CBG MEB

Public Assessment Report

Scientific discussion

Srivasso 18 microgram, inhalation powder, hard capsule

(tiotropium bromide)

NL/H/3137/001/DC

Date: 27 January 2016

This module reflects the scientific discussion for the approval of Srivasso 18 micrograms, inhalation powder, hard capsule. The procedure was finalised on 24 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse event
BDI	Baseline Dyspnea Index
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CV	Coefficient of Variation
DPI	Dry Powder Inhaler
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ET	Exercise Tolerance
EU	European Union
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GI	Gastrointestinal
HR	Hazard Ratio
HRQoL	Health-related quality of life
ICH	International Conference of Harmonisation
ICS	Inhaled Corticosteroids
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MCID	Minimal Clinical Important Difference
MDI	Metered dose inhaler
MEB	Medicines Evaluation Board in the Netherlands
MRP	Mutual Recognition Procedure
NfG	Note for Guidance
PAR	Public Assessment Report
PEFR	Peak Expiratory Flow Rate
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QTcF	QT interval using Fridericia's formula
QTcN	Population-specific QT correction
RH	Relative Humidity
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SVC	Slow Vital Capacity
TDI	Transition Dyspnea Index
TSE	Transmissible Spongiform Encephalopathy
VA	Alveolar Volume
VSRQ	Visual Simplified Respiratory Questionnaire

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Srivasso 18 micrograms, inhalation powder, hard capsule from Boehringer Ingelheim International GmbH.

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

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

Tiotropium is a long acting bronchodilating drug. The bronchodilating effect is due to slow dissociating binding and antagonism at muscarinic receptors. Following systemic administration, tiotropium induces antimuscarinic effects in a discernible sequence of sensitivity. Tiotropium appears to be two to four-fold more potent than ipratropium bromide. It has a slower onset of action. The duration of action for tiotropium is over 24 hours compared to 6 hours for ipratropium bromide. Tiotropium does not cross the blood-brain barrier and therefore does not elicit antimuscarinic CNS-effects. The expected adverse events are those of any anti-cholinergic drug; such as dry mouth, constipation and urinary retention.

This decentralised procedure concerns a duplicate application referring to the original product Spiriva 18 micrograms, inhalation powder, hard capsule (NL License RVG 26191), which has been registered in the Netherlands by Boehringer Ingelheim International GmbH since 9 October 2001. Subsequently, the product was registered in other EU countries via the Mutual Recognition Procedure (MRP) (NL/H/0299/001).

The application for Srivasso is made as a full application under Art 8(3) of Directive 2001/83/EC.

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

The clinical documentation included in this dossier consists of the dossier submitted for the initial marketing authorization application for Spiriva (NL/H/0299/001/MR). This application was supported by a full dossier containing ten pharmacokinetic studies, eight pharmacodynamic studies, four large pivotal clinical one-year studies, two large salmeterol-compared 6-month studies and four additional studies.
The Spiriva program was sufficient: the design of the pivotal studies is in accordance with the Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD of the CPMP (CPMP/EWP/562/98). The study duration was long enough and the amount of participants is large enough.
Two placebo-controlled and two active comparator studies were performed (double dummy). The chosen selection criteria provide the participation of “true” COPD patients, and the exclusion of asthma patients. The comparators were acceptable at that time.
Allover, the clinical program is sufficiently compelling for current standards. The supportive trials are conducted with salmeterol. In addition several relevant studies are submitted that were performed after registration addressing several important domains of COPD. An overview of the clinical dossier is given in section IV of this report.

II. QUALITY ASPECTS

II.1 Introduction

Srivasso 18 micrograms is a light green hard capsule containing the inhalation powder, with the product code TI 01 and company logo printed on the capsule.
Each capsule contains 22.5 microgram tiotropium bromide monohydrate equivalent to 18 microgram tiotropium.

The delivered dose (the dose that leaves the mouthpiece of the HandiHaler device) is 10 microgram tiotropium.

The hard capsules are packed in Aluminium/PVC/Aluminium peel-off blisters containing 10 capsules. The HandiHaler is a single dose inhalation device made from plastic materials (ABS) and stainless steel.

Lactose monohydrate is used as excipient.

II.2 Drug Substance

Tiotropium bromide monohydrate is a well-known active substance, described in the European Pharmacopoeia. The drug substance is a white or yellowish-white powder or crystals, sparingly soluble in water, soluble in methanol, and practically insoluble in methylene chloride. It is an ester formed of dithienylglycolic acid and of a quarternary tropanol derivative. The anion is bromide, and the substance contains one molecule of crystal water. The substance has no chiral centre. Tiotropium bromide monohydrate is a hydrophilic substance.

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 tests and specifications of the Ph. Eur. monograph are applied supplemented with a number of additional tests.
Batch analysis data of 3 production-scale batches demonstrating compliance to the specification have been included in the dossier.

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 product has been described, the choice of excipients is justified and their functions explained. Compatibility of the drug substance with the excipients was demonstrated. In order to penetrate the airways ducts of the lungs, particle size of the active ingredient is critical. As tiotropium bromide monohydrate cannot be produced directly as microfine powder, the active ingredient is micronised. The pharmaceutical development of the product has been adequately performed. Clinical phase III studies have been performed with the final formulation. The formulation is characterized by a delivered dose of about 10 mcg tiotropium and a fine particle dose in the range of 3 mcg tiotropium.
HandiHaler is the dedicated inhalation device for tiotropium inhalation powder. According to EU directive 93/42/EEC of 14 June 1993, the HandiHaler is a medical device. It has been categorised as class I device. A CE mark to indicate its compliance with the EU directive has been affixed.

Manufacturing process
The powder is manufactured by dry mixing. Validation studies of the micronized drug substance and drug product manufacturing have been performed on three full scale batches. The manufacturing process has been described in sufficient detail including in-process controls and relevant process parameters

Control of excipients
Lactose monohydrate is adequately controlled, in line with the requirements of the current Ph.Eur monograph. A specification for the gelatin capsules has been provided.

Quality control of drug product
The product specification includes tests for appearance, dimensions, odour, identification of drug substance, particulate contamination, water content, assay of drug substance, degradation products, uniformity of delivered dose, fine particle dose and microbiological purity. The shelf-life criteria for fine particle dose, active substance content and related substances deviate from the criteria applied for release. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from recent batches confirm the quality of the product.

Stability of drug product
The approved shelf life for Spiriva 18 microgram, inhalation powder, hard capsule is 24 months, and the storage conditions are 'Do not store above 25°C' and 'Do not freeze'. For Srivasso the same shelf life and storage conditions are applied. Stability data for recent full scale batches covering the shelf life of 24 months have been included. In-use stability data is included to support the proposed shelf life of 9 days after first opening of the blister.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is sourced under the same conditions as milk collected for human consumption. Therefore, the TSE risk is negligible. Adequate CEPs and TSE declarations for gelatin are in place.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Srivasso 18 micrograms, inhalation powder, hard capsule has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Pharmacodynamic effects
The pharmacodynamic effects of tiotropium bromide have been investigated in established and relevant preclinical *in vitro* and *in vivo* models.

The *in vitro* pharmacodynamic characteristics of tiotropium bromide can be summarized as follows:
- High selectivity towards all muscarinic receptor subtypes (hm1-hm5).
- In comparison with ipratropium slow dissociation from all muscarinic receptor subtypes (hm1-hm5).
- No significant activity towards several other relevant pharmacological receptors.
- Like ipratropium, potent bronchodilator effects.
- Like ipratropium, reversible anticholinergic activity.

The *in vivo* pharmacodynamic studies reveal that tiotropium bromide:
- inhibits ACh-induced bronchospasm in a dose dependent manner.
- provides significant bronchoprotection over 24 hours following daily administration.
- shows a dissociation between bronchoprotective and several systemic anticholinergic effects after inhalation,

- is 1-3 times more potent than ipratropium bromide.
- has a longer duration of action than ipratropium bromide.

In conclusion, the pharmacodynamic studies clearly show that tiotropium bromide is a potent bronchodilator without cardiovascular effects. For comparison tiotropium bromide is 1-3 times more potent than ipratropium, has a marked longer duration of action than ipratropium and acts like ipratropium as a selective and reversible muscarinic receptor antagonist.

Active metabolites
The degradation products of tiotropium bromide show negligible affinity for muscarinic receptors.

General pharmacodynamics
The general pharmacodynamic studies have shown that several systemic anticholinergic effects of tiotropium bromide do not occur after inhalation of therapeutic effective dosages. Not all possible systemic effects were evaluated after inhalation of tiotropium bromide, however in human pharmacology studies tiotropium is well tolerated with known anticholinergic effects manifesting in healthy volunteers at some 2-8 times the recommended therapeutic dose of 18 µg. Effects at doses closer to the therapeutic dose are primarily dry mouth of tolerable intensity.

Product interactions
No *in vitro* studies on product interactions were performed.

III.2 Pharmacokinetics

Absorption
Oral absorption was low in mice, rats and rabbit (< 19%) and higher in dogs (46%). Absorption after single intratracheal instillation in rats was high in the lung (96%) and C_{max} was achieved in 5 min.

Pharmacokinetics after a single dose/repeated administration
Single dose pharmacokinetics of tiotropium bromide were determined in mice, rats, rabbits and dogs and resulted in high plasma drug levels, that declined rapidly. The mass-balance was nearly complete (> 92% in 72 hours). Terminal elimination half-life of the parent is claimed to be less than 10 h in all species in the single dose studies, however when sampling was extended (>24 h) more reliable half-lives of approximately 20 hours were found. Although a small accumulation of tiotropium bromide in certain tissues (but not in plasma) could not be excluded, there is no toxicopathological correlate.

Repeated dose studies showed dose-proportional increase in plasma C_{max} levels following inhalatory administration. In some studies increases in plasma concentrations was noted between the sampling weeks. In several studies tiotropium-positive blood samples from control animals in toxicology studies were found. At the request of the Dutch MEB the MAH reviewed these data again. It was concluded that the positive control samples were not due to inhalation but were attributable to later sample contamination and/or analytical limitations. The lack of adverse clinical, histopathological and toxicological findings indicative of anticholinergic activity confirms the lack of actual drug exposure in control animals; therefore the positive control samples have no impact on the interpretation of the studies.

Distribution in normal and pregnant animals used in reproduction studies
The protein binding of tiotropium bromide was much lower in animal species (16-22%) compared to humans (71%).
A broad and rapid distribution was observed in rats following single intravenous and intratracheal administration of the drug. Following oral administration of the drug radioactivity was only detectable in the contents of the gastrointestinal tract. Drug-related radioactivity crossed the placenta and tissue organ concentrations in the foetus were lower than in maternal tissue. Drug-derived radioactivity was excreted in the milk of lactating rats resulting in milk : plasma ratios of 0.4 (0.5 h) to 18 at 24 h. Approximately 1.9% of the dose was excreted in the milk over two days.

Biotransformation
Hydrolytic cleavage of the ester bond on tiotropium bromide was the main reaction in plasma. The main metabolites N-methylscopine and dithienylglycolic acid were found in all species. After intravenous administration the parent compound was the main component in urine samples in mice,

rats and man. Metabolism occurred mainly in the liver and phase II metabolites were directly excreted into the bile.
There was no evidence of enzyme induction and no evidence of drug interactions. Metabolism of the drug seems to be a much more important clearance mechanism in animal species than in human.

Excretion
Single dose excretion balance studies demonstrated that the majority of radioactivity was recovered in the urine, with the remainder appearing in the faeces following intravenous administration in animals. Excretion in humans was mainly renal but in animal species approximately 30-40% of the dose was excreted in faeces.

III.3 Toxicology

Dose extrapolation
The total tiotropium bromide doses achieved in the inhalatory toxicology studies usually easily exceed the human therapeutic dose. The lowest doses were used in the latter 39 weeks of the second (male) mouse carcinogenicity study, where - based on µg/kg bodyweight/day - average doses achieved were 0.8, 1.9 and 6.7 times the human therapeutic dose. When tiotropium bromide plasma levels measured in toxicology studies after inhalatory administration of tiotropium bromide are compared with the human C_{max} (21.6 pg/ml), plasma levels reached in mid and high dose animals surpass human therapeutic plasma levels by far. However in low dose animals these plasma levels are closer to human therapeutic plasma levels. For example, in the 52-week repeated dose toxicity study in rats, plasma levels in the low dose animals were 1-5 times the C_{max} in humans. In the second mouse carcinogenicity study plasma levels were expected to be too low to be measured. Based on comparisons of doses achieved and plasma levels measured, the MAH concludes that exposure in the toxicology studies greatly exceeded human therapeutic exposure.
Technical and analytical limitations prevented multiple blood sampling in most toxicology studies. Therefore, AUC values were not determined. Thus, plasma levels measured in the toxicology studies 1-30 minutes after exposure, and the human C_{max} value were used to compare systemic exposure in animals and man. This may be considered a conservative method, as plasma values in animals will be highest during or right after exposure. Furthermore, on request of the MEB, the MAH provided a method for estimation of local exposure of tissues in the respiratory tract.

Single dose toxicity
Tiotropium bromide monohydrate has low toxicity in rats and mice after oral administration. Inhalation of tiotropium bromide at dose levels of 40.43 mg/kg (mice), 334.5 mg/kg (rat, the highest dose level), and 3.6 mg/kg (dog, the highest dose level) have low toxicity and caused no deaths, whereas the dose of 131 mg/kg (mice) was toxic and caused deaths. The effects in the acute inhalation toxicity studies were independent of the formulation type used (aerosol, lactose powder). Intravenous doses of $\geq$ 16 mg/kg and $\geq$ 20 mg/kg in mice and rats, respectively, were toxic and caused deaths, whereas intravenous administrations 12.5 mg/kg (mice) and 16 mg/kg (rats) were well tolerated.
Non-lethal dose levels led to clinical signs characteristic for the pharmacological action such as specific signs as 1) dry mouth/nose and 2) mydriasis. Non-specific signs observed were: 1) dyspnea, 2) tremor, 3) ataxia, 4) convulsions, 5) loss of motility, 6) loss of body weight, 7) irregular breathing, 8) vocalisation, 9) prone or lateral position, and 10) increased heart rate.
Based on comparison of effects after single oral and intravenous administration, the toxicity potential of impurity/degradation products was lower or similar to tiotropium bromide.

Repeated dose toxicity
Repeated dose toxicity was studied in mice, rats and dogs. Besides the route intended for clinical use, *i.e.* the inhalatory route, oral and intravenous toxicity was studied as well. Most adverse effects observed in the studies were the result of the systemic effects of a potent anticholinergic agent. Some of these effects were mild of nature, but others were more severe or even fatal. Next to these pharmacodynamic effects pathological changes were observed that were not explained by the pharmacology of tiotropium bromide and should be designated as toxic effects. Below, all relevant effects are grouped by organ system.

Gastro-intestinal tract
Many glands are under cholinergic control, including salivatory glands and other glands of the GI-tract. Reduced secretion of these glands, combined with a reduced motility caused a reduction of intestinal

transit time. A species and strain-specific effect was noted in Fisher-F344 rats, were inhalatory tiotropium bromide administration caused food impaction in the proximal oesophagus, following diminished salivation, followed by asphyxiation (see IIIQ Special toxicity studies). In CD-1 mice (carcinogenicity studies), inhalatory doses of tiotropium bromide similar to those intended for clinical use, caused swollen abdomens, due to dilated intestinal tracts, associated with reactive mucosal hyperplasia and inflammation, ultimately causing premature death.
Dry mouth and obstipation may be considered as the clinically relevant counterparts in humans.

Heart
Tachycardia, a known anticholinergic effect was observed in many studies. In the one-year inhalatory toxicity study in dogs all dose groups showed reduced heart weights. Although this effect was not explained, it was observed in this study only. Further, no histopathological signs were seen in heart tissue. For these reasons this observation was not considered a safety concern.

Eyes
As expected, tiotropium bromide caused reduced tear secretion and mydriasis. In dogs this was followed by (kerato)conjunctivitis sicca. In rats, histopathological changes of the Harderian glands were noted, including discoloration, accumulation of secretory product and distension of the lumen. In the 13- and 52-week rat inhalatory studies cataracts were noted. This was probably related to long-term eye exposure occurring in the inhalation tubes allowing the compound to cross the corneal epithelium and enter the eye. Acute and repeated local tolerance studies in rabbits were without adverse effects (see IIIH local tolerance). Although the mechanism of this effect is unexplained, its species and strain-specificity and its dependence on the ocular exposure route make this finding without clinical relevance for patients using the Handihaler device, provided inadvertent eye exposure is avoided.

Urinogenital tract
In rats, proteinaceous deposits and lithiasis were found in the bladder, in some cases related with minimal cystitis, diffuse hyperplasia of the transitional epithelium and (in the carcinogenicity study) prostatitis. The initial pathology was most probably a reflux of proteinaceous secretions from accessory genital glands into the urinary bladder, which was caused by the anticholinergic relaxing effect on the bladder and glands. Prostatitis may be related to the continuous stimulation of the muscarinic receptors in this organ due to tiotropium's low dissociation rate. The urogenital syndrome was not observed in other species and its clinical relevance for humans is unknown. In common with other anticholinergic drugs, tiotropium bromide should be used with caution in patients with bladder-neck obstruction or prostatic hypertrophy.

Respiratory tract and lungs
In rodents an increased incidence of rhinitis and a number of changes in the nasal cavity and larynx were observed. These included focal squamous metaplasia, focal inflammatory cell infiltrates, focal goblet cell hyperplasia and inflammatory exudate in anterior and posterior lumens. From these findings it may be concluded that tiotropium bromide is a mild irritant to the respiratory tract in rodents and/or renders the animals more susceptible to respiratory tract infections. Using a method provided by the MAH a safety margin of 7-10 was estimated for these effects.
In the one-year rat inhalatory toxicity study increased lung weights were observed. Treatment-related changes in body weight could only partially explain the changes in lung weights. However, as no histopathological correlates were observed, the changes in lung weights were not considered to be a safety issue.

Adrenals
In a 13-week inhalatory toxicity study in dogs decreased weights of the adrenals, histologically accompanied by atrophy of the zona fasciculata was observed. However, the weight reductions only attained statistical significance in females at the mid and high dose levels, there was no evidence of a dose-related response, and weights were within historical control data. The clinical picture in mid and high-dose animals did not suggest a diagnosis of canine adrenocortical insufficiency and similar adrenal findings (weight reduction and/or atrophy) have not been recorded in other repeated-dose dog studies. Thus, it was concluded that the apparent adrenal change in one isolated dog study does not have any adverse impact on human safety assessment.

Impurities

Addition of impurities and degradation products did not alter the toxicity profile of tiotropium bromide in a 4-week inhalatory toxicity study in rats. Batches used in toxicology studies contained representative levels of impurities, warranting exposure as well. Furthermore, due to the low dose intended for therapeutic use (22.5 µg tiotropium bromide/day), the maximum possible human dose of impurities and degradation products is so low that exposure in man will be very small (maximally 1.12 µg/day). There is no genotoxicity concern. Several degradation products were also metabolites found in toxicology species. For these reasons the presence of impurities and degradation products up to the specified limits is no safety concern.

Reproduction studies

Reproductive toxicity of tiotropium bromide was studied in rats and rabbits. In all inhalatory reproductive toxicity studies maternal toxicity was observed at or close to doses of 100 µg/kg/day, as demonstrated by chromodacryorrhea and reduced body weight, water intake and food consumption. In studies where tiotropium bromide was administered orally, maternal toxicity occurred at doses of 10 mg/kg/day and above in rabbits and at 25 mg/kg/day and above in rats.

In rat fertility studies, maternal toxicity was accompanied by reduced ovulation and implantation rates, resulting in reduced litter sizes.

In rat and rabbit embryo/foetotoxicity studies maternal toxicity was followed by embryo/foetotoxicity, as demonstrated by complete abortions, foetal resorption, change of foetal body weight, poorly ossified sternebrae and foetuses with 13^{th} rib. Foetuses with 13^{th} rib are a well-known spontaneous variation in both animals.

In peri/postnatal developmental rat studies maternal toxicity was associated with total litter loss, lower pup weights, delayed sexual maturity, and delays in development of startle and air righting reflexes. At the high dose pup survival at day 4 post partum was reduced as well. No effect on reproductive capacity of F_1 generation was noted.

Toxicokinetic data of rat and rabbit reproduction toxicity studies showed adequate systemic exposure.

Mutagenic potential

Standard *in vitro* and *in vivo* genotoxicity tests did not indicate any genotoxic potential of tiotropium bromide or any of the relevant impurities or degradation products.

Oncogenic/carcinogenic potential

Four inhalatory carcinogenicity studies were initiated (two in rats and two in mice), however, only one rat study was completed until 104 weeks. No carcinogenic potential of tiotropium bromide could be demonstrated. Relevant non-neoplastic findings are discussed in the section on repeated dose toxicity.

The first rat carcinogenicity study, using Fisher F-344 rats was terminated after 16 weeks owing to the high mortality rate probably caused by food impaction followed by asphyxiation. The second rat carcinogenicity study was done in Wistar rats and could be completed till the end. There was no evidence of a treatment-related increase in the incidence of neoplastic findings.

The first mouse carcinogenicity study had to be terminated in males after 51 weeks and in females after 83/84 weeks, owing to the high mortality rate caused by the effects on the GI-tract. As the duration of treatment was considered too short for the males, a second mouse carcinogenicity study was initiated (males only). However, owing to the sensitivity of the male mice for the GI-effects very low doses were used, that were not confirmed toxicokinetically, but by a salivary gland output assay. Both females from the first study and males from the second study were fully evaluated. No increase in the incidence of neoplasms was observed. Despite the limitations in duration and dose levels in the mouse carcinogenicity studies, taken together they are considered sufficient.

Although results from repeated dose toxicity studies and carcinogenicity studies indicated that tiotropium bromide is a mild irritant to the respiratory tract in rodents, the observed changes did not progress to neoplasia.

Local tolerance

Repeated dose toxicity studies and oncogenicity studies in rats and mice produced evidence that tiotropium bromide has mild local irritant properties for the respiratory tract. This is discussed in the section on repeated dose toxicity.

Tiotropium bromide was well tolerated in local tolerance studies in rabbits by single and repeated dose inoculations into the conjunctival sac, by intra-arterial and intravenous injection, and in rats by paravenous injection. Instillation into the conjunctival sac caused mydriasis and when very high

dosages were given, decreased food consumption and defecation were noted.

Tiotropium bromide solution produced no haemolytic effect *in vitro* at a final concentration of 0.0015%.

Special toxicity studies
In an investigatory study on the mechanism of sudden death in Fisher F-344 rats evidence was provided that the anticholinergic activity of tiotropium bromide attenuated the secretory capacity of the salivary glands and that the rats died of asphyxia due to impaction of food in the nasopharyngeal region when fed dry pellets.

Tiotropium bromide did not reveal a sensitising potential when tested in Magnusson and Kligman's 'Guinea Pig Maximisation Test'.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH indicated that the environmental risk associated with the use and disposal of tiotropium bromide is negligible. Tiotropium bromide is currently authorised in all Member States. Authorisation of Srivasso will only substitute for other tiotropium bromide containing medicinal products and therefore not increase the environmental burden. An increase of environmental risk, if any, is not anticipated.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Tiotropium bromide is a quaternary ammonium salt and there is no other ionisable functional group on the molecule. The active substance is not optically active. The recommended dose is 18 µg once daily by inhalation.
Ten pharmacokinetic studies were submitted. Pharmacokinetics of tiotropium in healthy volunteers and COPD patients, intravenous, inhalation and oral administration routes were evaluated in plasma and urine. Effect of renal function on pharmacokinetics was characterised. In two pharmacodynamic studies also a limited number of pharmacokinetic parameters were estimated.

Characterisation of the pharmacokinetics of tiotropium was hampered by the low plasma concentrations. Even when using a sensitive analytical method (lower limit of qualification 2.5 pg/ml) plasma levels were often below the limit of quantitation.
In urine higher amounts are found, so pharmacokinetic evaluation is mainly based on data from urine samples.
The absolute bioavailability of tiotropium after inhalation is about 20% and after oral administration only 2-3%. Tiotropium is rapidly absorbed with maximal plasma concentration 5 min after inhalation. The terminal half-life was estimated as 4 to 5 days and steady state is reached between 7 and 14 days.
After repeated dosing by inhalation an accumulation factor of two-three is observed. Pharmacokinetics of tiotropium was dose proportional.
Distribution of tiotropium after inhalation is fast and the protein binding is about 74%.
Renal excretion is the major elimination pathway for tiotropium. The total amount of unchanged tiotropium in urine after intravenous administration was estimated on 74% of the dose.
Renal clearance and excretion of tiotropium decreased with decreasing renal function. Systemic exposure of tiotropium was doubled in patients with renal function <50 ml/min compared to subjects with normal renal function.
Renal clearance of tiotropium was lower in the elderly population compared to the younger group, which can be explained by lower renal function in the elderly. As a result AUC values were slightly increased in elderly patients.
No formal interactions studies have been conducted. *In vitro* studies indicated that tiotropium did not inhibit cytochrome P450. It is unlikely that tiotropium affects pharmacokinetics of other co-medications.

IV.2 Pharmacodynamics

Primary pharmacology
An overview of primary pharmacology studies is given below in table 1.

Table 2. Description of the primary pharmacology studies

Study No. Report No.	Description of Study	Total No. Subjects	Country
205.129 (Subset of 122/126A)	Multiple dose, double-blind, ipratropium controlled study of 18 u g tiotropium (dry powder via the HandiHaler) to assess the onset of pharmacodynamic steady state in adults with COPD with a mean FEV1 of 1.1 l).	31	Netherlands
205.123	Effect of dosing A.M. vs P.M. in COPD with a mean FEV1 of 1.1 l: a six-week, double-blind, randomized, placebo-controlled, parallel group, 18 µg dry powder via the HandiHaler	121	United Kingdom
205.116	Safety of 18 µg (dry powder via the HandiHaler) on mucociliary clearance in COPD: a four- week, double-blind, randomized, placebo-controlled, parallel group.	38	United Kingdom
205.132	Study of the flow rate characteristics of the HandiHaler in patients with COPD	26	United States

The mode of action of tiotropium is similar to other muscarinic antagonists in that they block the action of acetylcholine at the receptor level. The cholinergic mechanisms mediated by acetylcholine account for a proportion of airway narrowing in both health and disease; counteraction of these effects results in bronchodilation.

Regarding the onset of pharmacodynamic steady state, the results of study 205.129 showed that within one week trough FEV1, peak FEV1, average FEV1 and FVC reached a pharmacodynamic steady state. Further, Study 205.123 showed that there was no difference in bronchodilator effect between the time of dosing (AM or PM).

Secondary pharmacology
Trial 205.302
COPD is often associated with concomitant (cardiac) diseases along with multiple comorbidities and medications that may influence QTc interval. Trial 205.302 was conducted assessing the influence of inhaled tiotropium on the QTC interval of the ECG.
In a three way cross-over design 56 healthy volunteers were exposed to 2 doses of tiotropium, i.e. the recommended dose of 18 mcg and 54 mcg, and placebo. The primary endpoint was the mean change of QTcF values from baseline. Additionally, adequate determinations and corrections of the QT parameter were included.

Results
The use of the initially planned primary endpoint, QTcF, was not deemed appropriate as Fridericia correction was poor for the study population. The applied primary endpoint of the study was the mean change from baseline of the corresponding QTcN values (frequency correction performed based on the baseline data of the study population). This is accepted, as the use of an alternative correction was prespecified in the protocol.

The difference to baseline of QTcN-from 5 minutes to 2 hours on day 12 was -1.4 ms for placebo, +0.6 ms for 18 mcg tiotropium, and -2.1 ms for 54 mcg tiotropium. The highest upper bound of the 95% one sided confidence intervals of the placebo-adjusted difference from baseline was +4.9 ms for 18 mcg tiotropium and +2.2 ms for 54 mcg tiotropium and thus well below the predefined non-inferiority margin of 10 ms.

Table 2. Adjusted means of the primary endpoint: the mean time-matched change from baseline of the QTcN interval in the time frame 0:05 to 2:00 hours post-drug administration on day 12.

	Adjusted mean [ms]	Difference to Placebo [ms]	
Treatment	Mean (SE)	Mean (SE)	Upper 95% CI
Placebo	-1.37 (1.27)		
Tiotropium 18 µg	0.55 (1.31)	1.92 (1.81)	4.93
Tiotropium 54 µg	-2.13 (1.30)	-0.77 (1.80)	2.23

For moxifloxacin, mean QTcN prolongation (time frame 1-4h) on day 1 was 8.4 ms. The study was able to detect any changes in the QTcN interval length.

Conclusions and discussion on secondary pharmacology
It may be concluded that tiotropium 18 and 54 mcg did not induce prolongation of the QT interval in a small population of young, healthy volunteers. However, this result cannot be extrapolated to COPD patients who are commonly older and who have frequently concomitant (cardiac) diseases and comedication. Secondly, QTc prolongation is a rare adverse event which may not be detected in such a small trial population despite the inclusion of moxifloxacin, an antibiotic which is known to prolong the QT interval modestly.

IV.3 Clinical efficacy

IV.3.1 Dose response studies

Four dose response studies are performed (Table 3). The results of these trials were used for the dose selection of the phase III studies.

Table 3. COPD-Dose Ranging Studies

Study No. Report No.	Description of Study	Total number of patients	Country
205.119	Single dose-escalation (10, 20, 40, 80, 160 µg as aqueous solution for inhalation on separate days) open label crossover pilot study in COPD with a mean FEV1 of 1.4 l and a partial reversibility on ipratropium.	6	Netherlands
205.120	Single dose and time responses (10, 20, 40, 80 µg dry powder inhalation) in COPD with a mean FEV1 of 1.3 l. Double-blind, placebo-controlled crossover.	35	Netherlands
205.108	Multiple dose, double-blind, placebo-controlled, parallel group chronic dose ranging study over 4 weeks (4.4, 8.8, 17.6 and 35.2 µg dry powder inhalation) in COPD with a mean FEV1 of 1.1 l.	169	United States
205.139	Single dose ranging, placebo-controlled, double-blind, four-way crossover (9, 18, 36 µg dry powder inhalation) in COPD	27	Japan

The three single dose studies (205.119, 205.120, and 205.139) showed a dose related bronchodilator effect of inhaled tiotropium of ± 24 hours. Furthermore, these studies exhibited general dose ordering with evidence of a plateau at the highest doses, i.e. 40 to 160 mcg tiotropium bromide. In the range of 10 to 40 mcg, dose-dependent increases in effectiveness were generally seen, and 10 mcg always was the least effective dose.
The multiple dose study (205.108) showed that all doses were more efficacious than placebo. The trough FEV1 increased after one week and remained the same during the further 3 weeks. The trough FEV1 response was -0.02 (placebo), 0.12 (4.5 mcg), 0.09 (9 mcg), 0.13 (18 mcg) and 0.17 (36 mcg) (Figure 1).

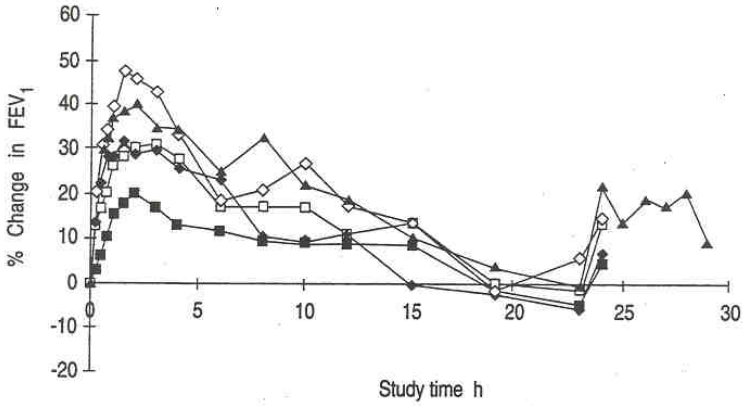

Fig. 2. – Percentage change in FEV_1 (*l*) from baseline for Ba 679 Br 10, 20, 40, 80 and 160 µg. —■—: 10 µg (baseline 1.43 *l*); —□—: 20 µg (baseline 1.39 *l*); —◆—: 40 µg (baseline 1.39 *l*); —◇—: 80 µg (baseline 1.31 *l*); —▲—: 160 µg (baseline 1.41 *l*). FEV_1 forced expiratory volume in one second.

Figure 1. Percentage change in FEV1

Table 4. Frequency of most reported adverse events in dose response study 205.108

	0 µg	4.5 µg	9 µg	18 µg	36 µg
Percent of Patients Reporting Dry Mouth	0%	5.9%	0%	6.1%	8.8%
Percent of Patients Reporting Adverse Events	37.1	29.4	18.2	30.3	50.0

In conclusion, the efficacy and safety findings of the multiple dose ranging trial and the consistent dose ordering observed in the single dose ranging trials do provide guidance for dose selection of 18 mcg for phase III trials. A dose of 9 mcg appeared less effective than 18 mcg, and 36 mcg showed a trend in more adverse events than the dose of 18 mcg.

IV.3.2 Main studies (registration trials)

To support the application four large pivotal clinical one-year studies, two large salmeterol-compared 6-months and four additional studies are enclosed.

The main purpose of these studies was to evaluate the short and long-term efficacy and safety of tiotropium in COPD patients.

The methodology of four pivotal studies, comparing tiotropium with placebo/ipratropium is summarised in the next tables.

Table 5. Description of the pivotal studies

Study No.	Description of the studies	Number of patients	Country
205.114/ 205.117	Efficacy/safety one-year study in COPD. Double-blind, randomized, placebo-controlled, parallel group, tiotropium DPI 18 mcg once a day.	470	United States
205.115/ 205.128	Efficacy/safety one-year study in COPD. Double-blind, randomized, placebo-controlled, parallel group, tiotropium DPI 18 mcg once a day.	451	United States
205.122A/ 205.126A	Efficacy/safety one-year study in COPD: tiotropium DPI 18 mcg once a day in comparison to ipratropium MDI 40 mcg four times a day. Double-blind, randomized, parallel group.	288	Netherlands
205.122B/ 205.126B	Efficacy/safety one-year study in COPD: tiotropium DPI 18 mcg once a day in comparison to ipratropium MDI 40 mcg four times a day. Double-blind, randomized, parallel group.	247	Netherlands and Belgium

Table 6. In- and exclusion criteria, efficacy variables and measurement

	Placebo-controlled studies 205.114/117 and 205.115/128	Ipratropium controlled studies 205.122/126A and 205.122B/126B
Inclusion criteria	FEV1 ≤65% of pred, FEV1/FVC≤70%, >40 years, >10 pack years smoking	FEV1 ≤65% of pred, FEV1/FVC≤70%, >40 years, >10 pack years smoking
Exclusion criteria	Asthma, allergic rhinitis, atopy, blood eosinophils >600/mm3	Asthma, allergic rhinitis, atopy, blood eosinophils >320-400mm3
Pulmonary function test (FEV1, FVC)	At 1 hour prior to and just prior to drug administration and at 30, 60, 120 and 180 minutes post dosing	At 1 hour prior to and just prior to drug administration, at 30, 60, 120, 180, 240, 300, 360 min. post dosing
Pulm. function test (FEV1, FVC) Quality of life instruments (SGRQ and SF36) Mahler Dyspnea indices (BDI/TDI)	At baseline, after 1, 7, 13, 25, 37 and 49 weeks	At baseline, after 1, 7, 13, 26, 39 and 52 weeks
PEFR by the patient	Twice daily	Twice daily
COPD symptom score Physician's global evaluation Energy-fatigue questionnaire	Every 3 weeks Every 3 weeks At 1, 4, 10, 19, 31 and 43 weeks	– – –
Salbutamol rescue medication	Number of doses daily (each dose is one or two puffs)	Number of inhalations daily (each inhalation is one puff)
Primary efficacy variable	Trough FEV1 (response)	Trough FEV1 (response)
Secondary efficacy variable	Peak FEV1 response, average FEV1 response, FVC, PEFR, Mahler dyspnea indices, energy fatigue questionnaire symptom scores, rescue medication, SGRQ, SF-36, prop. of patients with exacerbation, with hospitalisation, time to 1rst exacerbation, physician's evaluation	Peak FEV1 response, average FEV1 response, FVC, PEFR, Mahler dyspnea indices, rescue medication, energy fatigue questionnaire symptom scores, SGRQ, SF-36, proportion of patients with an exacerbation, with a hospitalisation, time to first exacerbation

For the efficacy evaluation the following criteria were used: trough FEV1 response after 13 weeks of treatment administration; trough FEV1 response was defined as change from baseline in trough FEV1, baseline FEV1 was calculated as the mean of the two FEV1 readings measured in the morning of the randomization visit prior to the first administration of study medication.
The St. George's Respiratory Questionnaire (SGRQ) was the primary instrument used to evaluate disease specific HRQoL with the impact domain stated as the primary endpoint.

Table 7. Definitions and abbreviations

Trough FEV1	Mean of the two FEV1 readings at the end of the dosing interval, 23 to 24 hours post drug administration
Trough FEV1 response	Change from baseline in trough FEV1
Baseline FEV1	Mean of the two FEV1 readings measured in the morning of the randomisation prior to the first drug administration
Peak FEV1 response	Maximum value post treatment administration minus baseline
Average FEV1 response	Change from baseline in average value over the first 3 hours
Mahler Dyspnea Indices	BDI and TDI
BDI	Baseline Dyspnea Index; three components,

	score 0-4
TDI	Transitional Dyspnea Index; change in score compared to baseline; score –9 to +9 (one unit difference is meaningful)
SGRQ	St. George's Respiratory Questionnaire; disease specific QoL; 4 components, score 0-100 (4 units difference is meaningful)
SF-36	Short-Form-36; non specific QoL; 8 components, score 0-100
Exacerbation	Complex of respiratory events reported as adverse events with a duration of 3 or more days

The design of the pivotal studies is in accordance with the Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD of the CPMP. The study duration is long enough and the amount of participants is large.

The comparator ipratropium 40 mcg four times a day is an obvious and rational choice since ipratropium is widely used as short-acting anti-cholinergic bronchodilator in COPD patients. The chosen selection criteria provide the participation of "true" COPD patients, and the exclusion of asthma patients. The chosen efficacy variables; lung function, quality of life, symptoms and exacerbation parameters cover the goals of treatment for COPD patients and are therefore all clinically relevant outcome parameters. The choice of the primary efficacy variable, trough FEV1, is in accordance with current CHMP guideline.

The other, secondary variables provide information about the maximal bronchodilatory effect and the duration of action, and health related quality of life and symptoms.
The frequency and severity of exacerbations is considered more and more of importance in the treatment of COPD patients. The incidence of exacerbations is dependent on the rate of exposure, and therefore the company calculated the number of exacerbations and the number of hospitalisations (days) expressed in exposure units.

The statistical model was analysis of covariance with terms for treatment, centre and treatment-by-center interaction. The intent-to-treat principle is used in the efficacy analysis. Since both placebo-controlled and both comparator-controlled studies used the same design, the two are analysed as combined studies.
The null hypothesis was that there is no difference between placebo/ipratropium and tiotropium in mean trough FEV1 response after 13 weeks.

In total 906 patients were treated with tiotropium, 179 with ipratropium and 371 with placebo.
In the salmeterol/placebo studies, 402 patients were exposed to tiotropium, 405 to salmeterol, and 400 to placebo.

All baseline patient characteristics such as age (±65 yrs) and sex were similar in the two placebo-controlled studies as well as in the two comparator studies.

The mean FEV1 of the participants was 1.0 and 1.2 liter in the placebo-controlled and in the comparator studies respectively, which means that mainly patients with severe COPD participated. The patients in the placebo trials had more pack years (63 yrs) than those in the ipratropium trials (34 yrs).

The results for the two placebo-controlled studies as well as for the two comparator trials were consistent and therefore results can be pooled. All results are presented below in Table 8. The primary endpoints are presented in detail.

Lung function
All lung function data over one year show that tiotropium therapy results in a statistically significant long-term bronchodilator efficacy in comparison to placebo as well as to ipratropium (Table 8).
The primary efficacy variable mean trough response with tiotropium is 0.11 and 0.12 liter in the placebo and comparator trials respectively.

The peak response with tiotropium is 0.26 and 0.31 liter in the placebo and comparator studies respectively. This response is not only statistically significant but also clinically relevant. A small improvement of 110-260-310 ml in FEV1 implicates a much larger improvement in airway resistance in patients with a low baseline FEV1. The mean trough FEV1 reached a steady state after one week tiotropium treatment and remained the same during the following year (Figure 2).
The secondary efficacy lung function variables confirm the results of the primary efficacy variable. The results after 13 weeks are similar to those after one year study.

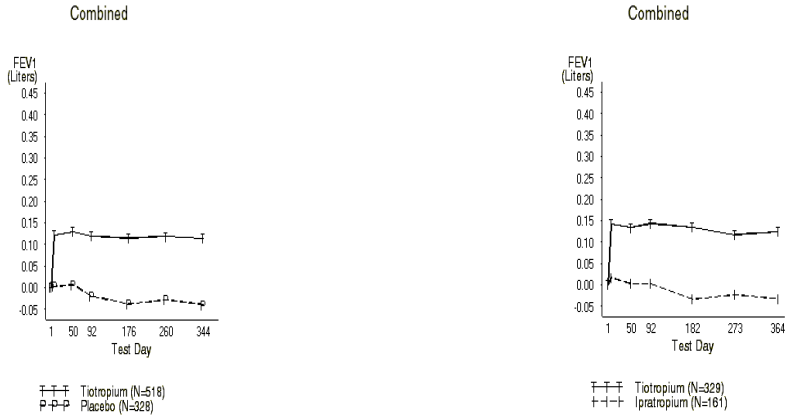

Figure 2. The mean FEV1 trough response over time in the placebo and comparator controlled trials

Quality of life
The results of the disease specific SGRQ clearly shows a beneficial efficacy of tiotropium in quality of life compared to placebo as well as compared to ipratropium. Quality of life is considered an important parameter for treatment in patients with COPD. With tiotropium 19% and 17% more patients experienced a clinically meaningful improvement in quality of life than with placebo and ipratropium respectively. It is noted that in the placebo-group, only in the first 3 months, an improvement in SGRQ score is seen as well.
Within the limitations of cross-sectional comparison, the results of the current study tiotropium seems to show more benefit than fluticasone in the ISOLDE study[1].

Symptoms
The results of the Mahler's dyspnea scores over the whole year show a statistically significant beneficial effect of tiotropium compared to placebo on the focal score as well as on the three different components; functional impairment, magnitude of task and magnitude of effort. The difference in focal score varies trough the year from 0.81 to 1.14 between tiotropium and placebo. Seventeen percent more patients experienced a meaningful benefit in dyspnea score (TDI) with tiotropium compared to placebo. This beneficial efficacy on dyspnea score of tiotropium is supported by the results of the COPD symptom scores, the energy fatigue score, the number of rescue medication, the number of nocturnal awakenings and the physician's global evaluation.
The results of tiotropium on symptoms compared to ipratropium follow the results compared to placebo, yet the differences are smaller. Tiotropium is at least as good, or on several points even better than ipratropium with respect to symptoms.

Exacerbations
Less patients experienced exacerbations and hospitalizations with tiotropium treatment than with placebo or ipratropium. After normalisation for the extent of exposure, the number of exacerbations per 100 patient years was 76 in the tiotropium group and 95 in the placebo group ($p<0.05$). The number of exacerbation days was not different. Kaplan-Meier curves were presented that show that the propensity for a exacerbation or hospitalization is reduced with tiotropium. Tiotropium delays the occurrence of an exacerbation.

[1] Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000; 320:1297-1303.

Table 8. Efficacy results over 1 year of the four pivotal studies

	Placebo 205.114/117 and 205.115/128	**Tiotropium 205.114/117 and 205.115/128**	**Ipratropium 205.122/126A and 205.122B/126B**	**Tiotropium 205.122/126A and 205.122B/126B**
Lung function				
Trough FEV1 response (l)(SE)	-0.04 (0.01)	0.11 (0.01)*	-0.03 (0.01)	0.12 (0.01)*
Average FEV1 response (l)(SE)	-0.02 (0.01)	0.19 (0.01)*	0.13 (0.01)	0.23 (0.01)*
Peak FEV1 response (l)(SE)	0.04 (0.01)	0.26 (0.01)*	0.21 (0.01)	0.31 (0.01)*
Trough FVC response (l)(SE)	-0.04 (0.02)	0.26 (0.02)*	0.11 (0.04)	0.32 (0.03)*
Trough FEV1 (l)	1.0 to 1.0	1.0 to 1.1*	1.2 to 1.2	1.2 to 1.3*
Peak FEV1 (l)	1.0 to 1.1	1.0 to 1.3*	1.2 to 1.4	1.2 to 1.5*
PEFR morning (l/min)	193 to 206	192 to 227*	252 to 257	263 to 273*
Symptoms				
TDI focal score (SE)	-0.09 (0.15)	1.06 (0.12)*	-0.44 (0.23)	0.46 (0.16)*
BDI focal score plus/minus TDI	6.2 to 6.1	6.0 to 7.1*	7.4 to 7.0	7.1 to 7.6*
Percentage of patients with a TDI focal score $\geq$ 1	29	46*	18	31*
Mean number of rescue salbutamol weekly	3.6 to 4.1	3.6 to 3.2*	2.7 to 2.6	2.7 to 2.2
Energy fatigue quest severity of condition fatigue level energy level	 2.9 to 3.0 3.3 to 3.3 3.0 to 3.0	 2.9 to 3.1 3.3 to 3.4* 3.0 to 2.9*	 3.5 to 3.3 3.4 to 3.4 2.7 to 2.7	 3.5 to 3.6* 3.4 to 3.5 2.7 to 2.6
Symptom score wheezing	0.8 to 0.9	0.8 to 0.8*		
Symptom score shortness of breath	1.5 to 1.7	1.5 to 1.5*		
Mean number of awakenings per night (13 weeks)	0.5 to 0.4	0.5 to 0.3*		
Physician's global evaluation	4.5 to 4.6	4.5 to 5.0*		
Mean COPD symptom scores	0.82 to 0.94	0.82 to 0.79*		
Withdrawals (%)	27.8*	18.7	21.2	15.2
Quality of life				
SGRQ symptoms	59 to 58	59 to 55*	53 to 51	53 to 47
SGRQ activities	64 to 64	64 to 60*	58 to 56	58 to 55
SGRQ impacts score	33 to 34	33 to 30*	35 to 35	35 to 31*
SGRQ total score	47 to 47	47 to 44*	45 to 44	45 to 41*
% of patients with change $\geq$4 in SGRQ total score	30	49*	35	52*
SF-36 physical sum.	35 to 33	35 to 36*	39 to 38	39 to 40*

Exacerbations				
% of patients with exacerbations	42	36*	46	35*
% of patients with hospitalizations	9	6*	12	7*
% of patients with oral steroid courses	25	16*	28	22

***p<0.05.**

IV.3.3 Supportive registration studies

The main purpose of the two studies was to confirm the short and long-term efficacy and safety of tiotropium in COPD patients and to compare the efficacy with the long-acting bronchodilator salmeterol.

The methodology of the studies is very similar to the pivotal studies in the initial application.

All lung function data over one year clearly show that tiotropium as well as salmeterol therapy results in statistically significant long-term bronchodilator efficacy in comparison to placebo, while most lung function variables show a statistically significant benefit of tiotropium compared to salmeterol.

The results of the Mahler's dyspnea scores over the whole year show a statistically significant beneficial effect of tiotropium and salmeterol compared to placebo. Many patients experienced a meaningful benefit in dyspnea score (TDI) with tiotropium and salmeterol compared to placebo. Tiotropium shows a beneficial trend compared to salmeterol. The beneficial efficacy on dyspnea score of tiotropium and salmeterol is supported by the other secondary endpoints.

The results of the disease specific SGRQ shows a beneficial efficacy of tiotropium in quality of life compared to placebo. In the data of salmeterol, only a positive trend is seen. Quality of life is considered an important parameter for treatment in patients with COPD. More patients with tiotropium experienced a clinically meaningful improvement in quality of life than with placebo and salmeterol (change $\geq$ 4).

Fewer patients experienced with tiotropium treatment exacerbations and hospitalizations than with placebo. Salmeterol shows only a positive trend.

Table 9. Efficacy results over 6 months of the two salmeterol studies

	Trial 205.130			**Trial 205.137**		
	Placebo	*Tiotropium*	*Salmeterol*	*Placebo*	*Tiotropium*	*Salmeterol*
Lung function						
Through FEV1 response (l)(SE)	-0.03 (0.02)	0.11(0.01)*#	0.05 (0.01)*	-0.03 (0.02)	0.07 (0.02)*	0.05 (0.02)*
Average FEV1 response (l)(SE) 0-3 hour	0.01 (0.02)	0.19 (0.02)*#	0.15 (0.02)*	0.01 (0.02)	0.22(0.02)*#	0.14 (0.02)*
Average FEV1 response (l)(SE) 0-12 hour	-0.02 (0.02)	0.20 (0.02)*#	0.12 (0.02)*			
Peak FEV1 response (l)(SE) 0-3 hours	0.08 (0.02)	0.27 (0.02)*#	0.21 (0.02)*	0.08 (0.02)	0.30 (0.02)*#	0.21 (0.02)*
Through FVC response (l)(SE)	-0.02 (0.03)	0.23 (0.03)*#	0.12 (0.03)*	-0.03 (0.03)	0.15 (0.03)*	0.10 (0.03)*
PEFR morning (l/min)	224 to 234	228 to 261*	226 to 255*	254 to 255	252 to 272*	245 to 278*
Symptoms						
TDI focal score (SE)	-0.63 (0.31)	0.39 (0.28)*#	-0.39 0.28)*	-0.42 (0.29)	0.80 (0.28)*	0.85 (0.29)*
Patients with TDI focal	26	42*	35	33	45*	48*

score ≥ 1 (%)						
Mean number of rescue salbutamol weekly	3.2 to 4.5	3.3 to 3.0*	4.0 to 3.0*	2.7 to 3.4	3.2 to 3.3	3.1 to 2.9
Symptom score wheezing	0.9 to 1.0	0.9 to 0.8*	0.9 to 0.8*	0.8 to 0.8	0.8 to 0.8	0.8 to 0.8
Symptom score shortness of breath	1.4 to 1.5	1.5 to 1.2*#	1.5 to 1.3*	1.5 to 1.4	1.6 to 1.4	1.5 to 1.3
Physician's global evaluation	4.6 to 4.4	4.5 to 5.0*	4.5 to 4.8*	4.6 to 4.6	4.4 to 4.7	4.4 to 4.7
Quality of life						
SGRQ symptoms	53 to 51	54 to 44*	52 to 46*	49 to 46	47 to 44	48 to 44
SGRQ activities	63 to 59	61 to 59	61 to 58	58 to 59	60 to 56*	60 to 57
SGRQ impacts score	35 to 31	33 to 29*#	33 to 31*	33 to 33	34 to 31	33 to 32
SGRQ total score	47 to 43	45 to 40*	45 to 42	43 to 43	45 to 41*	44 to 42
Patients with change ≥4 in SGRQ total score (%)	42	51*#	40	37	46	47
Exacerbations						
Events/100 patient years	149	107*	123	135	111	110
Event days/100 pat years	2500	1724*	2408	2076	1677	2015
Patients with hospitalizations (%)	6	3	5	4	4	5
Withdrawals due to exacerbation (%)	17.9	5.7	13.6	14.1	8.8	16.1
Patients with exacerbations (%)	39	32	35			

* p<0.05 to placebo, # tiotropium to salmeterol

In conclusion, the results are similar as the data in the four initial pivotal studies. The results of the two supportive studies confirm that tiotropium improves lung function, symptoms, quality of life and exacerbations in patients with moderate to severe COPD, in comparison with placebo. Furthermore, the efficacy results of tiotropium with respect to lung function, symptoms, quality of life and exacerbations are at least as good as the results of salmeterol.

IV.3.4 Post-marketing studies

The following studies were submitted after registration in order to update the SmPC with the results of the studies:

- trial 205.302 assessing the influence of inhaled tiotropium on the QTC interval of the ECG
- trial 205.235 (UPLIFT study) assessing the rate of decline of lung function in patients with COPD
- trial 205.256 (TIPHON study) evaluating HRQoL in patients with COPD
- trial 205.389 (POET study) evaluation the effect of inhalation of tiotropium once daily 18 mcg versus salmeterol twice daily 50 mcg on time to first exacerbation in COPD patients
- trial 205.266 (VETERAN STUDY) testing the hypothesis that tiotropium 18 mcg once daily reduces exacerbations and associated hospitalizations in COPD patients in the Veteran's Administration Medical System in the United States
- trial 205.214 (MISTRAL STUDY) evaluating the effect of long-term treatment with inhaled tiotropium bromide on am PEFR, and influence on severity, type and incidence of acute exacerbations.
- trial 205.131 investigating whether six weeks treatment with tiotropium (18µg/day) improves exercise tolerance in COPD patients.
- trial 205.223 investigating whether six weeks treatment with tiotropium (18µg/day) improves exercise tolerance in COPD patients.

- trial 205.230 determining whether tiotropium inhalation capsules, compared to placebo, enhances the improvement in exercise tolerance seen in patients with COPD who participate in pulmonary rehabilitation.
- trial 205.365 assessing the efficacy and safety of tiotropium in subjects with COPD [GOLD] Stage 2 who had not previously been treated with maintenance and with symptomatic shortness of breath.
- trial 205.368 determining the effect of long-term treatment with tiotropium on treadmill endurance time (ET) compared with placebo on top of usual care in patients with COPD

- **Long-term studies**

TRIAL 205.235 (UPLIFT STUDY - JANUARY 2003 TO FEBRUARY 2008)
UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) is a randomized, double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease (COPD).

Diagnosis and main criteria for inclusion and criteria are in general comparable with the pivotal phase III studies. Patients were offered a smoking cessation program.

Criteria for evaluation
The co-primary efficacy endpoints were:
- Yearly rate of decline in trough (pre-bronchodilator) FEV1 from day 30 (steady state) until completion of double-blind treatment
- Yearly rate of decline in post-bronchodilator FEV1 from day 30 (steady state) until completion of double-blind treatment.

The key secondary endpoints were:
- Time to first COPD exacerbation
- Time to first COPD exacerbation leading to hospitalization

The safety endpoints included all adverse events (including serious adverse events), all-cause mortality, and lower respiratory mortality.

Results
In total, there were 9,468 person years of exposure to tiotropium and 8,746 person-years of exposure to placebo, which includes the D30 follow-up period (no study drug taken).
Of patients randomized, 4,383 (73%) completed 2 years, 3,891 (65%) completed 3 years, and 3,569 (60%) completed ≥45 months. A higher proportion of patients failed to complete ≥45 months of treatment in the placebo group (45%) compared with the tiotropium group (37%, p<0.001).

A higher proportion of patients failed to complete ≥45 months of treatment in the placebo group (44.6%) compared with the tiotropium group (36.2%, p<0.001). The majority of discontinuations was due to adverse events.

The two treatment arms were well matched for all baseline characteristics, including age, gender, and baseline respiratory medications. The mean age was 65 ± 8 years, approximately 75% were men, and approximately 30% were current smokers.

Mean pre-bronchodilator FEV1 was approximately 1.10 ± 0.40 L (39% predicted) and post-bronchodilator FEV1 was approximately 1.32 ± 0.44 L (48% predicted). Mean increase in FEV1 following maximal bronchodilation was 23 ± 18%.
Patients classified as GOLD Stages II, III and IV comprised 46, 44, and 9%, respectively. Over 90% of patients were receiving respiratory medications at baseline, including 60% who were receiving long-acting beta-agonists and 62% who were receiving inhaled corticosteroids.

In the setting of allowing all other classes of respiratory medications during the study period, the rate of decline in pre- or post-bronchodilator FEV1 was comparable between the tiotropium and placebo groups. The rate of decline in prebronchodilator FEV1 was 30 mL/year for both the tiotropium and

placebo groups. The rate of decline in post-bronchodilator FEV1 was 40 and 42 ml/year for the tiotropium and placebo groups, respectively (Table 10).

Table 10. Mean (SE) rate of decline in FEV1 and FVC from Day 30 until end of treatment (including 30 days post treatment) in the tiotropium and placebo groups

	Tiotropium		Placebo				
	N	Mean (SE)	N	Mean (SE)	Δ Tio – Pla	95% CI	P-value
Day 30 to End of treatment[2]							
Pre-bronchodilator FEV_1	2557	-30 (1)	2413	-30 (1)	0 (2)	-4, 4	0.95
Post-bronchodilator FEV_1	2554	-40 (1)	2410	-42 (1)	2 (2)	-2, 6	0.21
Pre-bronchodilator FVC	2557	-43 (3)	2413	-39 (3)	-4 (4)	-12, 4	0.30
Post-bronchodilator FVC	2554	-61 (3)	2410	-61 (3)	-1 (4)	-9, 7	0.84

P-values are unadjusted.

Key secondary endpoints
• Time to first COPD exacerbation/ Time to first COPD exacerbation leading to hospitalization

Tiotropium delayed the time to the first exacerbation and the time to first hospitalization for an exacerbation. The HRs (95% confidence intervals [CI]) for an exacerbation or exacerbation leading to hospitalization were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively. The HRs indicate a 14% reduction in the risk of an exacerbation as well as a 14% reduction in the risk of an exacerbation hospitalization with tiotropium compared to placebo.
The mean number of exacerbations as well as exacerbation days was significantly less for the tiotropium group. The mean number of exacerbations leading to hospitalizations was low and not significantly different between treatment arms.

Conclusions on long-term studies
In the setting of allowing all other classes of respiratory medications during the study period, the rate of decline in pre- or post-bronchodilator FEV1 was comparable between the tiotropium and placebo groups.
Tiotropium delayed the time to the first exacerbation and the time to first hospitalization for an exacerbation. The HRs indicate a 14% reduction in the risk of an exacerbation as well as a 14% reduction in the risk of an exacerbation hospitalization with tiotropium compared to placebo.

Following wording is included in section 5.1 to reflect the efficacy results of the Uplift trials:
In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving Spiriva), the improvement in FEV1 resulting from Spiriva, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Spiriva group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV1 compared to placebo was similar between Spiriva and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

- **Quality of life studies**

TRIAL 205.256 (TIPHON TRIAL, 07 MAY 2002 - 19 APR 2004)
The TIPHON trial is a 9-month, randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg once daily evaluating HRQoL in patients with COPD. In addition, as a secondary

endpoint, the trial sought to validate a newly developed simple questionnaire, the Visual Simplified Respiratory Questionnaire (VSRQ) for measuring HRQoL questionnaire in daily practice.

The primary endpoint is the proportion of patients achieving at least a 4-unit improvement in the SGRQ total score. The choice for 'at least 4 units' is based on the generally accepted definition of "the minimal clinically important difference (MCID)".

The SGRQ is a disease-specific questionnaire. It has been designed for use in patients with respiratory disease. The questionnaire has three components:

- Symptoms – distress due to respiratory symptoms;
- activities –disturbance of physical activity;
- impacts – overall impacts on the daily life and well-being.

Secondary efficacy endpoints included SGRQ total score and sub scores, the VSRQ scores, spirometry, exacerbations and a physician global evaluation of the patient's COPD.

Compared with the placebo group, significantly more patients in the tiotropium group achieved a minimal clinically important difference (i.e. a reduction of ≥4 units) in the SGRQ total score at 9 months. At study end, 59.1% patients in the tiotropium group had clinically meaningful improvements in SGRQ total score compared with 48.2% of patients in the placebo group (p=0.029).

Table 11. Response rate of SGRQ total score - FAS population (N = 554)

	Months	Tiotropium (N=247)	Placebo (N=245)	Diff.	P-value
SGRQ : Responders	9 Months	146/247 (59.1)	118/245 (48.2)	10.9	0.029

A post hoc sensitivity analysis on the per protocol set excluding all patients who had no assessment at month 3 or later has been performed did not alter the results.
Tests of homogeneity of odds ratio allowed to assume that the subgroups share a common odds ratio except for the severity of illness at 3 months. Tests were performed on the severity of disease at entry, baseline HRQoL, reversibility, concomitant use of inhaled corticosteroids (ICS) and gender.

The results show that a nine-month treatment by tiotropium led to a consistent and clinically significant improvement in HRQoL.
The adjusted change from baseline in the tiotropium group on Month 9 was -8.50 points and was -4.32 in the placebo group. The difference tiotropium vs placebo was -4.19 points (p = 0.0011).
The difference was mainly driven by the domain "symptoms". The MCID was not achieved in all three domains: "activity" (3.9) and "impact on daily life" (3.6), they lie close to 4 and point is the same direction as the total score.

Conclusion of quality of life studies
The improvement of HRQoL in moderate to severe COPD patients in the tiotropium group has been demonstrated well. The outcome of both primary and secondary endpoints shows a statistically significant benefit from tiotropium. However, the difference in proportions of patients who achieved the minimal clinically important difference of 4 units improvement in SGRQ is only 10.9% in favour of tiotropium, because of the relatively high placebo result. The difference was statistically significant, 59.1% in the Spiriva group; 48.2% in the placebo group (p=0.029).
The MCID was not achieved in all three domains; "activity" (3.9) and "impact on daily life" (3.6), they lie close to 4 and point in the same direction as the total score.

The following wording for the results is included in the SmPC after a second variation for editorial improvements:
In a 9-month, randomized, double-blind, placebo-controlled clinical trial of 492 patients, SPIRIVA improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with SPIRIVA which achieved a meaningful improvement in the SGRQ total score (i.e. > 4 units) was 10.9% higher compared with placebo (59.1% in the SPIRIVA groups vs. 48.2% in the placebo group (p=0.029). The mean difference between the groups was 4.19 units (p=0.001; confidence interval: 1.69 – 6.68). The improvements of the

subdomains of the SGRQ-score were 8.19 units for "symptoms", 3.91 units for "activity" and 3.61 units for "impact on daily life". The improvements of all of these separate subdomains were statistically significant.

- **Exacerbation studies**

POET-COPD study (trial 205.389)
This was a 1-year, multicentre, multinational, randomised, double-blind, double-dummy, parallel group trial to evaluate the effect of inhalation of tiotropium once daily 18 mcg versus salmeterol twice daily 50 mcg on time to first COPD exacerbation in patients with COPD.

Inclusion Criteria
COPD patients, 40 years of age or older with post-bronchodilator FEV1 ≤70% of predicted normal and FEV1 ≤70% of FVC postbronchodilator (i.e., 30 min after inhalation of 4 puffs of 100 mcg salbutamol or equivalent short-acting β2-agonist).

The primary endpoint was time to first COPD exacerbation (moderate or severe, as defined below) during the 360-day randomised treatment period. A COPD exacerbation was defined as a complex of respiratory events/symptoms (increase or new onset) of more than 1 of the following: cough, sputum, wheezing, dyspnea, or chest tightness with at least 1 symptom lasting at least 3 days requiring treatment with antibiotics and/or systemic steroids and/or hospitalisation.
More specifically, a moderate COPD exacerbation was defined as increase or new onset of at least 2 of the respiratory events/symptoms mentioned above with at least 1 symptom lasting at least 3 days, requiring treatment with antibiotics and/or systemic steroids (but not requiring hospitalisation).

A severe COPD exacerbation was defined as increase or new onset of at least two of the respiratory events/symptoms mentioned above with at least 1 symptom lasting at least 3 days, requiring hospitalisation. Note that in this document, whenever the term "COPD exacerbation" is used, a moderate or severe exacerbation is meant if not explicitly stated otherwise. In addition, the primary endpoint refers to moderate and severe exacerbations.

Secondary Endpoints: Time-to-Event Endpoints, Number of Events, Number of Patients with Events.

Results
Baseline characteristics were balanced between the treatment groups with respect to demographics, COPD characteristics, lung function, and pulmonary medication use at baseline
During the study, concomitant use of pulmonary and other medication was also balanced between both treatment groups. Patients were allowed to continue inhaled corticosteroid (ICS) therapy during the trial and the use of ICS during the trial (overall 45.1% of treated patients)

The study demonstrated superiority of tiotropium over salmeterol for the primary endpoint: tiotropium significantly reduced the risk of the first moderate or severe COPD exacerbation (for hazard ratio) (Table 12).

Sensitivity analyses on the primary endpoint (on the per-protocol set of patients or excluding COPD exacerbations with imaging-confirmed pneumonia) confirmed the results of the primary analysis.

The pattern of benefit with tiotropium was consistently observed in all major subgroups considered in this trial (i.e. age, gender, GOLD stage, smoking status, BMI, pulmonary medication use at baseline).

The effect of tiotropium was consistent across a set of secondary endpoints assessing exacerbations (Table 12). Compared to salmeterol, tiotropium reduced the risk of both a moderate and severe (i.e. hospitalised) exacerbation ($p<0.001$) and tiotropium reduced the number of exacerbations ($p<0.05$ for moderate and/or severe exacerbations).

Table 12. Results primary and secondary endpoints POET-COPD study

	Ratio (95% CI) tiotropium vs. salmeterol	p-value
Primary endpoint:		
Time to first moderate or severe COPD exacerbation	0.83 (0.77, 0.90) [1]	<0.0001
Secondary endpoints		
Number of moderate or severe COPD exacerbations	0.89 (0.83, 0.96) [2]	0.0017
Time to first severe COPD exacerbation	0.72 (0.61, 0.85) [1]	<0.0001
Number of severe COPD exacerbations	0.73 (0.66, 0.82) [2]	<0.0001
Time to first moderate COPD exacerbation	0.86 (0.79, 0.93) [1]	0.0004
Number of moderate COPD exacerbations	0.93 (0.86, 1.00) [2]	0.0479

[1] Hazard ratio: Cox's proportional hazards model; p-value: Wald's Chi-square test
[2] Rate ratio based on Poisson regression model correcting for overdispersion

In conclusion, the study demonstrated superiority of tiotropium over salmeterol for time to the first moderate or severe COPD exacerbation: tiotropium significantly reduced the risk of the first moderate or severe COPD exacerbation. The results of the secondary endpoints were consistent with the primary analysis.

VETERAN STUDY (Trial 205.266)
This was a 6-month, prospective, randomized, double-blind, parallel-group, placebo-controlled trial tested the hypothesis that tiotropium 18 mcg once daily reduces exacerbations and associated hospitalizations in COPD patients in the Veteran's Administration Medical System in the United States.

The co-primary outcomes were the proportion of patients experiencing an exacerbation and the proportion of patients hospitalized due to an exacerbation.

The inclusion and exclusion criteria were similar to the one-year and the six-month registration trials other than liberalization of exclusion criteria to permit a broader sample of patients.

A COPD exacerbation was defined as more than one respiratory symptom (new onset or increase) for at least 3 days requiring treatment with antibiotics, steroids, or hospitalization. Patients kept a daily record about their COPD, and exacerbation data was collected during interviews at study visits (at three and six months) and by monthly telephone follow up between visits.

A total of 1,829 patients were randomized (tiotropium=914, placebo=915). The mean age was 68 years, 99% were male and mean baseline FEV1 was 1.04 L (35% predicted).

Tiotropium reduced the percent of patients experiencing an exacerbation compared to placebo (27.8% vs. 32.3% respectively, p=0.037) and reduced associated hospitalizations (7.0% vs. 9.4% respectively, p=0.056). Tiotropium significantly delayed the time to the first exacerbation or associated hospitalization (p<0.05). The tiotropium group had fewer exacerbations (82.1 vs. 100.4 events/100 patient years, p=0.004) and hospitalizations due to exacerbations (17.5 vs. 25.2 events/100 patient years, p=0.013). Exacerbation days and total days in hospital due to exacerbations were lower in the tiotropium group (p<0.001). Tiotropium also reduced the number of treatment days of antibiotics and of steroids for exacerbations (p<0.001 for both comparisons).

Compared with placebo, tiotropium increased the FEV1 response at 90 minutes after administration of study medication at study days 0, 90, and 180 by 0.13 L, 0.16 L, and 0.17 L, respectively (p < 0.0001 for all comparisons). Additionally, the morning trough FEV1 prior to administration of study drug was higher in tiotropium-treated patients than in placebo-treated patients at study days 90 and 180 (0.10 L and 0.09 L, respectively; p < 0.0001 for both comparisons).

MISTRAL STUDY (study 205.214)
The objectives of this study were to evaluate the effect of long-term treatment with inhaled tiotropium bromide on am PEFR, and influence on severity, type and incidence of acute exacerbations.

The MISTRAL study was a one-year parallel group, double-blind, randomized, placebo-controlled study in COPD patients aged, 40 years or older, with 30% ≤ FEV1 ≤ 65% of predicted value, FEV1/SVC ratio ≤ 70%, smoking history ≥ 10 pack-years and history of exacerbation in the past year.

Tiotropium significantly improved morning PEFR and through FEV1 compared to placebo and this effect was maintained over the 48-week treatment period without rebound effect after tiotropium stop. The changes in morning PEFR were significantly greater in the tiotropium group than with placebo from week 1 on with an average treatment difference of 25 L/min over the 1-year period.

Tiotropium significantly reduced the frequency of exacerbations and the number of days on exacerbations compared to placebo. The number of exacerbations per patient and per year was reduced by 34% with tiotropium compared to placebo (p=0.0008). The number of days of exacerbations per patient-year was also reduced by 37% in the tiotropium group (21.1 vs 33.3 days in placebo; p=0.0004).

This effect was observed irrespecive of the concomitant use of ICS. It was also significant for moderate to severe exacerbations. The average duration of exacerbations was not significantly modified overall.
Tiotropium significantly reduced the consequences of acute exacerbations in terms of health resource utilization. The number and duration of short courses of steroids and antibiotics, unscheduled visits and phone calls to physicians were significantly reduced compared to placebo. Number and duration of hospitalizations were lower in the tiotropium group but not statistically different from the placebo group in this trial.

- **Re-analysis of data of registration trials**

The one year placebo-controlled studies were pooled together and the one year active controlled trials together. Altogether the four one-year trials included 1,456 patients with COPD. In addition, the two multinational six-month studies were pooled together in 1,207 patients.

Definitions
A COPD exacerbation was defined in the protocols as a complex of COPD-related symptoms (i.e., cough, wheeze, dyspnea or sputum production) lasting longer than three days. Exacerbation information was taken from the adverse event data. The events were generally full-blown acute worsening of the underlying disease, usually associated with infection and requiring antibiotic and/or oral steroid therapy.

Patients with pneumonia who met the criteria for exacerbation, were included as having a COPD exacerbation in the pooled analysis.

Analysis
The treatment groups were compared in terms of time to first COPD exacerbation and in terms of time to hospitalisation associated with exacerbation by the Log rank test in each combined trial.

In addition, the proportion of patients with at least one COPD exacerbation and those with at least one hospitalisation associated with COPD exacerbation over the treatment period were compared across treatment groups using Logistic regression adjusted for extent of exposure and by Fisher's Exact test.

Results
The number of COPD exacerbations, the number of COPD exacerbation days, the number of hospitalisations and the number of hospitalisation days have been expressed in exposure units.

The three sets of registration trials show consistent trends upon re-analysis. As pooling was pre-specified in the six-month trials, and patients in the tiotropium treated group had significantly fewer COPD exacerbation days during the treatment period compared to placebo (p = 0.025; Wilcoxon-Mann-Whitney test), there is statistically significant evidence that 'tiotropium bromide significantly reduced exacerbation of COPD' on secondary data. The six-month trial data also show that tiotropium significantly delayed the time to exacerbation compared to placebo (p = 0.005, Log rank test). However, statistical significance of pre-specified groups could not be achieved in the two pairs of one year trials.

Nevertheless, given the consistency of the overall results and the relative lack of hospitalisation from COPD exacerbations in the placebo-controlled clinical trials, data support the claim that tiotropium is effective in reducing the risk of hospitalisation associated with COPD exacerbation.

Conclusions on exacerbation studies

The POET study demonstrated superiority of tiotropium over salmeterol for time to the first moderate or severe COPD exacerbation: tiotropium significantly reduced the risk of the first moderate or severe COPD exacerbation. The results of the secondary endpoints were consistent with the primary analysis.

In the VETERAN Trial the proportion of patients experiencing an exacerbation and the proportion of patients hospitalized due to an exacerbation was of borderline statistical significance. For the secondary endpoint, a reduction of exacerbations was shown with a statistical significance.

In addition, in the MISTRAL study, it was shown that tiotropium reduced the frequency of exacerbations and the number of days on exacerbations compared to placebo.

More support was provided by a re-analysis of the data of the registration trials on the secondary outcome exacerbation of COPD. The three sets of registration trials show consistent trends.

Altogether, the clinical documentation provided in the variation dossier of the MAH supports the therapeutic benefit of tiotropium, with evidence of clinical effect of tiotropium on exacerbations of COPD and exacerbations associated with hospitalisations.

The results of the POET study and VETERAN study have lead to a change of the label, i.e. section 5.1 of the SmPC.

Based on the results of the VETERAN study:

Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001)."SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

Based on the results of the POET study:

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of SPIRIVA once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.

Table 1: Summary of exacerbation endpoints

Endpoint	***SPIRIVA 18 microgram (HandiHaler) N = 3,707***	***Salmeterol 50 microgram (HFA pMDI) N = 3,669***	***Ratio (95% CI)***	***p-value***
Time [days] to first exacerbation†	*187*	*145*	*0.83 (0.77 - 0.90)*	*<0.001*
Time to first severe (hospitalised) exacerbation§	*-*	*-*	*0.72 (0.61 - 0.85)*	*<0.001*
*Patients with ≥1 exacerbation, n (%)**	*1,277 (34.4)*	*1,414 (38.5)*	*0.90 (0.85 - 0.95)*	*<0.001*
*Patients with ≥1 severe (hospitalised) exacerbation, n (%)**	*262 (7.1)*	*336 (9.2)*	*0.77 (0.66 - 0.89)*	*<0.001*

† *Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.*

§ *Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st*

quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.

* *Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.*

Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001)."SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

- **Exercise trials**

Five exercise trials were submitted post-registration in two different variations: TRIAL 205.131, TRIAL 205.223, TRIAL 205.230, TRIAL 205.365 and TRIAL 205.368.

The two placebo-controlled exercise trials, TRIAL 205.131 and TRIAL 205.223 were submitted post-registration in order to obtain a new wording in section 5.1 of the SmPC. The other trials did not lead to further change of the label.

TRIAL 205.131 and TRIAL 205.223
The 205.131 and 205.223 trials were multi-centre, randomised, double blind, placebo-controlled studies, conducted to investigate whether six weeks treatment with tiotropium (18 µg/day) improves exercise tolerance in COPD patients.

Study subjects included outpatients of either sex, between 40 and 75 years old, with a diagnosis of chronic obstructive pulmonary disease, FEV1 < 65% predicted normal and the presence of static lung hyperinflation (TGV(FRC) > 120% predicted normal).

Criteria for evaluation
The primary endpoint for both trials was the constant work rate exercise tolerance (ET) during a constant work rate cycle ergometry test performed 2 hours and 15 minutes after trial medication administration on Day 42 of treatment.
There were multiple secondary endpoints related to the ET like dyspnea lung function parameters single breath inert gas dilution parameters (Alveolar Volume [VA]), TDI, COPD symptom scores, Physician Global Assessment, and rescue medication use.

Safety parameters included adverse events, physical examination, ECGs, and vital signs. Constant work rate cycle ergometry was also performed on Day 0 (post-first dose) and Day 21 in both trials and 8 hours post-dosing in trial 205.223 on Day 42.

Statistical methods: ANCOVA with baseline as covariate

Results
Study 205.131
A total of 198 patients were randomized. A total of 187 (96 subjects receiving tiotropium and 91 subjects receiving placebo) completed at least 3 weeks of treatment and were included in the primary analysis. Twenty (20) patients discontinued the study prematurely with as most frequent reason worsening of disease under study (placebo group (9.0%), tiotropium group (3.1%)).

Overall the groups were comparable regarding the demographics and baseline characteristics.

Study 205.223
In study 205.223, a total of 261 patients were randomised. A total of 248 (131 subjects receiving tiotropium and 117 subjects receiving placebo) completed at least 3 weeks of treatment and were included in the primary analysis. Twenty 20 subjects prematurely withdrew from trial with as most frequent reason worsening of disease under study (4.6%, all in the placebo group).

Overall the groups were comparable regarding the demographics and baseline characteristics.

Efficacy results
The pre-specified primary parametric treatment comparison for ET, based on an ANCOVA model with terms treatment and centre and using baseline as a covariate, showed that tiotropium significantly improved ET compared with placebo at 2 hour 15 minutes post-dose on Day 42 of treatment:

- 205.131 (adjusted mean (SE)): 640.2 (30) seconds with tiotropium vs. 535.0 (31) seconds with placebo (treatment difference of 105.2 (40.3) seconds, p = 0.0098, 95% CI, 25.7 seconds, 184.7 seconds)
- 205.223 (adjusted mean (SE)): 803.2 (39.5) seconds with tiotropium vs. 567.6 (41.8) seconds with placebo, a treatment difference of 235.6 (57.7) seconds, p = 0.0001 (95% CI, 122.0 seconds, 349.3 seconds).

Table 13. Parametric treatment comparison for ET (sec, imputed), based on an ANCOVA model with terms treatment and centre and using baseline as a covariate - 205.131 and 205.223

	Baseline ET (Day -5)	ET on Day 42 of treatment		Treatment difference	95% CI
		tiotropium	placebo		
205.131 (U02-1202)	491.7 seconds	640.2 (30) seconds	535.0 (31) seconds	105.2 (40.3) seconds p = 0.0098	25.7 seconds, 184.7 seconds
205.223 (U04-3016)	534.9 seconds	803.2 (39.5) seconds	567.6 (41.8) seconds	235.6 (57.7) seconds p = 0.0001	122.0 seconds, 349.3 seconds

Additional statistical considerations in study 205.223
The data showed skewness, generally more apparent in the tiotropium group. Moreover, two outliers were present. Therefore, a non-parametric analysis of change in ET from baseline (Wilcoxon Rank Sum test stratified by Investigator) was performed. The results of these analyses confirmed the significant improvement in ET at all timepoints with tiotropium compared with placebo.

The outliers had ET >3000 secs, whereas in study 205.131 the adjusted mean (SE) was 640.2 (30) seconds with tiotropium vs. 535.0 (31) seconds with placebo (treatment difference of 105.2 (40.3) seconds, p = 0.0098, 95% CI, 25.7 seconds, 184.7 seconds).
The most reasonable estimate for the magnitude of the treatment effect in 205.223 is found in the analysis after removal of the 2 patients with outlying values of ET on Day 42, which decision is supported by non-parametric analyses.

Conclusions
It was demonstrated in trials 205.131 and 205.223 that:

(i) there is a statistically significant effect of 6 weeks treatment with tiotropium on ET compared with placebo,
(ii) the most reasonable estimate for the magnitude of the treatment effect in 205.223 is found in the analysis after removal of the 2 patients with outlying values of ET on Day 42, which decision is supported by non-parametric analyses
(iii) the magnitude of the treatment effect can consistently be described in terms of percent-increase in ET compared to placebo.

The results are reflected by the following wording in the SmPC:
The impact of improvements in dyspnoea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with Spiriva significantly improved symptom-limited exercise endurance time

during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A: 640 seconds with Spiriva vs. 535 seconds with placebo, compared with a pre-treatment baseline of 492 seconds) and 28.3% (Trial B: 741 seconds with Spiriva vs. 577 seconds with placebo, compared with a pre-treatment baseline of 537 seconds).

The MAH provided the summarized safety from the pooled Handihaler safety database for the different age classes. These data did not raise new concerns.

IV.4 Clinical safety

Adverse events

Dry mouth, including dry throat, was reported by a significantly greater proportion of patients in the tiotropium groups in both the placebo (16% vs 2.7%) and ipratropium (12.1% vs 6.1%) controlled trials. This was also seen in the salmeterol/placebo-controlled trials (8.2% tiotropium patients, 1.7% salmeterol and 2.3% placebo). Dry mouth was the most prominent adverse event overall and was reported as related in the majority of cases.

Events in theory potentially associated with dryness of mucous membranes in the upper respiratory tract and reported more frequently in tiotropium than placebo included epistaxis (3.6% vs. 1.9%), pharyngitis (8.9% vs. 7.3%), moniliasis (3.6% vs 2.4%) and sinusitis (11.3% vs. 9.4%). Only one such upper respiratory event was serious; sinusitis (in the tiotropium group) and withdrawals due to upper respiratory events (System Organ Class) were greater in placebo group (1.3%) vs. tiotropium group (0.4%).

In the one-year ipratropium-controlled trials, the frequency of these reports relative to ipratropium were epistaxis (1.1% vs. 1.1%), moniliasis (2.8% vs. 1.7%), pharyngitis (6.5% vs. 2.8%), and sinusitis (3.4% vs. 2.2%). In patients receiving tiotropium, only one (0.3%) was discontinued due to such upper respiratory events.

Additionally, urinary tract infection was reported by more tiotropium (7.3%) than placebo (5.1%) patients. A similarly higher rate of urinary tract infection was reported in the active-controlled trials on tiotropium (3.9%) than ipratropium (2.2%) therapy.

Constipation was reported in a higher proportion of tiotropium (3.5%) vs. placebo (1.6%) patients. There were no ascertainable differences between tiotropium (0.6%) and ipratropium (1.1%) in the active comparative trials.

Reports of chest pain coded under the System Organ Class (SOC) Body as a Whole were reported by a higher proportion of tiotropium-treated patients than in the placebo (6.9% vs. 4.6%) or ipratropium (5.3% vs. 2.2%) treated patients. The chest pains were not considered drug related except in one patient each in the two trials and were generally single transient events or non-specific events.

Observations in the six-month salmeterol/placebo-controlled trials are generally comparable to the one-year trials with the exception of a lower incidence of dry mouth and fewer imbalances seen with regard to anticholinergic effects.

Cardiovascular adverse events

Proportions were greater in the tiotropium group than placebo for overall (4.4% vs. 2.2%) and serious events (1.3% vs. 0.5%), while slightly lower for tiotropium vs. ipratropium in the ipratropium-controlled trials for overall (3.9% vs. 5.0%) and serious (0 vs. 1.1%) events. Discontinuations for events in this system organ class were restricted to four patients receiving tiotropium (arrhythmia, cardiac arrest, atrial fibrillation, and tachycardia). Two cases of palpitation, one AV block, one atrial fibrillation and one case of tachycardia in the tiotropium group were considered related.

Tachycardia was reported by four patients (1.0%) receiving tiotropium, no patients receiving salmeterol and one patient (0.3%) receiving placebo in the six-month salmeterol/placebo-controlled trials. Supraventricular tachycardia occurred in one patient each in the tiotropium and salmeterol groups. One case of ventricular tachycardia was noted in each group, salmeterol and placebo. The supraventricular and ventricular tachycardias were all reported as serious, whereas none of the tachycardia cases were reported as serious. Discontinuations in this category were more frequent in the placebo group (four) with one case in each of the active treatment groups.

There were no imbalances in number or type of ECG changes from the dose-ranging, one-year and six-month trials.

Additionally, there were no significant findings observed in the Holter monitoring observations in the 6 week trial (205.123) including assessments of arrhythmias, cardiac intervals, and heart rate variability.

A similar proportion of reports of myocardial infarction and ischemia were also observed. However, it can be noted that two of three cases of myocardial infarction in the control groups of the one-year trials (one with placebo and one with ipratropium) were reported as non-serious and found to be restricted to ECG evidence for myocardial infarction coding. In the six-month trials myocardial infarction was recorded in two patients in the tiotropium group, four patients in the salmeterol group and three patients in the placebo group.
Deaths from myocardial infarction occurred in four patients receiving tiotropium in the one-year trials and none in the six-month trials.

Serious adverse events
The proportion of serious adverse events (SAE) was less in the tiotropium group relative to the comparators.
No individual event occurred in more than 2% of patients with the exception of COPD exacerbation and pneumonia. Fewer tiotropium treated patients experienced exacerbation and pneumonia than their respective comparator groups of placebo and ipratropium.

There were only eleven patients with serious adverse events reported in other completed COPD trials; one patient (18 mcg tiotropium) with cystitis, hematuria and orchitis (205.123), one patient (placebo) with a fractured wrist, one patient (9 mcg tiotropium) with COPD exacerbation (205.108) and one patient (placebo) with dyspnea. One patient died of non-Hodgkins lymphoma 108 days after treatment (205.120). In trial 205.127, six patients reported serious adverse events during the treatment period. One pneumonia and one household accident in the tiotropium 1.25 mg Respimat group; one COPD exacerbation and one hematuria in the tiotropium 2.5 mg Respimat group and one COPD exacerbation and one gastrointestinal disorder in the placebo capsule group.
The hematuria was considered unexpected and related to the study drug. While the relationship could not be ruled out, the patient had a history of hematuria and prostate problems.

Deaths
Deaths in the one year trials occurred in less than 2% of patients which was balanced across groups. Specifically, in placebo-controlled trials, 1.3% of patients treated with tiotropium died as compared to 1.9% on placebo. Likewise, in ipratropium controlled trials 2.5% of patients treated with tiotropium died as compared to 1.7% receiving ipratropium. There was no obvious temporal relationship between time on drug and fatal events. No fatal events were considered related to drug.

The causes of death varied. In the one-year trials, there were four deaths due to myocardial infarction (one associated with respiratory failure and one with renal failure) and one death was due to arrhythmia in the tiotropium groups. No deaths due to myocardial infarction occurred in the control population. In the six-month trials cardiac deaths were limited to one patient in the salmeterol group (cardiac failure) and two patients in the placebo group (cardiac arrest).
Deaths reported in the other completed trials in the clinical program include a patient with non-Hodgkin's lymphoma occurring 108 days following placebo therapy and a patient with myocardial infarction and nephrotic syndrome who died 10-weeks after termination of two weeks treatment with tiotropium 18 mcg. There were no deaths in the early human pharmacology trials in healthy volunteers.

Adverse events leading to discontinuation Fewer patients in the tiotropium group discontinued the study due to adverse events than in the placebo and ipratropium group.
Withdrawals for lower respiratory events were more frequent in the control groups than for tiotropium.
Dry mouth leading to withdrawal was observed in three patients receiving tiotropium (0.5%) and one patient (0.3%) receiving placebo (placebo-controlled trials). There was one tiotropium patient in the six-month trials who withdrew due to dry mouth.
Other non-respiratory events leading to withdrawal in more than one patient in the one-year trials included cardiac failure (tiotropium 0.4% vs. placebo 0.8%), coronary artery disorder (tiotropium 0.4% vs. placebo 0.3%), and myocardial infarction (tiotropium 0.2% vs. placebo 0% and tiotropium 0.6% vs. ipratropium 0.6%). In the six-month trials non-respiratory events leading to withdrawal in more than one patient included pulmonary carcinoma (tiotropium 0.5% vs. 0% in controls), agitation (0.5% in placebo vs. 0% in tiotropium and salmeterol) and anxiety (0.5% in salmeterol vs. 0% in tiotropium and placebo).

Table 14. Adverse events (% of patients)

	Placebo	Tiotropium	Ipratropium	Tiotropium
Dry mouth	3	16	6	12
Epistaxis	2	4	1	1
Pharyngitis	7	9	3	7
Rhinitis	5	6	2	3
Sinusitis	9	11	2	3
Dysphonia	1	2	2	3
Upper airway infection	37	41	35	43
Moniliasis	2	4	2	3
Constipation	2	4	1	1
Urinary tract infection	5	7	2	4
Adverse events leading to discontinuation	14	10	12	10

Other findings
No obvious paradoxical bronchospasms was observed in any of the patients. No differences were seen in laboratory values, electrocardiograms, vital signs or physical examination.

- **Safety data of post-marketing trials**

The safety data of trial 205.235 (UPLIFT study) and trial 205.389 (POET study) are presented and discussed more extensively while the safety data of the other trials are presented only very shortly, i.e. SAE and deaths. Both studies were long-term studies (4 years for UPLIFT trial and 1 year for POET trial) and included a large population.
The results of the UPLIFT trial provided safety information that was included in SmPC.

UPLIFT TRIAL (205.235)
Of the 5,993 patients randomized, 4,383 (73%) completed 2 years, 3,891 (65%) completed 3 years, and 3569 (60%) completed ≥45 months. A higher proportion of patients failed to complete ≥45 months of treatment in the placebo group (44.6%) compared with the tiotropium group (36.2%, p<0.001).
The majority of discontinuations were due to adverse events.

Most patients reported at least one adverse event during the course of the trial (92%) and SAEs were reported by approximately half the patients (51%). The most frequently reported adverse events were due to respiratory causes. COPD exacerbations were reported for 65% of patients, pneumonia for 14% and dyspnea for 14% of patients. Of the respiratory events reported in at least 1% of patients, tiotropium was associated with a lower risk for COPD exacerbation, dyspnea and respiratory failure.

SAEs reported by >1% of patients were either respiratory or cardiac in nature. SAEs in the tiotropium group were observed for several events under these two SOC, with a lower risk of respiratory failure and a relative risk for myocardial infarction of 0.71 (0.52, 0.99) with 95% CI. Other SAEs that occurred at a lower frequency in the tiotropium group were cardiac failure congestive, COPD exacerbation, dyspnea and respiratory failure. The most frequently reported SAE was COPD exacerbation, occurring in 24% of patients overall.

Adverse events that led to discontinuation were reported for 23% of patients and their occurrence was more frequent in the placebo treatment group (25% placebo, 21% tiotropium). The most common reason for discontinuation was due to an exacerbation of a patient's underlying respiratory disease and fewer patients in the tiotropium treatment group discontinued treatment due to respiratory events.

Additional analyses were performed to evaluate the safety of tiotropium. An evaluation of stroke events did not identify an increased risk of stroke events or death from stroke in patients taking tiotropium. Similarly, an evaluation of cardiac events showed no adverse effect on ischemic heart disease and there was some evidence for reduced cardiac morbidity. There was also a reduction in reporting of respiratory failure that was supportive of meaningful reductions in respiratory morbidity from COPD.

Deaths

During the trial two amendments associated with mortality data were implemented. As originally written, the protocol follow-up of patients ceased 30 days post treatment discontinuation. The first amendment established procedures for the collection of vital status information on patients who prematurely discontinued from the trial extending to the protocol defined 4-year treatment period post-randomization (listed as day 1440 in the protocol) + the 30 day follow-up period (listed as day 1470 in the protocol). The second amendment established procedures for the adjudication of the primary cause of death by an independent committee.

Time to death was defined as time to the end date of the fatal AE. All patients were censored at 1470 days for the Kaplan-Meier estimates and Cox regression. In addition, as the protocol defined end-of-treatment protocol was day 1440, an analysis was performed using the cut-off of day 1440. The mortality endpoints for these analyses included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients.

Fatal events are presented in two ways: 1) deaths on-treatment and 2) all deaths including post-discontinuation vital status collection. Both 1 and 2 were analyzed with a cut-off of 1440 days (4 years), 1470 days (4 years and 30 days) and with no cut-off. A tabulated summary of all cause mortality is provided in Table 15 below. In the primary analyses the cause of death assessed by the adjudicated committee was utilized.

Table 16. Fatal adverse event summary - treated set

	Control	Tiotropium	ΔRates	Hazard Ratio Tiotropium vs. Control		
	N (%)	N (%)		HR	95% CI	P-value
On-Treatment (day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.009
On Treatment (day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On-Treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital Status (day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital Status (day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital Status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

On-treatment mortality (days 1440, 1470 and all)
The total number of deaths from any cause during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. The hazard ratio (HR) for death from any cause (tiotropium/placebo) was 0.84 (95% CI = 0.73, 0.97).

It is evident from the Kaplan-Meier estimate of no death on-treatment by day 1470 figure that the two curves show clear separation after 12 months with the curve for tiotropium on top and the separation is maintained until month 48. The Kaplan-Meier figure and the hazard ratio suggest a benefit of tiotropium on on-treatment mortality.

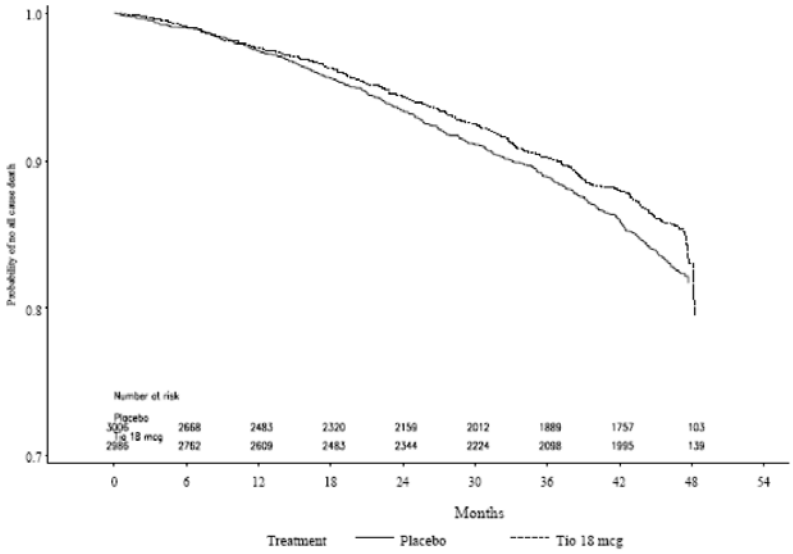

Figure 3. Kaplan-Meier estimates of probability of no all cause on-treatment deaths-treated set-censored at day 1470

The HR for lower respiratory deaths by day 1470 (271 cases) was 0.85 (95% CI= 0.67, 1.08). The HR for cardiac deaths (49 cases) at day 1470 was 0.88 (95% CI=0.50, 1.55).

The preferred terms sudden death, sudden cardiac death, and death (of unknown cause) are reported in MedDRA under the General disorders SOC, yet these terms are often considered cardiac events. Combining these three preferred terms, 70 on treatment deaths (day 1470, adjudicated) were reported with placebo and 57 with tiotropium (HR 0.75, 95% CI=0.53, 1.06).

The most common causes of death (reported in >1% of patients in either treatment group) during study drug treatment as assessed by the adjudication committee were COPD exacerbation (121 on placebo, 103 on tiotropium), lung neoplasm malignant (66 on placebo, 73 on tiotropium) and death of unknown cause (36 on placebo, 29 on tiotropium). The associated rate ratios (95% CI) are: 0.79 (0.60, 1.02), 1.02 (0.73, 1.43) and 0.74 (0.46, 1.21), respectively.

The proportion of patients reporting events was less in the tiotropium group in 4 of the 5 SOCs where an adjudicated cause of death was reported. For the SOC Respiratory Systems Disorders Other, which is primarily the SOC where cancers are reported, there were 82 deaths in the tiotropium group and 72 in the placebo group. The differences were not significant.

Table 17. Deaths reported in >1% of patients by SOC- adjudicated; on treatment mortality-treated set-day 1470.

System Organ Class	Placebo N = 3006 N (%)	Tiotropium 18 mcg N = 2986 N (%)	Hazard ratio (95% CI) [Tio vs. Pla]	P-value*
Respiratory system disorders (lower)	140 (4.7)	131 (4.4)	0.85 (0.67, 1.08)	0.1936
General disorders and administration site conditions	70 (2.3)	57 (1.9)	0.75 (0.53, 1.06)	0.1072
Respiratory system disorders (other)	72 (2.4)	82 (2.7)	1.04 (0.76, 1.42)	0.8229
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	41 (1.4)	36 (1.2)	0.80 (0.51, 1.25)	0.3187
Cardiac disorders	25 (0.8)	24 (0.8)	0.88 (0.50, 1.55)	0.6630

The HR for on-treatment death from any cause at 4 years (Day 1440) was 0.83 (95% CI=0.72, 0.95). The most common causes of death were COPD exacerbation, lung neoplasm malignant and death of unknown cause. There was a lower risk of death during treatment with tiotropium 12.8% than with placebo 13.7%, which included 30 days post last day of study drug.

Time to death was defined as time to the end date of the fatal AE. All patients were censored at 1470 days for the Kaplan-Meier estimates and Cox regression. In addition, as the protocol defined end-of-treatment protocol was day 1440, an analysis was performed using the cut-off of day 1440. The mortality endpoints for these analyses included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients. Fatal events are presented in two ways: 1) deaths on-treatment and 2) all deaths including post-discontinuation vital status collection. Both 1 and 2 were analyzed with a cut-off of 1440 days (4 years), 1470 days (4 years and 30 days) and with no cut-off.

Vital status information was known for 97.6% of patients. For the period of 4 years +30 days (day 1470) including vital status the number of deaths was reduced (n=446) in the tiotropium group compared with the placebo group (n=495). Analyses for death at day 1440 (end of protocol defined treatment period) indicated a reduction in all cause mortality.

Serious adverse events

Other than lung cancer, serious adverse events reported by >1% of patients in either treatment group were either cardiac or respiratory in nature. The incidence of all serious adverse events combined for the system organ classes (SOC) cardiac and lower respiratory system disorders was lower with tiotropium. On a preferred term basis, this included reduced risks for the terms cardiac failure congestive, COPD exacerbation, dyspnea, and respiratory failure.

Table 18. Incidence rate (per 100 person years) of patients experiencing serious adverse events[1] reported by >1/% of patients in any treatment group according to organ class during the treatment period (from first to last day of study drug + 30 days).

	Tiotropium n=2986	Placebo n=3006	Rate Ratio[3]	95% CI
Cardiac SOC	3.56	4.22	0.84	0.73, 0.98[2]
Angina	0.51	0.36	1.44	0.91, 2.26
Atrial fibrillation	0.74	0.77	0.95	0.68, 1.33
Cardiac failure	0.61	0.48	1.25	0.84, 1.87
Cardiac failure congestive	0.29	0.48	0.59	0.37, 0.96[2]
Coronary artery disease	0.21	0.37	0.58	0.33, 1.01
Myocardial infarction	0.69	0.97	0.71	0.52, 0.99[2]
Respiratory (lower) SOC	11.32	13.47	0.84	0.77, 0.92[2]
Bronchitis	0.37	0.31	1.20	0.73, 1.98
COPD exacerbation	8.19	9.70	0.84	0.76, 0.94[2]
Dyspnea	0.38	0.62	0.61	0.40, 0.94[2]
Pneumonia	3.28	3.46	0.95	0.81, 1.11
Respiratory failure	0.90	1.31	0.69	0.52, 0.92[2]

[1]excluding lung cancer (multiple different terms); [2]$p<0.05$; [3]rate ratio (tiotropium/placebo)

This study enhanced the understanding and confirmed the safety profile of tiotropium in terms of adverse events, both serious and non serious. Anticholinergic events such as dry mouth, constipation,

intestinal obstruction, gastroesophageal reflux disease, dysuria, dysphonia and urinary retention were more common with tiotropium. However, atrial fibrillation, an event usually associated with tiotropium, was balanced compared to placebo. There was no imbalance overall with ischemic heart disease nor was there evidence of an increased risk of stroke. In addition, tiotropium reduced all-cause mortality, exacerbations of COPD and reports of respiratory failure.

TRIAL 205.389 (POET STUDY)
Overall, 7,376 patients were randomised and treated with at least 1 dose of randomised study medication (tiotropium: 3,707 patients, salmeterol: 3,669 patients). The planned study duration was 360 days.
The median exposure to study drug was similar in both treatment groups (363 days tiotropium and 362 days for salmeterol). The total exposure was longer in the tiotropium group (3,308.4 patient years versus 3,209.6 patient years for salmeterol).
At the planned end of the study (exposure ≥360 days), a higher proportion of patients in the tiotropium group were still on study medication (76.6% versus 73.7% for salmeterol).

Patients in the tiotropium and the salmeterol group were comparable with regards to all major characteristics like demographic data, smoking history, lung function/COPD severity, pulmonary medication and comorbidities at baseline

In the POET-COPD trial (Phase IV) the collection of safety data was modified compared with standard clinical trials because the study medications were approved and had already well established safety profiles. Only serious adverse events and certain categories of non-serious adverse events were systematically collected.

With respect to cardiovascular events and cardiovascular mortality, the composite endpoints of major adverse cardiovascular events (MACE), fatal MACE, and stroke were analysed.

Collection of non-serious adverse events:
- For all AEs leading to treatment discontinuation.
- non-serious AEs prospectively foreseen to be related to any of the study drugs by the investigators.
- In Poland, all non-serious AEs were collected.
- In Norway, unexpected study drug-related AEs were collected.

Following additional analyses were preplanned:
- Analysis of major adverse cardiovascular events and stroke (MACE)
- Analysis of pneumonia
- Mortality analysis

Results
No study-drug related AE was reported in Norway. Overall the frequency of AEs was balanced across the treatment groups (tiotropium: 24.5%, salmeterol: 27.3%).

SAE
SAEs were reported for a smaller proportion of patients in the tiotropium group (14.7%) than in the salmeterol group (16.5%, rate ratio tiotropium versus salmeterol: 0.86; 95% CI: 0.77, 0.97), which is mostly caused by a reduction of SAEs in the 'respiratory, thoracic and mediastinal disorders' SOC and COPD exacerbations in particular. Patients in the tiotropium group had a reduced risk for respiratory disorders (incidence rate ratio: 0.79, 95% CI: 0.68, 0.92) at a frequency of 8.1% of patients in the tiotropium groups versus 10.0% of patients in the salmeterol group.

The incidence rate ratio of cardiac disorders was 1.12 (95% CI: 0.84, 1.50).

On MedDRA preferred term level, the most frequently reported SAE was COPD with a reduced risk for tiotropium patients (incidence rate ratio: 0.77, 95% CI: 0.66, 0.91) at a frequency of 7.3% of patient in the tiotropium group versus 9.1% in the salmeterol group.

All deaths
Overall, 171 deaths (2.3%) were reported for randomised and treated patients until database lock, irrespective of planned or actual treatment. Numerically smaller proportions of deaths were reported in the tiotropium group in all periods. Fatal events (including vital status of prematurely discontinued patients until Day 360) occurred in 1.7% and 2.1% of tiotropium and salmeterol treated patients.

Table 19. Overall summary of death/Treated Set

	Tiotropium		Salmeterol	
	n	(%)	n	(%)
Patients treated	3,707	(100.0)	3,669	(100.0)
All deaths[1]	79	(2.1)	92	(2.5)
Fatal AEs with onset during actual treatment	44	(1.2)	52	(1.4)
Fatal AEs with onset during actual treatment + 30 days	66	(1.8)	73	(2.0)
Fatal AEs with onset during planned treatment	70	(1.9)	82	(2.2)
Fatal AEs with onset during planned treatment and date of death on or before day 360	64	(1.7)	78	(2.1)

[1] All deaths reported up to the date of database lock for the Treated Set, i.e. excluding 5 deaths of patients who were screened but not randomised or patients who were randomised but not treated

The most frequent adjudicated primary causes of death on MedDRA system organ class (SOC) level were general disorders and respiratory disorders. Various mortality analyses were performed, based on different definitions of treatment periods and based on either adjudicated or investigator-reported causes of death.

There were numerically fewer fatal cases in the tiotropium group relative to the salmeterol group for each of the analyses; however, in all cases the 95% CI of the hazard ratio included the value 1.

Other post-marketing safety data
The safety of the following trials is summarized. The reported events did not change the safety labelling of Spiriva.

TRIAL 205.266
A total of 1829 patients were randomized and received at least one dose of study medication; 914 patients were treated with tiotropium and 915 patients received placebo. Fewer patients in the tiotropium group compared to the placebo group prematurely discontinued from trial medication (149 patients, 16.3% vs. 245 patients, 26.8%, respectively).

The planned exposure was 180 days. The median duration of exposure and maximal extent of exposure was comparable in the two treatment groups.

TRIAL 205.214
A total of 1010 patients were randomized and received at least one dose of study medication; 500 patients were treated with tiotropium and 510 patients received placebo. Fewer patients in the tiotropium group compared to the placebo group prematurely discontinued from trial medication (117 patients, 23.4% vs. 147 patients, 28.8%, respectively). The planned exposure was 336 days. The median duration of exposure was comparable in the two treatment groups. Overall, mean extent of exposure was slightly greater in the tiotropium group compared to the placebo group.

Analysis of adverse events was consistent with the core registration studies and with the population under study.

TRIAL 205.256
Analysis of adverse events during the conduct of the TIPHON study was consistent with the core registration studies, other than a lower reporting of dry mouth. The adverse events were consistent with the population under study.

Two hundred and sixty-six (266) patients were treated with tiotropium and 288 patients received placebo. Fewer patients in the tiotropium group compared to the placebo group prematurely discontinued from trial medication (39 patients, 14.7% vs 74 patients, 25.7%, respectively).

TRIAL 205.131
A total of 198 patients were randomized and received at least one dose of trial medication, 98 patients in tiotropium group, 100 patients in placebo group. The planned exposure time was 43 days.

Twenty patients (10.1% of total randomized) withdrew from the trial prior to completion. Seven were on tiotropium at the time of withdrawal (7.1% of patients on tiotropium) and 13 on placebo (13.0% of patients on placebo).
Analysis of adverse events was consistent with the core registration studies and with the population under study.

TRIAL 205.223
One hundred and thirty-one (131) subjects received tiotropium (18 mcg/d) and 130 subjects received placebo. One subject (0.8%) in the tiotropium group and 19 subjects (14.6%) in the placebo group withdrew from the trial prior to completion.

Analysis of adverse events was consistent with the core registration studies and with the population under study.

TRIAL 205.365
Tiotropium was well tolerated and the safety results were consistent with the previous safety experience for this drug and label.

TRIAL 205.368
A total of 519 patients were randomised and received at least one dose of study medication (259 placebo, 260 tiotropium). Placebo patients were more likely to discontinue the trial than tiotropium patients (HR 0.61, 95%CI, 0.44, 0.83; p=0.0018). Subsequently, exposure between the two groups at 96 weeks was different with 47.8 fewer patient years in the placebo group (359.1 patient years) compared to the tiotropium group (406.9 patient years).

The safety assessment from this trial was consistent with the overall safety database from previous tiotropium clinical trials. The trial did not identify any previously unsuspected important adverse reaction to tiotropium. There was no disparity between treatment groups with respect to fatal events during the double-blind phase of the trial. Over the entire course of the trial (100 weeks, including deaths reported from vital status collection) the number of fatal events was numerically lower in the tiotropium group than placebo.

Table 20. Serious adverse events and deaths

	SAEs	Deaths
205.266	17.7% of the tiotropium group and 17% of the placebo group most frequently were lower respiratory system disorders: tiotropium group 7.8% placebo 9.9% COPD exacerbations were the most commonly reported serious adverse events. The incidence of COPD exacerbations reported as SAEs was lower in the tiotropium group compared to placebo group (4.2% vs. 6.7% of patients, respectively).	67 in total. Treatment period Tio 22 (2.4%), placebo19 (2.1%) None of the deaths were treatment related 15 deaths in lower respiratory system disorders, 2 in Tio, 7 in placebo group. Fatal cardiac events: 3 in tio group, 6 in placebo group. 5 deaths unknown cause (4 in tio, 1 in placebo group) 5 in screening period, 21 of post-

		treatment period.
205.214	Serious lower respiratory events: Tio 11.2%, placebo 12.9% , COPD exacerbation Tio 4.6%, placebo 6.1% SAE of cardiac etiology: Tio group compared to placebo (2.2% vs. 3.7%, no relevant imbalance in the incidence of heart rhythm disorders	
205.256	Tio 15.8%, placebo 13.2%, Lower respiratory disorders: Tio 7.1% , placebo 6.3%. Vascular disorders: Tio 1.9%, placebo 1.0%. Cardiac SAEs Tio (0.8%), placebo 2.1%. no other relevant imbalance	9 deaths: Tio 3 (1.1%), placebo 6 (2.1%).
205.131	Tio 3.1%, placebo 3.0%, none as TAEA . COPD exacerbation 2.0% on Tio, 1.0% on placebo.	1 patient (placebo)
205.223	SAEs Tio 2 (1.5%), placebo 2 (1.5%). None was related to trial medication	1 patient (placebo) appr. 4.5 months after conclusion of participation
205.365	Serious AEs tiotropium 10 (4.2), placebo 11 (5.0); none were considered treatment related.	No deaths occurred
205.368	SAEs were reported by 22.8% of placebo patients and 24.2% of tiotropium patients during the double-blind treatment period. The most frequently reported (>3%) SAEs were exacerbation of COPD and pneumonia.	Blinded phase: 12 deaths, 6 placebo, 6 tiotropium), mostly malignant neoplasms, cardiac and lower respiratory disorders. The HR (95% CI) for death from any cause (tio/placebo) was 1.041 (0.317, 3.411). A total of 19 deaths were reported for the full 100 week study period, including vital status (11, 4.2% in the placebo group and 8, 3.1% in the tiotropium group). The HR (95% CI) was 0.72 (0.29, 1.79).

Conclusion
In the registration trials, the overall proportion of patients with adverse events, serious adverse events, events leading to withdrawal, and events leading to death were either balanced among treatment groups or occurred less frequent in the tiotropium groups.
Based on this critical assessment of the data, there were no special conditions identified beyond those existing for the class, i.e. use with caution in patients with predisposition to narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction and other than monitoring closely in patients with moderate to severe renal insufficiency where slightly increased plasma levels of drug could possibly result in anticholinergic side effects.

Out of all the post-marketing studies, the UPLIFT study provided additional safety information: during the 4 years of treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

IV.5 Risk Management Plan

The MAH has submitted a risk management plan (RMP), 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 Srivasso 18 micrograms, inhalation powder, hard capsules.
The RMP has been updated in line with the established RMP in the type IB variations for Spiriva (NL/H/0718/001/IB/015, NL/H/0299/001/IB/063, February 2015).

Table 21. Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
None	Not applicable	Not applicable
Important potential risks		
Cardiac mortality Blood and lymphatic system disorders Blood glucose increased Psychiatric disorders Syncope Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris). Vascular disorders (aneurysm, hypertension) Renal failure Overdose	Routine pharmacovigilance	Not applicable
Missing information		
Treatment of pregnant and breast-feeding women Treatment of paediatric patients Long-term safety for indication asthma Patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure	Not applicable	Not applicable

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

IV.6 Discussion on the clinical aspects

The two one-year registration studies show that tiotropium therapy results in statistically significant long-term bronchodilator efficacy in comparison with both placebo and ipratropium. The primary

efficacy variable mean trough FEV1 response with tiotropium is 0.11 and 0.12 liter in the placebo and comparator trials respectively. The peak (and average) response with tiotropium is 0.26 (average; 0.19) and 0.31 (average; 0.23) liter in the two pooled studies.

The results of tiotropium on symptoms and quality of life compared to the results with ipratropium, follow the results compared to placebo, yet the differences are smaller. Tiotropium is at least as good, or on several points better than ipratropium.

Tiotropium showed also a beneficial effect on exacerbations. Fewer patients experience exacerbations and hospitalizations with tiotropium treatment than with placebo or ipratropium. Tiotropium reduces the number of exacerbations per patient years. Furthermore, tiotropium delays the occurrence of an exacerbation.

The results of the salmeterol-compared registration studies confirm that tiotropium improves lung function, symptoms, quality of life, and exacerbations. Furthermore, the efficacy results of tiotropium with respect to lung function, symptoms, and quality of life are at least as good as the results of salmeterol therapy.

The twelve post-marketing studies provided further evidence of the efficacy of tiotropium Handihaler 18 mcg compared with salbutamol or placebo. The studies showed improvement in important domains of the treatment of COPD. The UPLIFT and POET trials are of great interest because they were long-term and included a high number of patients. The 4 year, randomised placebo-controlled UPLIFT study (5993 patients) showed an improvement in FEV1 resulting from tiotropium, compared with placebo, that remained constant throughout 4 years. The annualized rate of decline of FEV1 compared to placebo was similar between tiotropium and placebo.
The one-year randomised, salmeterol controlled POET trial (7376 patients) showed a reduction of exacerbations in favour of tiotropium compared with salmeterol.

The expected anticholinergic events are dry mouth, tachycardia, urinary retention, constipation and glaucoma.
The overall proportion of patients with adverse events, serious adverse events, events leading to withdrawal, and events leading to death were either balanced among treatment groups or less frequent in the tiotropium groups in the placebo-controlled, the ipratropium-controlled, and the salmeterol/placebo-controlled trials.

Out of all the post-marketing studies, the UPLIFT study provided additional safety information: during the 4 years of treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

Overall, based on the study data on efficacy and safety present in the Spiriva dossier, the benefit=risk profile for Srivasso is positive from a clinical point of view.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The interviews were conducted in two rounds. Firstly, ten respondents were interviewed. 24 questions in the questionnaire related to the product description and a further 8 to the use of the HandiHaler device.
Since there were no difficulties encountered in either locating the important information or understanding the information in the leaflet, it was decided to proceed with the second round of interviewing (a further ten respondents) without making any amendments to the leaflet.
Overall the readability test demonstrated that at least 18 out of 20 patients (90% of the sample) were able to find the information within the leaflet and at least 90% showed that they understood the information. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Srivasso 18 micrograms, inhalation powder, hard capsule has a proven chemical-pharmaceutical quality. As in the Spiriva dossier, the non-clinical and clinical sections are adequate to support the efficacy and safety of tiotropium.

The beneficial efficacy of the active substance with respect to lung function, symptoms, quality of life and exacerbations is considered clinically relevant in the treatment of COPD patients. The efficacy of tiotropium is favourable in comparison with ipratropium and as least as good as salmeterol. Anticholinergic adverse events occur more often with tiotropium than with ipratropium, especially dry mouth, which is in most cases temporarily. Upper airway infections are more frequently reported as well. Overall, the safety profile is sufficiently established.

The Board followed the advice of the assessors.

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 the product demonstrated adequate evidence of efficacy for the approved indication, and an acceptable level of safety. As for Spiriva, the overall benefit/risk balance of Srivasso is positive. The decentralised procedure was finalised with a positive outcome on 24 June 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
Any minor adjustment of the quantitative composition of the finished product with respect to excipients.	NL/H/3137/001/ WS/001	II/WS	30-9-2015	29-11-2015	Approval	No
Deletion of manufacturing sites; replacement or addition of a site where batch control/ testing takes place; deletion of a supplier; replacement or addition of a supplier.	NL/H/3137/001/ IA/002/G	IA/G	24-9-2015	24-10-2015	Approval	No
Other variation.	NL/H/3137/001/ WS/003	II/WS	30-9-2015	29-11-2015	Approval	No
Minor changes to an approved test procedure; other changes to a test procedure (including replace-ment or addition).	NL/H/3137/001/ WS/004	II/WS	30-9-2015	29-11-2015	Approval	No
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	NL/H/3137/001/ WS/005	II/WS	30-9-2015	18-1-2016	Approval	Yes, Annex I
Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier).	NL/H/3137/001/ IA/006/G	IA/G	21-12-2015	7-1-2016	Approval	No

Annex I – Update of the SmPC with the results of Tiospir study 205.452 and with PK/PD study 205.458 (NL/H/3137/001/WS/005)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the member states consider that the variation for Srivasso 18 microgram, inhalation powder, hard capsule (tiotropium bromide), for the proposed changes to the SmPC, Package Leaflet and labelling is approvable.

The changes are specified in section IV of this annex.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

The scope of this variation was to update the SmPC driven by the results of the TioSpir™ study. The MAH's main proposals concern the addition of the key results of TioSpir (205.452) to the SmPC, as well as the addition of the results of PK/PD study 205.458.
The same variation was approved for Spiriva 18 microgram, inhalation powder, hard capsule on 21 November 2015 through variation NL/H/0299/001/II/057.

SmPC section 5.1 pharmacodynamic properties: new proposed text (results of TioSpir study):

- Description of the study
- Efficacy results COPD exacerbations, bronchodilator effect)
- Safety (all-cause mortality)

Update of Pharmacokinetic properties
SmPC section 5.2: Update of this section considering the new PK/PD results (study 205.458)

Commitment of the label variation for Spiriva: NL/H/0299/001/II/0046 (POET-COPD trial 203.389)
During this variation the MAH committed to shorten section 5.1 Pharmacodynamic properties in one of the next SmPC updates. The study results are then presented in the same way as presented in the SmPC of Spiriva Respimat. This section has been structured with some sub-headers in a similar way to the SmPC of Spiriva Respimat.

Additional revisions/amendments
SmPC section 4.5 Interaction: One statement on common concomitant medications used by COPD patients has been added.

SmPC section 4.6 Fertility, pregnancy and lactation:
Pregnancy wording adapted according to current 'EU Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation'.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The proposed changes to the product information are already approved for the original product Spiriva 18 microgram, inhalation powder, hard capsule in variation NL/H/0299/001/II/057.
The member states consider the changes to the SmPC, Package Leaflet and labelling justified. The product information is updated with the results of the TioSpir study and PK/PD study 205.458.

The variation was completed on 18 January 2016.

IV. CHANGES IN PRODUCT INFORMATION

The revised paragraphs of the SmPC and package leaflet are outlined below, new text underlined, deleted text strikethrough.

- SmPC

4.4 Special warnings and precautions for use

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

4.5 Interaction with other medicinal products and other forms of interaction

Use of LABA or ICS was not found to alter the exposure to tiotropium.

4.6 Fertility, pregnancy and lactation

Pregnancy
~~For tiotropium bromide, no documented clinical data on exposed pregnancies are available.~~
~~Studies in animals have shown reproductive toxicity associated with maternal toxicity (see section 5.3). The potential risk for humans is unknown. Srivasso should therefore only be used during pregnancy when clearly indicated.~~
There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Srivasso during pregnancy.

5.1 Pharmacodynamic properties

Lung function
Tiotropium~~In the aforementioned studies~~, tiotropium bromide, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance.

A randomised, placebo-controlled clinical study in 105 COPD patients demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether the drug was administered in the morning or in the evening.

~~The following health outcome effect was demonstrated in the long term (6-month and one-year) trials:~~
Clinical trials (up to 12 months)

Dyspnoea, Exercise tolerance
Tiotropium bromide significantly improved dyspnoea ~~dyspnea~~ (as evaluated using the Transition Dyspnoea ~~dyspnea~~Index.). This improvement was maintained throughout the treatment period.

The impact of improvements in dyspnoea ~~dyspnea~~on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with Srivasso significantly improved symptom-limited exercise endurance time during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A) ~~640 seconds with Srivasso vs. 535 seconds with placebo, compared with a pre-treatment baseline of 492~~

~~seconds) and 28.3% (Trial B: 741 seconds with Srivasso vs. 577 seconds with placebo, compared with a pre-treatment baseline of 537 seconds)~~ and 28.3% (Trial B) compared with placebo.

~~In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).~~

Health-related Quality of Life
In a 9-month, randomized, double-blind, placebo-controlled clinical trial of 492 patients, Srivasso improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with Srivasso which achieved a meaningful improvement in the SGRQ total score (i.e. > 4 units) was 10.9% higher compared with placebo (59.1% in the Srivasso groups vs. 48.2% in the placebo group (p=0.029). The mean difference between the groups was 4.19 units (p=0.001; confidence interval: 1.69 – 6.68). The improvements of the subdomains of the SGRQ-score were 8.19 units for "symptoms", 3.91 units for "activity" and 3.61 units for "impact on daily life". The improvements of all of these separate subdomains were statistically significant.

COPD Exacerbations
In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).

~~In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3,006 receiving placebo and 2,987 receiving Srivasso), the improvement in FEV_1 resulting from Srivasso, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Srivasso group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV_1 compared to placebo was similar between Srivasso and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).~~

Long-term clinical trials (more than 1 year, up to 4 years)
In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving Srivasso), the improvement in FEV_1 resulting from Srivasso, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Srivasso group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV_1 compared to placebo was similar between Srivasso and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

Tiotropium active-controlled study
A long-term, large scale randomised, double-blind, active-controlled study with an observation period up to 3 years has been performed to compare the efficacy and safety of Srivasso HandiHaler and Spiriva Respimat (5,694 patients receiving Srivasso HandiHaler; 5,711 patients receiving Spiriva

Respimat). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).

The time to first COPD exacerbation was numerically similar during the study with Srivasso HandiHaler and Spiriva Respimat (hazard ratio (Srivasso HandiHaler/Spiriva Respimat) 1.02 with a 95% CI of 0.97 to 1.08). The median number of days to the first COPD exacerbation was 719 days for Srivasso HandiHaler and 756 days for Spiriva Respimat.

The bronchodilator effect of Srivasso HandiHaler was sustained over 120 weeks, and was similar to Spiriva Respimat. The mean difference in trough FEV1 for Srivasso HandiHaler versus Spiriva Respimat was 0.010 L (95% CI -0.018 to 0.038 L).

In the post-marketing TioSpir study comparing Spiriva Respimat and Srivasso HandiHaler, all-cause mortality including vital status follow up was similar during the study with Srivasso HandiHaler and Spiriva Respimat (hazard ratio (Srivasso HandiHaler/Spiriva Respimat) 1.04 with a 95% CI of 0.91 to 1.19).

5.2 Pharmacokinetic properties

b) General Characteristics of the Active Substance after Administration of the Medicinal Product

Absorption: Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable~~. It is expected from the chemical structure of the compound (quaternary ammonium compound) and from in vitro experiments that tiotropium bromide is poorly absorbed from the gastrointestinal tract (10-15%).~~ Oral solutions of tiotropium ~~bromide~~ have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed ~~five~~ 5-7 minutes after inhalation. ~~Food is not expected to influence the absorption of this quaternary ammonium compound.~~

~~*Distribution:* The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 L/kg.~~
At steady state, peak tiotropium ~~bromide~~ plasma levels in COPD patients ~~at peak~~ were ~~17 - 19~~ 12.9 pg/ml ~~when measured 5 minutes after dry powder inhalation of a 18 microgram dose~~ and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were ~~3 - 4~~ 1.71 pg/ml. Systemic exposure following the inhalation of tiotropium via the HandiHaler device was similar to tiotropium inhaled via the Respimat inhaler.

Distribution: Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium bromide does not penetrate the blood-brain barrier to any relevant extent.

Elimination: The ~~terminal elimination~~ effective half-life of tiotropium ~~bromide is~~ ranges between ~~5 and 6 days following inhalation~~ 27-45 h in COPD patients. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers ~~with an interindividual variability of 22%~~. Intravenously administered tiotropium ~~bromide~~ is mainly excreted unchanged in urine (74%). After dry powder inhalation by COPD patients to steady-state urinary excretion is 7% (1.3 µg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. The renal clearance of tiotropium ~~bromide~~ exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached ~~after 2 – 3 weeks~~ by day 7 with no accumulation thereafter.

Linearity / Nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range ~~after both intravenous administration and dry powder inhalation~~ independent of the formulation.

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, ~~advanced~~advancing age was associated with a decrease of tiotropium ~~bromide~~ renal clearance (365 mL/min in COPD patients < ~~58~~65 years to ~~163~~271 mL/min in COPD patients > ~~70~~65 years) ~~which may be explained by~~

~~decreased renal function. Tiotropium bromide excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients), however plasma concentrations~~ This did not ~~change significantly with advancing age within COPD patients if compared to inter- and intraindividual variability (43% -~~result in as corresponding increase in AUC_{0-6ss} ~~after dry powder inhalation -~~or $C_{max,ss}$ values.

Renally Impaired Patients ~~In common with all other drugs that undergo predominantly renal excretion, renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both intravenous infusion and dry powder inhalations. Mild~~ Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50-80 ml/min) ~~which is often seen in elderly patients increased tiotropium bromide plasma concentrations~~ resulted in slightly ~~(39% increase in AUC_{0-4h} after intravenous infusion)~~ higher $AUC_{0-6,ss}$ (between 1.8-30% higher) and similar $C_{max,ss}$ values compared to patients with normal renal function(CL_{CR} >80 ml/min).

In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min) the intravenous administration of tiotropium ~~bromide~~resulted in doubling of the ~~plasma concentrations~~ total exposure (~~82% increase in AUC_{0-4h}~~ higher AUC_{0-4h} and 52% higher C_{max}) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation..

Hepatically Impaired Patients: Liver insufficiency is not expected to have any relevant influence on tiotropium ~~bromide~~ pharmacokinetics. Tiotropium ~~bromide~~ is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Japanese COPD Patients: In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post-dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.

- PACKAGE LEAFLET

2. What you need to know before you use Srivasso 18 microgram

Warnings and precautions
Talk to your doctor or pharmacist before using Srivasso 18 microgram:

(…)
- In case you have suffered from a myocardial infarction during the last 6 months or from any unstable or life threatening irregular heart beat or severe heart failure within the past year, please, inform your doctor. This is important to decide if Srivasso is the right medicine for you to take