protocol was followed for medication washout time pre pulmonary function testing. The sponsor concluded that the reliability of the source documents could not be confirmed and that the integrity of the data was questionable. The site was closed down as a result of these findings and a decision was made to exclude the data of the 9 randomised subjects at this site (3 in the placebo group, 2 in the olodaterol 5 µg group, 1 in the olodaterol 10 µg group and 3 in the formoterol 12 µg group) from the FAS efficacy analysis. The safety data for these 9 randomised subjects was included in the safety analysis.

In Study 1222.14, one study site (in Canada) was identified as having potential compliance issues and was closed by the sponsor. Non compliance was noted for a sub investigator at the site during audits of other trials that the sub investigator was conducting as a principal investigator. The sponsor did not elaborate on the nature of the non compliance, but stated that prior to database lock, the decision was made by the sponsor to close the study site and to not include the data for the one subject enrolled in the study (randomised to the placebo group) in the FAS efficacy analysis, but safety data for this subject was included in the safety analysis.

> Comments: The exclusion of 9 subjects at the study site in India from the FAS in Study 1222.13 due to non compliance issues is appropriate, as the nature of the non compliance was not related to treatment assignment nor likely to be influenced by treatment assignment, and hence the exclusion of these subjects from the efficacy analysis is unlikely to introduce potential bias.
>
> The sponsor did not provide details on the nature of the non compliance issue in Study 1222.14 involving a study site in Canada. Although the exclusion of efficacy data at this site from the FAS involved only a single subject and was done prior to database lock and unblinding, and hence was unlikely to have introduced major bias into the efficacy analysis, the lack of information on the nature of the non compliance issue means nonetheless that the evaluator is unable to determine definitively if the exclusion of the single subject at this site from the FAS was appropriate. This will be raised as a clinical question.

6.2.1.2.10. Major protocol violations/deviations

In Study 1222.13, the incidence of important protocol violations was comparable between the 4 treatment groups. Overall, a total of 86 (9.5%) subjects had an important protocol violation (8.9% (20 out of 225), 9.7% (22 out of 227), 9.3% (21 out of 225), and 10.1% (23 out of 227) in the placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg treatment groups, respectively). The most commonly reported important protocol violations overall was "prohibited medication use during the treatment period" (3.0%, 27 out of 904) and “informed consent given too late” (2.8%, 25 out of 904).

In Study 1222.14, the incidence of important protocol violations was also comparable between the 4 treatment groups. Overall, a total of 120 (12.8%) subjects had an important protocol violation (15.3% (36 out of 235), 10.8% (25 out of 232), 12.0% (28 out of 234), and 13.3% (31 out of 233) in the placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg treatment groups, respectively).The most commonly reported important protocol violations overall was

[33] During a routine monitoring visit, a note was found on the returned medication kit of patient. The medication box had been returned full by the patient but the note indicated that some medication should be removed. It was assumed that it had been placed there by a study nurse, who meant to return to remove the medication to make it appear that the patient had been compliant with the medication.

"prohibited medication use during the treatment period" (5.3%, 50 out of 934) and “informed consent given too late” (3.2%, 30 out of 934).

Treatment compliance was monitored via a patient specific electronic Diary, into which subjects recorded whether they took their daily dose of study drug. Treatment compliance was high and comparable across the treatment groups in both Studies 1222.13 (mean (SD) compliance of 96.96% (7.91), 97.33% (7.18), 98.25% (2.97) and 97.29% (8.18) in the placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg treatment groups, respectively) and 1222.14 (mean (SD) compliance of 97.36% (9.14), 98.26% (3.92), 97.49% (6.77) and 96.70% (12.26) in the placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg treatment groups, respectively).

6.2.1.2.11. Baseline data

In Study 1222.13, the baseline demographic characteristics were comparable among treatment groups. The majority of subjects in each treatment group were male (76% to 80%) and White (71% to 72%). The mean age was 63 to 65 years. Baseline mean BMI was similar among treatment groups (mean BMI of 25 to26). The mean smoking history was also similar among treatment groups (43 to 46 pack years, respectively).

The baseline disease characteristics were also comparable among treatment groups. COPD disease history was comparable among treatment groups, with a mean (SD) duration from COPD diagnosis to trial enrolment of 6.6 (5.2), 6.6 (4.7), 7.3 (5.9) and 7.1 (5.6) years in the placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg treatment groups, respectively. Screening pre bronchodilator and post bronchodilator spirometry parameters were comparable among treatment groups. Concomitant pulmonary medications taken during the treatment period were generally comparable among treatment groups. Randomisation was stratified by concomitant tiotropium use at randomisation, and analyses showed that the proportions of subjects in the tiotropium stratum and the non tiotropium stratum were comparable across treatment groups (placebo group: 168 and 57 subjects in the non tiotropium stratum and tiotropium stratum, respectively; olodaterol 5 µg treatment group: 167 and 60 subjects, respectively; olodaterol 10 µg treatment group: 167 and 58 subjects, respectively; formoterol 12 µg treatment group: 169 and 58 subjects, respectively).

In Study 1222.14, the baseline demographic characteristics were also comparable among treatment groups. The majority of subjects in each treatment group were male (79% to 83%) and White (66% to 68%). The mean age was 64 to 65 years. Baseline mean BMI was similar among treatment groups (mean BMI of 25 to 26). The mean smoking history was also similar among treatment groups (41 to 45 pack years, respectively).

The baseline disease characteristics were also comparable among treatment groups. COPD disease history was comparable among treatment groups, with a mean (SD) duration from COPD diagnosis to trial enrolment of 6.7 (5.9), 6.3 (5.7), 7.0 (6.4) and 6.6 (6.4) years in the placebo, olodaterol 5 µg, olodaterol 10 µg and formoterol 12 µg treatment groups, respectively. Screening pre bronchodilator and post bronchodilator spirometry parameters were comparable among treatment groups. Concomitant pulmonary medications taken during the treatment period were generally comparable among treatment groups. Randomisation was stratified by concomitant tiotropium use at randomisation, and analyses showed that the proportions of subjects in the tiotropium stratum and the non tiotropium stratum were comparable across treatment groups (placebo group: 174 and 61 subjects in the non tiotropium stratum and tiotropium stratum, respectively; olodaterol 5 µg treatment group: 173 and 59 subjects, respectively; olodaterol 10 µg treatment group: 175 and 59 subjects, respectively; formoterol 12 µg treatment group: 175 and 58 subjects, respectively).

Baseline demographic and disease characteristics were also comparable between Studies 1222.13 and 1222.14, as were concomitant pulmonary medications taken during the treatment period.

Comments: Overall, the baseline demographic and disease characteristics were comparable among treatment groups in each study. The concomitant pulmonary medications taken during the treatment period were also comparable among treatment groups. The study population in each study was reflective of the target patient population, with mean (SD) age of 63.8 (8.7) years and 64.1 (8.3) years in Studies 1222.13 and 1222.14, respectively, mean (SD) duration from COPD diagnosis to trial enrolment of 6.9 (5.4) years and 6.6 (6.1) years, respectively, and with 92.2% and 91.0% of the respective study populations in GOLD grades II and III of COPD (representing moderate and severe COPD, respectively).

The baseline demographic and disease characteristics were comparable between Studies 1222.13 and 1222.14. Given this and the fact that both studies were replicate studies with the same study design, the analysis based on pooled datasets of these 2 studies is appropriate.

6.2.1.2.12. Results for the primary efficacy outcome

In both studies, there was a statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response at Day 169 compared to placebo, for both the olodaterol 5 µg group (Study 1222.13: difference of 151mL over placebo, p<0.0001; Study 1222.14: difference of 129mL over placebo, p<0.0001) and the olodaterol 10 µg group (Study 1222.13: difference of 165mL over placebo, p<0.0001; Study 1222.14: difference of 154mL over placebo, p<0.0001). There was also a statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response at Day 169 in the formoterol 12 µg group compared to the placebo group (Study 1222.13: difference of 177mL over placebo, p<0.0001; Study 1222.14: difference of 150mL over placebo, p<0.0001).

There was a statistically significantly greater mean trough FEV1 response at Day 169 compared to placebo for both the olodaterol 5 µg group (Study 1222.13: difference of 78mL over placebo, p=0.0002; Study 1222.14: difference of 53mL over placebo, p=0.0055) and the olodaterol 10 µg group (Study 1222.13: difference of 85mL over placebo, p<0.0001; Study 1222.14: difference of 69mL over placebo, p=0.0003). There was also a statistically significantly greater mean trough FEV1 response at Day 169 in the formoterol 12 µg group compared to the placebo group (Study 1222.13: difference of 54 mL over placebo, p=0.0088; Study 1222.14: difference of 42 mL over placebo, p=0.0270).

Integrated analyses with the combined datasets of Studies 1222.13 and 1222.14 showed similar results, with statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response and mean trough FEV1 response at Day 169 compared to pooled placebo group, for both pooled olodaterol 5 µg group and pooled olodaterol 10 µg group (FEV1 $AUC_{0\text{-}3h}$: difference of140mL for olodaterol 5 µg over placebo, p<0.0001; difference of 159mL for olodaterol 10 µg over placebo, p<0.0001; trough FEV1: difference of 65mL for olodaterol 5 µg over placebo, p<0.0001; difference of 76 mL for olodaterol 5 µg over placebo, p<0.0001). There was also a statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response and mean trough FEV1 response at Day 169 in the pooled formoterol 12 µg group compared to the pooled placebo group (FEV1 $AUC_{0\text{-}3h}$: difference of 163mL over placebo, p<0.0001; trough FEV1: difference of 48mL over placebo, p=0.0006).

Analysis of the mean Mahler TDI focal score at Day 169, which was pre specified as a co primary endpoint to be analysed in the combined dataset, showed that there was no statistically significant difference compared to the pooled placebo group, for the pooled olodaterol 5 µg group, pooled olodaterol 10 µg group, and pooled formoterol 12 µg group.

Although the formal pre specified hypothesis testing for the Mahler TDI focal score at Day 169 was to be based on the combined dataset from Studies 1222.13 and 1222.14, analyses had also been performed in the individual studies and showed a lack of consistency in the results between the 2 individual studies. While the results for the active treatment groups were similar across the two studies, there was an improvement in the Mahler TDI focal score over time in the placebo group in Study 1222.13 which was not seen in Study 1222.14. The sponsor had stated

that since a pre requisite for an analysis of the combined dataset was comparability in results in the two individual studies, an analysis of the combined dataset in this case would not be able to provide a reliable estimate of the effect size for the Mahler TDI focal score scores. This will be discussed in the overall comments on the results of Studies 1222.13 and 1222.14.

6.2.1.2.13. Results for other efficacy outcomes

6.2.1.2.13.1. Other analyses on the primary efficacy endpoints

The sponsor had performed additional analysis with tiotropium use stratum included as a covariate in the model for the primary endpoints analyses. Results showed that when the analysis of FEV1 $AUC_{0\text{-}3h}$ response at Day 169 was performed by tiotropium stratum, both doses of olodaterol (5 µg and 10 µg) as well as the formoterol 12 µg group had mean FEV1 $AUC_{0\text{-}3h}$ responses at Day 169 that were statistically significantly greater than that of placebo in both the tiotropium stratum and the non tiotropium stratum, in both individual studies and in the combined dataset. When analysis of trough FEV1 response at Day 169 was performed by tiotropium stratum, the mean trough FEV1 responses at Day 169 were statistically significantly greater than that of placebo for both doses of olodaterol and for the formoterol 12 µg group in the non tiotropium stratum in both individual studies and in the combined dataset. In the tiotropium stratum, the difference in mean trough FEV1 response at Day 169 from the placebo group for the olodaterol 5 µg group was statistically significant (in favour of olodaterol) in Study 1222.13 and in the combined dataset, but not in Study 1222.14. In the tiotropium stratum, for the olodaterol 10 µg group, the difference in mean trough FEV1 response at Day 169 from the placebo group was not statistically significant in either individual studies, but was statistically significant (in favour of olodaterol) in the combined dataset. The difference in mean trough FEV1 response at Day 169 between the placebo group and the formoterol 12 µg group was not statistically significant in the tiotropium stratum in the individual studies and in the combined dataset.

Key secondary endpoints for the combined analysis of Studies 1222.13 and 1222.14 included the comparison of the pooled olodaterol treatment groups (5 µg and 10 µg) with the pooled formoterol group, for the co primary endpoints of FEV1 $AUC_{0\text{-}3h}$ response at Day 169, trough FEV1 response at Day 169, and the Mahler TDI focal score at Day 169. Results showed that for mean FEV1 $AUC_{0\text{-}3h}$ response at Day 169, there were no statistically significant differences between either dose of olodaterol and the formoterol 12 µg group. For mean trough FEV1 response at Day 169, there was a statistically significant difference in favour of olodaterol between the olodaterol 10 µg group and the formoterol 12 µg group (0.021 versus -0.007, respectively; p=0.0410). There was no statistically significant difference in trough FEV1 response at Day 169 between the olodaterol 5 µg group and the formoterol 12 µg group. There was no statistically significant difference in the Mahler TDI focal score at Day 169 between either dose of olodaterol and the formoterol 12 µg group.

Subgroup analyses based on demographic subgroups and on baseline spirometry subgroups yielded results consistent with the primary efficacy analysis, showing results in favour of both olodaterol dose groups over placebo across the subgroups. There appeared to be a trend for an increased treatment effect in subjects with lesser baseline disease severity (compared to those with greater baseline disease severity), and in those with higher baseline pre bronchodilator FEV1 (compared to those with lower).

6.2.1.2.13.2. Secondary endpoints evaluating FEV1

Secondary endpoints evaluating FEV1 included FEV1 $AUC_{0\text{-}3h}$ response, trough FEV1 response, and FEV1 $peak_{0\text{-}3h}$ response over 48 weeks, and FEV1 at individual time points during the 3 hour post dose period over 48 weeks.

Analyses on the effects of olodaterol on FEV1 $AUC_{0\text{-}3h}$ response over 48 weeks showed that for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group, there were statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ responses compared to the

placebo group on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset.

Analyses on the effects of olodaterol on trough FEV1 response over 48 weeks showed that there were statistically significantly greater mean trough FEV1 responses compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, 337) for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group in both individual studies and in the combined dataset, except for the olodaterol 5 µg group on Day 281 (p=0.0537) and the formoterol 12 µg group on Day 281 (p=0.2579) in Study 1222.13, and for the formoterol 12 µg group on Day 337 in Study 1222.14 (p=0.0664).

Analyses on the effects of olodaterol on FEV1 $peak_{0\text{-}3h}$ response over 48 weeks showed that for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group, there were statistically significantly greater mean FEV1 $peak_{0\text{-}3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset.

Analyses of FEV1 at individual time points up to 3 hour post dose over 48 weeks (at 5, 15, and 30 minutes, and at 1, 2 and 3 hours after inhalation of study drug, at Day 1 and after 2, 6, 12, 24 and 48 weeks) showed that differences from placebo (in favour of olodaterol) were statistically significant for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group at all post dose time points in both individual studies and in the combined dataset.

In both studies, the mean FEV1 increased within 5 minutes after the administration of both olodaterol dose levels, and these increases were sustained over the 3 hour post dose evaluation period. The sponsor had tabulated the FEV1 by time points up to 30 minutes post dose on Day 1, which showed that in both studies, FEV1 increased within 5 minutes after the first administration (Day 1) of olodaterol 5 µg (increase from pre treatment baseline in mean FEV1 of 0.136 L in Study 1222.13 and of 0.121 L in Study 1222.14) and of olodaterol 10 µg (increase from pre treatment baseline in mean FEV1 of 0.133 L in Study 1222.13 and 0.131 L in Study 1222.14) with further increases after 15 minutes (olodaterol 5 µg: 0.176L and 0.154L in Studies 1222.13 and 1222.14, respectively; olodaterol 10 µg: 0.167L and 0.166L, respectively) and 30 minutes (olodaterol 5 µg: 0.191L and 0.167L in Studies 1222.13 and 1222.14, respectively; olodaterol 10 µg: 0.187L and 0.186L, respectively). A similar pattern was observed in the formoterol 12 µg group in both studies.

6.2.1.2.13.3. Secondary endpoints evaluating FVC

Secondary endpoints evaluating FVC included FVC $AUC_{0\text{-}3h}$ response, trough FVC response, and FVC $peak_{0\text{-}3h}$ response over 48 weeks, and FVC at individual time points during the 3 hour post dose period over 48 weeks.

Analyses on FVC $AUC_{0\text{-}3h}$ response over 48 weeks showed that for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group, there were statistically significantly greater mean FVC $AUC_{0\text{-}3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset. Analyses on trough FVC response over 48 weeks (Days 15, 43, 85, 127, 169, 225, 281, 337) showed that in Study 1222.13, there were statistically significantly greater mean trough FVC responses compared to placebo in the olodaterol 10 µg group only on Days 15, 43, 85, and 169, in the olodaterol 5 µg group only on Days 43, 85, and 337, and in the formoterol 12 µg group only on Days 15, 43, and 85. The difference between the active treatment groups and the placebo group was not statistically significant on other test days. In Study 1222.14, there were statistically significantly greater mean trough FVC responses compared to placebo on most test days (Days 15, 43, 85, 127, 281, and 337 for both the olodaterol 5 µg and olodaterol 10 µg groups, and also Day 225 in the olodaterol 5 µg dose group). There was statistically significantly greater mean trough FVC responses compared to placebo in the formoterol 12 µg group only on Days 15, 43, 85 and 127. In the combined analyses, there were statistically significantly greater mean trough FVC

responses compared to placebo on all test days (Days 15, 43, 85, 127, 169, 225, 281, and 337) for both the olodaterol 5 µg and olodaterol 10 µg groups. There was statistically significantly greater mean trough FVC responses compared to placebo in the formoterol 12 µg group only on Days 15, 43, and 85.

Analyses on the effects of olodaterol on FVC $peak_{0\text{-}3h}$ response over 48 weeks showed that for both the olodaterol 5 µg and olodaterol 10 µg groups as well as for the formoterol 12 µg group, there were statistically significantly greater mean FVC $peak_{0\text{-}3h}$ responses compared to placebo on all test days (Days 1, 15, 43, 85, 169, 337), in both individual studies and in the combined dataset.

Analyses of FVC at individual time points up to 3 hour post dose over 48 weeks (at 5, 15, and 30 minutes, and at 1, 2 and 3 hours after inhalation of Study drug, at Day 1 and after 2, 6, 12, 24 and 48 weeks) showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all post dose time points in both individual studies and in the combined dataset. In both studies, the mean FVC increased within 5 minutes after the administration of both olodaterol dose levels on each test day (Day 1 and Weeks 2, 6, 12, 24, and 48), and these increases were sustained over the 3 hour post dose evaluation period and were statistically significantly higher compared to placebo. Results were similar in the formoterol 12 µg group.

6.2.1.2.13.4. Secondary endpoints evaluating PEFR

Analyses of the weekly mean values for morning PEFR showed that differences from placebo (in favour of olodaterol or formoterol) were statistically significant for the olodaterol 10 µg group and the formoterol 12 µg group at all time points in both individual studies and in the combined dataset. The differences from placebo (in favour of olodaterol) in weekly mean values for morning PEFR were statistically significant for the olodaterol 5 µg group at all time points in both individual studies and in the combined dataset except at Weeks 36, 39, 40, and 41.

Analyses of the weekly mean values for evening PEFR showed that differences from placebo (in favour of olodaterol) were statistically significant for both olodaterol doses at all time points in both individual studies and in the combined dataset. Results were similar in the formoterol 12 µg group.

6.2.1.2.13.5. Secondary endpoints evaluating SGRQ scores and Mahler TDI scores

SGRQ total score at Day 169 (pooled olodaterol vs. pooled placebo) was a pre specified key secondary efficacy endpoint in the combined dataset, with the SGRQ component scores at Day 169 (pooled olodaterol versus pooled placebo) pre specified as other secondary efficacy endpoints. In the individual studies, SGQR total and component scores after 12 and 48 weeks were secondary efficacy endpoints.

In the combined dataset, there was a statistically significantly lower SGRQ total score (that is, better outcome) and lower SGRQ score for each component at Day 169 for both the olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group; however, there was no statistically significant difference in the SGRQ total score or each SGRQ component at Day 169 between the formoterol 12 µg group and the placebo group.

In the individual studies, analysis of total and component SGRQ scores at 12 and 48 weeks showed that in Study 1222.13, there was a statistically significantly lower SGRQ total score at Day 85 (that is 12 weeks) for both the olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group, but there was no statistically significant difference in SGRQ total score at Day 85 between the formoterol 12 µg group and the placebo group. Analyses of the SGRQ component scores showed that at Day 85, the mean SGRQ scores were statistically significantly lower compared to placebo for the olodaterol 10 µg group across all 3 SGRQ components (symptom, activity and impact), but only for the component of "symptom" for the olodaterol 5 µg group. There was no statistically significant difference between the formoterol 12 µg group

and the placebo group across all 3 SGRQ components at Day 85. In Study 1222.13, at Day 337 (that is 48 weeks), there was a statistically significantly lower SGRQ total score only for the olodaterol 10 µg group compared to the placebo group, while there was no statistically significant difference in the SGRQ total score between the formoterol 12 µg group or the olodaterol 5 µg group and the placebo group. There was no statistically significant difference between the placebo group and the active treatment groups across all 3 SGRQ components at Day 337, except for the olodaterol 10 µg group for the component of "symptom".

In Study 1222.14, there was a statistically significantly lower SGRQ total score at Day 85 for the olodaterol 5 µg and formoterol 12 µg groups compared to placebo, but no statistically significant difference between the olodaterol 10 µg group and the placebo group. The difference between the active treatment groups and the placebo group across the SGRQ components at Day 85 were mostly not statistically significant. There was no statistically significant difference in the SGRQ total score as well as all the component scores at Day 337 between the olodaterol 5 µg, olodaterol 10 µg, or formoterol 12 µg groups and the placebo group.

The Mahler TDI focal score (that is, total score) at Day 169 was a primary endpoint and results had been presented. Mahler TDI component scores at Day 169 (pooled olodaterol vs. pooled placebo) were secondary endpoints in the combined analysis, while the Mahler TDI total and component scores after 6, 12, 18, 24, 32, 40 and 48 weeks were secondary endpoints in the individual studies.

In the combined analysis, the analyses of the Mahler TDI component scores at Day 169 showed that the difference between the active treatment groups and the placebo group were not statistically significant, for all 3 components. In the individual studies, analyses of the Mahler TDI total and component scores over 48 weeks showed that in Studies 1222.13 and 1222.14, the differences between the active treatment groups and the placebo group were mostly not statistically significant.

6.2.1.2.13.6. Other secondary endpoints

Analyses of the weekly mean number of daytime rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in Study 1222.13 and in the combined analysis. In Study 1222.14, the difference between the olodaterol 5 µg group and the placebo group was not statistically significant across all time points, while that for the olodaterol 10 µg group was only statistically significant (in favour of olodaterol) in about half of the time points (Weeks 4 to 6, 8, 9, 11, 16, 20, 22 to 24, 26 to 34, 37 to 41, 43, 45 to 48; $p<0.05$).

Analyses of the weekly mean number of night time rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in Study 1222.13 and in the combined analysis. In Study 1222.14, the difference between the olodaterol 10 µg group and the placebo group was statistically significant (in favour of olodaterol) across all time points, while that for the olodaterol 5 µg group was only statistically significant (in favour of olodaterol) in about a quarter of the time points (Weeks 9, 10, 12, 13, 20, 26 to 29, 31, 32; $p<0.05$).

Analyses of daily (24 hour) rescue medication use (measured weekly) showed that reductions from placebo were statistically significant for both olodaterol doses at all time points in both in Study 1222.13 and in the combined analysis. In Study 1222.14, the difference between the olodaterol 10 µg group and the placebo group was statistically significant (in favour of olodaterol) across all time points, while that for olodaterol 5 µg, was only statistically significant (in favour of olodaterol) in a minority of time points (Weeks 19, 20, 26 to 29, 31,32; $p<0.05$).

Analyses of the Patient's Global Rating over 48 weeks showed that in Study 1222.13, the mean score at 6, 12, 24, and 48 weeks ranged from 2.9 to 3.1 in both olodaterol treatment groups and in the formoterol group, and from 3.1 to 3.4 in the placebo group. The lower scores in the olodaterol treatment groups compared to placebo were statistically significant at all time points

up to 24 weeks (that is, the difference at Week 48 was not statistically significant for either olodaterol dose). The lower scores in the formoterol treatment groups compared to placebo were statistically significant at only Weeks 6 and 12 (that is, the differences at Weeks 24 and 48 were not statistically significant). In Study 1222.14, the mean score after 6, 12, 24, and 48 weeks ranged from 3.0 to 3.2 in both olodaterol treatment groups and in the formoterol group, and from 3.2 to 3.4 for the placebo group. The lower scores in the olodaterol 5 µg group compared to the placebo group were statistically significant at only Weeks 6 and 12, while those for the olodaterol 10 µg group and for the formoterol group were statistically significant at time points up to Week 24. In the combined analyses, the mean score at 6, 12, 24, and 48 weeks ranged from 2.9 to 3.1 in both pooled olodaterol treatment groups, from 3.0 to 3.1 in the pooled formoterol group, and from 3.1 to 3.4 in the pooled placebo treatment group. The lower scores in the pooled olodaterol 10 µg group compared to pooled placebo group were statistically significant at all time points up to 48 weeks, while those for the pooled olodaterol 5 µg group and for the pooled formoterol group were statistically significant at time points up to Week 24.

Cox proportional hazards regression analysis showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between the olodaterol treatment groups and the placebo group and between the formoterol group and the placebo group, in both individual studies and in the combined datasets. There were also no statistically significant differences between the olodaterol treatment groups and the placebo group and between the formoterol group and the placebo group, for the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in both individual studies and in the combined datasets.

> Comments on Studies 1222.13 and 1222.14: Overall, efficacy results in these 2 studies supported the efficacy claim for olodaterol over placebo. Results in both studies showed statistically significantly greater mean FEV1 $AUC_{0\text{-}3h}$ response and greater mean trough FEV1 response at Day 169 (primary endpoints) for both the olodaterol 5 µg and 10 µg groups compared to the placebo group. Pooled analyses on the combined dataset of both studies yielded the same results. However, analysis of the other primary endpoint, the Mahler TDI focal score at Day 169, which was pre specified to be analysed only in the combined dataset, showed that there was no statistically significant difference between the pooled placebo group and the pooled olodaterol 5 µg group or pooled olodaterol 10 µg group.
>
> Although the sponsor had stated that the results of the Mahler TDI focal score in the combined dataset might not be reliable as the analyses in the individual studies yielded inconsistent results between the 2 studies, it was noted that despite the inconsistency between studies, both individual studies had yielded results that were not statistically significant. However, it is acknowledged that the studies had not been powered to show statistical significance for this endpoint at the level of analyses in the individual studies, only for analysis in the combined dataset. Nonetheless, analyses of the Mahler TDI component scores at Day 169 in the combined dataset (secondary endpoint) showed that the difference between both olodaterol groups and the placebo group were not statistically significant across all 3 components. Analyses of the Mahler TDI total and component scores over 48 weeks in the individual studies also showed that the differences between both olodaterol groups and the placebo group were mostly not statistically significant. However, it is noted that analyses in the formoterol group yielded similar results, showing no statistically significant difference between formoterol and placebo mean Mahler TDI focal and component scores at Day 169 in the pooled dataset. In addition, comparison between the olodaterol groups and formoterol group in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between both olodaterol doses and formoterol in the Mahler TDI focal score at Day 169.

Comparison between the olodaterol treatment groups and the formoterol group (pre specified to be analysed only in the combined dataset) showed that there was no statistically significant difference between the pooled olodaterol 5 µg group and the pooled formoterol group across all 3 co primary endpoints (that is, FEV1 AUC_{0-3h} response, trough FEV1 response and the Mahler TDI focal score at Day 169). For the pooled olodaterol 10 µg group there was a statistically significantly greater mean trough FEV1 response at Day 169 compared to the pooled formoterol group, but no statistically significant difference for the other 2 primary endpoints. The comparison between the olodaterol treatment groups and the formoterol group had been designed as a superiority test and not a test of non inferiority. Hence, the statistical inference would be that olodaterol 5 µg qd had not been found to be superior to formoterol 12 µg bid after 24 weeks of treatment in terms of FEV1 AUC_{0-3h} response, trough FEV1 response and the Mahler TDI focal score, and that olodaterol 10 µg qd had been found to be superior to formoterol 12 µg bid after 24 weeks of treatment in terms of trough FEV1 response, but had not been found to be superior to formoterol 12 µg bid after 24 weeks of treatment in terms of FEV1 AUC_{0-3h} response and the Mahler TDI focal score. No inference on non inferiority of olodaterol compared to formoterol could be made. The statistical method as a test of superiority rather than of non inferiority between olodaterol and the active control is consistent with the EMA guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease, which stated that

> *'The three arm placebo and active controlled study would aim to demonstrate that the test product is superior to placebo and allow putting results into perspective; the two arm study would aim to demonstrate that the test product is at least non inferior to the active comparator'.*

This guideline wording suggested that for a 3 arm study like Studies 1222.13 and 1222.14, the aim is to demonstrate superiority of test product against placebo, while the comparison between the test product and the active control is to allow the results to be put into perspective; a non inferiority study is recommended if it had been a 2 arm study between the test product and an active control, without a placebo arm.

Additional analysis with tiotropium use stratum included as a covariate in the model for the analyses of FEV1 AUC_{0-3h} response and trough FEV1 response at Day 169 showed that both doses of olodaterol (5 µg and 10 µg) had mean FEV1 AUC_{0-3h} responses at Day 169 that were statistically significantly greater than that of placebo in both the tiotropium stratum and the non tiotropium stratum, in both individual studies and in the combined dataset. The mean trough FEV1 responses at Day 169 were statistically significantly greater than that of placebo for both doses of olodaterol across the individual studies and the combined dataset only in the non tiotropium stratum, while the results comparing mean trough FEV1 response at Day 169 between olodaterol 5 µg and placebo, and between olodaterol 10 µg and placebo, in the tiotropium stratum were inconsistent for statistical significance across the individual studies and the combined dataset (olodaterol 5 µg versus placebo: statistically significant in Study 1222.13 and combined dataset, but not in Study 1222.14; olodaterol 10 µg versus placebo: not statistically significant in both Studies 1222.13 and 1222.14, but statistically significant in the combined dataset). However, it is noted that the results for the formoterol group followed a similar pattern: mean FEV1 AUC_{0-3h} response at Day 169 was statistically significantly greater than that of placebo in both the tiotropium stratum and the non tiotropium stratum, in both individual studies and in the combined dataset, but there was no statistically significant difference from placebo for mean trough FEV1 response at Day 169 across the individual studies and the combined dataset.

The FEV1 time profile up to 3 hours post dose on Day 1 yielded results similar to those in Studies 1222.11 and 1222.12, and showed that FEV1 increased within 5 minutes after

the first administration of olodaterol 5 µg and of olodaterol 10 µg, with further increases after 15 and 30 minutes, and was sustained over the 3 hour post dose evaluation period. A similar pattern was observed in the formoterol 12 µg group in both studies.

Evaluation of FEV1 and FVC profile over 48 weeks (that is, duration of treatment in the studies) also yielded results similar to those in Studies 1222.11 and 1222.12, and showed that there were statistically significant differences in FEV1 and FVC at individual time points up to 3 hour post dose over 48 weeks between placebo and both olodaterol doses (in favour of olodaterol) at all post dose time points in both individual studies and in the combined dataset. Similar results were seen in the formoterol group.

Analyses on the effects of olodaterol on FEV1 AUC_{0-3h} response, trough FEV1 response, and FEV1 $peak_{0-3h}$ response over 48 weeks showed statistically significantly greater responses for both olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group on all test days in both individual studies and in the combined dataset, except for olodaterol 5 µg on Day 281 (Week 40) in Study 1222.13 for the endpoint of trough FEV1 response. These results were similar to those obtained for Studies 1222.11 and 1222.12. Results in the formoterol group were generally comparable, showing statistically significantly greater responses compared to the placebo group on all test days in both individual studies and in the combined dataset, except for Day 281 (Week 40) in Study 1222.13 and Day 337 (Week 48) in Study 1222.14 for the endpoint of trough FEV1 response.

Analyses on the effects of olodaterol on FVC AUC_{0-3h} response and FVC $peak_{0-3h}$ response over 48 weeks also showed statistically significantly greater responses for both olodaterol 5 µg and olodaterol 10 µg groups (as well as for the formoterol group) compared to the placebo group on all test days in both individual studies and in the combined dataset. These results were similar to those obtained for Studies 1222.11 and 1222.12. Consistent with the results in Studies 1222.11 and 1222.12, analyses on the effects of olodaterol on trough FVC response over 48 weeks showed more variability between studies compared to those for FVC AUC_{0-3h} response and FVC $peak_{0-3h}$ response. The difference in mean trough FVC responses compared to placebo for both olodaterol 5 µg and olodaterol 10 µg groups was not statistically significant on most test days in Study 1222.13, statistically significant (in favour of olodaterol) on most test days in Study 1222.14, and statistically significant (in favour of olodaterol) on all test days in the combined dataset. Analyses on the effects on trough FVC response over 48 weeks in the formoterol group yielded results that were not statistically significant on most test days in both individual studies and the combined dataset (statistically significant in favour of formoterol only up to Week 12 in Study 1222.13 and the combined dataset, and only up to Week 18 in Study 1222.14).

Analyses of the SGRQ total and component scores at Day 169 in the combined dataset showed that there were statistically significantly lower SGRQ total and component scores (that is, better outcome) at Day 169 for both the olodaterol 5 µg and olodaterol 10 µg groups compared to the placebo group. By comparison, there was no statistically significant difference in the SGRQ total or component scores at Day 169 between the formoterol 12 µg group and the placebo group.

Other secondary endpoints evaluating PEFR, rescue medication use and the Patient's Global Rating yielded results which were less consistently in favour of olodaterol compared to those in Studies 1222.11 and 1222.12, but were generally supportive of the efficacy claim for olodaterol over placebo.

Analyses of the secondary endpoints of exacerbations of COPD yielded results similar to those in Studies 1222.11 and 1222.12, and showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD

exacerbation, or first COPD exacerbation leading to hospitalisation between both olodaterol treatment groups and the placebo treatment group, in both individual studies and in the combined datasets. There were also no statistically significant differences between both olodaterol treatment groups and the placebo treatment group in the mean number of COPD exacerbations, mean number of moderate COPD exacerbations, or mean number of COPD exacerbations leading to hospitalisation in both individual studies and in the combined datasets. However, comparisons between the formoterol group and the placebo group yielded the same results showing no statistically significant difference for these endpoints.

Subgroup analyses on the co primary endpoints yielded results that were consistent with the primary efficacy analysis. However, it is noted that with regards to interaction between smoking status and efficacy, only the smoking status at baseline was considered. A look through the study protocols of Studies 1222.13 and 1222.14 showed that smoking status of subjects was reviewed at Weeks 24 and 48. However, the potential interaction between smoking status at these time points and efficacy was not explored or presented. This will be raised as a clinical question.

6.2.2. Other efficacy studies

6.2.2.1. Studies 1222.24 and 1222.25

Both Studies 1222.24 and 1222.25 were multi centre,[34] randomised, double blind, double dummy, placebo controlled, four way cross over studies to characterise the 24 hour FEV1 time profiles of orally inhaled olodaterol 5 µg and 10 µg, administered qd with the Respimat Inhaler, and of orally inhaled formoterol 12 µg, administered bid with the Aerolizer Inhaler, after 6 weeks of treatment in patients with COPD. The primary objective of both studies was to evaluate whether once daily treatment with olodaterol 5 µg and 10 µg was superior to placebo using FEV1 $AUC_{0\text{-}12h}$ and FEV1 $AUC_{12\text{-}24h}$ responses after 6 weeks of treatment. The secondary objective was to evaluate whether once daily treatment with olodaterol 5 µg and 10 µg was superior to formoterol 12 µg twice daily using FEV1 $AUC_{0\text{-}12h}$ and FEV1 $AUC_{12\text{-}24h}$ responses after 6 weeks of treatment.

The study inclusion and exclusion criteria were the same as those for Studies 1222.11, 1222.12, 1222.13 and 1222.14. The study treatments were olodaterol 5 µg (2 actuations of 2.5 µg qd with the Respimat inhaler), olodaterol10 µg (2 actuations of 5 µg qd with the Respimat inhaler), formoterol Aerolizer 12 µg bid, placebo matching olodaterol Respimat qd, and placebo matching formoterol Aerolizer bid. Subjects underwent four 6 week treatment periods, each separated by a 2 week wash out period. Both studies had a double dummy four way cross over design, such that over the duration of the study, each subject would have received one 6 week treatment period of olodaterol 5 µg qd with placebo matching formoterol bid, one 6 week treatment period of olodaterol 10 µg qd with placebo matching formoterol bid, one 6 week treatment period of placebo matching olodaterol qd with formoterol 12 µg bid, and one 6 week treatment period of placebo matching olodaterol qd with placebo matching formoterol bid.

The co primary efficacy endpoints in both studies were FEV1 $AUC_{0\text{-}12h}$ response and FEV1 $AUC_{12\text{-}24h}$ response after 6 weeks of treatment. The primary efficacy outcome was the comparison of olodaterol 5 µg and10 µg with placebo for these primary endpoints. The key secondary efficacy outcomes were the comparison of olodaterol 5 µg and10 µg qd with formoterol 12 µg bid for these primary endpoints (pre specified to be performed only on the combined dataset), and the comparison of olodaterol 5 µg and10 µg with placebo for the endpoint of FEV1 $AUC_{0\text{-}24h}$ response after 6 weeks of treatment. Additional secondary endpoints

[34] Study 1222.24 was conducted across 10 study centres in the US, while Study 1222.25 was conducted across 13 study centres in the US.

included FVC AUC_{0-12h} response, FVC AUC_{12-24h} response and FVC AUC_{0-24h} response after 6 weeks of treatment.

In Study 1222.24, a total of 187 subjects were enrolled, and 99 subjects were randomised. In Study 1222.25, a total of 187 subjects were enrolled, and 100 subjects were randomised. Baseline demographic characteristics were comparable between both studies.

There was a statistically significant ($p<0.0001$) greater mean FEV1 AUC_{0-12h} response as well as FEV1 AUC_{12-24h} response at Day 43 (that is, Week 6) for olodaterol 5 µg qd, olodaterol 10 µg qd and formoterol 12 µg bid compared to placebo in both studies. There was also a statistically significant ($p<0.0001$) greater mean FEV1 AUC_{0-24h} response at Day 43 for olodaterol 5 µg qd, olodaterol 10 µg qd and formoterol 12 µg bid compared to placebo in both studies and showed that FEV1 increased within 30 minutes following the morning dose for both olodaterol doses, peaked at around 2 hours post dose and then reduced progressively towards baseline.

Analyses in the combined dataset comparing olodaterol 5 µg qd and olodaterol 10 µg qd with formoterol 12 µg bid showed that for mean FEV1 AUC_{0-12h} response at Day 43, there was no statistically significant difference between either dose of olodaterol and formoterol. However, the mean FEV1 AUC_{12-24h} response for formoterol 12 µg bid was statistically significantly greater than that for olodaterol 10 µg qd (−40 mL difference, $p=0.0024$) and for olodaterol 5 µg qd (−50 mL difference, $p=0.0001$). Overall mean FEV1 AUC_{0-24h} response at Day 43 showed no statistically significant difference between either dose of olodaterol and formoterol. There were no statistically significant differences in mean trough FEV1 response between olodaterol 10 µg qd and formoterol 12 µg bid or between olodaterol 5 µg qd and formoterol 12 µg bid.

There was a statistically significant ($p<0.0001$) greater mean FVC AUC_{0-12h} response, FVC AUC_{12-24h} response, and FVC AUC_{0-24h} response at Day 43 for olodaterol 5 µg qd, olodaterol 10 µg qd and formoterol 12 µg bid compared to placebo in both individual studies.

6.2.2.2. Studies 1222.39 and 1222.40

Both Studies 1222.39 and 1222.40 were multi centre,[35] randomised, double blind, double dummy, placebo controlled, four way cross over studies to characterise the 24 hour FEV1 time profiles of orally inhaled olodaterol 5 µg and 10 µg, administered once daily with the Respimat Inhaler, and of orally inhaled tiotropium bromide 18µg, administered once daily with the HandiHaler, after 6 weeks of treatment in patients with COPD. The primary objective of both studies was to evaluate whether once daily treatment with olodaterol 5 µg and 10 µg was superior to placebo using FEV1 AUC_{0-12h} and FEV1 AUC_{12-24h} responses after 6 weeks of treatment. The secondary objective was to evaluate whether once daily treatment with olodaterol 5 µg and 10 µg was superior to tiotropium bromide 18µg once daily using FEV1 AUC_{0-12h} and FEV1 AUC_{12-24h} responses after 6 weeks of treatment.

The study inclusion and exclusion criteria were the same as those for Studies 1222.11, 1222.12, 1222.13 and 1222.14. The study treatments were olodaterol 5 µg (2 actuations of 2.5 µg qd with the Respimat inhaler), olodaterol10 µg (2 actuations of 5 µg qd with the Respimat inhaler), tiotropium bromide HandiHaler 18µg qd, placebo matching olodaterol Respimat qd, and placebo matching tiotropium bromide HandiHaler qd. The study design and the study efficacy endpoints were the same as those for Studies 1222.24 and 1222.25, except that the active control was tiotropium bromide instead of formoterol, and the washout period was 3 weeks instead of 2 weeks.

In Study 1222.39, a total of 147 subjects were enrolled, and 108 subjects were randomised. In Study 1222.40, a total of 155 subjects were enrolled, and 122 subjects were randomised. Baseline demographic characteristics were comparable between both studies.

[35] Study 1222.39 was conducted across 15 study centres (3 in Belgium, 3 in Denmark, 3 in Germany and 6 in Hungary), while study 1222.40 was conducted across 12 study centres (3 in the Netherlands, 3 in Germany, 3 in the United States and 3 in Norway).

There was a statistically significant (p<0.0001) greater mean FEV1 AUC_{0-12h} response as well as FEV1 AUC_{12-24h} response at Day 43 (that is, Week 6) for olodaterol 5 µg qd, olodaterol 10 µg qd and tiotropium bromide 18 µg qd compared to placebo in both studies. There was also a statistically significant (p<0.0001) greater mean FEV1 AUC_{0-24h} response at Day 43 for olodaterol 5 µg qd, olodaterol 10 µg qd and tiotropium bromide 18 µg qd compared to placebo in both studies. FEV1 time profiles on Day 43 for Studies 1222.39 and 1222.40 showed that FEV1 increased within 30 minutes following the morning dose for both olodaterol doses peaked at around 2 hours post dose and then reduced progressively towards baseline. Tiotropium 18 µg qd showed similar FEV1 time profile on Day 43.

Analyses in the combined dataset comparing olodaterol 5 µg qd and olodaterol 10 µg qd with tiotropium 18 µg qd showed that for mean FEV1 AUC_{0-12h} response at Day 43, there were no statistically significant differences between either dose of olodaterol and tiotropium. However, the mean FEV1 AUC_{12-24h} response for tiotropium 18 µg qd was statistically significantly less than that for olodaterol 10 µg qd (30 mL difference, p=0.0306). There was no statistically significant difference in mean FEV1 AUC_{12-24h} response between olodaterol 5 µg qd and tiotropium 18 µg qd. Overall mean FEV1 AUC_{0-24h} response at Day 43 showed no statistically significant differences between either dose of olodaterol and tiotropium.

There was a statistically significant (p<0.0001) greater mean FVC AUC_{0-12h} response, FVC AUC_{12-24h} response, and FVC AUC_{0-24h} response at Day 43 for olodaterol 5 µg qd, olodaterol 10 µg qd and tiotropium 18 µg qd compared to placebo in both individual studies.

6.2.2.3. Studies 1222.37 and 1222.38

Both Studies 1222.37 and 1222.38 were multi centre,[36] randomised, double blind, placebo controlled, 3 way cross over studies to determine the effect of 6 weeks treatment of orally inhaled olodaterol 5 µg and 10 µg, administered once daily with the Respimat Inhaler on exercise endurance time during constant work rate cycle ergometry in patients with COPD.

The primary objective of both studies was to compare the effects of olodaterol (5 µg and 10 µg) versus placebo on constant work rate exercise tolerance after 6 weeks of treatment in patients with COPD. The secondary objectives were to compare the effects of olodaterol (5 µg and 10 µg) versus placebo on lung hyperinflation during constant work rate exercise in patients with COPD as measured by inspiratory capacity (IC), and on the intensity of breathing discomfort experienced during constant work rate exercise in patients with COPD. The intensity of breathing discomfort was rated by the patients using the Borg Category Ratio Scale.

The study inclusion and exclusion criteria were the same as those for Studies 1222.11, 1222.12, 1222.13 and 1222.14. The study treatments were olodaterol 5 µg (2 actuations of 2.5 µg qd with the Respimat inhaler), olodaterol 10 µg (2 actuations of 5 µg qd with the Respimat inhaler), and placebo matching olodaterol Respimat qd. Subjects underwent three 6 week treatment periods, each separated by a 2 week wash out period. Both studies had a 3 way cross over design, such that over the duration of the study, each subject would have received one 6 week treatment period of olodaterol 5 µg qd, one 6 week treatment period of olodaterol 10 µg qd, and one 6 week treatment period of placebo matching olodaterol qd.

The primary efficacy endpoint in both studies was the endurance time during constant work rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wcap) after 6 weeks of treatment (Day 43). Key secondary endpoints were the IC[37] at isotime during constant

[36] Study 1222.37 was conducted across 19 study centres (4 in Australia, 2 in Austria, 3 in Canada, 6 in France, and 4 in Germany), while study 1222.38 was conducted across 19 study centres (2 in Austria, 4 in Belgium, 4 in Canada, 6 in Germany, and 3 in Russia).

[37] For each individual subject, isotime was defined as the endurance time of the constant work rate exercise test of shortest duration from Visit 2 (screening), Visit 4 (Week 6 of first treatment period), Visit 6 (Week 6 of second treatment period) and Visit 8 (Week 6 of third treatment period).

work rate cycle ergometry to symptom limitation at 75% Wcap, [38] and the intensity of breathing discomfort (Borg Category Ratio Scale) at isotime during constant work rate cycle ergometry to symptom limitation at 75% Wcap.

In Study 1222.37, a total of 201 subjects were enrolled, and 151 subjects were randomised. In Study 1222.38, a total of 204 subjects were enrolled, and 157 subjects were randomised. Baseline demographic characteristics were comparable between both studies.

After six weeks of treatment, mean endurance time during constant work rate cycle ergometry was statistically significantly longer for both olodaterol doses compared with placebo in both studies. Compared to placebo, endurance time was longer by 14.0% with olodaterol 5 µg qd (p= 0.0002) and 13.8% with olodaterol 10 µg qd (p= 0.0003) in Study 1222.37 and by 11.8% with olodaterol 5 µg qd (p= 0.0018) and 10.5% with olodaterol 10 µg qd (p= 0.0052) in Study 1222.38. Analyses of the key secondary endpoint of IC at isotime showed that in both studies, there was a statistically significantly greater mean IC (indicating a lower end expiratory lung volume) at isotime compared to placebo for both olodaterol 5 µg (Study 1222.37: 2.099L versus 1.917L in placebo, p<0.0001, Study 1222.38: 2.246L versus 2.162L in placebo, p=0.0155) and olodaterol 10 µg (Study 1222.37: 2.091L versus 1.917L in placebo, p<0.0001, Study 1222.38: 2.328L versus 2.162L in placebo, p<0.0001). Analyses of the key secondary endpoint of the intensity of breathing discomfort at isotime showed that in Study1222.37, there was a statistically significantly lower intensity of breathing discomfort at isotime for both olodaterol 5 µg and olodaterol 10 µg compared to placebo. However, in Study 1222.38, the differences in the intensity of breathing discomfort at isotime for olodaterol 5 µg and for olodaterol 10 µg compared to placebo were not statistically significant.

> Comments: Although the results in these 2 studies showed that compared to placebo, endurance time was statistically significantly longer by 12 to 14% with olodaterol 5 µg qd and by 11 to 14% with olodaterol 10 µg qd, the difference in treatment means between olodaterol 5 µg and placebo was 42 to 52 seconds, and that between olodaterol 10 µg and placebo was 37 to 51 seconds. A direct translation of these increases in mean endurance time on the cycle ergometer at 75% maximal work capacity to normal effort tolerance in daily activities is not available, thus making interpretation of the clinical relevance of these findings difficult. A look through the currently approved Australian PI for indacaterol showed no mention of effect on endurance time during constant work rate cycle ergometry, thus not allowing any comparison to be made. It is recommended that these statistically significant results be acknowledged, but that caution should be taken in the presentation of these results in the proposed PI to ensure that these statistically significant findings are considered within the context that the difference in treatment means between olodaterol and placebo was less than 1 minute. This will be discussed later.

6.2.2.4. Studies 1222.3, 1222.5 and 1222.26

Studies 1222.3, 1222.5 and 1222.26 were Phase II studies in COPD patients. The efficacy results of Studies 1222.3 and 1222.5 have been previously described.

Study 1222.26 was a 3 week, randomised, double blind, 4 way cross over study to evaluate the 24 hour FEV1 time profile of orally inhaled olodaterol when administered once daily (5 µg qd, 10 µg qd) versus twice daily (2 µg bid, 5 µg bid) in COPD patients, in order to test the validity of once daily posology of olodaterol. The primary endpoints were FEV1 $AUC_{0\text{-}12h}$ response and FEV1 $AUC_{12\text{-}24h}$ response after 3 weeks of treatment. Results showed that for all olodaterol dose regimens there were statistically significantly greater FEV1 $AUC_{0\text{-}12h}$ and FEV1 $AUC_{12\text{-}24h}$ responses compared with pre treatment baseline (p<0.001). With regards to comparison of

[38] Maximal work capacity was the maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at Visit 1.

olodaterol 5 µg qd versus olodaterol 2 µg bid, results showed that the FEV1 AUC_{0-12h} response for olodaterol 5 µg qd was significantly increased compared with olodaterol 2 µg bid (0.209 L versus 0.155 L, p = 0.0003), but that there was no statistically significant difference in FEV1 AUC_{12-24h} response between olodaterol 5 µg qd and olodaterol 2 µg bid (0.155 L versus 0.167 L, p=0.4111). Analyses of FEV1 AUC_{0-24h} response showed that there was no statistically significant difference between olodaterol 5 µg qd and olodaterol 2 µg bid (0.182 L versus 0.160 L, p=0.1161). With regards to comparison of olodaterol 10 µg qd versus olodaterol 5 µg bid, results showed that there was no statistically significant difference in FEV1 AUC_{0-12h} response between olodaterol 10 µg qd and olodaterol 5 µg bid (0.204 L versus 0.189 L, p=0.3011), but that the FEV1 AUC_{12-24h} response for olodaterol 10 µg qd was significantly less compared with olodaterol 5 µg bid (0.149 L versus 0.201 L, p=0.0006). Analyses of FEV1 AUC_{0-24h} response showed that there was no statistically significant difference between olodaterol 10 µg qd and olodaterol 5 µg bid (0.176L versus 0.195L, p=0.1753).

> Comments: The rationale for the dose selection for the Phase III studies based on the results of the Phase II Studies 1222.3 and 1222.5 has been previously discussed. Study 1222.26 was not conducted for the purpose of dose regimen selection for the Phase III studies, but was conducted to evaluate alternative dosing frequencies of olodaterol in order to lend support to the proposed once daily dose regimen of olodaterol. The results in Study 1222.26 suggested that olodaterol 5 µg qd had a statistically significantly greater effect than olodaterol 2 µg bid in the first 12 hours post dose (FEV1 AUC_{0-12h}) after 3 weeks of treatment, but that despite the additional evening dose of olodaterol 2 µg there was no statistically significant difference in the effect on FEV1 between olodaterol 5 µg qd and olodaterol 2 µg bid in the 12 to 24 hours post dose period (FEV1 AUC_{12-24h}), and overall in the 24 hour post dose period (FEV1 AUC_{0-24h}), there was no statistically significant difference in the effect on FEV1 between olodaterol 5 µg qd and olodaterol 2 µg bid. These results supported the dose regimen of olodaterol 5 µg qd instead of olodaterol 2 µg bid.

6.2.2.5. Other Phase II studies

As previously described four 4 week Phase II studies in COPD patients which are not relevant to the evaluation of this submission.[39] These studies were reviewed for the purpose of this evaluation, and the study results did not raise any concerns relevant to this submission.

6.2.3. Analyses performed across trials (pooled analyses and meta analyses)

The sponsor had submitted 9 study reports involving combined or pooled analyses of studies. These consisted of the combined analyses of respective sets of replicate Phase III studies (Studies 1222.11/1222.12 (report 1222-9992), Studies 1222.13/1222.14 (report 1222-9993), Studies 1222.24/1222.25 (report 1222-9991) and Studies 1222.39/1222.40 (report 1222-9994)), a Summary of Clinical Efficacy Supplement (report 1222-9995), a Summary of Clinical Safety Supplement (report 1222-9996), a meta analysis of ADRB2 haplotypes across Studies 1222.11, 1222.12, 1222.13 and 1222.14 (report 1222-0050), a combined analysis of 2 Phase II Studies, 1222.5 and 1222.6, evaluating the covariate effects on olodaterol PK parameters in patients with COPD (Study 1222.5) and persistent asthma (Study 1222.6) (report 1222-9956), and an "embellished narrative summary table", which is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 with SAE or Non SAE leading to discontinuation.

The combined analyses of the respective sets of replicate studies have been previously described and evaluated together with those of the individual studies. The Summary of Clinical Safety Supplement and the "embellished narrative summary table" involved only safety data

[39] One study was a dose-response and PK study in Japanese COPD patients (Study 1222.22), while the other 3 studies were efficacy dose-response studies of a fixed-dose combination of tiotropium and olodaterol in COPD patients (studies 1237.4, 1237.9 and 1237.18).

and will be described and evaluated in the Safety Section of this report. The Summary of Clinical Efficacy Supplement consisted of a listing of tables on efficacy data from the Phase III studies, which were referenced in the Summary of Clinical Efficacy, but not found in the individual or combined study reports (for example, combined dataset from all 4 pivotal Phase III studies). As such, it will not be discussed separately, but data drawn from this report will be incorporated and discussed (Evaluator's conclusion on clinical efficacy).

Report 1222-0050 was a report on a meta analysis of ADRB2 haplotypes across the Phase III Studies 1222.11, 1222.12, 1222.13 and 1222.14. The sponsor had stated that the β2 adrenoceptor is a G protein coupled receptor encoded by the gene ADRB2, located on chromosome 5q31. Eleven ADRB2 polymorphisms had been genotyped. These ADRB2 polymorphisms may influence baseline airway function or the response to β2 adrenergic receptor agonists. The sponsor had stated that most investigations on the ADRB2 polymorphisms were focused on asthma instead of COPD, and that a thorough analysis of the interaction between ADRB2 polymorphisms and β2 agonist response in COPD patients was important. The study was conducted to investigate the genetic variability of the gene ADRB2 by calculation of haplotypes. The data resulting from this analysis were to be used in future to investigate the influence of ADRB2 polymorphisms and haplotypes on efficacy and safety parameters. Results showed that using only the two most frequent polymorphisms in ADRB2, 3 different haplotypes were calculated, with frequencies of 21.23% to 39.81%. Using all 11 genotyped polymorphisms in ADRB2, 66 different haplotypes were calculated, with frequencies of 0.03% to 30.97%. The study results did not raise any concerns relevant to this submission.

Report 1222-9956 was a combined analysis of Studies 1222.5 and 1222.6, evaluating the covariate effects on olodaterol PK parameters in patients with COPD (Study 1222.5) and persistent asthma (Study 1222.6). Study 1222.5 was a four week, randomised, double blind, placebo controlled parallel group study evaluating the efficacy and safety after 4 weeks of once daily treatment of orally inhaled olodaterol (2 µg, 5 µg, 10 µg, and 20 µg) in COPD patients, and has been previously described. Study 1222.6 was a study of similar design, but in patients with persistent asthma. The covariates tested were disease (COPD or asthma), olodaterol dose, gender, age, weight, height, creatinine clearance, smoking history, alcohol history, and pre treatment baseline FEV1. The results did not show definitively a significant effect of any of the investigated covariates on the PK of olodaterol in COPD and asthma patients. The study results did not raise any concerns relevant to this submission.

7.1.4. Evaluator's conclusions on clinical efficacy for the long term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD

The bronchodilator efficacy of olodaterol was evaluated through effects on FEV1 as well as effects on symptom relief and health related quality of life. Overall, analyses on effects of olodaterol on FEV1 compared to placebo yielded results which were supportive of the efficacy claim of both doses of olodaterol (5 µg qd and 10 µg qd) over placebo. Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of both doses of olodaterol over placebo.

With regards to effects on FEV1, efficacy results in the 4 pivotal Phase III studies showed that both olodaterol 5 µg qd and olodaterol 10 µg qd had statistically significantly greater mean change from pre treatment baseline in FEV1 $AUC_{0\text{-}3h}$ and in trough FEV1 compared to placebo, after 12 weeks of treatment (Studies 1222.11 and 1222.12) and after 24 weeks of treatment (Studies 1222.13 and 1222.14).

Secondary endpoints in Studies 1222.11 and 1222.12 characterising the 12 hour post dose FEV1 profile on Day 85 (that is, after 12 weeks of treatment) showed that the mean FEV1 increased within 5 minutes after the administration of both olodaterol dose levels, peaked around 2 to 3 hours post dose and then reduced progressively towards baseline, although at 12 hours post

dose, the difference from placebo was still statistically significant in favour of both doses of olodaterol. The statistically significantly greater mean trough FEV1 response at Day 85 with both doses of olodaterol compared to placebo suggested that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval. This FEV1 time profile of olodaterol was supported by that found in Studies 1222.13 and 1222.14. The statistically significantly greater mean trough FEV1 response at Day 169 with both doses of olodaterol compared to placebo suggested that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval after 24 weeks of treatment. The 24 hour bronchodilatory profile of olodaterol was also supported by the results in the 2 sets of replicate, non pivotal 6 week Phase III studies conducted to evaluate FEV1 profile of olodaterol over a continuous 24 hour dosing interval (Studies 1222.24/1222.25 and1222.39/1222.40). In these studies, there were statistically significantly greater mean FEV1 $AUC_{0\text{-}12h}$ response, FEV1 $AUC_{12\text{-}24h}$ response, and FEV1 $AUC_{0\text{-}24h}$ response at Day 43 (that is, Week 6) for both olodaterol 5 µg qd and olodaterol 10 µg qd compared to placebo.

Evaluation of FEV1 profile over 48 weeks of treatment duration showed that there were statistically significant differences in FEV1 at all individual post dose time points up to 3 hour post dose over 48 weeks (at Day 1 and after 2, 6, 12, 24 and 48 weeks) between placebo and both olodaterol doses (in favour of olodaterol) in all 4 pivotal Phase III studies. Analyses on the effects of olodaterol on FEV1 $AUC_{0\text{-}3h}$ response, trough FEV1 response, and FEV1 $peak_{0\text{-}3h}$ response over 48 weeks also showed statistically significantly greater responses for both olodaterol 5 µg qd and olodaterol 10 µg qd compared to placebo on all test days (at Day 1 and after 2, 6, 12, 24 and 48 weeks) in all 4 pivotal Phase III studies, except for olodaterol 10 µg on Day 225 (Week 32) in Study 1222.12 for the endpoint of trough FEV1 response, and olodaterol 5 µg on Day 281 (Week 40) in Study 1222.13 for the endpoint of trough FEV1 response confirming the long term efficacy of olodaterol.

Comparison between the olodaterol and the formoterol in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between olodaterol 5 µg qd and formoterol 12 µg bid for the primary endpoints of FEV1 $AUC_{0\text{-}3h}$ response and trough FEV1 response at Day 169, and between olodaterol 10 µg qd and formoterol 12 µg bid for the primary endpoint of FEV1 $AUC_{0\text{-}3h}$ response. For the primary endpoint of trough FEV1 response, there was a statistically significantly greater mean trough FEV1 response at Day 169 with olodaterol 10 µg qd compared to formoterol 12 µg bid. In addition, the post dose FEV1 time profile was similar between both olodaterol doses and formoterol, with increase in FEV1 occurring within 5 minutes post dose and then sustained over the 3 hour post dose evaluation period. These results were generally supported by those in the replicate non pivotal Phase III Studies 1222.24 and 1222.25, showing that there was no statistically significant difference between both olodaterol doses and formoterol in the pooled dataset in the mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43, although evaluating the mean FEV1 $AUC_{0\text{-}12h}$ response and the mean FEV1 $AUC_{12\text{-}24h}$ response at Day 43 separately showed that while there were no statistically significant differences between either dose of olodaterol and formoterol in the mean FEV1 $AUC_{0\text{-}12h}$ response, the mean FEV1 $AUC_{12\text{-}24h}$ response for formoterol 12 µg bid was statistically significantly greater than that for olodaterol 10 µg qd (−40 mL difference, p=0.0024) and for olodaterol 5 µg qd (−50 mL difference, p=0.0001), likely due to the second evening dose of formoterol.

Comparison with tiotropium 18 µg qd in the replicate non pivotal Phase III Studies 1222.39 and 1222.40 also showed that there was no statistically significant difference between both olodaterol doses and tiotropium in the pooled dataset in the mean FEV1 $AUC_{0\text{-}24h}$ response at Day 43. Evaluating the mean FEV1 $AUC_{0\text{-}12h}$ response and the mean FEV1 $AUC_{12\text{-}24h}$ response at Day 43 separately showed that there were no statistically significant differences between either dose of olodaterol and tiotropium in the mean FEV1 $AUC_{0\text{-}12h}$ response, and between olodaterol 5 µg and tiotropium in the mean FEV1 $AUC_{12\text{-}24h}$ response. The mean FEV1 $AUC_{12\text{-}24h}$ response for olodaterol 10 µg qd was statistically significantly greater than that for tiotropium 18 µg qd.

The evaluation of the effects of olodaterol on symptom relief and health related quality of life was assessed primarily in the replicate pivotal Phase III Studies 1222.13 and 1222.14 using the Mahler TDI focal score at Day 169 (co primary endpoint; pooled dataset) and the St. George's Respiratory Questionnaire (SGRQ) total score at Day 169 (key secondary endpoint; pooled dataset). This was supplemented by analyses of rescue medication use, the 7 point Patient's Global Rating (PGR) scale (used by the subjects to rate perceived changes in their respiratory condition), and COPD exacerbations in the 4 pivotal Phase III studies, and of exercise endurance time during constant work rate cycle ergometry in the replicate non pivotal Phase III Studies 1222.37 and 1222.38.

Analysis of the mean Mahler TDI focal (that is, total) score at Day 169 in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between both olodaterol doses and placebo. The sponsor had stated that the results of the Mahler TDI focal score in the combined dataset might not be reliable as the analyses in the individual studies yielded inconsistent results between the 2 studies. However, it was noted that despite the inconsistency between studies, both individual studies had yielded results that were not statistically significant, although it is acknowledged that the studies had not been powered to show statistical significance for this endpoint at the level of analyses in the individual studies, only for analysis in the combined dataset. Nonetheless, analyses of the Mahler TDI component scores at Day 169 in the pooled dataset also showed no statistically significant difference between both olodaterol doses and placebo across all 3 components, and analyses of the Mahler TDI focal and component scores over 48 weeks in both individual studies showed that the differences between both olodaterol doses and placebo were mostly not statistically significant. However, it is noted that analyses in the formoterol group yielded similar results, showing no statistically significant difference between formoterol and placebo in the mean Mahler TDI focal and component scores at Day 169 in the pooled dataset. In addition, comparison between olodaterol and formoterol group in the pooled dataset showed that there was no statistically significant difference between both olodaterol doses and formoterol in the Mahler TDI focal score at Day 169.

Analyses of the SGRQ total and component scores at Day 169 in the pooled dataset of studies 1222.13 and 1222.14 showed that there were statistically significantly lower SGRQ total and component scores (that is, better outcome) at Day 169 for both olodaterol doses compared to placebo. By comparison, there was no statistically significant difference in the SGRQ total or component scores at Day 169 between formoterol and placebo.

Analyses of rescue medication use and the PGR generally supported the efficacy claim for olodaterol over placebo. Analyses of the weekly mean number of daytime rescue medication, night time rescue medication, and daily (24 hour) rescue medication showed that reductions from placebo were statistically significant for both olodaterol doses at most time points in the pooled dataset of Studies 1222.11 and 1222.12, and that of 1222.13 and 1222.14 (although in the individual Study 1222.14, while the results were mostly statistically significant in favour of olodaterol 10 µg over placebo, they were mostly not statistically significant for olodaterol 5 µg). Analyses of the PGR over 48 weeks (Weeks 6, 12, 24 and 48) showed that there were statistically significantly lower scores (that is, better rating) for both olodaterol doses compared to placebo, at all (in pooled dataset of Studies 1222.11 and 1222.12) or most (in pooled dataset of Studies 1222.13 and 1222.14) time points. The results comparing formoterol and placebo were similar.

However, analyses of the endpoints of exacerbations of COPD showed that there was no statistically significant difference in the time to first COPD exacerbation, first moderate COPD exacerbation, or first COPD exacerbation leading to hospitalisation between both olodaterol doses and placebo, in all 4 individual pivotal Phase III studies, as well as their respective pooled datasets. There were also no statistically significant differences between both olodaterol doses and placebo in the mean number of COPD exacerbations, mean number of moderate COPD

exacerbations, or mean number of COPD exacerbations leading to hospitalisation in all 4 individual pivotal Phase III studies and their respective pooled datasets. It is, however, noted that analyses comparing formoterol and placebo also yielded similar results, with no statistically significant difference observed between formoterol and placebo for these endpoints.

Results in the replicate non pivotal Phase III Studies 1222.37 and 1222.38 showed that after six weeks of treatment, mean endurance time during constant work rate cycle ergometry was statistically significantly longer for both olodaterol doses compared with placebo. Compared to placebo, endurance time was longer by about 12% to14% with olodaterol 5 µg qd and about 11% to 14% with olodaterol 10 µg qd, although the difference in treatment means between both olodaterol doses and placebo was less than 1 minute.

Although 2 doses of olodaterol were tested in the Phase III studies, the recommended dose in the proposed Product Information (PI) was 5 µg of olodaterol given as two puffs from the Respimat inhaler once daily. The sponsor had provided a comparison of the difference from placebo in mean FEV1 $AUC_{0\text{-}3h}$ response and trough FEV1 response for olodaterol 5 µg and for olodaterol 10 µg in the Phase III studies, which showed that the results were similar between the 2 doses. A comparison of the difference from placebo in mean FEV1 $AUC_{0\text{-}12h}$ response and FEV1 $AUC_{0\text{-}24h}$ response for olodaterol 5 µg and for olodaterol 10 µg in the Phase III studies also showed results were generally comparable between the 2 doses. The FEV1 time profiles on Day 1 were also similar between olodaterol 5 µg and olodaterol 10 µg in the 4 pivotal Phase III studies. For both doses, FEV1 increased within 5 minutes after the first administration (increases from pre-treatment baseline in mean FEV1 of 0.128 L and 0.129 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.135 L and 0.133 L, respectively, in Study 1222.12, 0.136 L and 0.133 L, respectively, in Study 1222.13, and 0.121 L and 0.131 L, respectively, in Study 1222.14), with further increases after 15 minutes (increases from pre treatment baseline in mean FEV1 of 0.168 L and 0.166 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.169 L and 0.166 L, respectively, in Study 1222.12, 0.176 L and 0.167 L, respectively in Study 1222.13, and 0.154 L and 0.166 L, respectively, in Study 1222.14), and 30 minutes (increases from pre treatment baseline in mean FEV1 of 0.183 L and 0.181 L for olodaterol 5 µg and olodaterol 10 µg, respectively, in Study 1222.11, 0.187 L and 0.188 L, respectively, in Study 1222.12, 0.191 L and 0.187 L, respectively in Study 1222.13, and 0.167 L and 0.186 L, respectively, in Study 1222.14).

With regards to effects on symptomatic relief and health related quality of life between olodaterol 5 µg and olodaterol 10 µg, the TDI focal scores for both doses of olodaterol were similar throughout the 48 weeks of treatment in the pooled dataset of Studies 1222.13 and 1222.14, and analysis showed there was no statistically significant difference between the 2 doses for this endpoint. There was also no statistically significant difference between the 2 doses for the SGRQ total score at Day 85, Day 169 and Day 337.

Overall, these results showed that there was no obvious clinically meaningful increase in benefit with olodaterol 10 µg once daily compared to olodaterol 5 µg once daily. The selection of olodaterol 5 µg once daily as the recommended therapeutic dose in the proposed PI is appropriate.

With regards to the proposed posology of once daily administration instead of twice daily, results in the pivotal Phase III studies showed statistically significantly greater mean trough FEV1 response at Day 85 and at Day 169 with olodaterol 5 µg qd compared to placebo, suggesting that the bronchodilator effect of both doses of olodaterol was sustained at the end of the 24 hour dosing interval after 12 and 24 weeks of treatment. Comparison of olodaterol 5 µg qd with formoterol 12 µg bid (pooled dataset of Studies 1222.13 and 1222.14) also showed that there were no statistically significant difference in trough FEV1 response between olodaterol 5 µg qd and formoterol 12 µg bid at Day 169. This was supported by results in the pooled dataset of the replicate Phase II Studies 1222.24 and 1222.25, showing that there were no statistically

significant differences in mean FEV1 AUC_{0-24h} and mean trough FEV1 responses between olodaterol 5 µg qd and formoterol 12 µg bid. Results in the Phase II Study 1222.26 supported the dose regimen of olodaterol 5 µg qd instead of olodaterol 2 µg bid, showing that despite the additional evening dose of olodaterol 2 µg there was no statistically significant difference in the effect on FEV1 between olodaterol 5 µg qd and olodaterol 2 µg bid in the 12 to 24 hours post dose period (FEV1 AUC_{12-24h}), and that overall in the 24 hour post dose period (FEV1 AUC_{0-24h}), there was no statistically significant difference in the effect on FEV1 between olodaterol 10 µg qd and olodaterol 5 µg bid.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies (Studies 1222.11, 1222.12, 1222.13 and 1222.14), the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit
- AEs of particular interest
  - The sponsor had stated that in Studies 1222.11 and 1222.12, particular attention was to be paid to respiratory events indicative of bronchoconstriction related to administration of the study drug. Specifically, a drop in FEV1 greater than or equal to15%, the need for rescue medication, cough, wheeze or dyspnoea within 30 minutes after inhaling randomised treatment on each test day were to be characterised. This was due to the occurrence of administration related bronchoconstriction observed with some marketed bronchodilators.
  - In the 4 pivotal studies, Holter monitoring was to be performed (in a subset of subjects at selected sites; 50 subjects per treatment group) over a 24 hour period prior to the randomisation visit (Visit 2), and repeated after the completion of all study related tests at Visits 5, 7, 9, and 10. Across the 4 pivotal studies, Holter monitoring was done in 772 subjects: 225, 234, 233 and 80 subjects in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively.
- Laboratory tests performed included haematology, blood chemistry (alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, serum potassium, sodium, chloride, creatinine, blood urea nitrogen (BUN), fasting glucose, calcium, inorganic phosphorus, uric acid, creatine phosphokinase (CPK)[40]), and urinalysis. Laboratory tests were performed according to a schedule. In addition, serum potassium was to be collected at 1 and 3 hours post dose at Visits 4 (Week 6; Day 43) and 5 (Week 12; Day 85).
- Other safety endpoints included vital signs (seated pulse rate and blood pressure) and 12 lead electrocardiogram (ECG) performed according to a schedule.

[40] In cases where CPK values were greater than 1.5 times ULN, both CPK and fractionated CPK were analysed at all subsequent visits for that subject.

7.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable

7.1.3. Dose response and non pivotal efficacy studies

The dose response and non pivotal efficacy studies provided safety data, as follows:

- The 6 non pivotal Phase III studies (Studies 1222.24, 1222.25, 1222.39, 1222.40, 1222.37 and 1222.38) provided data on adverse events, vital signs, routine laboratory evaluations and 12 lead ECG.
- The 7 Phase II studies (COPD: Studies 1222.3, 1222.5, 1222.26; asthma: 1222.4, 1222.6, 1222.27 and 1222.29) provided data on adverse events, vital signs, routine laboratory evaluations and 12 lead ECG.

The Phase II studies in asthma patients have not been described in the efficacy section in this report.

7.1.4. Other studies evaluable for safety only

As previously described, the sponsor had submitted a "Summary of Clinical Safety Supplement" and an "embellished narrative summary table" which contained only safety data.

The Summary of Clinical Safety supplement consisted of a listing of tables on safety data from the Phase III efficacy/safety studies which were referenced in the Summary of Clinical Safety but not found in the individual or combined study reports (for example, combined dataset from all 4 pivotal Phase III studies). The "embellished narrative summary table" is an additional tabulation of subjects in Studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 with SAE or non SAEs leading to discontinuation.[41] These 2 reports will not be discussed as separate sections, but the content evaluated and incorporated into the safety evaluation.

> Comments: The sponsor had not provided details on how the Holter subset of subjects had been selected. This will be raised as a clinical question.
>
> In this evaluation, the safety data of the 4 pivotal Phase III studies were evaluated individually, and were found to be consistent among all 4 studies. In addition, the study design of the 4 pivotal Phase III studies were similar and the baseline demographic and disease characteristics were also comparable across these 4 studies. In view of the above, the combined safety data in the 4 pivotal studies (drawn from the Summary of Clinical Safety supplement) will be presented.
>
> In this evaluation, the safety data of the 6 non pivotal Phase III studies were also evaluated individually, and were found to be consistent among all 6 studies. The study design of these 6 non pivotal Phase III studies were similar and the baseline demographic characteristics were also comparable across these 6 studies. In view of the above, the combined safety data in the 6 non pivotal studies (drawn from the Summary of Clinical Safety supplement) will be presented.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

[41] In the Phase III studies SAEs or non-SAEs leading to discontinuation were categorised as fatal SAEs, drug-related or trial-related SAEs, SAEs leading to discontinuation, all other SAEs, or non-SAEs leading to discontinuation. The "embellished narrative summary table" is an additional tabulation of subjects in studies 1222.11, 1222.12, 1222.13, 1222.14, 1222.39 and 1222.40 according to these categories, with hyperlinks to the corresponding narrative documents.

7.3. Patient exposure

For the 4 combined pivotal (48 week, parallel group) Phase III Studies (1222.11, 1222.12, 1222.13, and 1222.14), the overall mean (SD) exposure was 300 (90.6) days. By treatment group the mean (SD) exposure was 287.5 (104.0, 308.4 (78.4) , 304.7 (84.8) and 299 (93.1) days in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively. Overall, the majority of subjects (54.5%) had an exposure to study drug of between 282 to 337 days. By treatment group, 51.6%, 56.2%, 56.2% and 53.9% of subjects in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively, had an exposure in this range.

For the 6 combined non pivotal (6 week, cross over) Phase III Studies (1222.24, 1222.25, 1222.37, 1222.38, 1222.39, 1222.40), the overall mean (SD) exposure was 147.4 (34.8) days. By treatment group the mean (SD) exposure to placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg, and formoterol 12 µg was 43.6 (4.6) , 44.1 (5.5) , 43.9 (5.1) , 43.0 (2.6) and 42.8 (3.1) days, respectively. Overall, 75.9%, 74.8%%, 76.7%, 87.4% and 92.5% of subjects were exposed to placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg, and formoterol 12 µg, respectively, for between 23 and 43 days.

With regards to the Phase II studies in COPD patients, in Study 1222.3 (placebo controlled cross over study evaluating single doses of olodaterol 2 µg, 5 µg, 10 µg and 20 µg in the main part of study and single dose open label 40 µg olodaterol in the extension part of study), all 36 subjects in the safety set participated in the main part of the study, and 34 completed the main part of the study. These 34 subjects each had 4 days on treatment with olodaterol (1 day each on each dose level) and one day on treatment with placebo. Of the 36 subjects in the safety set, 14 subjects also participated in the extension period and these subjects had 1 additional day on treatment with olodaterol (40 µg). In the Phase II Study 1222.5 (placebo controlled, parallel group study evaluating once daily olodaterol 2 µg , 5 µg, 10 µg and 20 µg for 4 weeks), the overall mean (SD) exposure was 29.24 (4.52) days. By treatment group, the mean (SD) exposure was 28.95 (4.65), 29.32 (3.32), 28.59 (5.19) , 29.16 (3.22) and 30.20 (5.73) days to placebo, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg and olodaterol 20 µg, respectively. Overall, the majority of subjects (89.1%) had an exposure to study drug of greater than 28 days. By treatment group, 84.8%, 92.6%, 86.3%, 88.4% and 93.7% of subjects had an exposure to placebo, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg and olodaterol 20 µg groups, respectively, of greater than 28 days. In the Phase II Study 1222.26 (a 3 week cross over study evaluating olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd), a total of 47 subjects received at least 1 dose of study medication, with 47, 46, 47 and 46 subjects receiving olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd, respectively. Overall, the mean (SD) exposure to olodaterol 2 µg bid, olodaterol 5 µg bid, olodaterol 5 µg qd, and olodaterol 10 µg qd was 20.7 (1.92) days, 20.98 (0.26) days, 21.0 (0.29) days and 20.98 (0.26) days, respectively with 93.6%, 95.7%, 97.8% and 97.8% of subjects, respectively exposed for 15 and 21 days.

Drug exposure in the Phase II studies in asthma patients (Studies 1222.4, 1222.6, 1222.27, 1222.29) overall, a total of 731 asthma patients were treated across these studies. The overall mean exposure across these studies combined ranged from 22.8 to 29.5 days across the treatment groups.

> Comments: Overall, the study drug exposure is adequate to assess the safety profile of olodaterol.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. 8.4.1.1. Pivotal studies

The percentages of subjects with any AEs were comparable among treatment groups (70.8% (627 out of 885), 71.0% (622 out of 876), 72.7% (642 out of 883) and 69.1% (318 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

The most commonly reported AEs by preferred term in the olodaterol 5 µg and olodaterol 10 µg groups were COPD (28.8%, 25.9%, 30.1% and 28.5% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively), nasopharyngitis (7.7%, 11.3%, 10.3% and 10.0%, respectively), and upper respiratory tract infection (7.5%, 8.2%, 7.0% and 7.0%, respectively).

7.4.1.2. Other studies

7.4.1.2.1. Supportive 6 week cross over Phase III trials

The percentages of subjects with any AEs were comparable among treatment groups (29.4% (204 out of 693), 32.2% (226 out of 701), 31.1% (215 out of 691), 34.1% (73 out of 214) and 26.9% (50 out of 186) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively).

AEs that occurred in greater than 2% of subjects in any treatment group are presented in. The most commonly reported AEs by preferred term in the olodaterol 5 µg and olodaterol 10 µg groups were COPD (6.2%, 6.3%, 4.2%, 2.8% and 4.8% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively), and nasopharyngitis (2.9%, 2.9%, 2.6%, 5.1% and 0.5%, respectively).

7.4.1.3. Phase II studies

7.4.1.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

In each study, the percentages of subjects with any AEs were comparable among treatment groups, and results did not show increased incidence of AEs with increasing doses of olodaterol. In the open label extension Phase of Study 1222.3 (evaluating single dose olodaterol 40 µg), 2 subjects reported AEs. No subjects in the extension set experienced AEs which were severe, serious, or defined by the investigator as drug related. The most commonly reported AEs in each study did not raise major safety concerns.

7.4.1.3.2. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

The percentages of subjects with any AEs were comparable among pooled treatment groups except in the pooled formoterol 12 µg group where the incidence was lower (14.9% (61 out of 409), 18.1% (38 out of 210), 14.9% (15 out of 101), 18.5% (59 out of 319), 18.8% (19 out of 101), 16.3% (52 out of 319), 21.5% (46 out of 214) and 6.4% (8 out of 125) in the pooled placebo, olodaterol 2 µg qd, olodaterol 2.5 µg bid, olodaterol 5 µg qd, olodaterol 5 µg bid, olodaterol 10 µg qd, olodaterol 20 µg qd, and formoterol 12 µg bid groups, respectively). The safety data of these 4 Phase II asthma studies in terms of AEs had also been evaluated individually, and did not raise major safety concerns.

7.4.2. Treatment related adverse events (adverse drug reactions)

7.4.2.1. Pivotal studies

The incidences of any treatment related AEs were comparable between the pooled placebo and olodaterol 5 µg treatment groups, but lower in the olodaterol 10 µg group and higher in the formoterol 12 µg group (8.9% (79 out of 885), 7.2% (63 out of 876), 5.9% (52 out of 883) and

11.3% (52 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

The most commonly reported treatment related AE by preferred term in the pooled olodaterol 5 µg and olodaterol 10 µg groups was COPD (0.6%, 1.4%, 1.4% and 2.8% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively) and headache (1.1%, 0.3%, 0.7% and 0.7%, respectively).

7.4.2.2. Other studies

7.4.2.2.1. Supportive 6 week cross over Phase III trials

The incidences of any treatment related AEs were generally comparable among treatment groups except with a higher incidence in the pooled formoterol group (1.4% (10 out of 693), 2.0% (14 out of 701), 2.2% (15 out of 691), 1.4% (3 out of 214) and 5.4% (10 out of 186) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively).

The most commonly reported treatment related AE by preferred term in the olodaterol 5 µg group was cough (0.3%, 0.4%, 0.0%, 0.5% and 0.0% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively).

7.4.2.3. Phase II studies

7.4.2.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

None of the AEs in Study 1222.3 were considered treatment related. In Study 1222.5, there was no trend of increased incidence of treatment related AEs with increasing doses of olodaterol (4.9%% (4 out of 81), 3.8% (3 out of 80), 2.3% (2 out of 86), 1.3% (1 out of 79) and 6.3% (5 out of 79) for the olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg, olodaterol 20 µg, and placebo groups, respectively). In Study 1222.26, the incidence of treatment related AEs was comparable for olodaterol 2 µg bid, olodaterol 5 µg qd, and olodaterol 5 µg bid groups (2.1% (1 out of 47), 4.3% (2 out of 47) and 4.3% (2 out of 46), respectively. The incidence of treatment related AEs for the olodaterol 10 µg qd group was higher, at 13.0% (6 out of 46).

7.4.2.3.2. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

The incidences of any treatment related AEs were generally comparable among treatment groups (2.0% (8 out of 409), 1.4% (3 out of 210), 0.0% (0 out of 101), 2.8% (9 out of 319), 3.0% (3 out of 101), 2.8% (9 out of 319), 5.6% (12 out of 214) and 0.0% (0 out of 125) in the pooled placebo, olodaterol 2 µg qd, olodaterol 2.5 µg bid olodaterol 5 µg qd, olodaterol 5 µg bid, olodaterol 10 µg qd, olodaterol 20 µg qd and formoterol 12 µg bid groups, respectively). The safety data of these 4 Phase II asthma studies in terms of treatment related AEs had also been evaluated individually, and did not raise major safety concerns.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal studies

In the 4 pivotal studies, deaths occurring throughout the conduct of the studies were categorised into on treatment deaths, post treatment deaths and post study deaths.[42] Overall, in the pivotal studies, there were 53 on treatment deaths, 7 post treatment deaths and 16 post study deaths. The incidence of on treatment deaths were comparable among treatment groups (1.5% (13 out of 885), 1.5% (13 out of 876), 1.9% (17 out of 883) and 2.2% (10 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups,

[42] On-treatment deaths were events with an onset any time following the first dose of study drug and up to 12 days after the last study drug intake. Post-treatment deaths were events with an onset greater than 12 days after the last dose of study drug up to trial completion date. Post-study deaths were events with an onset after the trial completion date.

respectively). The most frequently reported cause of deaths in the olodaterol 5 µg group was COPD (0.5%, 0.4%, 0.1% and 0.2% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The most frequently reported cause of deaths in the olodaterol 10 µg group was pneumonia (0.1%, 0.2%, 0.3% and 0.2% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). One of the deaths (in the placebo group) was considered related to study treatment by the investigators. The cause of death reported by the investigator was myocardial infarction. However, the assessment of primary cause of death by the Mortality Adjudication Committee (MAC) [43] was COPD exacerbation, and the MAC did not consider the event to be related to trial medication.

Overall there were 23 post treatment and post study deaths in the four 48 week Phase III studies (10, 6, 4 and 3 deaths in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). None of the deaths were considered related to study treatment by the investigators.

The incidence of SAEs was comparable among treatment groups (16.4% (145 out of 885), 15.8% (138 out of 876), 16.6% (147 out of 883) and 15.0% (69 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The most frequently reported SAE by preferred term in the olodaterol 5 µg and olodaterol 10 µg groups were COPD (6.0%, 4.7%, 6.9% and 5.9% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively) and pneumonia (1.5%, 1.6%, 2.5% and 1.5%, respectively). The incidence of SAEs in the SOC of "Neoplasms benign, malignant and unspecified (including cysts and polyps)" was higher in the olodaterol 5 µg group (1.6%; 14 out of 876), olodaterol 10 µg group (2.2%; 19 out of 883) and formoterol 12 µg group (1.7%; 8 out of 460) compared to the placebo group (1.0%; 9 out of 885). None of these SAEs were judged by the investigator to be treatment related.

The incidence of treatment related SAEs were comparable among treatment groups (0.8% (7 out of 885), 0.8% (7 out of 876), 0.3% (3 out of 883) and 1.5% (7 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The only treatment related SAE with an incidence of greater than 0.1% (that is, greater than 1 patient) in either olodaterol groups was chronic obstructive pulmonary disease (0.1%, 0.3%, 0.0% and 0.7% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

> Comments: Although the overall incidence of SAEs was comparable between the olodaterol treatment groups and placebo, as was that of the most frequently reported SAE by preferred term of COPD, it is noted that the incidence of SAEs in the SOC of "Neoplasms benign, malignant and unspecified (including cysts and polyps)" was higher in the olodaterol 5 µg and 10 µg groups compared to the placebo group. However, the incidence was comparable between the olodaterol 5 µg group and the formoterol group. In addition, none of these SAEs were judged by the investigator to be treatment related. These SAEs were distributed over various preferred terms within this SOC and there was no pattern of an increased incidence of a particular type of neoplasm. The maximum incidence within any one preferred term within this SOC was 0.2% (or 2 subjects) across all treatment groups. The sponsor had also performed additional analyses on the incidence of malignant neoplasms, and the results showed that the incidence of malignant neoplasms was comparable among the olodaterol 5 µg group, placebo group and formoterol 12 µg group (incidence of 1.4%, 1.7%, 2.5% and 1.7% in the placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

[43] During the conduct of the 48-week, parallel group Phase III studies, an independent Mortality Adjudication Committee (MAC) was established before closure of the database. All deaths occurring in studies 1222.11, 1222.12, 1222.13, and 1222.14 were adjudicated by the MAC before unblinding of the studies.

7.4.3.2. Other studies

7.4.3.2.1. Supportive 6 week cross over Phase III trials

There were 3 deaths across the six 6 week cross over Phase III studies, 1 in the olodaterol 5 µg group (in Study 1222.24) and 2 in the olodaterol 10 µg group (1 each in Study 1222.25 and Study 1222.38). None of the deaths were considered by the investigator to be treatment related. The cause of death for the patient on olodaterol 5 µg was cardio pulmonary arrest, while that for the patient on olodaterol 10 µg in Study 1222.25 was COPD. The cause of death for the patient on olodaterol 10 µg in Study 1222.38 was unknown and coded (preferred term) as "Death".[44]

The incidence of SAEs was comparable among treatment groups (3.3% (23 out of 693), 3.3% (23 out of 701), 2.7% (19 out of 691), 3.3% (7 out of 214) and 3.2% (6 out of 186) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively). The most frequently reported SAE by preferred term in the olodaterol 5 µg and olodaterol 10 µg groups was COPD (1.2%, 0.4%, 1.0%, 0.9% and 2.2% , respectively). The incidence of treatment related SAEs were also comparable among treatment groups (0.0% (0 out of 693), 0.1% (1 out of 701), 0.1% (1 out of 691), 0.0% (0 out of 214) and 0.5% (1 out of 186), respectively). One patient each in the olodaterol 5 µg group and olodaterol 10 µg group had a treatment related SAE of atrial fibrillation, while the third patient in the formoterol group had a treatment related SAE of angioedema.

7.4.3.3. Phase II studies

7.4.3.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

There were no deaths reported for Studies 1222.3, 1222.5 and 1222.26. In Studies 1222.3 and 1222.5, there was no trend of increased incidence of SAEs with increasing doses of olodaterol. In Study 1222.3, the incidence of SAE was 2.9% (1 out of 35), 2.9% (1 out of 35), 5.7% (2 out of 35), 0.0% (0 out of 34) and 0.0% (0 out of 35) for the placebo, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg, and olodaterol 20 µg, respectively . None of the SAEs were considered by the investigator to be treatment related. In Study 1222.5, the incidence of SAE was 2.5% (2 out of 81), 2.5% (2 out of 80), 2.3% (2 out of 86), 2.5% (2 out of 79) and 0.0% (0 out of 79) for the olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg, and olodaterol 20 µg, respectively. None of the SAEs were considered by the investigator to be treatment related. In Study 1222.26, there was 1 patient who reported 1 SAE (COPD exacerbation) and this occurred during treatment with olodaterol 5 µg bd. The SAE was not considered to be treatment related.

7.4.3.3.2. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

There were no deaths reported for these studies. The incidence of SAEs was low across these studies (1.0%; 7 out of 731). The 7 subjects who reported any SAEs included 2 in the placebo group, 1 in the olodaterol 2.5 µg bid group, 1 in the olodaterol 5 µg bid group, 2 in the olodaterol 10 µg group and 1 in the olodaterol 20 µg. The safety data of these 4 Phase II asthma studies in terms of SAEs had also been evaluated individually, and did not raise major safety concerns.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal studies

The incidence of any AEs resulting in discontinuation of study drug was comparable among treatment groups (8.4% (74 out of 885), 6.2% (54 out of 876), 7.5% (66 out of 883) and 8.0% (37 out of 460) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The most frequently reported AEs resulting in discontinuation of study

[44] This patient began receiving 10 µg olodaterol on [information redacted] and died six days later. The investigator reported the event upon reading of the death in an obituary and confirming the death with the patient's family doctor. No autopsy was available.

drug in the olodaterol 5 and 10µg groups was COPD (2.3%, 2.1%, 2.0% and 2.6% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

7.4.4.2. Other studies

7.4.4.2.1. Supportive 6 week cross over Phase III trials

The incidence of any AEs resulting in discontinuation of study drug was comparable among treatment groups (2.6% (18 out of 693), 1.9% (13 out of 701), 1.7% (12 out of 691), 2.8% (6 out of 214) and 1.6% (3 out of 186) in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively). The most frequently reported AEs resulting in discontinuation of study drug was COPD (1.6%, 0.4%, 0.6%, 0.9% and 0.5% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively).

7.4.4.3. Phase II studies

7.4.4.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

In Study 1222.3, there were no AEs that led to discontinuation of study drug. In Study 1222.5, there was no trend of increased incidence of AEs leading to discontinuation of study drug with increasing doses of olodaterol (incidence of 1.2% (1 out of 81), 6.3% (5 out of 80), 0.0% (0 out of 86), 2.5% (2 out of 79) and 1.3% (1 out of 79) for the, olodaterol 2 µg, olodaterol 5 µg, olodaterol 10 µg, olodaterol 20 µg, and placebo groups respectively). In Study 1222.26, there was 1 AE leading to discontinuation of study drug, and this was the patient with the SAE previously described.

7.4.4.3.2. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

The incidence of AEs leading to discontinuation of study drug was low across these studies (1.2%; 9 out of 731). The 9 subjects who reported any AEs leading to discontinuation of study drug included 1 each in the placebo, olodaterol 2 µg, olodaterol 2.5 µg bid and olodaterol 5 µg bid group, 3 in the olodaterol 5 µg group, and 2 in the olodaterol 10 µg group. The safety data of these 4 Phase II asthma studies in terms of AEs leading to discontinuation had also been evaluated individually, and did not raise major safety concerns.

7.5. Laboratory tests

7.5.1. Clinical laboratory tests

7.5.1.1. Pivotal studies

Analyses of clinical laboratory tests (haematology, blood chemistry and urinalysis) did not raise any significant safety concerns. In particular, evaluating the pharmacodynamic parameters of olodaterol by laboratory test in terms of glucose, CPK and potassium showed that the incidence of possible clinically significant high glucose levels was generally comparable across treatment groups (2.6%, 3.7%, 2.8% and 1.7% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The sponsor analysed the mean CPK levels change from baseline of the active treatment groups compared to the placebo group at Days 85, 169 and 337, and results showed that at Days 85 and 337, there were statistically significantly difference in all active treatment groups compared to the placebo group. At Day 169, the difference between olodaterol 5 µg and placebo was not statistically significant, but that between olodaterol 10 µg and placebo, and between formoterol 12 µg and placebo were statistically significant. However, the results also showed that overall, there was a mean decrease from baseline in the CPK levels at Days 85, 169 and 337 in the placebo as well as the olodaterol 5 µg groups, and an increase from baseline in the formoterol group. In the olodaterol 10 µg group, there was a slight increase from baseline at Day 85, and slight decreases from baseline at Days 169 and 337.

As previously described, serum potassium levels as a pharmacodynamic marker was evaluated in the 4 pivotal studies at 1 and 3 hours post dose at Visits 4 (Week 6; Day 43) and 5 (Week 12; Day 85). The results showed that for the pooled olodaterol 5 µg group, there was a statistically significantly lower serum potassium level compared to the pooled placebo group at 1 and 3 hours post dose on Day 43(1 hour post dose: difference of -0.044mmol/L from placebo, p=0.0330; 3 hours post dose: difference of -0.040mmol/L from placebo, p=0.0444), but the difference between the pooled olodaterol 5 µg group and placebo group was not statistically significant at 1 and 3 hours post dose on Day 85. For the pooled olodaterol 10 µg group, there was no statistically significant difference in mean serum potassium levels compared to placebo at all time points except at 1 hour post dose on Day 43 (difference of -0.042mmol/L from placebo, p=0.0399). There was no statistically significant difference in mean serum potassium levels between the pooled formoterol group and the pooled placebo group at all time points.

Across the 4 test time points, the minimum serum potassium recorded was comparable across the pooled treatment groups (2.8 mmol/L, 2.4 mmol/L, 2.8 mmol/L and 3.2 mmol/L in the placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively). The proportion of subjects in each pooled treatment group with a minimum serum potassium level during the treatment period which was below the lower limit normal (LLN) was also comparable across the pooled treatment groups (10.2%, 10.1%, 10.1% and 13.2% in the placebo, olodaterol 5 µg, olodaterol 10 µg, and formoterol 12 µg groups, respectively).

7.5.1.2. Other studies

7.5.1.2.1. Supportive 6 week cross over Phase III trials

Analyses of clinical laboratory tests did not raise any safety concerns. The incidence of possible clinically significant high glucose levels was generally comparable across treatment groups (2.7%, 3.7%, 2.4%, 4.9% and 1.8% in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively). The incidence of possible clinically significant low potassium levels was 0% across all treatment groups. The mean last potassium value on treatment was 4.2 mmol/L, 4.2 mmol/L, 4.2 mmol/L, 4.2 mmol/L and 4.1 mmol/L in the pooled placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively. The change from baseline in the mean last potassium value on treatment was 0.0 mmol/L in all treatment groups. The proportion of subjects in each pooled treatment group with a minimum serum potassium level during the treatment period which was less than LLN was also comparable across the pooled treatment groups (1.2%, 1.3%, 0.9%, 0.5% and 1.1% in the placebo, olodaterol 5 µg, olodaterol 10 µg, tiotropium 18 µg and formoterol 12 µg groups, respectively).

7.5.1.3. Phase II studies

7.5.1.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

Analyses of clinical laboratory tests did not raise any safety concerns.

With regards to the pharmacodynamic parameter of potassium levels, in Study 1222.3, results showed a trend of lower potassium levels with higher doses of olodaterol at 1 hour and 2 hour post dose. At 1 hour post dose, the difference in geometric mean compared to placebo was statistically significant only for olodaterol 20 µg, but not statistically significant for the other doses. At 2 hour post dose, the difference in geometric mean compared to placebo was statistically significant for olodaterol 5 µg, 10 µg, and 20 µg , but not statistically significant for 2 µg. At 4 hour post dose, there was no statistically significant difference in the potassium geometric mean between placebo and any of the olodaterol groups. For the single dose olodaterol 40 µg, the difference in geometric mean compared to placebo was statistically significant at 1 hour, 2 hours and 4 hours post dose.

In Study 1222.5, after the first dose (Day 1) and after 1 week of treatment (Day 8), the difference in the maximum decrease from baseline in serum potassium compared to placebo

was statistically significant only for olodaterol 20 µg , but not statistically significant for the other doses. At Days 15 and 29, there was no statistically significant difference between placebo and any of the olodaterol dose groups.

Comments: The potassium results in Studies 1222.3 and 1222.5 support the dose selection of olodaterol 5 µg and 10 µg for the Phase III studies (previously discussed).

7.5.1.3.2. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

Analyses of clinical laboratory tests did not raise any safety concerns.

7.5.2. Electrocardiograph

7.5.2.1. Pivotal studies

Analyses of the ECGs showed that the incidence of notable increases or decreases from baseline in heart rate, PR interval, and QRS interval[45] was low and comparable across all treatment groups. The incidence of QTcF and QTcB greater than 450msec, greater than 480 msec and greater than 500 msec was low and comparable across all treatment groups.

7.5.2.2. Other studies

7.5.2.2.1. Supportive 6 week cross over Phase III trials

The incidence of notable increases or decreases from baseline in heart rate (HR), PR interval, and QRS interval was low (heart rate: 0.0% to 7.5%; PR interval: 0.0% to 0.6%; QRS interval: 0.0% to 3.1%) and comparable across all treatment groups.

7.5.2.3. Phase II studies

7.5.2.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

Analyses of ECGs in these studies did not raise any safety concerns.

7.5.2.4. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

Analyses of ECGs in these studies did not raise any safety concerns.

7.5.3. Vital signs

7.5.3.1.1. Pivotal studies

Analyses of vital signs in the 4 pivotal studies did not raise any safety concerns. Incidence of marked changes in vital signs in the pooled pivotal studies were comparable across pooled treatment groups.

7.5.3.2. Other studies

7.5.3.2.1. Supportive 6 week cross over Phase III trials

Analyses of vital signs in the six 6 week cross over studies did not raise any safety concerns. Incidence of marked changes from baseline in vital signs in the pooled Studies (1222.24, 1222.25, 1222.39 and 1222.40[46]) showed that the incidences were comparable across pooled treatment groups.

7.5.3.3. Phase II studies

7.5.3.3.1. COPD studies (Studies 1222.3, 1222.5 and 1222.26)

Analyses of vital signs in these studies did not raise any safety concerns.

[45] Notable HR increase was defined as greater than or equal to 25% increase and HR greater than 100 bpm; notable HR decrease was defined as greater than or equal to 25% decrease and HR less than 50 bpm; notable PR interval increase was defined as greater than or equal to 25% increase PR interval greater than 200 ms; notable QRS interval increase was defined as greater than or equal to 10% increase and QRS interval greater than 110 ms

[46] Studies 1222.37 and 1222.38 were not included as these studies were exercise studies

7.5.3.4. Asthma studies (Studies 1222.4, 1222.6, 1222.27 and 1222.29)

Analyses of vital signs in these studies did not raise any safety concerns.

7.5.4. Holter monitoring

7.5.4.1. Pivotal studies

Results of the Holter monitoring in the pivotal studies did not raise any safety concerns.

7.5.5. Administration related bronchoconstriction

7.5.5.1. Pivotal studies

The incidence administration related bronchoconstriction in Studies 1222.11 and 1222.12 was lower in the pooled olodaterol 5 µg (2.9% (12 out of 417)) and olodaterol 10 µg (4.7% (20 out of 424)) groups, respectively, compared to the pooled placebo group(13.6% (58 out of 425))

7.5.6. Adjudicated SAEs

The sponsor had stated that, as per previous LABA development programs, the FDA had requested an analysis evaluating the incidence of a respiratory related composite endpoint of death, hospitalisation and intubation (as well as the individual components) related to asthma, COPD or pneumonia in subjects treated with olodaterol compared to control. For this evaluation, each SAE reported in the olodaterol development program was reviewed by an Adjudication Committee (AC), who was blinded to study treatment. The AC independently assessed all SAEs to categorise deaths, hospitalisation and intubation events described in the patient narratives and patient profiles to determine if a death, hospitalisation, and or intubation was respiratory related, and if so, whether the respiratory event was related to asthma, COPD, pneumonia or another respiratory condition.

The safety database used for the adjudicated analysis included 5387 subjects across 18 studies[47] with 3380 treated with olodaterol, 1409 with placebo, 541 with formoterol and 57 with tiotropium. The majority of these subjects (87.0%; 4687 out of 5387) were treated for COPD (15 studies), with the remainder treated for asthma (3 studies).

Overall, the incidence of the composite endpoint of death, hospitalisation and intubation in the all treated safety population (that is, both COPD and asthma patients) was comparable among the combined olodaterol group (8.6%; 292 out of 3380), placebo group (10.4%; 146 out of 1409) and formoterol group (11.8%; 64 out of 541). The incidence of respiratory related composite endpoint was also comparable among these treatment groups (4.6% (156 out of 3380), 5.3% (74 out of 1409) and 7.2% (39 out of 541) in the combined olodaterol group, placebo group and formoterol group, respectively). In the individual components analysis, incidence of respiratory related deaths (0.6% (21 out of 3380), 0.4% (5 out of 1409) and 0.7% (4 out of 541), respectively), respiratory related hospitalisations (4.4% (148 out of 3380), 5.1% (72 out of 1409) and 6.7% (36 out of 541), respectively) and respiratory related intubations (0.5% (17 out of 3380), 0.6% (8 out of 1409) and 0.7% (4 out of 541), respectively) were comparable among these treatment groups.

7.6. Post marketing experience

Not applicable.

[47] These included the 4 pivotal and 6 supportive Phase III studies. Out of the 7 Phase II studies (3 in COPD and 4 in asthma patients), the 2 single-dose studies (1 in COPD and 1 in asthma patients) were excluded. Three additional studies were included in this evaluation: Study 1237.18, which was a 4-week Phase II efficacy dose-response study evaluating olodaterol versus a tiotropium-olodaterol fixed dose combination in COPD patients; Study 1222.22, which was a 4-week Phase II placebo-controlled efficacy dose-response study in Japanese subjects; and Study 1237.3, which was a 3-week Phase I study evaluating PK interaction between olodaterol and tiotropium in COPD patients.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Cardiovascular safety

The sponsor analysed cardiac related Special MedDRA Query (SMQ) and Pharmacovigilance (PV) endpoints on the combined dataset of Studies 1222.11, 1222.12, 1222.13 and 1222.14. Overall, the incidence of cardiovascular AEs were comparable across treatment groups (69.1% to 72.7%), as were the incidence of cardiac arrhythmias (4.2% to 5.6%), tachyarrhythmias (2.9% to 3.5%), palpitations (1.5% to 2.2%) and ventricular tachyarrhythmia (1.0% to 2.0%).

An analysis of major cardiac adverse events (MACE) was also undertaken on the combined dataset of Studies 1222.11, 1222.12, 1222.13 and 1222.14. The incidences were low and generally comparable across treatment groups.

7.7.2. β2 adrenergic class effects

The sponsor analysed adverse events related to β2 adrenergic class effects on the combined dataset of Studies 1222.11, 1222.12, 1222.13 and 1222.14. Overall, the incidences of these AEs were comparable across treatment groups. Effects on serum potassium have been previously described , and results did not raise major safety concerns.

7.8. Other safety issues

7.8.1. Safety in special populations

The sponsor performed subgroup analyses on the combined dataset of Studies 1222.11, 1222.12, 1222.13 and 1222.14 based on baseline demographics, baseline disease severity, concomitant disease at baseline (cardiac disease, diabetes mellitus, renal impairment), baseline β2 receptor agonist reversibility, concomitant medications at baseline (anticholinergic use, inhaled steroid use, xanthine use, LABA use, beta adrenoceptor blocker use), and smoking status at baseline. These subgroup analyses did not raise any major safety concerns. Overall, the incidences of AEs were comparable among treatment groups in each subgroup.

7.9. Evaluator's overall conclusions on clinical safety

Overall, the safety results did not raise any major safety concerns for olodaterol. The overall incidences of all causality AEs, treatment related AEs, SAEs and AEs leading to discontinuation were comparable between the olodaterol 5 μg and 10 μg treatment groups and the placebo group in the pivotal Phase III studies. The commonly reported AEs were those expected for a LABA. These results were generally supported by those of the non pivotal Phase III and Phase II studies.

Analyses of cardiovascular safety and of AEs related to β2 adrenergic class effects did not raise major safety concerns. Evaluating the effects of olodaterol on various systemic pharmacodynamic parameters (vital signs, serum potassium, glucose and CPK) also did not raise any major safety concerns. Evaluation of serum potassium in the pivotal studies showed that for both olodaterol doses, there were statistically significantly lower serum potassium levels compared to placebo mostly at the Week 6 time points, but no statistically significant difference compared to placebo at the Week 12 time points. By comparison, there was no statistically significant difference in mean serum potassium levels between formoterol and placebo at all time points. However, in the pooled pivotal studies, the proportion of subjects in each treatment group with a minimum serum potassium level during the treatment period which was less than LLN was comparable between the olodaterol groups and the placebo group, and between the olodaterol groups and the formoterol group (10.1% to 13.2% across all treatment groups). In addition, across all test time points, the minimum serum potassium recorded was comparable across the pooled treatment groups (2.4 to 3.2 mmol/L). The

incidence of AEs of "hypokalaemia" (preferred term) was also low in all treatment groups (0.0% to 0.5%).

Analyses of the incidence of administration related bronchoconstriction (pooled dataset of Studies 1222.11 and 1222.12) showed that it was lower in the pooled olodaterol 5 µg (2.9%) and olodaterol 10 µg groups (4.7%), respectively, compared to the pooled placebo group (13.6%).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The potential benefit of olodaterol in the proposed usage is as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients. The selection of the recommended therapeutic dose of olodaterol of olodaterol 5 µg once daily has been previously discussed and has been found to be appropriate. In view of this, in this section references will be made only to olodaterol 5 µg.

The bronchodilator efficacy of olodaterol was evaluated through effects on FEV1 as well as effects on symptom relief and health related quality of life. The results showed that olodaterol 5 µg once daily had statistically significantly greater mean change from pre treatment baseline in FEV1 $AUC_{0\text{-}3h}$ and in trough FEV1 (co primary endpoints in pivotal studies) compared to placebo, after 12 weeks of treatment and after 24 weeks of treatment. After 12 weeks of treatment there was a difference over placebo of 151mL to 172mL in FEV1 $AUC_{0\text{-}3h}$ response and of 47 mL to 91 mL in trough FEV1 response. After 24 weeks of treatment there was a difference over placebo of 129 mL to 151 mL in FEV1 $AUC_{0\text{-}3h}$ response and of 53mL to 78 mL in trough FEV1 response. Comparison between olodaterol and the formoterol (pooled dataset of Studies 1222.13 and 1222.14) showed that there was no statistically significant difference between olodaterol 5 µg qd and the formoterol 12 µg bid for the co primary endpoints of FEV1 $AUC_{0\text{-}3h}$ response and trough FEV1 response at Day 169. Mean FEV1 increased within 5 minutes after the administration of olodaterol 5 µg qd, and peaked around 2 to 3 hours post dose. The statistically significantly greater mean trough FEV1 response at Day 85 and at Day 169 with olodaterol 5 µg compared to placebo suggested that the bronchodilator effect of olodaterol was sustained at the end of the 24 hour dosing interval.

Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of both doses of olodaterol over placebo. Although the results showed no statistically significant difference between olodaterol 5 µg and placebo for the co primary endpoint of Mahler TDI focal score at Day 169 (in Studies 1222.13 and 1222.14), it is noted that formoterol group also failed to show statistically significant difference. In addition, direct comparison between olodaterol and formoterol group in the pooled dataset of Studies 1222.13 and 1222.14 showed that there was no statistically significant difference between olodaterol 5 µg and formoterol in the Mahler TDI focal score at Day 169.

Analyses of the SGRQ total and component scores at Day 169 in the pooled dataset of Studies 1222.13 and 1222.14 showed that there were statistically significantly lower SGRQ total and component scores (that is, better outcome) at Day 169 for olodaterol 5 µg compared to placebo.

Analyses of rescue medication use and the PGR were also generally supportive of the efficacy claim for olodaterol over placebo.

Results in the replicate non pivotal Phase III Studies 1222.37 and 1222.38 showed that after six weeks of treatment, mean endurance time during constant work rate cycle ergometry was

statistically significantly longer for olodaterol 5 µg compared with placebo. Compared to placebo, endurance time was longer by about 12% to14% with olodaterol 5 µg qd.

8.2. First round assessment of risks

The risks of olodaterol in the proposed usage are:

- administration related bronchoconstriction
- systemic β2 agonist effects

Analyses of the incidence of administration related bronchoconstriction (pooled dataset of Studies 1222.11 and 1222.12) showed that it was lower in the pooled olodaterol 5 µg (2.9%) compared to the pooled placebo group (13.6%).

Evaluating the effects of olodaterol on various systemic β2 agonist effects did not reveal any major safety concerns. Analyses of vital signs did not raise any safety concerns in both the pivotal and non pivotal studies evaluated. The incidence of possible clinically significant high glucose levels in the pivotal studies was generally comparable between the olodaterol 5 µg and placebo. Analyses of the CPK levels in the pivotal studies showed that there was an overall mean decrease from baseline in the CPK levels in the olodaterol 5 µg group across 48 weeks, instead of the expected increase. Evaluation of serum potassium in the pivotal studies showed that for olodaterol 5 µg, there was a statistically significantly lower serum potassium level compared to the pooled placebo group at 1 and 3 hours post dose at Week 6, but no statistically significant difference at 1 and 3 hours post dose at Week 12. However, in the pooled pivotal studies, the proportion of subjects in each treatment group with a minimum serum potassium level during the treatment period which was less than LLN was comparable between the olodaterol 5 µg (10.1%) and placebo (10.2%) groups, and the incidence of AEs of "hypokalaemia" (preferred term) was low (0.3% and 0.5% in the placebo, and olodaterol 5 µg groups, respectively).

Overall, the incidences of all causality AEs, treatment related AEs, SAEs and AEs leading to discontinuation were also comparable between olodaterol 5 µg and the placebo in the pivotal studies, and these results were generally supported by those of the non pivotal Phase III and Phase II studies.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of olodaterol, given the proposed usage, is favourable.

Overall, analyses on effects of olodaterol on FEV1 compared to placebo yielded results which were generally supportive of the efficacy claim of olodaterol 5 µg qd over placebo. Analyses on effects of olodaterol on symptom relief and health related quality of life compared to placebo also yielded results which were generally supportive of the efficacy claim of olodaterol 5 µg qd over placebo. Safety results did not raise any major safety concerns.

9. First round recommendation regarding authorisation

It is recommended that the application for the registration of olodaterol as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients be approved.

This is subject to a satisfactory response to the recommendations and clinical questions raised.

10. Clinical questions

10.1. Pharmacokinetics

Not applicable.

10.2. Pharmacodynamics

Not applicable.

10.3. Efficacy

10.3.1. Question One

Please provide clarification on how the "12 hour PFT set" in Studies 1222.11 and 1222.22 were selected.

Rationale for question:

As discussed, it was not clearly explained in the clinical study reports (CSR) or protocols how the "12 hour PFT set" of subpopulation was selected. In the CSR, it was stated that "Based on a regulatory authority request to provide a more complete description of the spirometric profile over time from the large parallel Phase III studies, a sub group of subjects performed additional serial PFTs up to 12 hours post dose on Day 85 in both Study 1222.11 and the replicate Study 1222.12, with the pre specified intention of describing the results in a separate report based on the pooled dataset.", and in the Clinical Overview, it was stated that "following a US FDA recommendation, lung function was measured up to 12 hours post dose at Day 85 in a subset of patients in 1222.11 (N=241) and 1222.12 (N=321)". These statements clarified that the reason for this subset was an FDA recommendation, and that the analysis of the 12 hour PFT in this subset was pre specified to be performed on the combined dataset rather than the individual studies. However no explanation or clarification was provided regarding how the selection of subjects into this subset was done.

10.3.2. Question Two

Please provide the baseline demographic and disease characteristics of the 12 hour PFT set.

Rationale for question:

As discussed in, the baseline demographic and disease characteristics of the 12 hour PFT set were not provided, and hence comparability of these baseline characteristics across the treatment groups in this subset of study population could not be ascertained.

10.3.3. Question Three

Please provide details on the nature of the noncompliance issue in Study 1222.14 involving a study site in Canada.

Rationale for question:

As discussed, the sponsor had not provided details on the nature of the noncompliance issue in Study 1222.14 involving a study site in Canada. Although the exclusion of efficacy data at this site from the FAS involved only a single subject and was done prior to database lock and unblinding, and hence was unlikely to have introduced major bias into the efficacy analysis, the lack of information on the nature of the noncompliance issue means nonetheless that the evaluator is unable to determine more definitively if the exclusion of the single subject at this site from the FAS was acceptable.

10.3.4. Question Four

Please provide additional analysis results looking at the potential interaction between smoking status at Weeks 24 and 48 and efficacy, in the 4 pivotal efficacy studies (Studies 1222.11/1222.12 and 1222.13/1222.14).

Rationale for question:

As discussed, it is noted that in the subgroup analyses on the co primary endpoints in Studies 1222.11/1222.12 and 1222.13/1222.14, only the smoking status at baseline was considered in exploring potential interaction between smoking status and efficacy. A look through the study protocols of these studies showed that smoking status of subjects was reviewed at Weeks 24 and 48. However, the potential interaction between smoking status at these time points and efficacy was not explored or presented.

10.3.5. Question Five

Please provide additional information on whether the use of smoking cessation aids such as varenicline was monitored during the conduct of the 4 pivotal studies, and on any known drug-drug interactions between varenicline and olodaterol.

Rationale for question:

As smoking cessation is an important part in the overall clinical management of patients with COPD, it is expected that in clinical settings, COPD patients being prescribed olodaterol would also be engaged in smoking cessation programs, which may include the use of varenicline. It would therefore be clinically relevant to explore any potential drug-drug interactions between these 2 medications.

10.4. Safety

10.4.1. Question Six

Please provide details on how the Holter subset of subjects in the 4 pivotal studies had been selected.

Rationale for question:

As discussed, in the 4 pivotal studies, Holter monitoring was performed in a subset of subjects at selected sites (50 subjects per treatment group) over a 24 hour period prior to the randomisation visit (Visit 2), and repeated after the completion of all study related tests at Visits 5, 7, 9, and 10. However, the sponsor had not provided details on how the Holter subset of subjects had been selected.

11. Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. The responses by the sponsor did not raise new efficacy or safety concerns.

11.1. Pharmacokinetics

Not applicable.

11.2. Pharmacodynamics

Not applicable.

11.3. Efficacy

11.3.1. Question One

The response by the sponsor adequately clarified the selection of the "12 hour PFT set". According to the sponsor, all participating sites were contacted (prior to study initiation) to determine their capacity to conduct 12 hour post dose spirometry. In sites deemed to have the necessary infrastructure, all patients were given the opportunity to participate in the 12 hour post dose spirometry sub set. The response by the sponsor did not raise additional concerns regarding the study design, data or conclusions.

11.3.2. Question Two

The sponsor clarified that the relevant data, while not available in the individual studies, was available in the combined clinical trial report for Studies 1222.11 and 1222.12, and provided the locations of the relevant tables. These tables are evaluated and showed that the baseline characteristics of the combined 12 hour PFT set were comparable across the treatment groups.

11.3.3. Question Three

The sponsor clarified that following inspections and audit, there was sufficient doubt as to the eligibility of the patients being enrolled into the clinical trials at this site. The response by the sponsor did not raise additional concerns regarding the study data or efficacy analysis conclusions.

11.3.4. Question Four

The sponsor clarified that the number of patients with a documented change in smoking status at week 24 or at week 48 was low (1.7% and 2.5% respectively; Table 5), and therefore, subgroup analysis based on smoking status at baseline is considered to be sufficiently representative of smoking status during the study.

It is noted by the evaluator that there is a relatively significant amount of missing data with regards to smoking status at Weeks 24 and 48 (12.9% at Week 24, and 7.6% at Week 48). Hence while the proportion of patients with documented change in smoking status at Week 24 or at Week 48 was low, the actual proportion with a change in smoking status at these timepoints could potentially be higher. However, the relatively significant amount of missing data at Weeks 24 and 48 also meant that attempts to analyse the potential interaction between smoking status at these timepoints and efficacy may not yield meaningful conclusions. Overall, the response by the sponsor did not raise additional concerns regarding the study data or conclusions drawn from the efficacy analysis.

Table 5. Change in smoking status – pooled dataset from 1222.11, 1222.12, 1222.13, and 1222.14 (treated set)

		Placebo	Olodaterol 5 µg	Olodaterol 10 µg	Formoterol	Total
	N (%)	885 (100)	876 (100)	883 (100)	460 (100)	3104 (100)
Week 24	Missing	150 (16.9)	91 (10.4)	99 (11.2)	60 (13.0)	400 (12.9)
	No change	716 (80.9)	769 (87.8)	772 (87.4)	394 (85.7)	2651 (85.4)
	Change	19 (2.1)	16 (1.8)	12 (1.4)	6 (1.3)	53 (1.7)
Week 48	Missing	69 (7.8)	56 (6.4)	66 (7.5)	45 (9.8)	236 (7.6)
	No change	793 (89.6)	792 (90.4)	799 (90.5)	406 (88.3)	2790 (89.9)
	Change	23 (2.6)	28 (3.2)	18 (2.0)	9 (2.0)	78 (2.5)

11.3.5. Question Five

The sponsor provided a listing of study patients who were on concomitant varenicline which showed that the use of varenicline in the 4 pivotal studies (1222.11, 1222.12, 1222.13, 1222.14) was low (Study 1222.11: 2.4% (5 out of 209), 3.4% (7 out of 208), 1.4% (3 out of 207) in the

placebo, olodaterol 5 µg, and olodaterol 10 µg groups, respectively; Study 1222.12: 1.9% (4 out of 216), 2.9% (6 out of 209) and 0.5% (1 out of 217), respectively; Study 1222.13: 0.4% (1 out of 225), 0.9% (2 out of 227), 1.8% (4 out of 225) and 0% (0 out of 227) in the placebo, olodaterol 5 µg, olodaterol 10 µg and formeterol groups, respectively; Study 1222.14: 0.9% (2 out of 235), 1.3% (3 out of 232), 1.7% (4 out of 234) and 0.4% (1 out of 233), respectively). The sponsor also stated that in vitro investigations had indicated that olodaterol had no potential to inhibit or induce CYP enzymes at the exposure levels expected to be achieved in clinical practice. According to the sponsor, in vitro studies had led to the conclusion that the effects of olodaterol on systemic exposure of other medications were not to be expected and hence these interactions were not investigated in clinical studies. In addition, the sponsor provided a copy of the Product Information for varenicline which stated that varenicline has no known clinically meaningful drug interactions. Based on this information, the sponsor had concluded that a drug-drug interaction between olodaterol and varenicline was not expected.

11.4. Safety

11.4.1. Question One

The response by the sponsor adequately clarified the selection of the Holter subset of subjects. According to the sponsor, all study sites were given the option to participate in the Holter sub study. If the site declined participation, no patients were enrolled into the sub study at that site. If the site opted to participate, the site was provided with the appropriate Holter monitoring equipment and instructions for use prior to study initiation. The Holter sub study was open to all patients at participating sites. All patients at participating sites who were screened for the study (that is, signed informed consent) was asked if they would be willing to participate in the Holter sub study, and were informed that their participation in the main study would not be impacted if they did not want to participate in the Holter sub study. Recruitment into the Holter sub study was monitored on an ongoing basis during the course of the study, and once the required number of patients had been randomised into the sub study (200 patients for Studies 1222.11 and 1222.12; 250 patients for Studies 1222.13 and 1222.14), recruitment into the Holter sub study was closed. The response by the sponsor did not raise additional concerns regarding the study design, data or conclusions.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of olodaterol in the proposed usage are unchanged from those identified earlier.

12.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of olodaterol in the proposed usage are unchanged from those identified previously.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of olodaterol, given the proposed usage, is favourable.

13. Second round recommendation regarding authorisation

It is recommended that the application for the registration of olodaterol as a long term, once daily maintenance bronchodilator treatment of airflow obstruction in COPD patients be approved.

14. References

1. Australian Lung Foundation. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease. 2010. http://www.wdhs.net/sites/default/files/pph-cc-resp-copd-x-plan2010.pdf (accessed 20th December 2012)
2. European Medicines Agency, Guideline on the requirements for clinical documentation for orally inhaled product (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. 22 January 2009. http://www.tga.gov.au/pdf/euguide/ewp415100enfin.pdf (accessed 7th January 2013)
3. European Medicines Agency, Guidelines on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease. 21 June 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf (accessed 20th December 2012)
4. European Medicines Agency, Points to consider on multiplicity in clinical trials. 19th September 2002. http://www.tga.gov.au/pdf/euguide/ewp090899en.pdf
5. FDA, Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. November 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071575.pdf (accessed 20th December 2012)
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of COPD. 2011. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf (accessed 7th January 2013)
7. ICH, Efficacy Guidelines E9: Statistical Principles for Clinical Trials. September 1998. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf (accessed 20th December 2012)

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au