CBG MEB

Public Assessment Report

Scientific discussion

Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution

(tiotropium and olodaterol)

NL/H/3157/001/DC

Date: 14 July 2015

This module reflects the scientific discussion for the approval of Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution. The procedure was finalised on 20 May 2015. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

µg	Microgram
AC	Active-controlled
ACh	Acetylcholine
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the time curve
AUC(x-yh)	Area under the time curve from x to y hours after dosing (normalized)
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CO	Crossover
COPD	Chronic obstructive pulmonary disease
DB	Double-blind
DC	Decentralised procedure
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
EWP	Efficacy Working Party (of EMA)
FAS	Full analysis set
FDA	Food and Drug Administration of the United States
FDC	Fixed-dose combination
FEV_1	Forced expiratory volume during 1 second
FVC	Forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
IC	Inspiratory capacity
ICH	International Conference on Harmonization
iCO	Incomplete crossover
L	Litre
LABA	Long-acting β2-adrenoceptor agonist
LAMA	Long-acting antimuscarinic antagonist
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
mL	Millilitre
MRD	Multiple rising dose
N	Number of patients
Olo	Olodaterol
PBT	Persistent, bioaccumulative and toxic
PC	Placebo-controlled
PD	Pharmacodynamics
PECsw	Predicted Environmental Concentration in surface water
PFT	Pulmonary function testing
PG	Parallel group
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PPS	Per protocol set
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMS	Reference Member State

RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product information
SRD	Single rising dose
TDI	Transition Dyspnea Index
Tio	Tiotropium
Tio + Olo	Tiotropium + Olodaterol fixed dose combination
TS	Treated set
TSE	Transmissible Spongiform Encephalopathy
US	United States
vPvB	Very persistent and very bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution from Boehringer Ingelheim International GmbH.

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

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

Spiolto Respimat inhalation solution is a fixed dose combination containing tiotropium, a long acting muscarinic receptor antagonist (LAMA), and olodaterol, a long acting beta2-adrenergic agonist (LABA), delivered via the Spiolto Respimat soft mist inhaler device.

The two active ingredients provide additive bronchodilation due to their different modes of action. Since muscarinic receptors appear to be more prominent in the central airways while ß$_2$ adrenoceptors have a higher expression level in the peripheral airways, a combination of tiotropium and olodaterol should provide optimal bronchodilation in all regions of the lungs.

This decentralised procedure concerns a fixed dose combination application in accordance with Article 10b of Directive 2001/83/EEC of an inhalation solution with two known active substances: tiotropium 2.5 microgram (as bromide monohydrate) and olodaterol 2.5 microgram (as hydrochloride) per delivered dose. Both active substances are approved treatments in the maintenance bronchodilation treatment of COPD and are available as monotherapy as a solution delivered via the same EC approved inhalation device Respimat. The development of the fixed dose combination is based on the formulation of the two monotherapy products registered by the same MAH:

- Spiriva Respimat 2.5 microgram containing tiotropium bromide, registered through procedure NL/H/2498/001/DC since 2007.
- Striverdi Respimat 2.5 microgram containing olodaterol, registered through procedure NL/H/0718/001/DC since 2013.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom. The application was withdrawn in Finland.

The clinical development programme included four phase I trials (2 in healthy volunteers, and 2 in patients with COPD), three phase II trials and six phase III trials (in COPD patients).

- The phase I trials established the pharmacokinetics in both healthy volunteers and COPD patients.
- The phase II trials were designed to characterise the dose-response for olodaterol in combination with tiotropium and the dose-response for tiotropium in combination with olodaterol
- The phase III trials include:
    - Two pivotal, randomised, double-blind, parallel twin trials of 52-week duration to establish the long-term efficacy and safety of the fixed-dose combination and to establish the superiority of the fixed dose combination (FDC) over the mono-components.
    - Supported with a double blind placebo controlled trial of 6 weeks duration to characterise the bronchodilation effect over a continuous 24 h dosing interval.
    - Supported with three additional trials to investigate the effect of tiotropium + olodaterol FDC on symptom-limited exercise tolerance.

Scientific advice

Authority interactions (scientific advice meetings) have taken place in 2011 with the Medicines Evaluation Board (MEB) in the EU as well as with the Food and Drug Administration (FDA) in US.

Additional advice was sought from the MEB in 2012. In these meetings the requirements of the clinical development plan were discussed.

Paediatric development
The requirement to submit a paediatric investigation plan has been waived by the European Medicines Agency (EMA) for products intended for the treatment of COPD, which is a condition that only occurs in adults (Waiver Decision Number: CW/1/2011). A confirmation of the applicability of this class waiver for the fixed dose combination tiotropium + olodaterol has been issued by the EMA (EMA/385813/2013; 09 Aug 2013).

CHMP guidelines
The clinical programme is developed according to the following guidelines:
EMEA/CHMP/483572/2012-corr1 'Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)' and CHMP/EWP/240/95 Rev. 1 'Guideline on clinical development of fixed combination medicinal products'.

II. QUALITY ASPECTS

II.1 Introduction

Spiolto Respimat is formulated as a clear, colourless inhalation solution. The drug product is filled into a 4.5 ml container made out of polyethylene/polypropylene material, closed with a polypropylene cap with integrated silicone sealing ring. The filled primary container is inserted into an aluminium cylinder with an air hole seal. The cartridges contain the active ingredients olodaterol (as hydrochloride) and tiotropium (as bromide monohydrate) and are used in combination with a soft-mist inhaler to deliver 2.5 µg olodaterol and 2.5 µg tiotropium per puff. Two puffs are one medical dose.
The labelled number of actuations per cartridge is 60 actuations (30 doses) for commercial product which corresponds to a one-month therapy.

The excipients are benzalkonium chloride, disodium edetate, purified water and 1M Hydrochloric acid (for pH adjustment).

II.2 Drug Substances

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

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

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

Stability of drug substance

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

Tiotropium bromide monohydrate
Tiotropium bromide monohydrate is a well-known active substance, described in the European Pharmacopoeia. The drug substance is white or yellowish-white powder or crystals, sparingly soluble in water, soluble in methanol, and practically insoluble in methylene chloride.

The CEP procedure is used for this active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The MAH applies the tests and specifications of the Ph. Eur. monograph with the additional test and requirement for residual acetone listed on the CEP. Results of batch analysis have been provided of the batches used for the manufacture of the clinical batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the formulation is based on the Spiriva Respimat formulation (tiotropium bromide, NL/H/0718/001/DC) and the Striverdi Respimat formulation (olodaterol, NL/H/2498/001/DC), which are very similar and use the same EC approved inhalation device Respimat.
The development of the product has been satisfactory performed and explained. The excipients used are common in the manufacture of a solution for inhalation. The packaging materials are usual and suitable for the product at issue. The minimum fill volume of 4.0 ml allows the extraction of 30 doses. The overfilling is required to guarantee a high dosing accuracy for the patient.
Comparison of the droplet size distribution by laser diffraction, the aerodynamic particle size distribution by Andersen Cascade impactor, the delivered dose (aerodynamic), the dynamic viscosity, the surface tension, and the pH demonstrated that, except for the pH, compared to Striverdi Respimat, there are no relevant differences between Spiolto Respimat and the monotherapy products and therefore no physical drug-drug interaction exist between tiotropium bromide and olodaterol in the fixed combination product. The comparison has been performed with batches used in the clinical studies. All clinical studies including phase III trials were performed with the same formulation and Respimat inhaler as intended to be marketed.
The pharmaceutical development has been described in sufficient detail.

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

Container closure system

The specifically developed cartridge corresponds to the cartridge used for the monoproducts: a 4.5 ml plastic container, closed with a plastic cap and sealed with a tamper protection seal prior to being inserted and crimped into an aluminium cylinder.
Compliance of the packaging components with legal requirements has already been founded.
No potential leachables were identified from the control extraction studies; therefore, no leachables investigations is part of the drug product control. This strategy is consistent with the strategy applied for the corresponding monoproducts for which identical materials of construction are used. The chemical and physical compatibility of the formulation with the primary packaging components has been confirmed in the stability studies

Microbiological attributes
The microbiological attributes of Spiolto Respimat solution for inhalation are in compliance with the harmonized requirements for preparations for inhalation use.
As a multidose administration form, the inhalation solution has to be preserved against microbial contamination. The same preservative system is used as applied for the mono-products. A preservative effectiveness study has been conducted which confirms that the concentration of 9 mg benzalkonium chloride/100 ml (corresponding to the lower specification limit) results in sufficient preservation complying with criterion A of Ph. Eur.
The preservative efficacy was also tested during the primary stability studies and in-use stability studies. The results conformed to the current Ph. Eur. 5.1.3-2, preparations for inhalation at all tested time points. These results confirm the adequate preservation of the solution against microbiological contamination.

Control of excipients
All excipients are known and used in approved inhalation products. All excipients are of compendial quality and each batch is controlled to all requirements of the monographs in the Ph. Eur. These specifications are acceptable.

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

Stability of drug product
Stability data has been obtained at 25ºC/60% RH (36 months) and 40ºC/75% RH (6 months) of the inhalation solution in the unopened cartridge. Investigations to cover the stability after insertion of the cartridge into the inhaler (in-use stability studies) were also performed, for up to 90 days.
The only trend observed is a slight increase in the known degradation products and a very slight decrease in assay. All results amply comply. Photostability studies were not conducted as the drug product is fully protected from light by the aluminium cylinder used as secondary packaging to encase the cartridge containing the inhalation solution.
On the basis of the submitted data, a shelf-life of 36 months can be granted. The in-use storage period of 3 months is supported by the in-use studies. The product should not be frozen.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The pharmacodynamic properties of tiotropium and olodaterol are well known, as both compounds are registered. For this application for a combination product, the focus lies on possible synergistic or additive effects.
The primary pharmacodynamics of the combination therapy was investigated in guinea pigs and dogs. In both models which investigated protection from bronchospasm induced by ACh, the combination treatment resulted in an additive effect with a longer duration, as compared to the individual treatments.
The combination of olodaterol and tiotropium is not expected to provide any secondary pharmacology effects apart from those associated with the use of the compounds alone.
Safety pharmacology studies revealed at supratherapeutic doses mainly beta-adrenegic effects which are also seen for olodaterol alone, including increased heart rate (with heart rate-dependent subsequent QTc prolongation) and decreased mean arterial blood pressure. No additional effects were seen after the combination treatment.

III.2 Pharmacokinetics

Absorption and systemic exposure was observed after inhalation dosing in rats and dogs. No differences in exposure between males and females were observed for either compound. No pronounced or consistent deviation from dose-proportionality or effect of repeated dosing was observed. Variability in rats was low, and moderate in dogs.
No studies with the combination regarding distribution, metabolism and excretion were performed. This is acceptable, since the ADME characteristics of both compounds are well known.
Pharmacokinetic interactions between tiotropium and olodaterol were studied at the level of metabolism and absorption. *In vitro* studies using human liver microsomes and human lung homogenate showed that the formation of the very small fraction “other metabolites” from tiotropium is slightly inhibited by addition of 10 µM or higher olodaterol. The formation of the main tiotropium metabolite dithienylglycolic acid was not effected by any olodaterol concentration. Since 10 µM is very much higher than the expected Cmax in patients and no effect was seen at lower concentrations, this small effect of olodaterol on tiotropium metabolism is not likely to be clinically relevant. Olodaterol had no effect on the metabolism of tiotropium in *in vitro* human liver microsomes.
Although some differences in exposure to tiotropium are evident after 13 weeks of dosing in dogs, where exposure is lowered when combined with olodaterol, this is not considered relevant. Likewise, exposure to olodaterol in rats appears to be lowered after a single dose when combined with tiotropium, but this is not considered meaningful.

III.3 Toxicology

In inhalation single-dose toxicity studies in mice and rats conducted with the dose ratio 1:1, the approximate lethal dosages (males and females combined) were 33.8 + 35.5 mg/kg and >17.9 + 18.8 mg/kg Tio+Olo, respectively. Therefore, the acute toxicity of tiotropium and olodaterol is considered to be low.
Inhalation repeat-dose toxicity studies with tiotropium and olodaterol were performed in Wistar Han rats (duration 4 weeks) and in Beagle dogs (duration up to 13 weeks). In all studies, toxicokinetic analyses showed substantial systemic exposure to tiotropium and olodaterol. All effects observed were also observed after dosing with the single components when compared to previous studies, except for increases in urine volume and subsequent decreases in electrolyte concentrations in rats, which persisted after 4 weeks of recovery. An opposite effect on urine volume was seen in the 4 week dog study, where urine volume was decreased. This effect was no longer apparent after 13 weeks of dosing. In the 13 week dog study a direct comparison between the combination and the mono compounds could be made, since mono groups were included in the study. No synergistic or additive effects were observed in this dog study, in comparison to the mono groups of the present studies and also in comparison to the respective dog studies that were performed for the Marketing Authorisation Applications for the mono components (olodaterol and tiotropium).

Tiotropium and olodaterol are not genotoxic when tested separately. No synergistic effect on genotoxicity from the combination is expected. Nevertheless, a micronucleus assay was included in the 4-week rat combination study, which revealed no genotoxic potential as expected.
No carcinogenicity studies with the combination were conducted, which is agreed. Carcinogenicity studies previously conducted with tiotropium were negative. Tumours seen in previous studies conducted with olodaterol were considered not relevant for humans.
No reproduction toxicity studies with the combination were conducted, and none are necessary. From previous studies conducted with the mono compounds, it was shown that adverse effects on reproduction were evident at maternally toxic doses in the case of tiotropium, and at very high exposures in the case of olodaterol. This is correctly reflected in the SmPC.

III.4 Ecotoxicity/environmental risk assessment (ERA)

PECsurfacewater is 2.5 x 10^{-5} µg/L for both compounds, which is below the action limit of 0.01 µg/L. A phase II environmental risk assessment is not deemed necessary. Olodaterol and tiotropium are not persistent, bioaccumulative and toxic (PBT), nor very persistent and very bioaccumulative (vPvB).

PBT-assessment				
Parameter	***Substance***	***Results***	***Criteria***	***Conclusion***
Bioaccumulation	Olodaterol	log P = 3.0 (free base) log D = 1.2 (pH = 7.4) log D < 0.5 (pH < 6)	log K_{ow} > 4.5	Not B
Bioaccumulation	Tiotropium	Log K_{ow} = -2.28 (pH 7.4)	log K_{ow} > 4.5	Not B
PBT-statement :	The compound is not considered as PBT nor vPvB			
Phase I				
Calculation	***Value***	***Unit***	***Conclusion***	
PEC $_{surface\ water}$	2.5 x 10^{-5}	µg/L	< 0.01 threshold	

Considering the above data, olodaterol and tiotropium are not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical programme was designed according to the COPD guideline (EMA/CHMP/483572/2012-corr-1) and the guideline on fixed dose combinations (CHMP/EWP/240/95 Rev.1). In this section the main results of the studies are presented.

The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. All clinical studies were performed with the same formulation and Respimat inhaler as intended to be marketed.

IV.2 Pharmacokinetics

Pharmacokinetics (PK) in healthy subjects was assessed in two Phase I trials (1237.1, 1237.2). PK in COPD patients was assessed in two Phase I trials (1237.3, 1237.24), one Phase II trial (1237.4) and one Phase III trial (1237.20). These trials are listed in Table 1.

Table 1 Clinical trials with PK and systemic PD data within the clinical development program for Tio+Olo FDC

Trial type	BI trial number	Description
Safety and PK in healthy volunteers	1237.1	SRD with free combinations of tiotropium and olodaterol
	1237.2	Two weeks MRD with Tio+Olo FDC
Safety and PK in COPD patients	1237.3	PK interaction of tiotropium and olodaterol administered as Tio+Olo FDC
Efficacy, safety and PK in COPD patients	1237.4	4 weeks dose finding with Tio+Olo FDC
	1237.20	24-hour lung function profiles after 6 weeks with Tio+Olo FDC
PK/PD in special populations	1237.24	3 weeks PK and safety of Tio+Olo FDC in Japanese COPD patients

The pharmacokinetics of tiotropium and olodaterol have been characterised previously for the respective monotherapy drug products. The PK studies aimed to demonstrate the absence of relevant pharmacokinetic interaction between tiotropium and olodaterol and on demonstration of comparable exposure for the Tio+Olo FDC compared to the approved monoproducts. This is in line with the recommendations in the 'Guideline on clinical development of fixed combination medicinal products' (CHMP/EWP/240/95 Rev. 1).

Bioequivalence

Spiolto Respimat inhalation solution consists of an aqueous solution of tiotropium and olodaterol delivered via the Respimat inhalation device. The formulation of the FDC is identical to the tiotropium Respimat monotherapy formulation, with the exception of the presence of olodaterol as a second drug substance. The FDC formulation is also similar to the olodaterol Respimat monotherapy formulation, with the exception of the pH (2.9 instead of 4), the acidifier used for pH adjustment (hydrochloride instead of citric acid), and the presence of tiotropium as a second drug substance. Throughout the entire clinical development, the to-be-marketed inhaler version Respimat A5 was employed, and except for the concentration of the active ingredients, the composition of the formulation was not changed. Therefore no bioequivalence studies are necessary.

Interaction

In order to justify that the PK properties of the individual compounds can be conferred to Tio+Olo FDC, the PK interaction Study 1237.3 was performed. This was a 3-way crossover study with 47 COPD patients designed to compare steady state systemic exposure to tiotropium and olodaterol after inhalation of Tio+Olo FDC (5/10 µg) and after inhalation of the corresponding monotherapies (Tio 5 µg, Olo 10 µg). This study design was in line with the recommendations in the applicable guideline (CHMP/EWP/240/95 Rev. 1.).

The results are summarized in Table 2. Results from study 1237.3 showed that the pharmacokinetic parameters for each component were similar to those observed when tiotropium and olodaterol were administered separately by the inhaled route. It further demonstrates comparable exposure of tiotropium and olodaterol following inhalation between the FDC and the registered monoproducts.

Table 2 Comparison of tiotropium steady state PK parameters between Tio+Olo 5/10 µg and tiotropium 5 µg – trial 1237.3

	Test (T): T+O 5/10		Ref. (R) T 5				2-sided 90% CI	
Parameter	N	Adj. gMean	N	Adj. gMean	Adj. gMean T/R Ratio [%]	Intra-indiv. gCV [%]	Lower Limit (%)	Upper Limit (%)
$Ae_{0-24,ss}$ (ng)	45	900.57	43	918.63	98	20.43	91	106
$C_{max,ss}$ (pg/mL)	47	15.55	45	16.15	96	29.92	87	107
$AUC_{0-4,ss}$ (pg·h/mL)	44	21.92	39	24.00	91	22.61	84	100
$AUC_{0-6,ss}$ (pg·h/mL)	36	29.97	35	33.24	90	19.81	83	98

The data from study 1237.3 were supported by the results of the Phase III Study 1237.20, dose rising 1237.1 and 1237.2 in healthy volunteers, and the dose finding study 1237.4 in COPD patients. Excretion of tiotropium and olodaterol was similar for the FDC and the monoproducts. Based on urinary excretion following single dose and at steady-state, pharmacokinetics of tiotropium and olodaterol were dose proportional over the range investigated: tiotropium 2.5-10 µg and olodaterol 2-40 µg.

The study data provided are satisfactory. Pharmacokinetics of tiotropium and olodaterol have been investigated sufficiently for the fixed dose combination application for Spiolto Respimat.

IV.3 Pharmacodynamics

The pharmacodynamics properties of tiotropium and olodaterol are well known, as both compounds are registered. No new pharmacodynamic studies have been conducted. No pharmacokinetic interaction was observed between tiotropium and olodaterol and the pharmacology properties of the individual compounds can be conferred to Spiolto Respimat. Dose selection was based on clinical efficacy.

IV.4 Clinical efficacy

The clinical programme for tiotropium + olodaterol FDC comprised four Phase I trials, three Phase II trials in COPD, and six Phase III trials in COPD (Table 3).

The phase II trials were designed to characterise the dose-response for olodaterol in combination with tiotropium (1237.4, 1237.9) and the dose-response of tiotropium in combination with olodaterol (1237.18).

The phase III trials include:

- Two pivotal, randomised, double-blind, parallel replicate trials of 52-weeks duration to establish the long-term efficacy and safety of the fixed dose combination and to establish the superiority of the FDC over the monocomponents (1237.5 & 1237.6).
- A supportive double-blind placebo controlled trial of 6-week duration to characterise the bronchodilation effect of tiotropium + oldaterol FDC over a continuous 24-h dosing interval (1237.20).
- Three supportive additional trials to investigate the effect of tiotropium + oldaterol FDC on symptom-limited exercise tolerance (1237.13 & 1237.14 & 1237.15).

Table 3 Summary of the randomised Phase II and III studies of the clinical programme.

Summary of the phase II dose-ranging studies

Study ID	No. of centres	Designs	No. patients Treated/Full analysis set	Primary efficacy variable	Key Secondary outcome
Dose/response of olodaterol in combination with tiotropium					
1237.4	38	DB, AC, PG 4w	T + O 5/2µg (89/89) T+ O 5/5 µg (93/93) T+ O 5/10 µg (88/88) T 5 µg (90/90)	Trough FEV_1 response after 4 weeks of treatment	
1237.9	24	DB, CO, 4 w	T + O 5/2 µg (141/136) T + O 5/5 µg (141/136) Total (141/136)	Trough FEV_1 response after 4 weeks of treatment.	
Dose/response of tiotropium in combination with olodaterol					
1237.18	34	DB, AC, iCO 4 w	T/O 1.25/5 µg (109/107) T/O 2.5/5 µg (113/109) T/O 5/5 µg (109/104) T/O 1.25/10 µg (110/105) T/O 2.5/10 µg (110/105) T/O 5/10 µg (111/107) O 5 µg (108/107) O 10 µg (117/108) Total (232/222)	Trough FEV_1 response [L] after 4 weeks of treatment	
Summary of the phase III pivotal studies					
Study ID	**No. of study centers**	**Design**	**No. patients Treated/Full analysis set**	**Primary efficacy variable**	**Key Secondary outcome**
52-week efficacy and safety study					
1237.5	239	DB, AC, PG 52 w	T+O 2.5/5 µg (522/522) T+O 5/5 µg (522/522) Tio 2.5 µg (525/524) Tio 5 µg (527/526) Olo 5 µg (528/528)	Day 169: FEV_1 AUC_{0-3h} response Day 170: Trough FEV_1 response Day 169: SGRQ total score [b] (combined with 1237.6)	Day 169: TDI focal score [b] (combined with 1237.6)
1237.6	241	DB, AC, PG 52 w	T+O 2.5/5 µg (508/508) T+O 5/5 µg (507/505) Tio 2.5 µg (507/505) Tio 5 µg (506/503) Olo 5 µg (510/507)	Day 169: FEV_1AUC_{0-3h} response Day 170: Trough FEV_1 response Day 169: SGRQ total score [c] (combined with 1237.5)	Day 169: TDI focal score [b] (combined with 1237.5)
6-week study					
1237.20	29	DB, PC, AC, iCO, 6 w	T+O 2.5/5 µg (136/135[a]) T+O 5/5 µg (139/138[a]) Tio 2.5 µg (137/136[a]) Tio 5 µg (135/135[a]) Olo 5 µg (138/136[a]) Placebo (138/132[a]) Total (219/212[a])	Day 43: FEV_1 AUC_{0-24h} response	Day 43: FEV_1AUC_{0-12h} response Day 43: FEV_1AUC_{12-24h} response
Supportive studies (Exercise endurance studies)					
Study ID	**No. of study centres**	**Design**	**No. patients Treated/Full analysis set**	**Primary efficacy variable**	**Key Secondary outcome**
6-week cross-over studies					
1237.13	43	DB, PC, AC, iCO, 6 w	T+O 2.5/5 µg (223/219) T+O 5/5 µg (226/222) Tio 5 µg (227/216) Olo 5 µg (217/214) Placebo (222/212) Total (295/252)	Day 43: IC pre-exercise Day 43: Exercise endurance time during constant work rate cycle ergometry	
1237.14	33	DB, PC, AC,	T+O 2.5/5 µg (219/212[b])	Day 43: IC pre-exercise Day 43: Exercise endurance	

		iCO, 6 w	T+O 5/5 µg (224/218[a]) Tio 5 µg (218/208[a]) Olo 5 µg (219/208[a]) Placebo (216/202[a]) Total (291/283[a])	time during constant work rate cycle ergometry	
12-week parallel group study					
1237.15	58	DB, PC, PG, 12w	T+O 2.5/5 µg (133/129) T+O 5/5 µg (139/135) Placebo (132/121)	Day 85: Exercise endurance time during constant work rate cycle ergometry	Day 85: Exercise endurance time during endurance shuttle walking test[c]

DB= double blind, PC= placebo- controlled, AC = active- controlled, PG = parallel group, CO= crossover, iCO = incomplete crossover, FEV_1=Forced expiratory volume during 1 second; T+O=tiotropium + olodaterol fixed dose combination; T/O = Tio + olodaterol in a free combination; Tio=tiotropium; O = olodaterol; AUC0-3h=area under the curve from 0 to 3 hours post-dose; IC=inspiratory capacity; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnoea Index

a. Full analyses set
b. Combined dataset.
c. In addition, IC pre-exercise (Day 85) from constant work rate cycle ergometry identified as a secondary endpoint and included in the hierarchical testing sequence.

Patient population

In general, patients with a diagnosis of COPD (post-bronchodilator < 80% predicted FEV_1 and FEV_1/FVC < 0.7) were included. Patients must be aged ≥ 40 years with a smoking history of >10 pack-years.

Patients with significant other diseases were excluded. Patients were specifically excluded if they suffered from asthma, thyrotoxicosis, paroxysmal tachycardia (>100 beats per minute), myocardial infarction within 1 year of the screening visit, unstable or life-threatening cardiac arrhythmia or hospitalisation for heart failure within the past year.

Analysed patient population

The clinical trials used the same definitions of the analysed patient population. The primary efficacy analyses were conducted on the full analysis set, i.e. all patients who had at taken 1 dose of study medication and who had the study baseline and at least 1 evaluable post-dose measurement for 1 of the primary endpoints.

Data monitoring

The conduct of the phase III studies were monitored by the Data Monitoring Committee (DMC).

- **Dose-response studies**

Study 1237.4

Title: randomised, double-blind, parallel group study to assess the efficacy and safety of 4 weeks of once daily treatment of 3 doses of orally inhaled olodaterol, each in fixed dose combination with 5 µg tiotropium bromide (delivered by the Respimat® inhaler) compared with 5 µg tiotropium bromide monoproduct (delivered by the Respimat® inhaler) in patients with COPD.

The fixed dose combination of tiotropium + olodaterol 5/2 µg, tiotropium + olodaterol 5/5 µg, tiotropium + olodaterol 5/10 µg was compared with tiotropium 5 µg monotherapy. All treatments were delivered by the Respimat inhaler.

After 4 weeks of treatment, a dose ordering between the different dose combinations of tiotropium + olodaterol was observed, with the largest improvement for the high-dose combination. A statistically significant improvement in trough FEV_1 response (change from baseline) was observed between the highest dose combination and tiotropium monotherapy (adjusted mean (SE) difference 0.057 (0.03) L, 95% CI 0.004-0.110, p=0.03).

The doses of olodaterol appeared to be on the steep part of the FEV_1 dose response curve, similar as previously observed in the dose response curve of olodaterol monotherapy.

Study 1237.9

Title: randomised, double-blind, cross-over study to assess the efficacy and safety of 4 weeks of once daily treatment of 2 doses of orally inhaled olodaterol, each in fixed dose combination (FDC) with 5 µg tiotropium bromide (delivered by the Respimat® inhaler) in patients with COPD.

Study 1237.9 compared tiotropium + olodaterol 5/2 µg with tiotropium + olodaterol 5/5 µg. The study consisted of two treatment periods separated by a two-week washout period. A total of 136 patients were included in the full analysis set.
On day 15, a dose ordering was observed, numerically in favour of the high-dose combination regarding trough FEV_1. However, after 4 weeks of treatment, the adjusted mean difference (SE) in trough FEV_1 between tiotropium + olodaterol 5/5 µg and tiotropium + olodaterol 5/2 µg dose was −0.002 (0.017) L (p=0.89). Study 1237.9 failed to show a dose ordering between the two fixed dose combinations after 4 weeks of treatment.

Study 1237.18
Title: A randomised, double-blind, 8 treatment, 4 period, incomplete crossover study to determine the optimal free dose combination of olodaterol and tiotropium (both delivered by the Respimat® inhaler) after 4 weeks once daily treatment in patients with COPD.

The treatment periods were of 4 weeks duration, separated with a washout period of 3 weeks. In this study, tiotropium 1.25 µg, 2.5 µg or 5 µg was added in free combination to olodaterol 5 µg or olodaterol 10 µg.

Results
At week 4, the primary efficacy endpoint trough FEV_1 response [in L] showed numerical differences between the monotherapies 5 µg olodaterol and 10 µg olodaterol (12 mL difference), and the combination regimens with 1.25 µg tiotropium (9 mL difference), 2.5 µg tiotropium (30 mL difference) and 5 µg tiotropium (8 mL difference).

Statistically significant increases in trough FEV_1 response were seen for all tiotropium doses in free combination with 5 µg olodaterol (1.25 µg/5 µg, 2.5 µg/5 µg, and 5 µg/5 µg tiotropium/olodaterol) compared with 5 µg olodaterol monotherapy; similarly, statistically significant increases in trough FEV_1 response were observed for all tiotropium doses in free combination with 10 µg olodaterol (1.25 µg/10 µg, 2.5 µg/10 µg, and 5 µg/10 µg tiotropium/olodaterol) compared with 10 µg olodaterol monotherapy.

The differences in trough FEV_1 response between tiotropium/olodaterol 5 µg/5 µg vs. tiotropium/ olodaterol 1.25 µg/5 µg approached statistical significance.
Similar effects were seen for olodaterol 10 µg: the differences in trough FEV_1 response between tiotropium/ olodaterol 5 µg/10.0 µg vs. tiotropium/olodaterol 1.25 µg/10 µg approached statistical significance as well.

Discussion on the dose-response programme
The dose response study 1237.4 showed that olodaterol 2 µg is still on the steep part of the dose-response curve when added to tiotropium 5 µg. The results of the comparison between olodaterol 10 µg and 5 µg in study 1237.18 are considered equal, both applied as monotherapy and in combination with tiotropium. Olodaterol 5 µg is an approved therapy, while olodaterol 10 µg is not. Therefore, olodaterol 5 µg would be the preferred dose in the fixed dose combination.
The doses of tiotropium 2.5 and 5 µg show dose ordering in study 1237.18 and, therefore, the MAH decided to proceed with both the 2.5 µg and 5 µg tiotropium doses. The tiotropium + olodaterol 2.5/5 µg and 5/5 µg doses were further developed in the phase III clinical trials.

- **Main studies**

The main studies to establish the long-term safety and efficacy of tiotropium + olodaterol FDC are the twin studies 1237.5 and 1237.6 of 52-week duration.

Title: a randomised, double-blind, parallel-group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg/5 µg; 5 µg/5 µg) (delivered by the Respimat inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD).

After a run-in period of 2 weeks, patients were randomized to olodaterol 5 µg, tiotropium 2.5 µg, tiotropium 5 µg, tiotropium + olodaterol 2.5/5 µg and tiotropium + olodaterol 5/5 µg. The primary

endpoints were measured on day 169 (week 24), and the study was continued in a blinded fashion up till 52 weeks to establish the maintenance effect and the safety.

The two pivotal studies were actively controlled trials to compare the fixed dose combination with separate component parts. The lack of placebo-arm is accepted because of the duration of the trial (52 weeks), and long-acting bronchodilators can be considered as standard of care in patients with moderate to very severe COPD (CPMP/EWP/562/98). The lack of the placebo arm was also discussed and agreed with the MEB in the scientific advice.

Objective
The objective of this study was to test the superiority of the fixed dose combinations over the monocomponents.

Endpoints
The study had three primary endpoints: two lung function endpoints and one symptomatic endpoint.

The two primary lung function endpoints were:
- FEV_1AUC_{0-3h} response on day 169
- trough FEV_1 response on day 170

The symptomatic endpoint was the total score of the Saint George Respiratory Questionnaire (SGRQ) on day 169.

Statistics
The 2 lung-function primary endpoints were analysed for each individual trial (1237.5 and 1237.6), while the SGRQ total score was only tested for the combined data from both trials.
The comparisons for the primary endpoints (assessed after 24 weeks) were first performed for tiotropium + olodaterol 5/5 µg in the following order:

1. Superiority of tiotropium + olodaterol 5/5 µg compared with olodaterol 5 µg for mean FEV_1AUC_{0-3h} response
2. Superiority of tiotropium + olodaterol 5/5 µg compared with tiotropium 5 µg for mean FEV_1AUC_{0-3h} response
3. Superiority of tiotropium + olodaterol 5/5 µg compared with olodaterol 5 µg for mean trough FEV_1 response
4. Superiority of tiotropium + olodaterol 5/5 µg compared with tiotropium 5 µg for mean trough FEV_1 response
5. Superiority of tiotropium + olodaterol 5/5 µg compared with olodaterol 5 µg for mean SGRQ total score using combined data from the 1237.5 and 1237.6 trials
6. Superiority of tiotropium + olodaterol 5/5 µg compared with tiotropium 5 µg for mean SGRQ total score using combined data from the 1237.5 and 1237.6 trials

If the above tests were successful, the comparisons for the primary endpoints were performed for tiotropium + olodaterol FDC 2.5/5 µg vs. olodaterol 5 µg and tiotropium 2.5 µg.

Populations studied
Trial 1237.5
Most patients were male (73.7%), and white (69.5%) or Asian (25.6%). Their mean (SD) age was 64.2 (8.3) years with a mean (SD) smoking history of 46.4 (25.6) pack-years. The mean (SD) pre-bronchodilator FEV_1 was 1.209 L (43.9% of predicted normal), mean (SD) FEV_1/FVC of 44.6% (11.5); the mean (SD) post-bronchodilator FEV_1 was 1.380 (0.5) L (50.1% of predicted normal); with a mean (SD) FEV_1 reversibility of 16% (14) of baseline after the inhalation of 400 µg salbutamol.
Patients were classified as COPD GOLD II (50%), COPD GOLD III (39%), or COPD GOLD IV (11%).

A total of 2624 patients were randomized. The FAS analyses included 2622 patients: olodaterol 5 µg 528 patients, tiotropium 2.5 µg 524 patients, tiotropium 5 µg 526 patients, tiotropium + olodaterol 2.5/5 µg 522 patients and tiotropium + olodaterol 5/5 µg 522 patients.

Trial 1237.6
Most patients were male (72.0%), and either white (72.5%) or Asian (25.0%). Their mean (SD) age was 63.8 (8.4) years, with a mean (SD) smoking history of 45.9 (25.4) pack-years. The mean pre-

bronchodilator FEV_1 at screening was 1.197 L (43.5% of predicted normal), with a mean pre-bronchodilator FEV_1/FVC of 44.2%. The mean (SD) post-bronchodilator FEV_1 was 1.368 (0.51) L (49.8% of predicted normal), with a mean (SD) FEV_1 reversibility of 17% (14) of baseline after inhalation of 400 µg salbutamol. Patients were classified as COPD GOLD II (50%), COPD GOLD III (38%) or COPD GOLD IV (12%).

A total of 2539 patients were randomized. The FAS included 2528 patients: olodaterol 5 µg (507) patients, tiotropium 2.5 µg 505 patients, tiotropium 5 µg 503 patients, tiotropium + olodaterol 2.5/5 µg 508 patients and tiotropium + olodaterol 5/5 µg 505 patients.

Results

Table 4 overview of the Efficacy outcome measures of the phase III programme - comparison of doses (FAS)

Pivotal trials 1237.5 and 1237.6

	Tio + Olo 5/5 µg		**Tio + Olo 2.5/5 µg**	
Trials 1237.5/6	**1237.5**	**1237.6**	**Trial 1237.5**	**1237.6**
FEV_1AUC_{0-3h} (l) day 169*	Adj. mean (SE)	Adj. mean (SE)	Adj. mean (SE)	Adj. mean (SE)
vs. Olo 5 µg	0.123 (0.012)	0.132 (0.013)	0.109 (0.012)	0.121 (0.012)
vs. Tio 2.5 µg			0.093 (0.012)	0.131 (0.012)
vs. Tio 5 µg	0.117 (0.012)	0.103 (0.012)	0.102 (0.012)	0.091 (0.012)
T+O 5/5 µg vs. T+O 2.5/5 µg			0.014 (0.012)	0.012 (0.012)
Trough FEV_1 (L) day 170*				
vs. Olo 5 µg	0.082 (0.012)	0.088 (0.013)	0.058 (0.012)	0.067 (0.013)
vs. Tio 2.5 µg			0.029 (0.012)	0.062 (0.013)
vs. Tio 5 µg	0.071 (0.012)	0.050 (0.013)	0.046 (0.012)	0.029 (0.013)
T+O 5/5 µg vs. T+O 2.5/5 µg			0.024 (0.012)	0.021 (0.013)
Combined set trial 1237.5/6				
	Tio + Olo 5/5 µg		**Tio + Olo 2.5/5 µg**	
SGRQ total score*[1]	**Adj. mean (SE)**	**p-value**	**Adj. mean (SE)**	**p-value**
vs. Olo 5 µg	-1.693 (0.553)	0.0022	-1.031 (0.552)	0.0620
vs. Tio 2.5 µg			-0.456 (0.548)	0.4051
vs. Tio 5 µg	-1.233 (0.551)	0.0252	-0.571 (0.550)	0.2988
T+O 5/5 µg vs. T+O 2.5/5 µg			-0.662 (0.545)	0.2249
SGRQ Responder rate (%)[2]	**Odds (SE)**	**p-value**	**Odds ratio (SE)**	**p-value**
vs. Olo 5 µg	1.67 (0.15)	<0.0001	1.40 (0.13)	0.0002
vs. Tio 2.5 µg			1.16 (0.11)	0.1071
vs. Tio 5 µg	1.43 (0.13)	0.0001	1.20 (0.11)	0.0453
T+O 5/5 µg vs. T+O 2.5/5 µg			1.19 (0.11)	0.0565
TDI score	**Adj. mean (SE)**	**p-value**	**Adj. mean (SE)**	**p-value**
vs. Olo 5 µg	0.420 (0.135)	0.0019	0.416 (0.135)	0.0020
vs. Tio 2.5 µg			0.290 (0.134)	0.0307
vs. Tio 5 µg	0.356 (0.135)	0.0082	0.352 (0.135)	0.0088
T+O 5/5 µg vs. T+O 2.5/5 µg			0.003 (0.134)	0.9801
TDI Responder rate[3]	**Odds ratio (SE)**	**p-value**	**Odds ratio (SE)**	**p-value**
vs. Olo 5 µg	1.31 (0.12)	0.0026	1.33 (0.12)	0.0014
vs. Tio 2.5 µg			1.20 (0.11)	0.0439
vs. Tio 5 µg	1.19 (0.11)	0.0546	1.21 (0.11)	0.0356
T+O 5/5 vs. T+O 2.5/5			0.98 (0.09)	0.8567
FEV_1 AUC_{0-24h} L day 169	**Adj. mean (SE)**	**p-value**	**Adj. mean (SE)**	**p-value**
vs. Olo 5 µg	0.098 (0.021)	<0.0001	0.051 (0.021)	0.0136

vs. Tio 2.5 µg			0.075 (0.021)	0.0003
vs. Tio 5 µg	0.106 (0.022)	<0.0001	0.059 (0.022)	0.0065
T+O 5/5 µg vs. T+O 2.5/5 µg			0.047 (0.021)	0.0277
Exacerbations (combined set)				
	Tio + Olo 5/5 µg		**Tio + Olo 2.5/5 µg**	
Moderate-to-severe COPD exacerbation				
Time to first exacerbation	**Hazard ratio**	**p-value**	**Hazard ratio**	**p-value**
vs. Olo 5 µg	0.81 (0.06)	0.0091	0.74 (0.06)	0.0002
vs. Tio 5 µg	0.93 (0.08)	0.3857	0.85 (0.07)	0.0541
T+O 5/5 µg vs. T+O 2.5/5 µg			1.10 (0.09)	0.2845
Annual rate[4]	**Risk ratio (SE)**	**p-value**	**Risk ratio (SE)**	**p-value**
vs. Olo 5 µg	0.83 (0.07)	0.0332	0.69 (0.06)	<0.0001
vs. Tio 5 µg	0.92 (0.08)	0.3631	0.76 (0.07)	0.0021
T+O 5/5 µg vs. T+O 2.5/5 µg			1.21 (0.11)	0.0286
severe COPD exacerbations				
Time to first exacerbation	**Hazard ratio (SE)**	**p- value**	**Hazard ratio (SE)**	**p-value**
vs. Olo 5 µg	1.06 (0.20)	0.7519	0.78 (0.16)	0.2225
vs. Tio 5 µg	1.29 (0.25)	0.2052	0.95 (0.20)	0.7976
T+O 5/5 µg vs. T+O 2.5/5 µg			1.35 (0.26)	0.1222
Annual rate	**Risk ratio (SE)**	**p-value**	**Risk ratio (SE)**	**p-value**
vs. Olo 5 µg	0.93 (0.19)	0.7210	0.66 (0.14)	0.0585
vs. Tio 5 µg	1.14 (0.24)	0.5406	0.81 (0.18)	0.3480
T+O 5/5 µg vs. T+O 2.5/5 µg			1.40 (0.30)	0.1186

*[1]Primary outcome measure reduction of the score indicates an improvement, the difference between the fixed dose combinations and the monocomponents are all statistically significant for the high dose (Tio+ Olo 5/5 µg), but not for the low dose (Tio + Olo 2.5/5 µg) ;
2. a responder is defined as patients with an improvement ≥ 4; 3 a responder is defined as a patient with an improvement ≥1;4 annual rate is exacerbations per patient years.; Adj. = adjusted; SE is standard error; Olo = olodaterol, Tio = tiotropium; T+O= tiotropium+ olodaterol

- FEV_1AUC_{0-3h}

The primary efficacy analysis was the FEV_1AUC_{0-3h} response. All active treatments showed an improvement from baseline. The largest improvement was observed with the high-dose combination (tiotropium + olodaterol 5/5 µg) in both trials.

The fixed dose combinations show a statistically significant improvement over the monocomponents (including tiotropium 5 µg) in both trials. The difference between the fixed dose combinations was numerically in favour of the high-dose combination.

- Trough FEV_1

The obtained results for the trough FEV_1 are comparable to FEV_1AUC_{0-3h}. All treatments showed an improvement from baseline; the largest improvement was observed with the high-dose combination.

The fixed dose combinations show a statistically significant improvement over the monocomponents in both trials; also for tiotropium + olodaterol 2.5/5 µg superiority over tiotropium 5 µg is shown. The difference between the fixed dose combinations was numerically in favour of the high-dose combination.

- Saint George Respiratory Questionnaire

The third primary endpoint of the pivotal studies was the total score in the Saint George Respiratory Questionnaire (SGRQ) after 24 weeks for the combined dataset. Both trials showed a consistent effect, an improvement of the SGRQ total score on day 169 compared to baseline.

In the combined dataset, for tiotropium + olodaterol 5/5 µg, the treatment difference in the SGRQ total score was -1.69 points compared with olodaterol 5 µg, -1.23 points compared with tiotropium 5 µg (p=0.002 and p=0.025, respectively). Statistical superiority over the individual components was demonstrated.

However, tiotropium + olodaterol 2.5/5 µg failed to show statistical superiority over the monocomponents with regard to the SGRQ total score on day 169. The treatment difference in the SGRQ total score was -1.03 points compared with olodaterol 5 µg (p=0.06), and -0.46 points compared with tiotropium 2.5 µg (p=0.4). No superiority over tiotropium 5 µg was shown either.

SGRQ responder rate
An SGRQ responder was defined as a patient with an improvement ≥ the minimal clinically important difference of 4 units from baseline. The odds ratio between tiotropium + olodaterol 5/5 µg and the monocomponents was nominally statistically significant since these treatment comparisons were not alpha-protected.

The responder rates showed a similar effect as the SGRQ total score. The highest scores were observed with the fixed-dose combination in both trials. On day 169, the combined responder rates were highest for the fixed dose combinations: olodaterol 5 µg (44.8%), tiotropium 2.5 µg (49.6%), tiotropium 5 µg (48.7%), tiotropium + olodaterol 2.5/5 µg (53.2%) and tiotropium + olodaterol 5/5 µg (57.5%).

The odds ratio for being an SGRQ responder between tiotropium + olodaterol 5/5 µg and the monocomponents was nominally statistically significant (p=<0.001). Tiotropium + olodaterol 5/5 µg vs. olodaterol 5 µg: odds ratio 1.67 (nominal p=<0.001); tiotropium + olodaterol 5/5 µg vs. tiotropium 5 µg: odds ratio 1.43 (nominal p=0.0001). Tiotropium + olodaterol 2.5/5 µg failed to show a nominally statistically significant improvement over tiotropium 2.5 µg: odds ratio 1.16 (nominal p=0.11).

- Mahler Transient Dyspnoea Index

In the pivotal studies, all treatments demonstrated a Transition Dyspnea Index (TDI) score > 1, the minimal clinically important difference. The descriptive statistics show a nominally statistically significant difference between tiotropium + olodaterol 5/5 µg and the monocomponents. This is supported by the responder analyses for the odds ratio between tiotropium + olodaterol 5/5 µg vs. olodaterol. Similar results were observed for tiotropium + olodaterol 2.5/5 µg against its monocomponents and tiotropium 5 µg.

- Exacerbations

Exacerbations were included as a further efficacy parameter. The trials 1237.5 and 1237.6 were of 52 week duration, which is sufficient duration to examine exacerbations. A moderate exacerbation was defined by the need for systemic steroids or antibiotics. A severe exacerbation required hospitalisation.

In the combined dataset, the percentage of patients with at least one moderate-to-severe COPD exacerbation was lower for the fixed dose combination than the monocomponents: 31.9% for olodaterol 5 µg, 29.6% for tiotropium 2.5 µg, 28.8% for tiotropium 5 µg, 25.8% for tiotropium + olodaterol 2.5/5 µg and 27.7% for tiotropium + olodaterol 5/5 µg.

In the combined dataset, the percentage of patients with at least one severe COPD exacerbation was 5.4% (n=56) for olodaterol 5 µg, 5.2% (n=54) for tiotropium 2.5 µg, 4.5% (n=47) for tiotropium 5 µg, 4.5% (n=46) for tiotropium + olodaterol 2.5/5 µg and 5.9% (n= 61) for tiotropium + olodaterol 5/5 µg.
For tiotropium + olodaterol 5/5 µg, the risk of having a severe exacerbation was inconsistent between trials 1237.5 and 1237.6. The combined risk ratio showed comparable incidences between the fixed dose combination and the monocomponents.

- **Supportive data: 12 h bronchodilation profile after 24 weeks of treatment**

- 12 h-response to support bronchodilation over the day

The period of maximal response (FEV_1AUC_{0-3h}) and trough FEV_1 are used as surrogate parameters to reflect the 24 h trial profile under trial conditions. Further characterisation of the bronchodilation profile of tiotropium + olodaterol was conducted in a subgroup of 890 patients who continued lung function measurements up to 12 h post-dose on day 169 and t=24 h on day 170. The FEV_1 AUC_{0-24h} results in the trial 1237.5 and 1237.6 combined dataset are shown in Table 5.
The fixed dose combinations showed a nominally statistically significant improvement over the monocomponents. The difference between tiotropium + olodaterol 5/5 µg and tiotropium + olodaterol 2.5/5 µg was also nominally statistically significant.

Table 5 Treatment comparisons for adjusted mean FEV_1 AUC_{0-24h} response (L) after 24 weeks: - 12 h PFT set.

Treatment	Adjusted mean (SE) difference	P-value	95% CI
Tio + Olo 5/5 µg – Olo 5 µg	0.098 (0.021)	<.0001	(0.057, 0.139)
Tio + Olo 5/5 µg – Tio 5 µg	0.106 (0.022)	<.0001	(0.063, 0.149)
Tio + Olo 2.5/5 µg – Olo 5 µg	0.051 (0.021)	0.0136	(0.010, 0.091)
Tio + Olo 2.5/5 µg – Tio 2.5 µg	0.075 (0.021)	0.0003	(0.035, 0.116)
Tio + Olo 2.5/5 µg – Tio 5 µg	0.059 (0.022)	0.0065	(0.016, 0.101)
Tio + Olo 5/5 µg – Tio + Olo 2.5/5 µg	0.047 (0.021)	0.0277	(0.005, 0.089)

Adjusted mean (SE) are obtained from fitting an ANCOVA model with categorical effect of treatment and baseline as covariate.
Tio+Olo= tiotropium + olodaterol; Olo = olodaterol; Tio= tiotropium

- Trial 1237.20

Study 1237.20 was a multicentre, multinational study to characterize the 24 h bronchodilation profile of the tiotropium + olodaterol combination after 6 weeks of treatment. The study had a double-blind, randomised incomplete crossover design and was active- and placebo-controlled. After a run-in period of 2 weeks, patients were randomized to 4 out of the 6 possible treatments: tiotropium + olodaterol 2.5/5 µg, tiotropium + olodaterol 5/5 µg, tiotropium 2.5 µg, tiotropium 5 µg, olodaterol 5 µg or placebo. The treatment periods were separated with a washout period of 3 weeks.

The primary endpoint was the FEV_1 AUC_{0-24h} response after 6 weeks of treatment. Key secondary endpoints were FEV_1 AUC_{0-12h} response and FEV_1 AUC_{12-24h} response after 6 weeks of treatment. Secondary outcomes included the trough FEV_1 response, after 6 weeks of treatment. The fixed dose combinations show a sustained 24 h bronchodilation over both monocomponents and placebo. The results are presented below in Table 5.

Table 6 Results of supportive study 1237.20 (24 h bronchodilation profile)

24 h bronchodilation profile				
Trial 1237.20 day 43	**Tio + Olo 2.5/5 µg**		**Tio + Olo 5/5 µg**	
FEV_1 AUC_{0-24h}	**Adj. mean (SE)**	**P-value**	**Adj. mean (SE)**	**P-value**
vs. placebo	0.277 (0.015)	<0.0001	0.280 (0.014)	<0.0001
vs. Olo 5 µg	0.111 (0.014)	<0.0001	0.115 (0.014)	<0.0001
vs. Tio 2.5 µg	0.124 (0.014)	<0.0001		
vs. Tio 5 µg	0.107 (0.014)	<0.0001	0.110 (0.014)	<0.0001
T+O 5/5 vs. T+O 2.5/5	0.003 (0.014)	0.8238		
Trough FEV_1 day 43	**Adj. mean (SE)**	**P-value**	**Adj. mean (SE)**	**P-value**
vs. placebo	0.201 (0.017)	<0.0001	0.207 (0.017)	<0.0001
vs. Olo 5 µg	0.086 (0.017)	<0.0001	0.092 (0.017)	<0.0001
vs. Tio 2.5 µg	0.101 (0.017)	<0.0001		
vs. Tio 5 µg	0.073 (0.017)	<0.0001	0.079 (0.017)	<0.0001
T+O 5/5 vs. T+O 2.5/5	0.006 (0.017)	0.7317		

➢ **Supportive studies 1237.13, 1237.14 and 1237.15: exercise endurance studies**

- Design

The MAH conducted three additional studies to provide evidence for the claim that the fixed-dose combination improves exercise performance.
Two replicate studies (1237.13 and 1237.14) were double blind, randomised, active- and placebo-controlled, incomplete crossover trials. Each treatment period had a duration of 6 weeks, separated by a washout of 3 weeks. The studies had two primary endpoints: the inspiratory capacity (IC) at rest 2 h after inhalation and the endurance time during constant work cycle ergometry to symptoms limitation. Both endpoints were measured after 6 weeks of treatment.

The primary endpoint IC at rest was introduced late in the trial (but prior to database lock and unblinding). The original efficacy parameter, IC at isotime, could not be adequately assessed due to the incomplete crossover design.

A separate, additional 12 week exercise study (1237.15) was conducted comparing both fixed dose combinations with placebo. In contrast to the other exercise studies, this study was parallel group designed, and therefore, a longer duration of treatment was considered possible (12 weeks). The primary aim was to show the exercise improvement compared to placebo after 12 weeks of treatment while a secondary aim was to compare the exercise improvement in COPD patients across different exercise modalities (cycling and walking) [sub-group of patients].

The exercise studies included patients based on spirometric values (post-bronchodilator FEV_1 >= 30% predicted normal and < 80% of predicted normal). The included patient population was sensitive to show statistically significant improvements in exercise performance compared to placebo, but was not sensitive to show statistically significant improvements in exercise performance between the fixed dose combinations.

The primary efficacy parameter was the treatment ratio.

- Results

Table 7 Results of supportive trials 1237.13, 1237.14 and 1237.15 (exercise endurance tests)

Exercise endurance tests				
	Tio + Olo 2.5/5 µg		**Tio + Olo 5/5 µg**	
Exercise improvement Constant Work Rate Cycle Ergometry (CWRCE)				
6 weeks	Treatment ratio	p-value	Treatment ratio	p-value
vs. placebo trial 1237.13	26%	<0.0001	21%	<0.0001
vs. placebo trial 1237.14	12%	0.0003	13%	<0.0001
vs. placebo trial 1237.15	22%	0.0004	23%	0.0002
12 weeks				
vs. placebo trial 1237.15	9%	0.1419	14%	0.0209
Exercise improvement endurance shuttle walk test (ESWT) after 12 weeks of treatment				
Vs. placebo trial 1237.15	21%	0.0562	21%	0.0552
Inspiratory capacity at rest	Adj. mean (SE)	p-value	Adj mean (SE)	p-value
vs. placebo trial 1237.13	0.218 (0.027)	<0.0001	0.244 (0.027)	<0.0001
vs. placebo trial 1237.14	0.274 (0.025)	<0.0001	0.265 (0.025)	<0.0001

Exercise endurance time

In the exercise studies 1237.13 and 1237.14, the fixed dose combinations showed statistically significant improvements as compared with placebo in the treatment ratio. The endurance time in seconds was also provided. The improvement of the fixed dose combination over placebo was considered clinically relevant when measured in seconds e.g. Tio + Olo 5/5 vs. placebo adjusted mean (SE) 91.56 (18.42) and 74.71 (18.50) seconds. The differences between the fixed dose combinations and the monocomponents were not consistently statistically significant.

The improvement in the exercise endurance shuttle walking test in the sub-group of patients, the improvement in the exercise endurance between placebo and the fixed dose combination did not reach statistical significance. More patients in the placebo group than in the active treatment groups prematurely left the trial, which may have contributed to the effect.

Inspiratory capacity

The improvement over placebo in the inspiratory capacity at the end of the treatment was for the high fixed dose combination 0.244 L and 0.265 L (p<0.0001). This improvement is in line with what was shown for other LABA/LAMA combinations (Anoro 198 mL and 0.238 mL, EMEA/H/C002751). A lower statistically significant difference was observed between the fixed dose combination and the monocomponents.

- **Additional analyses**

The MAH provided also a subgroup analysis according to baseline reversibility for the pivotal studies 1237.5 and 1237.6. These studies included a subgroup of 1829 patients (36%) that showed improvements in FEV_1 > 12% and 200 mL upon reversibility testing. The proportion of patients with reversible disease is comparable to previous trials conducted in COPD with budesonide/formoterol and in the trials included in the clinical package of the recently approved LABA/LAMA combinations umeclidinium/viladaterol and formoterol/aclidinium (EMEA/H/C/2751, EMEA/H/C/3751).
A greater improvement in lung function parameters was observed in those patients exhibiting greater reversibility at the beginning of the study than in those patients whose airways obstruction showed less reversibility. Patients with reversible disease showed also a larger improvement in the SGRQ or TDI, although the patients with irreversible disease also showed improvements. The observed improvement was nominally statistically significant with the high fixed dose combination compared to olodaterol 5 µg, but not with tiotropium 5 µg.

A subanalysis according to the severity of GOLD COPD was also conducted. The lung function shows a greater improvement in those patients with moderate COPD compared to those with severe COPD, but the symptomatic improvements were larger in patients with more severe disease. Patients with severe disease however, are not known to show large improvements in lung function.

IV.5 Clinical safety

The safety profiles of the two monotherapies have been previously characterised and are well known.

The safety profile of the fixed dose combination is based on 2664 COPD patients. The MAH conducted two large phase III studies comparing the FDC with the monoproducts. Long-term safety data was provided by > 800 patients.
In addition, one 12-week placebo controlled and three 6-week placebo-and active-controlled incomplete crossover trials were conducted, making a comparison with placebo possible.

In general, the incidence of adverse events was comparable between the fixed dose combination and the monocomponents. No dose ordering was observed in adverse events between the two fixed-dose combinations. The incidence of adverse events of the FDC was generally comparable with the highest incidence of one of the monocomponents. The number of (serious) adverse events was comparable to placebo. The most frequently reported adverse event was COPD.

Due to the pharmacological working mechanism, both tiotropium and olodaterol may have cardiac side effects. As they have a different mode of action, the question rises whether there might be an additive effect on the cardiac safety profile. Some side effects may overlap, but no increased incidence was observed in the treatment emergent adverse events tachycardia or palpitations.

Patients at high risk of cardiac events like paroxysmal tachycardia (>100 beats per minute), myocardial infarction within 1 year of the screening visit, unstable or life-threatening cardiac arrhythmia or hospitalisation for heart failure within the past year were excluded from participation.
In the subgroup of patients with a history of cardiac disorder, a higher incidence of cardiac arrhythmias was observed with the fixed dose combination compared to the monocomponents. Nevertheless the exposure adjusted risk ratio failed to show an increased risk.
The incidence of patients prematurely discontinuing the trials due to cardiovascular events was comparable for the high fixed dose combination compared with the monocomponents, but slightly higher for the low fixed dose combination.

The overall (fatal) MACE events were balanced in the treatment groups. The overall incidence of serious adverse events was comparable between the different treatments. An external adjudicated committee failed to identify differences between the adjudicated incidences of the composite endpoint of respiratory related, cardiovascular related cerebrovascular related or other related SAE endpoints The number of deaths was also comparable among the different treatment groups in the pivotal trials.

Beta2-agonists may prolong the QTc interval. The incidence of ECG with QTc prolongation was comparable between olodaterol and the fixed dose combinations. Also, comparable incidences were observed for the patients with hyperglycaemia and hypokalaemia.

The long term cardiovascular safety profile between the fixed dose combination and the mono-components is comparable. The comparison with placebo is limited to the 12-week and 6-week safety database (n=1209). These studies generally included a patient group with a more favourable cardiovascular safety profile, because they were selected on being able to conduct an exercise test. No increased risk was identified from this limited short-term database.

Other important adverse events or this fixed dose combination are respiratory infections and COPD exacerbations. The adverse events related to respiratory tract infection were numerically in favour of the tiotropium monotherapy arms compared with the fixed-dose combinations. The incidences between the fixed dose combination and olodaterol, however, were comparable.

Exacerbations are a major burden in the treatment of COPD. Exacerbations were included as a secondary endpoint. Both fixed dose combinations showed a lower incidence of moderate to severe COPD exacerbations compared to the monocomponents. The effect for the severe COPD exacerbation was however inconsistent among the two pivotal trials: Tio + Olo 5/5 µg showed a higher incidence of severe COPD exacerbations than the monocomponents in one study, but a comparable incidence in the other pivotal study. The observed differences were highest in the patient group with reversible disease.

In an adjudicated analysis, both the low and high dose tiotropium + olodaterol (2.1%, n=22 and 1.7%, n=18) showed a higher incidence of the SAE pneumonia compared with the monocomponent tiotropium (0.9%, n=9). The incidence for the high dose tiotropium + olodaterol 5/5 µg was comparable with olodaterol (1.4%, n=15).
The incidence of the SAE pneumonia was in both the general and adjudicated analyses low with tiotropium 5 µg arm (n=9) compared with the other treatments (range n=15-22), including tiotropium 2.5 µg (n=15). No dose ordering for the SAE pneumonia was observed between the two fixed-dose combinations. Therefore, the low incidence observed for tiotropium is most likely reflecting variability.

There are no clinical data to support the concomitant treatment with roflumilast for maintenance therapy. The effect of roflumilast on top of monotherapy with tiotropium or LABAs was established in the clinical development program for roflumilast and is well documented. The interaction between roflumilast and the combination is not known; olodaterol was not an approved LABA during the clinical development of roflumilast.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Spiolto Respimat.

Table 8 Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in the RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
None	N/A	N/A
Important Potential Risks		
Blood and lymphatic system disorders	Routine risk minimisation by routine pharmacovigilance	None
Blood glucose increased	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.4, 4.8, and 4.9	None
Psychiatric disorders	Routine risk minimisation by routine pharmacovigilance	None
Syncope	Routine risk minimisation by routine pharmacovigilance	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Cardiac disorders (myocardial ischaemia, cardiac arrhythmia, cardiac failure)	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.4, 4.8, and 4.9	None
Cardiac mortality	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.4, 4.8, and 4.9	None
Vascular disorders (aneurysm)	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.4, 4.8, and 4.9	None
Renal failure	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.2, 4.4, and 4.8	None
Overdose	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC section 4.9	None
Hypokalaemia	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.4, 4.5, and 4.9	None
Off-label use in asthma	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC section 4.4	None
Missing Information		
Long-term data beyond 1 year of use (adverse cardiovascular outcome)	Routine risk minimisation by routine pharmacovigilance	None
Pregnant and breast-feeding women	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC section 4.6	None
Patients with a recent history of: - myocardial infarction, - unstable or life-threatening cardiac arrhythmia - paroxysmal tachycardia - decompensated heart failure	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC section 4.4	None
Patients with hepatic impairment	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC section 4.2	None
Patients with severe renal impairment	Routine risk minimisation by routine pharmacovigilance and by means of labelling in SmPC sections 4.2 and 4.4	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

Periodic Safety Update Report (PSUR)
The Marketing Authorisation Holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

Efficacy conclusion

The clinical programme was designed according to the COPD guideline (EMA/CHMP/483572/2012-corr-1) and the guideline on fixed dose combinations (CHMP/EWP/240/95 Rev.1). The COPD guideline requires at least two co-primary outcome measures: a lung function improvement and a symptomatic improvement. The fixed-dose guideline requires that each substance must show a documented therapeutic contribution to the combination. The fixed-dose combination must, therefore, show a clinically relevant improvement in the lung function and symptomatic improvement over the monocomponents.

The pivotal studies 1237.5 and 1237.6 had two co-primary lung function endpoints: the FEV_1AUC_{0-3h} and the trough FEV_1 response measured at day 169 and day 170 respectively.
Both pivotal trials showed an improvement in the FEV_1AUC_{0-3h} > 100 ml for the fixed dose combination tiotropium + olodaterol 5/5 µg over both separately deployed monocomponents.

The trough FEV_1 is used as a surrogate parameter to measure the 24-h bronchodilation profile. The FDC tiotropium + olodaterol 5/5 µg showed an improvement of 82 mL and 88 mL over olodaterol monotherapy. The improvement over tiotropium 5 µg monotherapy was 71 mL and 50 mL respectively (all p<0.0001).

The fixed-dose combination tiotropium + olodaterol 2.5/5 µg showed an improvement on FEV_1 of 58 mL and 67 mL over olodaterol 5 µg; the improvement over tiotropium 2.5 µg monotherapy was 29 mL and 62 mL; the improvement over tiotropium 5 µg monotherapy was 46 mL and 29 mL (all p<0.02).

The third co-primary endpoint of the pivotal studies was the total score in the Saint George Respiratory Questionnaire (SGRQ) of the combined dataset of the pivotal studies. Only the high dose tiotropium + olodaterol 5/5 µg showed statistically significant improvements compared to the mono-components.

All treatments showed in the pivotal studies a Transition Dyspnea Index (TDI) score > 1 on day 169, the minimal clinically important difference. The descriptive statistics show a nominally statistically significant difference between tiotropium + olodaterol 5/5 µg and the monocomponents. This is supported by the responder analyses for the odds ratio between tiotropium + olodaterol 5/5 µg vs. olodaterol. Similar effects are observed for tiotropium + olodaterol 2.5/5 µg against its monocomponents and tiotropium 5 µg.

The bronchodilation effect of the fixed-dose combinations over the monotherapies was maintained throughout the 52-week observation period.

The fixed dose combination increased the endurance exercise time in the constant work rate exercise cycle ergometry (CWRCE) compared to placebo in three studies.
At week 6, the treatment ratio between tiotropium + olodaterol 5/5 µg and placebo was 21%, 13%, and 23% (all p-values <0.001). This is in line with previous studies conducted with other LABA/LAMA combinations (EMEA/H/C/002751)

The largest improvements in lung function were observed in the patients showing reversible disease on baseline lung function testing, but the benefit remained in the patients who were irreversible. This obervation is in line with the other approved LABA/LAMA combinations (EMEA/H/C002751, EMEA/H/C/003745).

Safety conclusion
The safety profile of the two monocomponents has been previously characterized. There is no evidence of additive effects when the two are combined in one inhaler. The comparison with placebo is limited to one 12 week and two 6 weeks trials, which hampers cross comparison of Spiolto Respimat with other approved LABA/LAMA combinations.
Olodaterol is an approved therapy since 2013. The knowledge regarding the long-term safety profile is limited, but the safety profile of LABAs is well known.

Both olodaterol and tiotropium may have adverse effects on the cardiovascular system. Differences between the fixed-dose combinations and the monocomponents in the adjudicated incidence of respiratory, cardiovascular or cerebrovascular serious adverse events were not identified.

Numerically a higher incidence in the serious adverse event pneumonia was seen with tiotropium + olodaterol compared with tiotropium 5 µg, but not with olodaterol.

Regarding the secondary endpoint exacerbations, the high fixed dose combination Tio + Olo 5 µg/5 µg showed numerical improvements in the number of moderate to severe exacerbations compared with the monocomponents. The effect on the severe exacerbations is inconclusive, because in one study a numerical imbalance in favour of the monocomponents was observed. However, the observed numbers are small.

V. USER CONSULTATION

The MAH performed a test to assess the impact of differences in the Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution package leaflet (PL) to the very similar successfully user tested PL for Striverdi Respimat 2.5 microgram, solution for inhalation. Both products are solutions for inhalation which contain active substances that belong to a group of medicines called long-acting bronchodilators (Striverdi: olodaterol, Spiolto: tiotropium and olodaterol). Both products are used in the indication chronic obstructive pulmonary disease (COPD).

Due to the additional active substance tiotropium in the product, the Spiolto Respimat PL contains additional information in section 2, 3 and especially section 4 of the leaflet. A focus test was performed to address sections in the daughter leaflet (Spiolto) which do not share enough similarities with the parent PL (Striverdi) to enable bridging. To comply with the European Commission Directive 2001/83 EC, modified 2004/27/EC (Articles 59 (3) and 61 (1)), a readability test was performed focussing on sections 2, 3 and 4 of the Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution PL. Ten participants were selected for focus test interviews. The results were satisfactory.
The bridging report and focus test submitted have been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Spiolto Respimat 2.5 microgram/2.5 microgram, inhalation solution has a proven chemical-pharmaceutical quality. Adequate information has been provided on the development, manufacture and control of the drug product. The non-clinical documentation in support of this fixed dose combination containing well known active substances is satisfactory.

The fixed dose combination showed statistically significant improvements in the lung function parameters over the monocomponents. The observed improvement with the high dose combination are in line with currently approved other fixed dose combinations and can be regarded as clinically relevant.

The adverse events of tiotropium and olodaterol have been previously characterised. From the clinical programme, there is no evidence that there is an additive effect when administered together via the same inhaler.

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

In the Board meeting of 4 September 2014 this application was discussed. With regard to the clinical data, the Board concluded that an improved bronchodilation effect was demonstrated for Spiolto Respimat compared to the monocomponents. Moreover, an improved effect on exacerbations was observed. The wording of the indication was also discussed. The Board expressed its positive opinion on the application for Spiolto Respimat 2.5/2.5 micrograms for the indication ‘maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)’.

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

The member states, on the basis of the data submitted, considered that Spiolto Respimat 2.5/2.5 micrograms, solution for inhalation demonstrated adequate evidence of efficacy for the approved indication, and an acceptable level of safety.
The member states considered the benefit/risk profile satisfactory and therefore granted a marketing authorisation. The decentralised procedure was finished with a positive outcome on 20 May 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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