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PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Spiriva Respimat 2.5 microgram, solution for inhalation
Boehringer Ingelheim International GmbH, Germany

tiotropium bromide monohydrate

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

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

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

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

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Pharmacotherapeutic group:	Other drugs for obstructive airway diseases, inhalants, anticholinergics
ATC code:	R03B B04
Route of administration:	inhalation
Therapeutic indication:	maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD)
Prescription status:	prescription only
Date of authorisation in NL:	24 September 2007
Concerned member states:	AT, BE, CY, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NO, PL, PT, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

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

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List of abbreviations

ACI	Anderson Cascade Impactor
ACQ	Asthma Control Questionnaire
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
ATS	American Thoracic Society
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic Fibrosis
CF	CF Questionnaire
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
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FDA	Food and Drug Administration of the USA
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRQoL	Health-related quality of life
ICH	International Conference of Harmonisation
ICS	Inhaled Corticosteroids
IRR	Incidence-Rate Ratio
LABA	Long-acting β_2 Agonist
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
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RR	Relative Risk
RSSQ	Respiratory and Systemic Symptoms Questionnaire
SAE	Serious Adverse Event
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire

SmPC	Summary of Product Characteristics
SOC	System-Organ Class
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TDI	Transition Dyspnoea Index
Tio HH 18	tiotropium 18 µg delivered by the HandiHaler
Tio R2.5	tiotropium 2.5 µg delivered by the Respimat inhaler per two actuations
Tio R5	tiotropium 5 µg delivered by the Respimat inhaler per two actuations
Tio R10	tiotropium 10 µg delivered by the Respimat inhaler per two actuations
Tio R20	tiotropium 20 µg delivered by the Respimat inhaler per two actuations
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Spiriva Respimat 2.5 microgram, solution for inhalation, 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 Summary of Product characteristics (SmPC).

Tiotropium is a specific antagonist of the muscarinic acetylcholine receptor of the pharmaco-therapeutic group of anticholinergic drugs that exerts local effects in the lungs when inhaled.

The dossier has been submitted as a full dossier according to art. 8(3). This decentralised application concerns an extension of the currently approved Spiriva® 18 µg inhalation powder hard capsules, which are delivered by an inhaler (Spiriva HandiHaler device). Spiriva 18 µg has been registered in the Netherlands by Boehringer Ingelheim International GmbH on 9 October 2001 (NL License RVG 26191). Subsequently, the product was registered in other EU countries via the Mutual Recognition Procedure (MRP) (NL/H/0299/001).

The currently approved indication of Spiriva/HandiHaler is maintenance of bronchodilator treatment to relieve symptoms of patients with COPD. The present application proposes the Respimat inhaler instead of the HandiHaler inhaler to deliver the same active ingredient tiotropium to the patient, and therefore the same indication as the HandiHaler is suggested. The MAH showed that 22.1 µl of solution of Spiriva Respimat (6.25 µg of tiotropium bromide monohydrate), which is equivalent to a 5 µg dose of tiotropium from the Respimat mouthpiece, is comparable to the registered dose of Spiriva 18 µg inhalation powder in conjunction with the HandiHaler, which delivers 10 µg tiotropium from the mouthpiece. To this end the MAH has submitted 10 new clinical studies. Two of them compared Spiriva solution 2.5 microgram for inhalation to Spiriva 18 µg inhalation powder hard capsules in combination with the HandiHaler.

The Respimat inhaler is part of the finished product and is a medical device class IIb according to the EU Medical Device Directive 93/42/EEC, and is certified to be marked with the CE symbol. The solution is expelled mechanically rather than by propellant gas. The inhaler has been used in other drug products such as the Berodual Respimat solution for inhalation.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC, a dossier with administrative, quality, pre-clinical and clinical data. This dossier contained data already submitted in the dossier of Spiriva HandiHaler 18 µg inhalation powder (NL RVG 26191).

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

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

Active substance and excipients
The active substance is tiotropium bromide monohydrate, an established active substance. Tiotropium bromide monohydrate is not described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 11 batches.

Full information on the manufacturing of the drug substance and the drug product is included in the dossier.

Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months with no special storage conditions in double LDPE bags in stainless steel drums. In addition, stability data on the active substance have been provided for 8 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months in laminated aluminium bags with no special storage conditions. The substance is only slightly sensitive to light.

The excipients used are common in the manufacture of a solution for inhalation, and comply with the relevant Ph.Eur. monographs.

Medicinal Product

Composition
Spiriva Respimat 2.5 microgram is a clear, colourless solution of tiotropium bromide monohydrate filled into a polyethylene/polypropylene 4.5 ml cartridge, closed with a polypropylene cap with integrated silicone sealing ring. The cartridge is inserted into an aluminium cylinder with an air hole seal. Each cartridge contains 30 labelled doses (60 actuations). The solution is to be used with a soft-mist inhaler, Respimat inhaler, which provides an aerosol cloud. Each actuation of the inhaler delivers 2.5 µg tiotropium (equivalent to 3.124 µg tiotropium bromide monohydrate) from the mouthpiece. One dose of 5 µg tiotropium consists of two actuations.

The excipients in the solution for inhalation are: benzalkonium chloride as preservative, edetate disodium as stabiliser, hydrochloric acid 3.6% (for pH adjustment), and purified water. The medium for pressure filtration is nitrogen.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging materials are usual and suitable for the product. The Respimat inhaler has been used for other drug products. The main goal was to provide an alternative tiotropium formulation to Spiriva 18 µg inhalation powder, hard capsule.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 4 batches (3 batches of the minimum batch size and 1 batch of the maximum batch size) in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification includes tests for appearance, colour and clarity of the solution, pH, volume, identification, degradation products, contents, microbiological purity, uniformity of delivered dose, fine particle fraction, aerodynamic fine particle dose and number of doses. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The MAH commits to the testing of 10 commercial-scale batches with regards to fine particle fraction by Anderson Cascade Impactor (ACI), in addition to the routine test by laser diffraction.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data have been provided for the solution for inhalation in the cartridge, the combination of device and the cartridge, and in-use stability. Stability data on the combination of cartridge and inhaler device have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The product should not be frozen. For the in-use stability, data of 3 batches were submitted. No out of specifications were observed but an upward trend of two impurities was seen, correlating to a decrease in content and an increase in the sum of impurities. An in-use period could be granted of 2 months.
Two post-approval IB variations were submitted: one to justify an extension of shelf life to 3 years, and another to extend the in-use period to 3 months (NL/H/0718/001/IB/003-004).

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

II.2 Non-clinical aspects

No new preclinical data have been submitted. The current application is sufficiently supported by the studies already presented with the application for Spiriva 18 µg hard capsules. A description of these non-clinical studies can be found in the Public Assessment Report of Spiriva 18 µg with EU-procedure number NL/H/0299/001. In view of the unchanged indication, the same active substance, the lower daily dose in humans and same route of administration, there is no need for additional non-clinical studies.

Environmental risk assessment
The product is intended as an alternative to another respiratory product on the market, i.e. Spiriva HandiHaler. The approval of this product will not result in an increase in the total quantity of tiotropium bromide released into the environment. It does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
Studies included in this dossier were conducted in accordance with the guideline provided in 1999 by the Committee for Proprietary Medicinal Products (CPMP) in the document Points to Consider on

Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD (G99-0010). Efficacy was evaluated with standard spirometric assessments to have a measure of dyspnoea. In addition health related quality of life by the St. George's Respiratory Questionnaire, and exacerbation rates were assessed.
The MAH confirms that trials were approved by institutional review boards or independent ethics committees. The MAH followed International Conference on Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines and conformed to the Declaration of Helsinki. Written consent was obtained from included patients.

Design of clinical studies
Ten clinical studies were submitted (Table 1). Two clinical studies focused on the toxicity (205.138; 205.248), while the pharmacokinetic profile of Spiriva Respimat was addressed in four studies (205.112; 205.127; 205.249; 205.250). The clinical Phase III development programme included two 4-week (205.249; 205.250), two 12-week (205.251; 205.252) and two 1-year (205.254; 205.255) randomised, double-blind studies in 2,916 patients with COPD. The 4-week studies were conducted to demonstrate the non-inferiority of Spiriva Respimat to the Spiriva 18 µg hard capsules, delivered with the HandiHaler. The two 12-week trials were both active (ipratropium)- and placebo-controlled, and were intended to proof superiority of Spiriva Respimat over placebo. Also the 1-year trials were intended to prove superiority of Spiriva Respimat over placebo.
Besides the trough FEV_1 as listed in the table below, the identical-protocol, placebo-controlled trials, (205.254 and 205.255) had three additional co-primary endpoints assessed at the one-year time point: quality of life (St. George's Respiratory Questionnaire), dyspnoea (Mahler TDI) and COPD exacerbations.

Table 1. Trials conducted in the Spiriva Respimat programme

Phase Study No Centres	Design	Study Posology	Study Objective	Subjs arm entred	Duration	Gender	Diagnosis Incl. crit.	Primary Endpoint
I 205.112 (U97-2426) 1	safety and tolerability + PK Multiple increasing doses, pl-c, rand	placebo, 10, 20, 40µg tiotropium bromide monohydrate o.d. vs. pl via RESPIMAT[A3]	dose finding	36 9/arm	14 days	male	healthy subjects	airway resistance
I 205.138 (U99-1355) 1	safety and tolerability after ocular administration pl-c	0.02, 0.04, 0.08, 0.16, 0.28, 0.40µg tiotropium vs pl (eyedrops)	eye toxicology	48 8/dose level 6 tio/ 2 placebo	single doses	male	healthy subjects	outcome eye
II 205.127 (U00-0077) 15	dose-ranging + PK md, rand, d-b, pg, pl-c and act-c	placebo, 1.25, 2.5, 5, 10, 20µg, tiotropium via RESPIMAT[A3] vs. pl vs. Tio HH18 o.d.	dose finding	202 25/arm	3 weeks	M&F	COPD	FEV increase
II 205.248 (U02-1222) 1	safety and tolerability sd, rand, d-b, pl-c, 4-way c-o	Respimat pl (pH=2.7) vs. (pH=3.4) vs. (pH=3.4) (pH=7) Vs. CFC-MDI /pl	acidic buffer/Tio toxicity	34 cross-over	single doses	M&F	Asthmatic	FEV decrease cough physical
III 205.249 (U05-1949) multinat	+PK md, rand, d-b, d-d, pl-c, act-c, c-o, 4	5, 10µg, tiotropium via RESPIMAT[A4] vs. pl vs. Tio HH18 o.d.	non-inferiority tiotropium in RESPIMAT vs. HANDIHALER	131 cross-over	4 weeks	M&F	COPD	FEV
III 205.250 (U04-2041) 2	+PK md, rand, d-b, d-d, pl-c, act-c, c-o, 4 multinat	5, 10µg, tiotropium via[A4] RESPIMAT vs. pl vs. Tio HH18 o.d.	non-inferiority tiotropium in RESPIMAT vs. HANDIHALER	76 cross-over	4 weeks	M&F	COPD	FEV
III 205.251 (U04-3400) multinat	Comparison of efficacy/safety of tiotropium in RESPIMAT to IB md, rand, d-b, d-d pg, pl-c, act-c	5, 10µg tiotropium via RESPIMAT[A4] o.d. vs. pl vs. 36µg IB via pMDI q.i.d.	superiority of tiotropium in RESPIMAT placebo	361 90/arm	12 weeks	M&F	COPD	FEV
III 205.252 (U04-3343)	ibidem study 205.251 multinat	ibidem study 205.251	ibidem study 205.251	358 90/arm	12 weeks	M&F	COPD	FEV
III 205.254 (U05-2112) multinat	efficacy, safety of tiotropium in RESP vs. pl, md, rand, d-b, pg, pl-c	5, 10µg tiotropium vs. pl via[A4] RESPIMAT o.d.	superiority of tiotropium in RESPIMAT placebo	983 320/arm	48 weeks	M&F	COPD	FEV
III 205.255 (U05-2113)	ibidem study 205.254 multinat	ibidem study 205.254	ibidem study 205.254	1007 335/arm	48 weeks	M&F	COPD	FEV

Patients included in the Phase III clinical studies

The six Phase III clinical trials included 2,916 patients with COPD. A total of 1,990 COPD patients were treated with Spiriva Respimat, of whom 214, 180 and 670 received 5 µg of Spiriva Respimat for up to 3-4, 12 and 48 weeks, respectively. A further 211, 180 and 667 patients received 10 µg of Spiriva Respimat for identical periods, respectively.

According to the protocol the patients who could participate in the Phase III studies were outpatients of either sex, 40 years or older, with a diagnosis of COPD. The patients were required to have relatively stable, moderate to severe airway obstruction with a Forced Expiratory Volume in 1 second (FEV_1) ≤65% of the predicted normal value and an FEV_1/Forced Vital Capacity (FVC) ≤70% and a smoking history of > 10 pack-years (with 1 pack- year defined as smoking 1 pack of 20 cigarettes per day for 1 year). The exclusion criteria for the Phase III trials were made less restrictive with special reference to patients with cardiac or prostate disease history or symptoms. For example, patients were allowed into the study with stable arrhythmia, prostate hypertrophy controlled by medication, with moderate to severe renal impairment (creatinine clearance of <50 mL/min), with appropriate medical supervision. Patients with asthma were carefully excluded otherwise. Only patients with significant disease other than COPD were excluded.

Table 2 summarises the mean age, smoking history and baseline pulmonary function of the patients, at screening, for each Phase III study. At baseline the physical characteristics, pulmonary function, smoking history and concomitant medication use were balanced between the various treatment groups in each of the studies.

Table 2. Mean age, tobacco consumption and pulmonary function

Trial	205.254	205.255	205.251	205.252	205.249	205.250
Number of treated patients*	983	1007	361	358	131	76
Planned treatment duration (weeks)	48	48	12	12	4	4
Mean age (yr)	65	65	62	66	64	65
Smoking history (pack-years)	47	48	42	60	60	36
FEV1 (L)	1.09	1.09	1.26	1.03	1.02	1.12
% predicted FEV1	38	39	44	38	36	40
FEV1/FVC (%)	43	42	50	45	45	38
% change in FEV1 following 4x100 µg salbutamol (albuterol)	19	21	17	22	21	18

* 15 patients were recruited in two Phase III studies.

In study 205.249 a total of 131 patients with COPD were randomised and participated in the pharmacokinetic part of the study. Of these, 129 patients were included in the analyses. The mean age of the patient population was 64 years, 65% of the trial population was male and 98% was Caucasian. The mean duration of COPD was 10 years. All patients were current (37%) or ex-smokers (62%) with a mean smoking history of 60 pack years. At the screening visit the mean FEV_1 was 1.02 L with a mean percent of predicted normal of 36% and a mean FEV_1/FVC ratio of 45%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg salbutamol from a metered dose inhaler (MDI) was 0.20 L and 21%.

In study 205.250 a total of 76 patients with COPD were randomised and participated in the pharmacokinetic part of the study. All 76 patients were included in the full analysis set. The mean age of the patient population was 65 years, 83% of the trial population was male and 99% was Caucasian. The mean duration of COPD was 11 years. All patients were current (37%) or ex-smokers (63%) with a mean smoking history of 36 pack years. At the screening visit the mean FEV_1 was 1.12 L, with a

mean percent of predicted normal of 40% and a mean FEV_1/FVC ratio was 38%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg of salbutamol from an MDI was 0.19 L and 18%.

In study 205.251 a total of 361 patients with COPD were randomised and received double-blind treatment: 88 to tiotropium 5 µg solution for inhalation; 93 to tiotropium 10 µg solution for inhalation; 89 to Atrovent® MDI (Ipratropium bromide MDI 36) and 91 to matching placebos (double-dummy). Of these, 320 (89%) patients completed the planned 12 weeks of treatment.
The mean age of the patient population was 62 years; 75% of the trial population was male and 99% was Caucasian. The mean duration of COPD was 10 years. All patients were current (43%) or ex-smokers (57%) with a mean smoking history of 42 pack years. At the screening visit the mean FEV_1 was 1.26 L with a mean percent of predicted FEV_1 of 44% and mean FEV_1/FVC ratio of 50%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg of salbutamol from an MDI was 0.20 L and 17%. The trial was conducted in Europe and South Africa.

In study 205.252 a total of 358 patients with COPD were randomised and received treatment: 92 to tiotropium 5 µg solution for inhalation; 87 to tiotropium 10 µg solution for inhalation; 89 to Atrovent® MDI (Ipratropium bromide MDI 36) and 90 to matching placebos (double-dummy). Of these, 312 (87%) patients completed the planned 12 weeks of treatment.
The mean age of the patient population was 66 years; 64% of the trial population was male and 96% was Caucasian. The mean duration of COPD was 10 years. All patients were current (35%) or ex-smokers (65%) with a mean smoking history of 60 pack years. At the screening visit the mean FEV_1 was 1.03 L with a mean percent of predicted FEV_1 of 38% and mean FEV_1/FVC ratio of 45%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg of salbutamol from an MDI was 0.20 L and 22%. The trial was conducted in the USA and Canada.

In study 205.254 a total of 983 patients with COPD were randomised and received double-blind treatment: 332 to tiotropium 5 µg solution for inhalation; 332 to tiotropium 10 µg solution for inhalation; and 319 to matching placebo. Of these 983 patients 80% completed the planned 48-week-treatment. The mean age of the patient population was 65 years; 76% of the trial population was male and at least 92% were Caucasian. The mean duration of COPD was 9 years. All patients were current (36%) or ex-smokers (64%) with a mean smoking history of 47 pack years. At the screening visit the mean FEV_1 was 1.09 L with a mean percent of predicted FEV_1 of 38% and a mean FEV_1/FVC ratio of 43%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg of salbutamol from an MDI was 0.18 L and 19%. The trial was conducted in North America.

In study 205.255 a total of 1007 patients with COPD were randomised and received double-blind treatment: 338 to tiotropium 5 µg solution for inhalation; 335 to tiotropium 10 µg solution for inhalation; and 334 to matching placebo. Of these 1007 patients 75% completed the planned 48-week-treatment period. The mean age of the patient population was 65 years; 72% of the trial population was male and at least 90% were Caucasian. The mean duration of COPD was 9 years. All patients were current (37%) or ex-smokers (63%) with a mean smoking history of 48 pack years. At the screening visit the mean FEV_1 was 1.09 L with a mean percent of predicted FEV_1 of 39% and mean FEV_1/FVC ratio of 42%. The mean change from baseline in FEV_1 30 minutes after inhaling 400 µg of salbutamol from an MDI was 0.20 L. The trial was conducted in the Netherlands and Belgium.

Respimat inhaler devices
Three versions of the Respimat inhaler were used during the developmental phase, mentioned as versions A3, A4 and A5 in the study report (Table 1). The Respimat A3 inhaler was used in the Phase I/II dose-ranging studies. The Respimat A4 device delivered a slightly higher volume of solution per actuation than the A3 version. The spray duration, spray velocity and particle size distribution are not affected by the optimization and are identical for both Respimat A3 and A4. The Respimat A4 version has been used in the Phase III Spiriva Respimat clinical trials. The to-be-marketed A5 inhaler is intended for use with a single cartridge for 30 days and differs from the A4 version only in the locking

mechanism, cap colour, and dose indicator. All three versions of the inhaler have the same nozzle type and are thus identical in terms of aerodynamic performance of the emitted aerosol. Consequently, the clinical results obtained with one version of the device can be considered comparable and relevant to those obtained with either of the other versions.

Primary endpoints

For the analysis it is considered acceptable that bronchodilation in terms of spirometric FEV_1 was primary endpoint in all six individual Phase III trials (Table 3). FEV_1 was measured approximately 24 hours after the previous treatment dose (approximately 10 min before the final dose in the clinic). Spirometry, conforming to the American Thoracic Society (ATS) criteria, was undertaken for the measurement of FEV_1 and FVC.

Table 3. Primary efficacy endpoints in Spiriva Respimat Phase III trials

Clinical Trial	Trough FEV_1§	SGRQ*	TDI#	No. of COPD Exacerbations†
One-year placebo controlled trials				
205.254	yes	yes	yes	yes
205.255	yes	yes	yes	yes
12-week active and placebo controlled trials				
205.251	yes	no	no	no
205.252	yes	no	no	no
4-week crossover trials				
205.249	yes	no	no	no
205.250	yes	no	no	no

§ Trough FEV_1 (i.e. 24-hours post-dose) recorded approximately 10 minutes before the last dose of randomised treatment.
* SGRQ Total Score at 48 weeks
# TDI Focal Score at 48 weeks assessment is only made by combining data for trials 205.254 and 205.255.
† Assessment is only made by combining data for trials 205.254 and 205.255.

Statistical analyses in the clinical development programme of Spiriva Respimat are similar to earlier statistical analyses of studies for registration and variations of Spiriva. As FEV_1 is about 1 litre in the patient population, which is about 40% of predicted FEV_1, it is considered acceptable that the non-inferiority margin is set at -50 mL.

The twin design of the Phase III trials is considered acceptable. The efficacy data relating to the primary endpoints have been provided from individual studies, pooled from twin studies, and overall. The data are presented with respect to a pre-specified statistical analysis of the pooled data from the twin studies, and also separately for each study. The decision to analyse pooled data was taken before data were un-blinded. The twin studies had the same protocol.

In addition, it is considered acceptable that in the 1-year trials (205.254; 205.255), three further sequential primary endpoints were investigated and sequentially analysed to give more indication of

clinical relevance of the product under investigation. These were (1) health-related quality of life (HRQoL), (2) dyspnoea, and (3) reduction in COPD exacerbations.

It is considered acceptable that a difference in treatment means of 4 units in the St. George's Respiratory Questionnaire (SGRQ) total score was pre-specified as the minimum clinically important difference in the 1-year protocol.

Methods for detection of tiotropium

The methods for assessing tiotropium in plasma and urine are the same as for the Spiriva 18 µg powder for inhalation application. Only the limit of quantitation in plasma was lowered to 2.5 pg/ml, which was validated.

Clinical Pharmacology

The clinical development programme of the MAH did not involve a pharmacological analysis of the active ingredient. Spiriva Respimat delivers tiotropium bromide monohydrate as a fine aerosol cloud from a mouthpiece. In contrast, registered Spiriva is dry powder tiotropium bromide. Once inhaled by a patient, however, Spiriva dry powder tiotropium bromide dissolves into body solutions of the patient, and thus converts to identical tiotropium bromide monohydrate of Spiriva Respimat. Therefore, it is considered acceptable that the MAH did not submit a pharmacological analysis of the active ingredient tiotropium, and that the majority of the basic pharmacological properties of tiotropium of Spiriva Respimat have been cross-referenced to the dossier for Spiriva 18 µg inhalation powder, hard capsules. A description of these studies can be found in the Public Assessment Report of Spiriva 18 µg with EU-procedure number NL/H/299/01. From the pharmacological Phase I and II studies the bronchodilator properties of tiotropium were established. Forced Expiratory Volume in 1 sec (FEV_1) improved significantly and this improvement was maintained over 24 hours after dosing compared to placebo. Approximately 90% of steady-state bronchodilation was achieved within 7 days of treatment and reached pharmacodynamic steady state within 14 days.

Tiotropium is poorly absorbed in the gastrointestinal tract; oral solutions of tiotropium have an absolute bioavailability of 2-3%. Absorbed tiotropium is mainly excreted via the kidney. The extent of biotransformation is small as 74% of unchanged substance was recovered in the urine after an intravenous dose to healthy volunteers. As the oral bioavailability of tiotropium is low, systemic exposure to tiotropium is mainly representative of lung disposition. Excretion of tiotropium in urine can be used as a measure of systemic exposure. The elimination half-life of tiotropium is approximately 5 to 6 days.

Dose ranging study in healthy volunteers (205.112)

This Phase I dose ranging study evaluated safety, tolerability and pharmacokinetics of different doses. It was a sequential, parallel group, multiple increasing dose tolerance study after inhalation of 8 µg, 16 µg and 32 µg tiotropium with the Respimat A3 inhaler for 14 days in 36 healthy volunteers. Twelve patients were studied in a double-blind design at each dose level, nine on active drug and three on placebo. One patient in the 32 µg tiotropium group was discontinued on study day 9 because of abnormal liver enzymes caused by excessive physical activity.

Blood samples were taken before tiotropium inhalation and after inhalation on day 1, 7 and 14 of the treatment. On day 1 also a 24h blood sample was taken. Taking into account the sparse data set, plasma concentrations increased with increasing dose and were approximately 2 and 3 fold higher at day 7 and day 14, respectively, compared to day 1. Pharmacokinetic investigation of tiotropium in plasma was only determined using sparse data (three time points) sampling, and therefore plasma data are considered as supportive data only.

Urine was collected in the intervals of 0-4h, 4-8h, and 8-24h on days 1, 7 and 14. An additional urine sample was collected before the first inhalation (Table 4).

Table 4. Geometric means of amount excreted (ng and % of dose) within 0-4h and 0-24h after inhalation of 8 µg, 16 µg and 32 µg tiotropium.

Dose tiotropium cation	n	8.0 µg			16 µg			32 µg		
		[ng]	% gCV	% of dose	[ng]	% gCV	% of dose	[ng]	% gCV	% of dose
$Ae_{0-4h,day1}$	9/9/9	120	75.7	1.49	478	104	2.99	716	91.3	2.24
$Ae_{0-4h,day7}$	9/9/9	363	43.6	4.54	1220	59.6	7.62	2183	64.0	6.82
$Ae_{0-4h,day14}$	9/9/8	433	38.2	5.41	1230	47.6	7.69	2368	56.6	7.40
$Ae_{0-24h,day1}$	8/9/9	453	36.0	5.66	1345	61.1	8.41	2063	55.3	6.45
$Ae_{0-24h,day7}$	0/7/4	---	---	---	4657	27.6	29.1	9397	28.7	29.4
$Ae_{0-24h,day14}$	9/9/6	1612	25.6	20.1	3927	34.0	24.5	6800	53.4	21.3
ratio Ae_{0-4h} values										
day 7 / day 1			3.05			2.55			3.04	
day 14 / day 1			3.63			2.57			3.30	
day 14 / day 7			1.19			1.01			1.09	
ratio Ae_{0-24h} values										
day 7 / day 1			---			3.46			4.56	
day 14 / day 1			3.55			2.91			3.30	
day 14 / day 7			---			0.84			0.73	

After inhalation, between 20% and 29% of the inhaled dose was excreted unchanged in urine. It is known from a former study that after intravenous administration of 14.4 µg tiotropium, 73.6% of the dose is excreted unchanged in the urine. This suggests that about 33% of the inhaled tiotropium dose reached the systemic circulation. This finding is in accordance with the results of a scintigraphic study, which revealed that about 39% of the inhaled dose was deposited in the lungs after administration of fenoterol hydrobromide via the Respimat inhaler.

The continued rise in plasma concentrations over 14 days is in accordance with the long terminal half-life (5-6 days) of tiotropium as was determined after dry powder inhalation. No deviation from dose proportionality for tiotropium was observed within the dose range of 8-32 µg tiotropium. As tiotropium is hardly absorbed after oral ingestion, urinary excretion of the unchanged tiotropium may be used as an estimate of relative absorption in the lungs.

Dose ranging study in COPD patients (205.127)

This second dose-ranging trial was a parallel group, multiple-dose, placebo controlled, intraformulation double-blind study conducted over a period of 3 weeks in COPD patients. Two hundred and two COPD patients were randomised and 191 completed as planned. The mean age was 60.2 years, 86% were male, the mean duration of COPD was 10.5 years, 45% were current smokers and 55% were ex-smokers. The objective of this study was to determine the optimal dose of tiotropium inhaled as a solution from the Respimat device once daily in comparison to tiotropium dry powder 18 µg delivered from the HandiHaler device. Doses of 1.25, 2.5, 5.0, 10 and 20 µg of tiotropium administered via the A3 inhaler were compared to tiotropium inhalation powder capsules given via the HandiHaler device (18 µg) and placebo. Tiotropium urine samples were collected over two periods: 2 hours pre-dose (-2-0h) and after drug administration on days 7, 14, and 21.

Table 5. Comparison of geometric mean tiotropium Ae values after inhalation of various tiotropium doses by the Respimat inhaler and 18 µg by dry powder inhalation.

Dose (µg) (number of subjects)	Day 7±2 Mean (%CV)	Day 14±2 Mean (%CV)	Day 21±2 Mean (%CV)
Respimat inhalation			
1.25 (N=10)	29 (65)	28 (88)	31 (106)
2.5 (N=9)	47 (100)	53 (83)	51 (107)
5.0 (N=10)	170 (60)	167 (66)	185 (50)
10 (N=12)	273 (60)	241 (90)	283 (55)
20 N=11)	759 (75)	690 (98)	706 (104)
Dry powder inhalation			
18 (N=9)	251 (63)	124 (121)	192 (140)

Urinary excretion of unchanged tiotropium indicated a comparable systemic exposure between 5 to 10 µg tiotropium delivered via the Respimat inhaler and 18 µg delivered via the HandiHaler (Table 5). The variability in urinary excretion was high for both formulations ranging from 50 to 144% CV. The short period of urine collection, 2 hours post-dose, may contribute to this high variability, as in study 205.112 in healthy volunteers it was shown that urinary excretion prolonged for a long period of time.

There was no change in tiotropium urinary excretion observed from day 7 onwards, plasma data in healthy volunteers study 205.112 indicated that steady-state had not been reached before day 14, which is in agreement with the long half-life of tiotropium. Probably due to the short period of urine collection (2h post-dose), the urinary excretion was less sensitive to establish steady-state.

Phase III studies in COPD patients (205.249 and 205.250)
These clinical trials were randomised, double-blind, placebo-controlled. These studies were used for kinetic comparison, as well as efficacy, of 5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg) of tiotropium inhalation solution delivered by the Respimat inhaler, and tiotropium inhalation powder capsule (18 µg) delivered by the HandiHaler. Plasma samples were collected pre-dose and at 10 min, 1h and 6h post-dose. Urinary excretion of tiotropium was collected up to 12h post-dose.

Secondary pharmacological plasma/urine chromatographic data show that Spiriva Respimat gives about 1.65 µg of tiotropium to the systematic circulation. This is similar to the plasma/urine chromatographic finding of about 1.7 µg of tiotropium released to the systematic circulation of the 18 µg registered dose by Spiriva/HandiHaler. Therefore, a comparable systemic safety profile can be expected for 5 µg Spiriva Respimat as for Spiriva HandiHaler 18 µg inhalation powder.

Since the systemic exposure for Tiotropium Respimat 5 µg and Tiotropium HandiHaler 18 µg are similar, it can be concluded that the dose deposited in the lungs is comparable between both doses due to the higher efficiency of the Respimat inhaler.

Although the variability in urinary excretion was high %CV (between 59 and 124%) (Table 6), the amount excreted was comparable for both studies. The short period of urine collection may contribute to this high variability. Nonetheless, it is considered acceptable to conclude that Spiriva Respimat delivers about equal amounts of tiotropium to the systematic circulation compared to Spiriva/HandiHaler.

Table 6. Urinary excretion of unchanged tiotropium following 5 µg and 10 µg inhalation solution and 18 µg powder capsule.

	Mean Ae (ng)			Mean fe (% of dose)		
Dose study	Pre-dose -2-0h	Post-dose 0-2h	Post-dose 0-12h	Pre-dose -2-0h	Post-dose 0-2h	Post-dose 0-12h
5 µg						
205.249	36	189	561	0.71	3.8	11.2
205.250	42	144	479	0.83	2.9	9.6
10 µg						
205.249	100	395	1230	1.0	4.0	12.3
205.250	74	290	892	0.74	2.9	8.9
18 µg						
205.249	26	110	428	0.14	0.61	2.3
205.250	34	126	410	0.12	0.70	2.4

Clinical studies in special populations

As subgroup differences were small and there is no evidence of cytochrome P-450 inhibition, there is no need for label considerations for special populations raised. As plasma concentration increases with decreased renal function, tiotropium bromide should only be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment. Warnings for impaired renal function are present in the proposed SmPC.

Genetic differences in pharmacodynamic response

No genetic differences in pharmacodynamic response have been reported.

Pharmacodynamic interactions with other medicinal products or substances

Subgroup analyses of adverse effects to assess drug-drug interactions were undertaken across all treatment groups from the combined data of the 1-year trials 205.254 and 205.255. Pharyngolaryngeal pain was more frequently seen in females than in males and at a higher rate for the active treatment groups compared to placebo. Pharyngolaryngeal pain appeared associated with inhaled corticosteroid use, as 78% of women reporting pharyngolaryngeal pain were using inhaled corticosteroids.

It is considered acceptable that the MAH does not provide a pharmacodynamic explanation for the signal of increased pharyngolaryngeal pain using tiotropium in conjunction with corticosteroids, as a pharmacodynamic interaction in women and not men, and pharynx only below the level of the nose is unlikely. There is no pertinent evidence of drug-to-drug interaction.

II.3.1 Clinical efficacy

Clinical efficacy and safety results have been demonstrated with tiotropium bromide as Spiriva 18 µg inhalation powder. Spiriva Respimat exerts local effects in the lungs. As a result the systemic bioavailability of tiotropium or bioequivalence (in terms of plasma concentrations) of Spiriva Respimat and Spiriva HandiHaler is not a determinant of efficacy. Six new clinical studies addressed the efficacy (205.249; 205.250; 205.251; 205.252; 205.254; 205.255). Both the dose-response and main clinical studies were placebo controlled blinded studies including sufficient numbers of subjects in sufficient number of study centres. Subsequent to dose finding, efficacy and safety studies compared, Spiriva Respimat to placebo, to Spiriva/HandiHaler and, within the anticholinergic class, to ipratropium.

Currently two classes of bronchodilator drugs are utilised, which are beta-agonists and anticholinergics. Tiotropium was not compared to beta-agonists, although an assessment of beta-agonistic response was made of all subjects pre-randomisation to characterise the study population, and it was used as rescue medication.

The MAH based the dose of the pivotal six Phase III trials of the clinical development programme on the Phase I dose-ranging study, 205.112, and the Phase II dose-ranging study, 205.127. From these dose response studies it is considered acceptable that the two plateau doses of tiotropium Respimat 5 µg (Tio R5) and 10 µg (Tio R10) of Spiriva Respimat were selected for further testing in Phase III trials. Lower doses did not show clinically relevant increases of FEV_1. Neither did more elevated doses increase FEV_1, but they did increase undesired systemic anticholinergic effects.

4-week Phase III trials in COPD patients (205.249 and 205.250)
These two studies were also used for pharmacodynamics, and compared the efficacy and safety of two doses 5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg) of tiotropium inhalation solution delivered by the Respimat inhaler both with placebo, and with tiotropium inhalation powder capsule (18 µg) delivered by the HandiHaler (Tio HH 18).

The differences between each of the 3 active treatments and placebo were statistically significant ($p<0.0001$) for both studies and pooled data thereof (Table 7). Non-inferiority of Tio R5 to Tio HH 18 was demonstrated in study 205.249 ($p<0.0001$) at day 29.

Table 7. Mean trough FEV_1 responses at day 29

Trial	Tio Respimat 5 µg	Tio Respimat 10 µg	Tio HandiHaler 18 µg	Placebo
205.249	0.116 L	0.128 L	0.069 L	-0.005 L
205.250	0.055 L	0.044 L	0.054 L	-0.072 L
205.249/.250	0.073 L	0.075 L	0.044 L	-0.052 L

Non-inferiority for Tio R10 was not established in the 205.250 study (treatment difference of -10 mL of no clinical relevance, $p<0.028$; required $p<0.025$). Therefore, non-inferiority could not be established for the Tio R5 dose due to the required sequential statistical testing (non-inferiority had first to be shown for Tio R10 before testing Tio R5).

Pooling of the data of the 4-week studies demonstrated that both Tio R5 and Tio R10 doses resulted in statistically significant ($p=0.03$ resp. $=002$) higher responses compared to Tio HH 18 for FEV_1 (peak and AUC_{0-3} after first dose and trough, peak, AUC_{0-12} at day 29). However, it should be mentioned that these observed differences, were nevertheless relatively small and clinically not relevant (range: 0.028-0.057 L).

12-week Phase III trials in COPD patients (205.251 and 205.252)
These trials were 12-week, double-dummy, double-blind, randomised, placebo and active-controlled. The active control was ipratropium MDI q.i.d. The 12 weeks of randomised treatment were preceded by a 2-week baseline period and followed by a 3-week post-treatment period.

Pulmonary function tests were conducted at clinic visits at the end of the 2-week baseline and after 1, 4, 8 and 12 weeks of randomised treatment. On each test day pulmonary function testing was performed prior to drug administration and 30, 60 minutes, 2, 3, 4, 5 and 6 hours post dose. The test day following 1 week of randomised treatment was included to determine if full efficacy had been reached by 1 week.

Tio R10 over Tio R5 had statistically significant increases in FEV_1 compared to placebo, both for the pooled data and the individual studies (Table 8). Tio R10 demonstrated a greater response compared to ipratropium bromide MDI 36 (ipratropium) in both studies. Tio R5 demonstrated a statistically significantly greater response in trial 205.252 and, numerically greater response in trial 205.251. Pooling of data from the 2 studies revealed a consistent clinically and statistically significant FEV_1 trough response differences for both tiotropium doses compared to ipratropium (Atrovent MDI).

Table 8. Mean FEV_1 treatment differences (L) for Tio R10, Tio R5, placebo and Atrovent MDI at day 85

Trial	Tio R10 – PL	Tio R5 – PL	Tio R10 – IB MDI 36	Tio R5 – IB MDI 36	IB MDI 36 - PL
205.251	0.182 L (p<0.0001)	0.109 L (p=0.0032)	0.119 L (p=0.0013)	0.046 L (p=0.2160)	0.063 L (p=0.0869)
205.252	0.115 L (p=0.0001)	0.125 L (p<0.0001)	0.071 L (p=0.0147)	0.081 L (p=0.0051)	0.044 L (p=0.1369)
205.251/ .252	0.149 L (p<0.0001)	0.118 L (p<0.0001)	0.095 L (p<0.0001)	0.064 L (p=0.0060)	0.054 L (p=0.0223)

1-year Phase III trials in COPD patients (205.254 and 205.255)
Clinical endpoints were recorded at the end of the 2-week baseline and after 2, 8, 16, 24, 32, 40 and 48 weeks of randomised treatment. On each test day pulmonary function tests (FEV_1 and FVC) were performed 10 minutes prior to test-drug inhalation and 5, 30 and 60 minutes and 2 and 3 hours after inhalation of trial medication.

Both 1-year studies and the pooled data thereof, demonstrated statistically (p<0.0001) and clinically significant differences in trough FEV_1 of Tio R5 and Tio R10 over placebo on test day 337 and earlier test days (Table 9).

Table 9. Mean trough FEV_1 treatment differences for the 1-year trials at day 337

Trial	Tio R5 – PL	Tio R10 - PL
205.254	0.142 L *	0.161 L *
205.255	0.113 L *	0.140 L *
205.254/ .255	0.127 L *	0.150 L *

* p<0.0001 vs. placebo

The analysis of the pooled data of both studies resulted on average in a greater (0.023 L) response for Tio R10 over Tio R5 on test day 337, which was clinically not relevant (<50 mL).

The clinical relevance of FEV_1 reduction of both Tio R5 and Tio R10 over placebo has been corroborated by the St. George's Respiratory Questionnaire, the Transition Dyspnoea Index (TDI) and several measures for COPD exacerbations. That investigation was predefined to be analysed in hierarchical framework to avoid multiplicity.

In these 1-year trials both Tio R5 and Tio R10 resulted in consistent statistically significant improvement in HRQoL (as measured using the SGRQ). For both Spiriva Respimat doses improvement from baseline exceeded 4.7 units (in each trial), although the pre-defined Minimal Clinical Important Difference (MCID) mean score of 4 versus placebo in SGRQ was not achieved. As measured by the SGRQ, both tiotropium doses had positive effects on the domains of the SGRQ, psychosocial impacts of COPD, activities affected by COPD and distress due to COPD symptoms. The improvement in mean total score between Tio R5 and Tio R10 both versus placebo at the end of the two 1-year trials was statistically significant.

Dyspnoea (as evaluated using the Mahler TDI) was significantly improved following both doses of tiotropium, achieving the pre-defined MCID reduction for the Mahler TDI, following either dose of tiotropium compared to placebo.

Data of studies 205.254 and 205.255 showed that for various measures of evaluating reduction of COPD exacerbations, there is evidence for reduction of COPD exacerbations by Spiriva Respimat. Both tiotropium doses gave a similarly significant reduction in the number of COPD exacerbations, and delay to the time of the first COPD exacerbation compared to placebo (Table 10). Those data observed with Spiriva Respimat are consistent with data recently reported for Tio HH 18 conducted in

a US Veterans Affairs setting, which concluded that tiotropium significantly reduced COPD exacerbations (Variation Dossier registered Spiriva/HandiHaler) (Niewoehner et al, 2005[1]). In this study 1,829 patients with moderate to severe COPD were treated for 6 months with either tiotropium or placebo. The two sequential primary endpoints were the percentage of patients experiencing at least one COPD exacerbation and the percentage of patients with at least one COPD-related hospitalisation. Tiotropium significantly reduced the percentage of patients experiencing 1 or more exacerbations compared with placebo (27.9% vs. 32.3%, respectively p=0.036). Fewer tiotropium patients were hospitalised due to a COPD exacerbation (7.0% vs. 9.5%, p=0.056). However, the second primary endpoint just failed to attain statistical significance.

Table 10. Mean COPD exacerbation data of Studies 205.254 and 205.255

Parameter		Tio R 5	Tio R 10	PL
COPD exacerbation rate per patient year (i.e. adjusted for treatment exposure)	Crude Mean	0.93	1.02	1.91
	Statistical Test	(p=0.002)*	(p=0.0008)*	
No. of exacerbations/patient (i.e. unadjusted for treatment exposure)	Crude Mean	0.66	0.59	0.73
	Statistical Test	(p=0.021)*	(p=0.0057)*	
% of patients with at least 1 exacerbation		37.2	36.9	44.1
Odds ratio of % of patients with at least 1 exacerbation		0.71 (p=0.0031)	0.71 (p=0.0028)	-
Time, in days, to 1st exacerbation(lower quartile)		160 (p<0.0001)	178 (p<0.0001)	86
% of time in exacerbation		4.0 (p=0.009)*	3.9 (p=0.003)*	5.6

p-values relate to vs. placebo (PL) * Based on Wilcoxon-Mann-Whitney test

The studies demonstrated only a difference of 10 exacerbations (8%) on a total of 122 exacerbations. The MAH was requested to include in the SmPC a statement about this difference, and numerical data including the p-values and the large 95% confidence intervals of each study.

The 1-year trials showed that there was reduction of use of rescue medication for both tiotropium doses compared to placebo.

Ancillary analyses of the Phase III studies

Ancillary analyses of smoking habits, medication compliance, tolerance and rebound effect do not raise concerns for bias between treatment groups in the presented Phase III clinical trials (Table 2).

The smoking status of the patients was checked again at the end of the treatment periods. During the conduct of the trials the patients were not instructed to change their smoking habits. The data from the 1-year trials show that the majority of patients (at least >89%) did not change their smoking habits during the course of the trials. The small number, who changed smoking habit these patients were distributed evenly amongst the three treatment groups.

Test medication compliance was evaluated in all 6 Phase III trials based on reporting by patients on daily diary cards and for all trials it was good, in excess of 92%, for the 80-100% range of prescribed medication.

Data from the 1-year multinational trials 205.254 and 205.255 for FEV_1 and the use of rescue medication do not support a tolerance effect on bronchodilation for the two tiotropium Respimat doses.

[1] Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, et al. (2005), Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial, Ann Intern Med. 143(5): 317-26.

The potential occurrence of a rebound effect when tiotropium dosing from the Respimat is stopped was studied in the 12-week and 1-year studies where the patients were followed-up for a further 3 weeks after cessation of the treatment period. In all studies no evidence was found of a rebound effect following cessation of treatment with tiotropium.

II.3.2 Clinical safety

Tiotropium plasma concentrations and excretion of tiotropium in urine are measures of systemic exposure, which is relevant for the safety of tiotropium. A major goal with regard of safety was to determine which dose of Spiriva Respimat was comparable to the already approved Spiriva 18 µg, inhalation powder drug product with regard to systemic exposure measured as C_{max} (maximum measured concentration of tiotropium in plasma) AUC (Area under the concentration-time curve of tiotropium in plasma), and Ae (Amount of tiotropium excreted unchanged in urine).

Due to their longer study periods, four out of six Respimat Phase III trials (1-yr trials 205.254 and 205.255 and 12-week trials 205.251 and 205.252) are regarded as pivotal for safety consideration. Most of the reported adverse effects were balanced (Table 11) across the treatment groups with, as expected, a higher incidence of anticholinergic events in the active treatment groups, which are reflected in the SmPC.

Table 11. Frequency [N (%)] of patients with selected adverse events occurring with incidence greater than or equal to 3% by treatment, for the 1-year trials 205.254 and 205.255

System organ class/	Tio Respimat 5 µg	Tio Respimat 10 µg	Placebo	Total
Preferred term	N (%)	N (%)	N (%)	N (%)
Number of patients	670 (100.0)	667 (100.0)	653 (100.0)	1990 (100.0)
Total with adverse events	505 (75.4)	525 (78.7)	502 (76.9)	1532 (77.0)
Gastrointestinal disorders	142 (21.2)	193 (28.9)	97 (14.9)	432 (21.7)
Mouth dry#	48 (7.2)	97 (14.5)	14 (2.1)	159 (8.0)
Infections and infestations	90 (13.4)	95 (14.2)	79 (12.1)	264 (13.3)
Urinary tract infection#	17 (2.5)	28 (4.2)	7 (1.1)	52 (2.6)
Respiratory syst. dis. (lower)	304 (45.4)	299 (44.8)	360 (55.1)	963 (48.4)
Bronchitis#	29 (4.3)	35 (5.2)	27 (4.1)	91 (4.6)
COPD exacerbation#	220 (32.8)	216 (32.4)	275 (42.1)	711 (35.7)
Lower respiratory tract infect.	25 (3.7)	24 (3.6)	20 (3.1)	69 (3.5)
Pneumonia#	22 (3.3)	22 (3.3)	11 (1.7)	55 (2.8)
Respiratory syst. Dis. (upper)	208 (31.0)	203 (30.4)	171 (26.2)	582 (29.2)
Nasopharyngitis	94 (14.0)	64 (9.6)	54 (8.3)	212 (10.7)

The incidence of angina was higher in tiotropium Respimat groups, while the incidence of myocardial infarction was lower (Table 12). Angina events were generally non-serious and were not associated with more serious events, such as myocardial infarction or death. An increase in urinary tract infections was seen in the tiotropium-treated patients. Although, these events occurred more frequently in women than in men, a decrease in urinary flow as a contributing factor cannot be ruled out. However, urinary retention (a known anticholinergic side effect) was an uncommon outcome of the programme.

Table 12. Rates (%) of most common serious adverse effects in 1-year trials 205.254 and 205.255

Preferred term	Tio Respimat 5 µg	Tio Respimat 10 µg	Placebo
Cardiac failure	0.9	0.4	0.6
Angina	0.4	1.0	0.2

Myocardial infarction	0.3	0.1	0.9
COPD exacerbations	4.9	6.0	5.7
Pneumonia	2.1	1.6	0.9

The severe adverse effects were balanced between the treatment groups. Most of the severe adverse effects were of the lower respiratory system organ class, as one would expect from this population of patients. The events leading to discontinuations from randomised treatment were similar across the treatment groups. The reduction seen in COPD exacerbations in the 1-year trials when on active treatment compliments the efficacy data on COPD exacerbations.

A clinical assessment of the deaths among patients treated with Spiriva Respimat strongly suggests the patients' underlying pathologies as the cause rather than being a result of treatment- or trial-related factors. The overall incidence of deaths in the Respimat active-treatment groups was comparable to that seen in the substantial database of Spiriva HandiHaler and HandiHaler placebo. The imbalance in deaths between the Spiriva Respimat active groups and placebo is likely due to an unusual low number of deaths in the placebo-treatment group. Such an imbalance was not observed in the Spiriva HandiHaler programme.

The dose-ranging study revealed no significant changes in mean laboratory values from baseline to end of trial. In the six Phase III trials, the changes in vital physical signs, ECG, Holter and clinical laboratory evaluations were minimal or none. The small changes observed were of no clinical significance. The formulation was well tolerated by patients and there was no evidence of paradoxical bronchoconstriction following inhalation.

Local tolerance study in healthy subjects (205.138)
A single, increasing dose, local tolerance study after ocular administration of tiotropium was undertaken in 48 healthy volunteers. The range of doses instilled into the eye (0.02-0.40 µg) corresponded to a range of 7-133 µg tiotropium nominal metered doses from the Respimat inhaler. Pupil diameter, pupil reflex, intraocular pressure and accommodation were not influenced by tiotropium. The transient burning sensation by accidental ocular administration of aerosol in 25% of patients is likely caused by excipients or low pH, as symptoms were in equal number also present in patients exposed to the placebo solution. Accidental ocular exposure seems an unimportant risk. Nevertheless, a precaution statement, that warns patients not to spray in their eyes, has been included in the labelling.

Tolerability study in asthmatic patients (205.248)
This trial was undertaken to evaluate the local tolerability of Respimat placebo solution with a pH 2.7 (more acidic than the active Spiriva Respimat solution of pH 2.9) in 32 hypersensitive asthmatic patients. The data showed that the Respimat formulation was well-tolerated at double the dose (4 actuations) expected to be administered to COPD patients. This is supported by the evidence generated in the six Phase III studies in which COPD patients were exposed to two actuations from the Respimat inhaler for up to 48 weeks with good tolerability.

Risk Management Plan
The safety of Spiriva Respimat is comparable to that of Spiriva HandiHaler, registered in 2001 in the Netherlands. While differences in the adverse event data between Spiriva Respimat and Spiriva HandiHaler are present they are not considered to reflect a basically different safety profile. Spiriva Respimat 2.5 microgram, given as two actuations, is an alternative clinically comparable formulation to Spiriva HandiHaler. Nevertheless, a couple of undesirable effects including cardiovascular events and lower respiratory tract infections should be monitored closely post-marketing and a risk management plan should monitor all cause and respiratory mortality with tiotropium, lower respiratory tract infections and cardiovascular events (in particular angina pectoris) for both Spiriva Respimat and Spiriva 18 µg HandiHaler.

The PSUR submission cycle is 3 years. An integrated PSUR schedule for Spiriva 18 µg inhalation powder and Spiriva Respimat 2.5 microgram is agreed, provided that the MAH spends all efforts to differentiate between data and events for each formulation. The MAH agreed to submit the first integrated PSUR in December 2008 (with first data lock point October 2008), and the next 3 yearly PSUR (with data lock point October 2011) in December 2011 with the Renewal application.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed. The MAH included only patients with COPD who have a certain experience using inhalation medication. This test is therefore not representative for newly diagnosed patients, however, this is considered acceptable in view of the indication as maintenance treatment.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality part of the dossier is of sufficient standard for authorisation. There is a small number of issues for which the marketing authorisation holder has provided commitments to address these issues post-authorisation (see below).

No new preclinical data have been submitted. The current application is sufficiently supported by the non-clinical studies already presented during the application for Spiriva 18 µg hard capsules.

The Spiriva Respimat clinical development programme is considered to have a sufficient testing strategy for registration. It is consistent with Points to consider on the requirements for clinical documentation for orally inhaled products (OIP) with number CPMP/EWP/4151/00 of 22 April 2004.

The pharmacokinetics of tiotropium and urinary excretion following inhalation with the Respimat inhaler were measured in healthy volunteers and patients with COPD over a dose range of 1.25 to 32 µg. The data were compared to the already approved tiotropium inhalation powder capsules given via the HandiHaler device (Spiriva 18 µg). Based on γ-scintigraphy and urinary excretion, 30-40% of the inhaled dose is deposited in the lungs. Dose proportionality of tiotropium pharmacokinetics was observed over the dose range 1.25 to 32 µg of tiotropium delivered via the Respimat inhaler. Phase III trials revealed that systemic exposure and urinary excretion of tiotropium after inhalation of 5 µg tiotropium via the Respimat inhaler was approximately 20% higher than 18 µg tiotropium delivered by the HandiHaler. Therefore, a comparable safety profile can be expected for 5 µg Spiriva Respimat as for Spiriva HandiHaler 18 µg. Spiriva Respimat is a formulation for inhalation that exerts local effects in the lungs. As a result the systemic bioavailability of tiotropium or bioequivalence (in terms of plasma concentrations) of Spiriva Respimat and Spiriva HandiHaler is not a determinant of efficacy and needs to be established in clinical studies.

Based on data from six pivotal Phase III Studies, it is concluded that bronchodilatory properties of Tio R5 and Tio R10 were demonstrated to be clinically relevant and statistically significant for FEV_1 with respect to placebo, and that these were maintained over trial periods ranging from 4-48 weeks of treatment with no evidence for tolerance.

In the 1-year trials, the mean improvement in FEV_1 at 30 minutes for tiotropium Respimat 5 µg compared to placebo was 0.11 and 0.12 L (11% and 12% of baseline) with an improvement at 3 hours of 0.19 and 0.17 L (18% and 16% of baseline) after first dose. An analysis of trough FEV_1 including the data from all 6 Phase III trials at pre-specified time points resulted in mean improvements over placebo of 0.122 L and 0.137 L for tiotropium Respimat 5 µg and tiotropium Respimat 10 µg respectively.
Pooled data from all six clinical studies showed a mean trough FEV_1 response over placebo of 0.137 L and 0.122 L ($p<0.0001$) for tiotropium Respimat 10 µg and tiotropium Respimat 5 µg, respectively. As similar differences were found on intermediate test days, it is considered acceptable to conclude that Spiriva Respimat in both doses gives a statistically significant, clinically relevant 24-hour bronchodilatory response. As tiotropium Respimat 5 and 10 µg provided a comparable effect on efficacy parameters with very little differentiation between the two doses, and as tiotropium Respimat 10 µg gives a doubled undesired anticholinergic systemic effect, it is considered acceptable the MAH proposed tiotropium Respimat 5 µg for registration.

The 1-year trials showed for both tiotropium doses a similarly significant reduction in the number of COPD exacerbations and a delay to the time of the first COPD exacerbation compared to placebo.

The MAH discussed satisfactorily the extrapolation to the requested indication of COPD in general, without any restriction for a smoking history.

Spiriva Respimat 5 µg shares an almost similar efficacy/safety profile with the marketed product Spiriva HandiHaler. From the safety perspective there are no special concerns. Spiriva Respimat 5 µg offers an alternative inhalation device and formulation of tiotropium, i.e. a mist rather than a dry powder, in a multi-dose inhaler that delivers the dose independent of the patient's inspiratory effort.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The member states, on the basis of the data submitted, considered that Spiriva Respimat 2.5 microgram demonstrated adequate evidence of efficacy for the approved indication(s) as well as satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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

A European harmonised birth date has been allocated (9 October 2001) and subsequently the first data lock point for tiotropium is October 2008. The first integrated PSUR is therefore expected in December 2008. The PSUR submission cycle is 3 years.

The renewal date is 24 July 2012.

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

Quality

- The MAH proposes to use only laser diffraction in the routine quality control and commits to test in parallel ACI and laser during the first 10 commercial batches before discontinuing the ACI testing in routine quality control.
- The MAH commits to further evaluate the stability profile of commercial batches and to consider further tightening (of specification limits) accordingly.

Pharmacovigilance

- A Risk Management Plan (RMP) for Spiriva® (covering the products Spiriva Respimat 2.5 microgram, solution for inhalation and Spiriva 18 microgram, inhalation powder) should be submitted in accordance with guideline EMA/CHMP/96268/2005. The RMP should monitor all cause and respiratory mortality with tiotropium, lower respiratory tract infections and cardiovascular events (in particular angina pectoris) for both Spiriva Respimat and Spiriva 18 microgram HandiHaler, as well as a detailed action plan for specific safety concerns, if applicable. Also data and a protocol outline of studies with respect to risks indicated above should be reported in the RMP.

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 procedure	Approval/ non approval	Assessment report attached Y/N
Submission of an updated drug substance documentation set reflecting a partly new route of synthesis for drug substance. Several minor changes are combined to one Type II variation.	NL/H/0718/ 001/II/001	II	29-5-2008	28-7-2008	Approval	N
Updated description of the Pharmacovigilance System, including change of responsible person for pharmacovigilance.	NL/H/0718/ 001/II/002	II	8-12-2008	12-2-2009	Approval	N
Extension of shelf life: 2 years -> 3 years.	NL/H/0718/ 001/IB/003	IB	17-7-2009	16-8-2009	Approval	N
Extension of in-use period: 2 months -> 3 months	NL/H/0718/ 001/IB/004	IB	17-7-2009	16-8-2009	Approval	N
Update of SmPC/PL with new safety information from study 205.372 and updated safety profile from 5 pooled studies: Section 4.4: Additional statement proposed as precautionary measure, Section 4.8: Re-evaluation of undesirable effects (based on pooled data of 5 Spiriva Respimat clinical trials), Section 5.1: Amendment to describe key efficacy results in clinical trial 205.372.	NL/H/0718/ 001/II/005	II	17-7-2009	5-8-2009	Approval	Y, Annex I
Repeat-use procedure with Bulgaria, Estonia, Liechtenstein, Malta and Romania.	NL/H/0718/ 001/E/001	E	2-2-2011	3-5-2011	Approval	Y, Annex II
Renewal of the marketing authorisation.	NL/H/0718/ 001/R/001	R	27-1-2012	6-8-2012	Approval	Y, Annex III
Pharmacovigilance system master file.	NL/H/0718/ 001/IA/006/ G	IA/G	25-9-2012	29-10-2012	Approval	N
Update of the SmPC with the results of the paediatric studies in cystic fibrosis according to the paediatric regulation. In addition, the SmPC is updated with the information on the paediatric waiver in the condition COPD according to the QRD template.	NL/H/0718/ 001/I/007	II	25-9-2012	16-5-2013	Approval	Y, Annex IV
Addition of 'anaphylactic reaction' to SmPC section 4.8. and to section 4 of the Package Leaflet with frequency 'unknown' as requested by PRAC on 28 June 2013.	NL/H/0718/ 001/IB/008	IB	15-8-2013	16-10-2013	Approval	N
Extension of the indication to the treatment of adult patients with asthma.	NL/H/0718/ 001/II/009	II	9-11-2013	7-8-2014	Approval	Y, Annex V
Submission of a new CEP from an already approved manufacturer of the active substance.	NL/H/0718/ 001/IA/010	IA	14-10-2013	13-11-2013	Approval	N
Update of SmPC section 5.1 with results of Tiospir study and section 5.2 with PK/PD study 205.458. Update of SmPC section 4.8 and minor amendments of 4.5, 4.9 and 5.1.	NL/H/0718/ 001/II/011/G	II/G	26-2-2014	20-11-2014	Approval	Y, Annex VI

Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmaco-vigilance System Master File (PSMF) location.	NL/H/0718/ 001/IA/012/ G	IA/G	26-4-2014	26-5-2014	Approval	N
Change in layout and colours outer packaging.	NL/H/0718/ 001/IB/013	IB	28-7-2014	27-8-2014	Approval	N
Submission of an updated CEP from an already approved manufacturer of the active substance.	NL/H/0718/ 001/IA/014	IA	30-6-2014	30-7-2014	Approval	N
Submission of updated RMP (version 6.0 and 7.0)	NL/H/0718/ 001/IB/015	IB	13-1-2015	13-4-2015	Approval	Y, Annex VII

Annex I – Update to SmPC/PL, new safety data (NL/H/0718/001/II/005)

Introduction

The variation application was submitted to the RMS and all CMS on 10 July 2009 to update the SmPC and package leaflet with new efficacy and safety information from the recently completed Spiriva Respimat study 205.372 and updated safety profile from 5 pooled long-term studies. In addition, data from previous trials with Spiriva HandiHaler were reviewed. Besides amendments of sections 4.8 and 5.1, an additional statement was proposed as precautionary measure for section 4.4 to highlight an increased incidence rate of fatal events for Spiriva Respimat versus placebo which was seen in the pooled analysis.

The RMS has performed a thorough evaluation and assessment of the data indicating a higher risk for fatal events with Spiriva Respimat compared to HandiHaler which cannot be explained within the current knowledge. After a first discussion in the Pharmacovigilance Working Party (PhVWP) of July 2009, it was decided to request the MAH for further information and not to start the variation procedure until the requested data and discussion from the MAH had been received and assessed. After assessment and discussion in the PhVWP of October 2009, further information was requested from the MAH in November 2009. In February 2010 the RMS provided an assessment report to the PhVWP with the conclusion for a revised SmPC wording (section 4.4 and 5.1) related to the imbalance in fatal events, which was endorsed by the PhVWP.

The MAH has accepted the proposed statements for the SmPC with a minor revision and provided revised product information documents on 4 March 2010.

Clinical aspects

Fatal events in patients treated with Spiriva® Respimat®

In July 2009 the MAH submitted the results of the 205.372 trial. Trial 205.372 is a randomised, double-blind, placebo-controlled, parallel group study to assess long term (one-year) efficacy and safety of Spiriva® Respimat® in patients with chronic obstructive pulmonary disease (COPD). 3,991 patients were enrolled in this study. The primary endpoints of this study were FEV1 (Forced Expiratory Volume in one second) and time to first COPD exacerbation. The secondary end points were other efficacy and safety of the product. The efficacy outcome of the study shows that treatment with tiotropium is associated with an improvement in lung function, a reduced risk of a COPD exacerbation and associated hospitalisation, and an improvement in health related quality of life (St. George's Respiratory Questionnaire) relative to the placebo group. Regarding the safety results, overall the numbers of patients reported with adverse events and serious adverse events were similar in both treatment groups, except for fatal events and other significant AEs. The total number of deaths was 52 (incidence density 2.94 per 100 patient-years) in the tiotropium group and 38 (incidence density 2.13) in the placebo group (RR 1.38, 95% CI 0.91, 2.10, p = 0.1297). An imbalance favouring placebo was seen in the SOC cardiac disorders (RR 2.27, 95% CI 0.70, 7.37), general disorders and administration site conditions (RR 1.60, 95% CI 0.78, 3.29) and lung (RR 2.52, 95% CI 0.49, 13.01) or other neoplasms (RR 2.02, 95% CI 0.37, 11.02). Fatal events had a higher rate ratio in patients who had a history of cardiac disease (RR= 4.03, 95% CI 1.15, 14.13; incidence rate of 2.86 for tiotropium and 0.71 for placebo (per 100 patient years)), and arrhythmia at baseline (RR = 8.61, 95% CI 1.10, 67.23; incidence rate of 4.51 for tiotropium and 0.52 for placebo (per 100 patient year)).

These conclusions were further confirmed by a pooled analysis of all studies of at least 24 weeks duration comparing tiotropium RESPIMAT to placebo (about 6000 COPD patients; 2,802 treated with RESPIMAT). This analysis shows a RR of 1.33 (95% CI 0.93, 1.92) for all-cause mortality. The subgroup of patients with 'cardiac disorder' at randomisation had an increased risk of IRR (incidence-rate ratio) 1.78 (95% CI 1.01, 3.16; 34 patients with tiotropium and 18 with placebo) and the subgroup

with the broad rhythm disorder high level group term had an increased risk of IRR 3.42 (95% CI 1.29, 9.07; 21 patients with tiotropium and 5 with placebo).

In contrast, for Spiriva® HandiHaler® no increase in fatal events was observed compared to placebo. The pooled trial database for Spiriva HandiHaler, includes 9,149 tiotropium patients and 7,865 placebo patients from 26 placebo-controlled (UPLIFT + HH (25 trials) clinical trials with treatment periods ranging between four weeks and four years. The results of this pooled analysis did not show a higher rate ratio for serious (0.82, 95% CI 0.72, 0.93) or fatal (0.75, 95% CI 0.56, 0.99) cardiac events; death (1.17, 95% CI 0.71, 1.92); sudden death (1.00, 95% CI 0.44, 2.27) and general fatal events (0.88, 95% CI 0.85, 0.92) in the tiotropium treated group compared to placebo. The rate ratio for fatal or serious cardiac events was also not higher in patients with baseline complications such as cardiac arrhythmia, cardiac disorder, atherosclerotic disease, coronary artery disease and cardio vascular disorders. In patients with baseline cardiac arrhythmia the rate ratio for fatal and cardiac related fatal events were 0.78 (95% CI 0.52, 1.16) and 0.29 (95% CI 0.10, 0.89), respectively. In patients with baseline cardiac disorder the rate ratio for fatal and cardiac related fatal events was 0.77 (95% CI 0.62, 0.97) and 0.48 (95% CI 0.30, 0.75), respectively.
These findings are in line with the FDA update (January 2010) on the safety of Spiriva HandiHaler.

The PhVWP (meeting of October 2009) decided that although there is a lack of biological and/or clinical explanation justifying a difference in the fatality rate (reported in the clinical trials with Spiriva Respimat compared to the placebo controlled trial using Spiriva HandiHaler); nevertheless, there appears to be a real difference between the two formulations and this warrants a further benefit-risk re-evaluation at some point.

A recent randomized, double-blind, parallel-group, placebo-controlled study (Celli et al Cardiovascular safety of tiotropium in patients with COPD. Chest 2010; 137; 20-30) has investigated the safety of tiotropium in 19,545 patients (10,846 tiotropium and 8,699 placebo) from 30 trials. The result of this study shows that tiotropium was associated with a reduction in the risk of all-cause mortality, CV mortality, and CV events. For all-cause mortality, the IR was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years (RR [95% CI] 0.88 [0.77-0.999]). IR for the CV end point was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR [95% CI] 0.83 (0.71-0.98]). The IR for the CV mortality excluding nonfatal MI and stroke was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years (RR [95% CI] 0.77 [0.60-0.98]). For total MI, cardiac failure, and stroke the RRs (95% CI) were 0.78 (0.59-1.02), 0.82 (0.69-0.98), and 1.03 (0.79-1.35), respectively. Although it is stated that studies from both tiotropium formulations (Respimat and HandiHaler) have been included in the pooled analysis, and the authors relate their safety findings to the term “tiotropium” in general; the assessor would like to point out that the outcome of this study is strongly affected by the higher number of HandiHaler trials. From almost 20,000 patients only 2,000 were treated with the Respimat formulation (study 205.254, 255); and the largest and most controversial trial on Respimat (205.372) has not been included (due to a later date of completion). Even if trial 205.372 would have been included, it seems unlikely that the outcome would differ, given that still the great majority of patients were treated with Spiriva HandiHaler.

The difference observed in the safety profile of Spiriva HandiHaler and Spriva Respimat can not be explained by the possible differences in the formulation of these two formulations, their systemic exposure, or differences observed in the patient populations. It seems unlikely that paradoxical bronchoconstriction related to use of Benzalkonium in the formulation of Spiriva Respimat is the cause of increased fatality. Additional follow-up analysis on the fatal cases in the trial 205.372 and comparison in the cardiovascular history of the patients (for further clarifying the cause of death) also didn’t provide sufficient explanation for an increased risk of fatality for Spiriva Respimat.
To further explain the increased risk for fatal events in a subgroup of patients with known arrhythmia at baseline (rate ratio (95% CI) 3.35 (1.11 - 10.09)), the MAH has evaluated a potential relatedness baseline arrhythmia and cause of death using an algorithm by Schosser et al. In the tiotropium group baseline arrhythmia was reported for 16 patients who died, and relatedness was determined

”excluded” or “unlikely” for eleven of 16 patients (69%). Similarly in placebo patients, relatedness was considered “excluded” or “unlikely” in three of five patients (60%). Although the reasoning of the MAH is considered acceptable, it should be noted that still the number of fatal cases, likely related to arrhythmia, is approximately 2.5 times higher in the Spiriva group in comparison to the placebo group.

A review of the effectiveness data between the two formulations indicates a small statistically significant difference in bronchodilatation favouring the Respimat formulation in Caucasian, but not in Japanese COPD patients. Moreover, reduction in COPD exacerbations and hospitalizations due to exacerbations for tiotropium compared to placebo appear to be slightly higher with the Respimat formulation. On the other hand when comparing trial 205.372 for Respimat with the UPLIFT study for HandiHaler, it seems that the estimated compliance to the trial medication for the proportion of “high use” patients (exceeded the 120% compliance) is higher for the Respimat treated patients (1.4%) compared to the HandiHaler treated patients (0.2%).
Information provided covers the compliance of the patients to test medication and not the possibility of overdose. It is comprehensible that based on this data the risk of overdose can not be calculated. However, the MAH is asked to closely monitor cases of overdose in future and include this topic to the list of potential risks of the risk management plan.

Although such data should be cautiously considered given the different methods of assessment in the trials, still a combination of higher compliance and effectiveness as well as the underlying condition of the patients can suggest an increase in the anticholinergic effect of Spiriva Respimat.

Conclusions
The MAH should include “overdose” in the list of potential risks of the RMP, and closely monitor the topic.
With respect to the SmPC, the agreed wording for section 4.4 - with cross reference to section 5.1 - is:
Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders.

Section 5.1 should be revised as follows:
In a retrospective pooled analysis of the three 1-year and one 6-month placebo-controlled trials with Spiriva Respimat including 6,096 patients a numerical increase in all-cause mortality was seen in patients treated with Spiriva Respimat (68; incidence rate (IR) 2.64 cases per 100 patient-years) compared with placebo (51, IR 1.98) showing a rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) for the planned treatment period; the excess in mortality was observed in patients with known rhythm disorders.

The proposed text is in line with the final decision of the PhVWP in February 2010 and is therefore acceptable.

Annex II – Repeat-use procedure (NL/H/0718/001/E/001)

The repeat-use procedure was started on 2 February 2011, with the following concerned member states:
Bulgaria, Estonia, Liechtenstein, Malta and Romania. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states mutually recognised the RMS's assessment, and have therefore granted a marketing authorisation. The repeat-use procedure was finished on 3 May 2011.

The date for the first renewal is: 24 July 2012.

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

- The requested and accepted changes in the SmPC, PL and Labelling will be considered in the proposed product information to be submitted with the renewal application for Spiriva Respimat.
- Regarding the pharmaceutical form: the current term "solution for inhalation" will be replaced by an appropriate new EDQM standard term for non-pressurised metered-dose preparations for inhalation as soon as this is available. The RMS will closely monitor the introduction of a new EDQM standard term following the revision of the Ph.Eur. monograph on Preparations for Inhalation and will initiate the submission to EDQM if necessary.

Annex III – Renewal of the marketing authorisation (NL/H/0718/001/R/001)

I RECOMMENDATION

Based on the review of the data submitted for the renewal application, the member states consider that the benefit/risk balance of Spiriva Respimat 2.5 microgram, solution for inhalation is positive. An additional five-year renewal is granted.

II SCIENTIFIC DISCUSSION

II.1 Introduction

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

The product has been licensed within the EU in 2007 through a decentralised procedure with the Netherlands acting as the Reference Member State, and a subsequent repeat-use procedure in 2011. The requested and accepted changes in the SmPC, PL and Labelling during the repeat-use procedure were taken into account in the product information submitted with the renewal application.

For the renewal the MAH submitted the following documents:

- PSUR covering the period 10 October 2008 to 9 October 2011
- Clinical Expert Statement (Clinical Overview) dated 11 November 2011
- Quality Expert Statement dated 26 October 2011

The provided PSUR is for tiotropium and covers both formulation of Spiriva Respimat® and HandiHaler®. In future PSUR, a separate analysis of number of ADRs (serious/non-serious) per formulation should be provided. The MAH will indicate if there was a difference in the safety profile of the two formulations.

Patient exposure to Spiriva® Respimat® 2.5 µg solution is estimated at 766,119 patient years within the reporting period.

II.2 GMP compliance statements

The following documents have been submitted:

- GMP compliance statements for all manufacturers listed in the application form beside the manufacturers of the active substance
- Declaration of the qualified person as regards the manufacturer of the active substance
- Contact person for pharmacovigilance
- Contact person with the overall responsibility for product defects and recalls
- Contact person for scientific service in charge of information about the medicinal product

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

II.3 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008) a quality expert statement has been submitted for this product confirming:
- That the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH to take account of technical and scientific progress and introduce any changes.
- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.
- The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

The MAH has provided a list of post-approval commitments and their status. The following quality commitments were made:

Description of post-approval commitments
I. The MAH proposes to use only laser diffraction in the routine quality control and commits to test in parallel ACI and laser during the first 10 commercial batches before discontinuing the ACI testing in routine quality control. This commitment has been fulfilled in January 2011.

II. The MAH committed to further evaluate the stability profile of commercial batches and to consider further tightening (of specification limits) accordingly.
Stability data of 7 commercial batches have been generated. The data do not support a further tightening of degradation specification limits. All batches are full-scale batches and have been manufactured at the commercial site according to the approved manufacturing process. For 3 of the batches, data over the full shelf-life of 36 months are available; 3 more batches have been stored for 24 months in the meantime, and one batch for 9 months.
The results were subject to statistical analysis and indicate that, for each batch, the prediction interval does not exceed the current decomposition specification. This means that the decomposition specifications will consistently be complied with by all batches. On the other hand, the prediction intervals of the batches with the highest degradation are quite close to the current decomposition specification limits. This means that there is no basis for a further meaningful tightening. This conclusion is agreed. The MAH has provided sufficient data and the post-approval commitment can be considered fulfilled.

III. At the end of the decentralised procedure of Spiriva Respimat (NL/H/0718/001/DC) it was committed by the MAH to provide a full validation for all residual solvents of the drug substance. The MAH has adequately resolved the issue. The commitment was considered fulfilled in January 2009.

Other changes
The other quality changes approved for Spiriva Respimat are given in the table on pages 24-25 of this report.

II.4 Clinical aspects

II.4.1 Clinical efficacy

Three studies in total have been completed since the submission of the dossier. Two of these studies

(205.372 and 205.291) are part of the clinical development programme for tiotropium solution for inhalation 5 µg via the Respimat® inhaler in the COPD indication.

In study 205.372, a placebo controlled randomised parallel group study of 48 weeks duration, the trough FEV_1 was significantly greater in the tiotropium group (119 mL) than the placebo (18 mL). The adjusted mean difference between treatments was 102 mL (95% CI 85, 118 ml; p<0.0001). The difference in Health Related Quality of life between tiotropium and palcebo was statistically significant, however did not meet the MCID of the SGRQ (4 units) which might possibly be due to the concomitant use of long acting β_2 agonist during the trial.

The time to the first exacerbation was delayed with tiotropium. During the treatment 685 (35.3% patients in the tiotropium group and 842 (43.1%) in the placebo group had at least one exacerbation, representing a significant risk reduction with tiotropium; hazard ration (HR) = 0.69 (95% CI: 0.63, 0.77; p<0.0001).
The rate of exacerbations per patient year was lower with tiotropium during the treatment period than with placebo (0.69 and 0.87 respectively; RR 0.79 (95 CI 0.72-0.87; p<0.0001).

In study 205.291, a randomised double blind, double dummy active controlled 2 period crossover study in Japanese patients, therapeutic equivalence between the Tiotropium Respimat (5 µg) and Tiotropium HandiHaler (18 µg) was demonstrated, see data below.

Table 1. Comparison in FEV1 between Tiotropium Respimat® hand Tiotropium HandiHaler®

	Adjusted mean Response (L)		Difference in response (Respimat HandiHaler® [95% CI]
	Tiotropium Respimat 5 µg	Tiotropium 18 µg HandiHaler®	
Peak FEV1 day, day 1	0.186	0.189	-0.003(-0.018, 0.011) p=0.65
Peak FEV1, day 29	0.220	0.205	+0.015 (-0.002, 0.032) p=0.09
FEV1, AUC0-3 hr, day 1	0.119	0.122	-0.003(-0.014, 0.009) p=0.64
FEV1, AUC0-3 hr, day 29	0.166	0.151	+0.015(-0.001, 0.030) p=0.07

Table 2. Pharmacokinetic data plasma tiotropium

	Tiotropium Respimat 5 µg	Tiotropium 18 µg HandiHaler®	Adjusted mean ratio (90% CI)
plasma exposures, geometric mean ($AUC_{T, ss}$)	94.4 pg.h./mL	89.6 pg.h./mL	105 (98.0-113.8)
Steady state Ae0-4, ss	342 ng	341	102.2 (92-5 -113.0)

The number of adverse events reported during the treatment were comparable between treatments 45.3% with Respimat and 41.27% with HandiHaler. The number of patients reporting AE considered to be related to study medication was low 4 (2.7%) and * (5.4%) during Respimat and HandiHaler respectively. A total of 11 SAE were reported 5 with Respimat and 6 with HandiHaler, non considered

to be related to study treatment.

The third study (1205.14) is part of a separate clinical development programme for another compound intended for the COPD indication where in tiotropium 5 µg delivered as two actuations of 2.5 µg from the Respimat® inhaler was used as an active comparator in addition to a placebo-treated group. The mortality data of this study was used in the retrospective analysis for all cause mortality. Five patients that received placebo and two patients that received the active comparator died.

Based on the provided data, the RMS concluded that no new efficacy findings were retrieved from these studies. No new data changing the efficacy knowledge of Spiriva Respimat® has become available during this period.

Two studies (205.458 and 205.452) were not yet finalised to provide further data on:
- the efficacy, safety and PK of tiotropium solution for inhalation 5 µg administered from the Respimat® inhaler to COPD patients and
- comparison of its efficacy, safety and pharmacokinetics of tiotropium inhalation solution 5 µg administered from the Respimat® inhaler with that of the tiotropium inhalation powder capsule 18 µg administered from the HandiHaler® to COPD patients.

The RMS noted that the safety profile of Tiotropium HandiHaler seems to be more favourable than Tiotropium Respimat. The reason for the possible difference might be differences in systemic availability, although study 205.291 did not confirm differences in bioavailability. This will be further investigated in study 205.458.
Study 205.452 will make a head to head comparison between Tiotropium HandiHaler and Tiotropium Respimat. The study is started in May 2010, the conduct of the study is estimated to last a total of approximately 3.5 years.

II.4.1 Clinical safety

Cumulative Experience October 2008 – October 2011
The benefit risk balance of tiotropium remains favorable in the indication COPD, the maintenance treatment of associated dyspnoea and for prevention of exacerbations.
Looking at the safety of tiotropium, although the relative risk (RR) of cardiac disorders does not reach a significant limit in the pooled clinical studies, in many cases the number of reported events is higher in the tiotropium arm compared to the placebo arm (although it varies between Respimat® and HandiHaler®).

The results of ongoing trial 205.452, where the efficacy and safety of tiotropium Respimat® and HandiHaler® are compared, are awaited. It is expected that this study further address the topics of sudden death and unspecified death, all-cause and cardiac mortality, cardiac disorders, vascular disorders, and renal failure.

Report of Post Marketing Experience October 2008 – October 2011
For this renewal the MAH submitted the following documents:
- PSUR for both tiotropium bromide formulations (Spiriva HandiHaler®, Spiriva Respimat®) covering the period 10 October 2008 to 9 October 2011
- Clinical Expert Statement (Clinical Overview) dated 11 November 2011

No new data that changes the current safety profile of Spiriva Respimat has become available. The results of trial 205.452, where the efficacy and safety of tiotropium Respimat® and HandiHaler® are compared, will be provided.
Based on assessment of submitted safety data, and in line with conclusions of PSUR assessment report under worksharing procedure NL/H/PSUR/0017/002, the MAH should continue close monitoring topics of overall mortality, hypertension, blood and lymphatic system disorders, blood

glucose increased, cardiac disorders, lower respiratory tract infections, arthralgia, myalgia and muscular weakness and renal failure (see below).

Cumulative analysis and full discussion on the topics of cataract and hallucination should be provided with the next PSUR.

Conclusion on safety
The benefit risk balance of Spiriva Respimat remains favorable in the indication COPD and the maintenance treatment of associated dyspnoea and for prevention of exacerbations.

The following safety issues should be monitored:

- Overall mortality
- Hypertension
- Blood and lymphatic system disorders
- Blood glucose increased
- Cardiac disorders (including stroke, angina pectoris, MI, syncope, arrhythmia and cardiac failure)
- Lower respiratory tract infections
- Arthralgia, myalgia and muscular weakness
- Renal failure
- Cataract (a cumulative data review)
- Psychiatric disorders (a cumulative analysis on topic of hallucination)

II.5 Product information

Only minor modifications/revisions in several sections of the SmPC, labelling and package leaflet are proposed based on the inclusion of the commitments of the repeat-use procedure, improvements of the patient's instructions for use and handling and on the adaptation to the CMDh annotated QRD template version.

The proposed changes are considered acceptable.

Summary of Product Characteristics
Section 4.6
Text on fertility is added, which is agreed and a reference to section 5.3 is included. In section 5.3 the fertility study is mentioned.

Section 4.9
The proposed wording of section 4.9, stating that no significant undesirable effects have been observed in long term-studies with a daily dose of 10 µg has been removed.
When the Core Safety Profile (CSP) of worksharing procedure NL/H/PSUR/0017/002 is finalised, the MAH should update the SmPC accordingly.

Package leaflet and labelling
The package leaflet and labelling are harmonised for this product. Minor changes have been proposed to implement the commitments of the repeat-use procedure in line with the QRD template. The changes are acceptable.

II.6 Outstanding commitments

The following post-approval commitments are still outstanding:

Pharmacovigilance

- PSURs should be submitted every five years.
- The safety issues listed should be monitored.
- In future PSUR, the MAH committed to also provide a separate analysis of number of ADRs (serious/non-serious) per formulation (Spiriva Respimat® and HandiHaler), and indicate if there was a difference in the safety profile of the two formulations.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The benefit risk balance of tiotropium remains favorable in the indication COPD, the maintenance treatment of associated dyspnoea and for prevention of exacerbations.
Looking at the safety of tiotropium, although the relative risk of cardiac disorders does not reach a significant limit in the pooled clinical studies, in many cases the number of reported events is higher in the tiotropium arm compared to the placebo arm (although it varies between Respimat® and HandiHaler®), with some signals for the Respimat inhaler that need further clarification.

It was expected that study 205.452 – comparing the efficacy and safety of tiotropium Respimat® and HandiHaler –, which was ongoing at the time of renewal, would further addresses the topics of sudden death and unspecified death, all-cause and cardiac mortality, cardiac disorders, vascular disorders, and renal failure especially regarding possible differences between the two different inhalation devices.

The assessment of the variation regarding the comparison between tiotropium Respimat and HandiHaler (NL/H/0718/001/II/011/G) is discussed in annex VI of this report.

The PSUR submission cycle is 5 years. Tiotropium takes part in the PSUR synchronisation project of the Heads of Medicine Agencies with a next data lock point of October 2016. The MAH is requested to submit the next PSUR within 60 days following this data lock point.

The common renewal date is set on 24 July 2012. The renewal procedure ended positively on 6 August 2012. As the results of trial 205.452 as well as other ongoing trials can strongly influence the benefit-risk balance of Spiriva Respimat, an additional five-year renewal can be granted.

Annex IV – Update to SmPC/PL, results of paediatric studies in cystic fibrosis (NL/H/0718/001/II/007)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the member states consider that the variation for Spiriva Respimat (tiotropium bromide), for the following proposed changes is approvable:

update of SmPC sections 4.2, 4.4, 5.1, 5.2 and 5.3 with the results of the paediatric studies in cystic fibrosis according to the paediatric regulation, and in addition with the information on the paediatric waiver in the condition COPD according to the QRD template.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

The MAH has completed a development program in the condition cystic fibrosis (CF) in adults and children according to an agreed Paediatric Investigation Plan (PIP). The overall conclusion is that efficacy and safety was not established in the population studied. This type II variation was submitted to update the SmPC with the results of the paediatric studies according to the paediatric regulation. In addition, the SmPC is updated with the information on the paediatric waiver in the condition COPD.

Article 8 of the Paediatric Regulation
Article 8 of the Paediatric Regulation applies to this variation since the application relates to a new indication for an authorized medicinal product, which is protected by a supplementary protection certificate under Regulation (EEC) No 1768/92.
The development of tiotropium in the condition cystic fibrosis was conducted according to an agreed PIP (P/0105/2012). PIP compliance has been confirmed by EMA/PDCO (EMEA/C/000035/PIP01/07 dated 17 Augustus 2012).
The agreed PIP included 4 trials: a handling study in children below 5 years of age, a phase I trial (205.338) to evaluate the single dose and multiple dose pharmacokinetics of the drug, its safety and tolerability, a phase II trial (205.339) addressing dose ranging, proof of concept, efficacy and safety and a phase III trial (205.438) to confirm the efficacy and safety of tiotropium delivered from the Respimat inhaler in CF patients.

COPD class waiver
EMA has adopted a class waiver (CW/1/2001) for products intended to treat chronic obstructive pulmonary disease (COPD). The applicability of the class waiver has been confirmed by EMA.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

The quality dossier was updated to include information to assure the pharmaceutical suitability for CF patients. Although the clinical studies conducted in line with the PIP do not lead to extension of the indication for CF in the paediatric population, section 5 of the SmPC is updated to include brief information on these clinical studies.

Studies related to presence of *Pseudomonas aeruginosa* on Respimat®:

- *Investigations for deactivation of Pseudomonas aeruginosa on the Respimat mouthpiece*
  Cleaning procedures studied are the same as already stated in the SmPC. The absence of *Pseudomonas aeruginosa* was confirmed by clinical study 205.438.

- *Survival of Pseudomonas aeruginosa on surfaces of the Respimat device*
  The normal drying process at room temperature revealed a powerful but simple process to eliminate *Pseudomonas aeruginosa* and no additional instructions with regard to cleaning or disinfection of the Respimat device need to be provided to CF patients beyond what is already known.

- *Influence of daily cleaning with isopropyl alcohol on the Respimat A5 inhaler for Spiriva Respimat for Cystic Fibrosis*
  According to the PIP, a one-time study to explore an adequate cleaning and disinfection method of the Respimat inhaler to avoid potential *Pseudomonas aeruginosa* contamination has to be conducted as this microorganism is of special harm for the lung of CF patients Wiping with 70% isopropyl alcohol once daily was proposed by the Paediatric Committee as a suitable disinfection method for the Respimat inhaler. As a result of the cleaning procedure only small gaps and stress whitening were observed in the mouthpiece section of the case upper part. These defects can hardly be seen without a microscope and have no influence on the inhaler performance and handling of the inhaler. The inhaler robustness is also verified by the results of the performance testing. All inhalers were within the specification limits. Furthermore the additional conducted stress test (drop test) showed no additional damage on the case upper part. All results were within the specifications.

- *Testing of used Respimat inhaler for Pseudomonas aeruginosa*
  The mouthpieces of Respimat inhalers used by CF patients and cleaned according to the instructions (damp cloths once a week) were analysed microbiologically for absence of *Ps. Aeruginosa*. On none of the returned Respimat inhalers of the clinical study 205.438 at the time point of analysis *Pseudomonas aeruginosa* could be detected.

Suitability of the inhaler and chamber for use in children

- *In vitro* determination of the dose to the lung for the Respimat inhaler equipped with a spacer was determined using representative mouth/throat models and inhalation air flow profiles of children.
  The results and conclusions of an *in vitro* study to characterize the inhalative treatment of children when using the Respimat inhaler equipped with the spacer AeroChamber PlusR with face mask are discussed. As model, tiotropium solution for inhalation was used. Based on the clinical findings, e.g. the handling assessment performed by the investigators and assessment of the flow profiles, children below 4 years of age should use Respimat inhaler with a spacer. The majority of 4-<5 year old subjects can handle Respimat inhaler without a spacer, but with considerable variability in the inhalation flow profile parameters which translate into predicted variability of the predicted dose to the lung. Thus, to ensure standardized dosing, children below 5 years of age are recommended to use Respimat with spacer. Respimat inhaler in connection with the Aerochamber Plus delivers a quantity of tiotropium to children that is comparable to the dose administered to adults in terms of µg/kg body weight.

Clinical batches

- Tiotropium bromide monohydrate clinical trial formulations and batches used in clinical studies are commercial batches. Hence no further assessment was needed.

III.2 Non-clinical aspects

Tiotropium (an anticholinergic drug) is currently marketed for the treatment of chronic obstructive pulmonary disease (COPD). As part of the investigation of tiotropium use for the treatment of cystic fibrosis (CF) and asthma in paediatric patients, studies in juvenile animals have been performed to

extend the existing non-clinical safety database. These data were submitted accompanied by a non-clinical overview focusing on the results of the juvenile toxicity testing.
A preliminary inhalation feasibility study (non-GLP, identification numbers U08-1024-01 and 668143) and a pivotal 13-week inhalation toxicity study (GLP, identification numbers U07-2438 and 667862) in juvenile rats have been performed.

The preliminary inhalation feasibility study in juvenile rats provided valuable information for the design of the subsequent 13-week inhalation toxicity study. No direct toxicity of tiotropium at daily doses of up to 1900 µg/kg was noted in this study. However, anticholinergic effects of tiotropium were evident by the reduced body weight gain in treated animals.
The feasibility study showed that snout-only inhalation of 988-1900 µg tiotropium/kg/day for 1-23 days to rats was feasible with inhalation tubes of various sizes through different growing phases. Data also indicated that juvenile rats were vulnerable to inhalation exposure at 5 days old as a significant drop in body temperature during dosing was noted. It was therefore recommended to start dosing juvenile rats from 7 days of age, and that a higher room temperature was needed to prevent a significant drop of body temperature and it was necessary to accommodate generation of smaller particle size. Furthermore whole body plethysmography chamber system to assess respiratory parameters proved to be suitable for the purpose.

In the pivotal 13 week juvenile toxicity study direct and indirect pharmacological changes were observed in all groups exposed to tiotropium. This included mydriasis and a reduced body weight gain which was in accordance with a reduced food consumption. A delay in sexual maturity in females was noted which was considered to be associated with reduced body weights. Ophthalmic investigations showed a dose-related increase in persistent pupillary membranes which was accompanied by histopathological detectable (minimal) pupillary membrane remnants. This effect was considered due to the mydriatic effect of tiotropium. This was considered of no toxicological concern due to species differences between rat and human ocular development. This is agreed as the apoptosis of the pupillary membrane in humans is usually complete at birth while this occurs postnatal in rats. It was concluded that there were no toxicologically relevant systemic effects on key developmental parameters and on tracheal or key organ development. Local toxicological effects, squamous metaplasia and rhinitis, were seen in the nasal cavity of rats in the mid- and high-dose group. However these effects were seen at doses and exposures (far) above the maximal clinical dose. These findings were already noted in the initial application for Spiriva.
It was agreed that no new toxicities and no toxicologically relevant effects on key developmental parameters and on tracheal or key organ development were observed. As such there is no safety concern based on non-clinical data for the use of tiotropium in the paediatric population.

III.3 Clinical aspects

Cystic fibrosis (CF) is an inherited autosomal recessive disease that disrupts ion transport in epithelial lined organs, including pulmonary airways. It is the most common autosomal recessive disease in Caucasians, with a variable incidence across the countries. It is classified as an orphan disease.
At birth, CF patients have normal lung structure and function, but their mucus is very sticky. As a result, the airways cannot easily be cleared, making the patient population vulnerable to infections and the destructive effects of the chronic inflammation of the airways, like in patients with COPD. Respiratory failure, secondary to obstruction of pulmonary airways, is the cause of death in more than 9% of the patients with CF.
There is no relevant paediatric component in the COPD population. However, there are similarities in terms of disease etiology and progression leading to the obstructive component that is part of both COPD and CF.
At present, the therapy of CF is supportive. Therapy includes antibiotics, airway clearance techniques and devices, pancreatic enzymes and nutritional supplements, and drugs like dornase alfa, ibuprofen and inhaled bronchodilators. The use of bronchodilators is widespread, although no bronchodilator is specifically approved for the treatment of CF.

Tiotropium has a long duration of action and therefore has to be administered only once daily, which is a benefit for patients using multiple medications. It may be speculated that the bronchodilation could facilitate clearance of secretions by cough. On the other hand, anticholinergics may dry in mucus, which will make it more difficult to clean the airways.
The Respimat inhaler is chosen for the clinical development plan in CF. The inhaler is an active device that releases drug substance via an aerosol and hence no minimal inspiratory flow is required by the patient. The inhaler and formulation can therefore be suitable for the entire population age range.

III.3.1 Clinical efficacy

The agreed PIP included 4 trials: a handling study in children below 5 years of age, a phase I trial (205.338) to evaluate the single dose and multiple dose pharmacokinetics of the drugs, its safety and tolerability, a phase II trial addressing dose ranging, proof of concept, efficacy and safety (205.339) and a phase III trial (205.438) to confirm the efficacy and safety of tiotriopium delivered from the Respimat inhaler in CF patients. An additional ECG analysis of a subset of the patient population included in the phase III study was performed following a scientific advice given in June 2011.

Table 1. Overview of clinical trials in patients with cystic fibrosis

Study ID	Design	Study Posology	Study Objective	Subjs by arm entred/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
205.338	SD MD P DB, Pl	SD: Tio R2.5, 5 ad 10 MD Tio R2.5 and Tio R5	PK safety and tolerability		1 day 28 day		CF, FEV1 > 25% of predicted value, clinically stable	FEV1
205.339	P DB Pl	Tio R2.5 and Tio R5	Dose ranging, proof of concept, efficacy and safety PK	465 (155 each treatment group)	12 weeks	53.9% male, mean age 20.9 years	CF, FEV1 > 25% of predicted value, clinically stable	FEV1 % predicted AUC0-4h Trough FEV1 at week 12
205.438	P DB Pl 12 weeks, extention open label single arm	Tio R5	Confirmation of efficacy and safety, PK < 5 yrs		12 weeks; then 12-38 w open label, then optional 4 weeks open label ECG sub-study	55.9% male, mean age 19.8 years.	CF, FEV1 > 25% of predicted value, clinically stable	FEV1 AUC0-4h Trough FEV1 at week 12

SD single dose; MD multiple dose; P parallel; Pl placebo; DB double blind; Tio R tiotropium Respimat, CF cystic fibrosis, FEV1 forced expiratory volume in 1 second.

Dose selection for the phase II studies was based on PK data provided from the phase I trial, comparison of systemic availability to COPD patients and evaluation of safety.
For phase III dose selection was based on the phase II proof of concept, dose ranging efficacy and safety trial (205.339) in which two doses of tiotropium bromide (2.5 µg and 5 µg) were administered once daily via de Respimat device for 12 weeks in patients with CF.

GCP aspects
The trials were carried out in compliance with the clinical trial protocol, in accordance with the

principles of Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice, in accordance with applicable regulatory requirements, and the MAH's standard operating procedures.

- **Studies 205.339 and 205.438**

Design

Main studies
The main studies are considered phase II study 205.339 and confirmatory phase III study 205.438. Study 205.339 was a dose response study. However, this study has the same in- and exclusion criteria, primary endpoints and duration as the confirmatory phase III study (205.438). The exception included the lower age limit (also patients < 5 years in study 205.438) and in study 205.339 patients were required to exhibit a longer duration of symptomatic stability prior to the screening visit.

Methods
Both studies were randomised, double blind, placebo controlled, parallel group studies of 12 weeks duration.
In addition, in study 205.438, all patients continued with an open label active treatment for at least another 12 weeks, resulting in a minimum of 24 weeks of treatment. Patients remained in the trial on active medication (up to 12 months) until the last patient had completed the trial.
After completion of the trial, patients were asked to participate in an optional ECG substudy which had an open label 4 week treatment.

Study participants
Male and female patients with a documented diagnosis of CF (positive seat chloride ≥ 60 mEq/L by pilocarpine iontophoresis) and/or a genotype with two identifiable mutations consistent with CF accompanied with one or more clinical features with the CF phenotype and a FEV1 ≥ 25% were included.
The main exclusion criterion was that patients should not start with a new chronic treatment for CF within 4 weeks of screening. Patients on a cycling tobramycine regimen were allowed to participate.

The inclusion criteria regarding CF are conform the 'Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis' (EMEA/CHMP/EWP.9147-2008/corr*).

Treatments
Study 205.339
Patients were randomised to tiotropium Respimat 2.5 µg, tiotropium Respimat 5 µg or placebo in a 1:1:1 ratio.

Study 205.438
Patients were randomised to tiotropium Respimat 5 µg or placebo in a 2:1 ratio.

Objectives
Study 205.339
In this dose finding study the primary objective was to evaluate the effects of 12 weeks treatment with two doses of tiotropium (2.5 µg q.d and 5 µg q.d) compared to placebo administered via the Respimat device on lung function in patients with CF.

Study 205.438
The primary objective of this study was to confirm the efficacy of 5 µg tiotropium versus placebo (i.e. on top of usual care) delivered by the Respimat inhaler over 12 weeks.

Additionally the long term safety was assessed over an open label active treatment (12 weeks) for a minimum of 12 weeks.
Per amendment, safety is further assessed based on electrocardiogram (ECG) measurement over a 4 week period of open label 5 µg tiotropium treatment.

The study duration is relatively short according to recommended study duration of 6 months regarding the primary outcome measure FEV_1 (guideline EMEA/CHMP/EWP/9147/2008-corr).
The study is performed on top of treatment. Concomitant treatments were not standardised, which makes the variability larger and differences (if any) between active treatment and placebo more difficult to demonstrate.

The additional ECG were performed in a subset of patients. The results are therefore considered supportive rather than conclusive.

Outcomes/endpoints
The co-primary endpoints of the study were the FEV_1 $AUC_{0\text{-}4h}$, and trough FEV_1 after 12 weeks of treatment. The trough FEV_1 response was defined as the change from baseline in trough FEV_1.

Secondary parameters were the proportion of patients experiencing at least one exacerbation of pulmonary CF assessed by the Respiratory and Systemic Symptoms Questionnaire (RSSQ) and the health related quality of life cystic as measured by change from baseline in CF Questionnaire (CFQ) scores at the end of week 12.

Other secondary parameters in study 205.339 were the residual and total lung capacity.

The study has two co-primary endpoints regarding the lung function. Preferably a symptomatic co-primary endpoint, like exacerbations and health related quality of life should be included. They are included as secondary endpoints.

Randomisation
Study 205.339
The MAH generated a randomisation schedule and prepared the randomisation list. After assessment of all in- and exclusion criteria the patients were assigned to the lowest available number at the investigational site.

Study 205.438
The randomisation code was generated using a validated system that involved a pseudo random number generator with a supplied seed number so that the resulting sequence of treatments was reproducible and non-predictable.

Statistical methods
In both trials, the main objective was to show superiority of tiotropium over placebo in change from baseline in percent predicted FEV_1 $AUC_{0\text{-}4h}$ and percent predicted trough FEV_1 at the end of 12 weeks.

The following null and alternative hypotheses were tested in hierarchical order, each at the 2.5% level of significance (one-sided) to control the overall probability of type I error at 2.5% (one-sided).
H10: Change from baseline in percent predicted FEV_1 $AUC_{0\text{-}4h}$ (Tio R5) ≤ Change from baseline in percent predicted FEV_1 $AUC_{0\text{-}4h}$ (placebo) versus
H11: Change from baseline in percent predicted FEV_1 $AUC_{0\text{-}4h}$ (Tio R5) > Change from baseline in percent predicted FEV_1 $AUC_{0\text{-}4h}$ (placebo),
H20: Change from baseline in FEV_1 percent predicted trough (Tio R5) ≤ Change from baseline in percent predicted FEV_1 trough (placebo) versus

H21: Change from baseline in percent predicted FEV_1 trough (Tio R5) > Change from baseline in percent predicted FEV_1 trough (placebo).

Four analysis populations were defined for each of the two trials: the randomised set included all randomised patients. The treated set included all patients who were documented to have taken at least one dose of investigational treatment. The full analysis set (FAS) included all patients in the treated set with at least one baseline pulmonary function test measurement and at least one on-treatment post-baseline pulmonary function test measurement, regardless of the washout compliance status. The per protocol set (PPS) included all patients in the FAS except those with important protocol violations related to efficacy.

The primary efficacy variable is a lung function measurement, therefore the FAS analyses were regarded as the primary efficacy analysis. No patients < 5 years were included in the FAS and according to the definition also not in the PP set.

Results

Study 205.339

Analysis description	**Primary Analysis**			
Analysis population and time point description	Change from baseline at week 12 (FAS–population)			
Descriptive statistics and estimate variability	Treatment group	Tiotropium 2.5 µg (A)	Tiotropium 5 µg (B)	Placebo (C)
	Number of subject	166	176	168
	FEV°AUC 0-4h (% predicted) Adjusted mean (SE)	1.20 (0.66)	1.65 0.63	-1.74 0.65
	Trough FEV1 % predicted Adjusted mean (SE)	0.81 (0.71)	0.78 (0.69)	-1.44 (0.71)
	FEV1 AUC 0-4h L Adjusted mean (SE)	0.03 (0.02)	0.03 (0.02)	-0.07 (0.02)
	Through FEV1 L Adjusted mean (SE)	-0.00 (0.00)	-0.00 (0.02)	-0.06 (0.02)
	RSSQ	7.8%	6.9%	9.6%
	Health related quality of life CFQ			
Effect estimate per comparison	FEV1AUC 0-4h % predicted	A vs. C		
		Adjusted mean % (SE) 95% CI P value	2.94 (0.89) (1.19, 4.70) 0.001	
		B vs. C		
		Adjusted mean % (SE) 95% CI P value	3.39 (0.88) (1.67, 5.12) <0.001	
	Trough FEV1	A vs C		

% predicted	Adjusted mean % (SE) 95% CI P value 95% CI B vs. C Adjusted mean % (SE) 95% CI P value	2.24 (0.95) (0.38, 0.41) 0.018 2.22 (0.93) (0.38, 4.06) 0.018

The lung function secondary endpoints were comparable to the co-primary endpoints.
The adjusted mean difference (SE) regarding the change from baseline regarding the FEV_1 $AUC_{0\text{-}4h}$ (L) after 12 weeks was for Tio R2.5-placebo 0.09 (0.03) L (95% CI 0.04, 0.14, p<0.001 and for Tio R5-placebo 0.09 (0.02) 95%CI [0.05-0.14], p< 0.001).
Regarding the trough FEV1, these values were Tio R2.5 – placebo 0.06 (0.03) L, 95% CI [0.00, 0.11], p=0.033 and for Tio R5 0.06 (0.03) L, 95% CI [0.01, 0.11] p=0.028.
The amount of patients experiencing at least one exacerbation was not statistically different between the active treatments and placebo. No clinically significant improvement was observed in the CFR-Q for neither treatment.

Tiotropium R5 µg was chosen for the phase III study because:

a) Best pulmonary function test compared to placebo for percentage predicted FEV_1 $AUC_{0\text{-}4H}$ (3.39% vs 2.94%)
b) Systemic exposure comparable to COPD
c) Similar safety profile between Tio R2.5 and Tio R5

The RMS noted that the improvement in FEV_1 is small, although statistically significant. The improvement is less than the minimum clinical value used in COPD of 100 mL and less than 5% of predicted, which are often used in CF trials. The symptomatic and health related measurements did not demonstrate a significant improvement.
A difference of at least 4 points in the respiratory domain of the CFQ-R is considered a minimal important difference. This difference was not achieved.

Study 205. 438

Analysis description	**Primary Analysis**		
Analysis population and time point description	Change from baseline at week 12/FAS		
Descriptive statistics and estimate variability	Treatment group	Tiotropium 5 µg (A)	Placebo (B)
	Number of subjects	293	147
	Through FEV_1 % predicted Adjusted mean (SE)	2.12 (0.58)	0.72 (0.80)
	FEV_1 $AUC_{0\text{-}4h}$ (L) Adjusted mean (SE)	0.059 (0.016)	-0.011 (0.022)
	Trough FEV_1 (L) Adjusted mean (SE)	0.043 (0.016)	-0.024 (0.22)
	RSSQ	8.9%	7.8%
	CFQ (mean SD)	-0.60 (14.52)	-1.50 (16.04)

Effect estimate per comparison (tiotropium R5-placebo)	FEV_1 AUC_{0-4h} % predicted	Tiotropium R5 – placebo	
		Adjusted mean % (SE)	1.64 (0.97)
		95% CI	-0.27 – 3.55
		P-value	0.09
	Trough FEV_1 % predicted	Tiotropium R5 – placebo	
		Adjusted mean % (SE)	1,40 (0.97)
		95% CI	-0.50-3.30
		P-value	0.15

For the secondary lung function parameters, the adjusted mean difference (SE) regarding the change from baseline for the FEV_1 AUC_{0-4h} after 12 weeks was for Tio R5-placebo 0.070 (0.027 L) 95%CI [0.017-0.24], ($p< 0.01$), and for the trough FEV_1 Tio R5/placebo 0.067 (0.027), 95% CI [0.015, 0.119], ($p=0.012$). In contrast to the previous trial, more patients randomised to Tio R5 experienced an exacerbation (Tio R5 6.9% and placebo 9.6%). No clinically significant improvement was observed in the CFR-Q for either treatment.

The improvement in FEV_1 % predicted did not reach statistical significance, although the improvement in FEV_1 in L did. However, the % predicted is considered more precise, as it is corrected for age, gender, race and height, but might be subject to a higher variability in children. In this trial also children are included, and then the use of FEV_1 % predicted is preferable due to the increase in lung function when children grow.
In contrast to the previous study, the amount of exacerbations is larger, although not significantly, in patients treated with tiotropium R5 compared to placebo, although it did not reach significance in the RSSQ.

- **Clinical studies in special populations**

Patients aged ≤ 11 years
Because of the orphan indication and the anticipated low number of patients per ICH subgroups, the subgroups were combined in two main subgroups: ≤ 11 years and ≥ 12 years. These two subgroups represent a split between paediatric and adolescent/adult patients, and maturation of the lung is considered fully complete by the age of 12.

At birth, patients with CF have normal lung structure and function. When patients with CF become older, structural changes and lung function decline may occur, due to the infectious and inflammatory burden. Like COPD, CF can be a progressive disease, with more pronounced lung disease when patients become older. The split between the paediatric and adolescent patients is accepted.

Study 205.339
At screening, for patients aged ≤11 years the mean FEV_1 was 1.642 L (94.3% predicted normal), while for patients aged ≥12 years the FEV_1 was 2.369 L (69.2%).

Study 205.438
At screening, for the patients aged ≤11 years the mean FEV_1 was 1.576 L (90.1%), while for the patients aged ≥12 years the FEV_1 was 2.371 L (70.0%).

The higher baseline mean FEV_1 observed in patients ≤11 years is as expected for this patient population.

Results
The primary efficacy variable is the change from baseline in % predicted $FEV_1AUC_{0-4\ h}$ and trough FEV_1. The results and the adjusted mean changes from baseline in percentage predicted FEV_1AUC_{0-}

$_{4h}$ after 12 weeks of treatment in study 205.339, 205.438 and the pooled analyses are summarised in the table below.

Table 2. Adjusted mean (SE) percentage predicted FEV_1AUC_{0-4h} change from baseline; comparison of Tio R5 to placebo after 12 weeks for the CF trials 205.339 and 205.438 by age group ≤ 11 years.

			Study 205.339		Study 205.438		Pooled	
			Tio R	Placebo	Tio R	Pla	Tio R	Pla
	N=		44	52	47	95	147	91
	FEV_1 AUC_{0-4h} % predicted	Adjusted mean (SE)	3.57 (116)	-0.32 (1.26	3.33 (1.14)	3.96 (1.64)	3.10 (0.91)	1.63 (1.15)
	Trough FEV_1 (% predicted)	Adjusted mean (SE)	1.85 (1.24)	-0.83 (1.35)	2.81 (1.14)	4.06 (1.24)	1.93 (0.98)	1.39 (1.22)
Estimate per comparison	FEV_1AUC_{0-4h} % predicted	Adjusted mean (SE)	3.89 (1.67)		-0.63 (2.00)		1.48 (1.46)	
		95% CI	(0.62-7.17)		(-4.58, 332)		(-1.41, 436)	
		P value	0.019					
	Trough FEV_1 (% predicted)	Adjusted mean (SE)	2.68 (1.78)		-1.24		0.55	
		95% CI	-0.81 -6.18		-5.20, 2.71		1.57-2.54	
		P value						

In study 205.438, an unexpected numerical improvement in FEV_1AUC_{0-4h} was observed for patients ≤ 11 years old receiving placebo, which was comparable to Tio R5.

In the pooled results, the adjusted mean values for percentage predicted FEV_1AUC_{0-4h} showed improvement from baseline at week 12 for Tio R, both in patients who were <11 years (adjusted mean (SE) 3.10 (0.91)%) and for those who were >12 years (1.41 (0.44)%). For placebo also an improvement in lung function was observed for patients ≤ 11 years, mostly driven by the change observed in 205.438.

The findings observed in the FEV_1 AUC_{0-4h} were also observed in the change from baseline in percentage predicted trough FEV_1 at week 12, in favour for placebo for those aged ≤ 11 years old.

According to the MAH a high variability was observed in the lung function in the patients ≤ 11 years old, which may in part explain the observed improvement with placebo.

Yet, the response on Tio R5 in trial 205.339 and 205.438 seems fairly constant for patients ≤ 11 years (adjusted mean (SE) 3.57 (1.16) and 3.33 (1.14)) compared to what is observed in patients ≥ 12 years (0.55 (0.75) and 1.86 (0.61)).

One patient ≤ 11 years in the study 205,339 experienced an exacerbation. In study 205.438, 4 patients ≤ 11 years (6.4%) randomised to tiotropium experienced at least one exacerbation as assessed in the RSSQ, compared to 1 patient in the placebo group (3.2%).
No significant improvements in health related quality of life as assessed with the CFQ-R was observed.

Overall, the effect of tiotropium in this younger patient population is modest and not supported with an improvement of quality of life or exacerbations.

- **Analysis performed across trials (pooled analyses and meta-analysis)**

The pooled results of the phase II and III studies are provided in the clinical overview. The results were pooled because the results point toward the same direction, despite the fact that one trial met the primary outcome, while the other did not. The results are pooled in order to assess the efficacy.
However, the comparability between the trials can be disputed due to the larger decrease in pulmonary function observed with placebo.

For the pooled analyses, the baseline demographic and lung function were comparable between placebo and TioR. Placebo mean age 20.5 ± 12.6 years, 57% male, proportion of patients ≤ 11 years 31%, mean FEV_1 2.17 ± 0.9L (71.8 ± 24%); Tio R mean age 19.8 ± 11.7 years, 54% male, proportion of patients ≤ 11 years 33%, mean FEV1 2.11 ± 0.84L (76 ± 22.5).

The lung function secondary endpoints were comparable to the co-primary endpoints. The adjusted mean difference (SE) regarding the change from baseline regarding the FEV_1 $AUC_{0\text{-}4h}$ (L) after 12 weeks was for Tio R5-placebo 0.070 (0.027) 95%CI [0.017-0.24], $p<0.01$; for the trough FEV_1 the difference was Tio R5 0.067 (0.027 L), 95% CI [0.015, 0.119], p=0.012.
The amount of patients experiencing at least one exacerbation was not statistically different between the active treatments and placebo (Tio R5 7.5%, placebo 8.6%).
No clinically significant improvement was observed in the CFR-Q for either treatment.

In both trials an improvement was observed in the group treated with Tio R5 µg. In study 205.339 the difference with placebo was larger, mainly due to the fact that the deterioration in the placebo group was larger. The difference in placebo effect might be due to between-trial variability. The subgroup analyses by age revealed that the response on placebo was large in the age group ≤11 years in study 205.438.

Due to the complex transformation of the litre data into % predicted data, which adjust for age, height, sex and race using one set or predicted equatations for adults and several set of predicted equatations for the different age groups in children, the variability is higher in the percentage predicted data compared with data expressed in litres.

The results remain limited, and below the minimal clinically relevant difference, either expressed as mL or as percentage predicted. They are also not supported by a reduction in the proportion of patients experiencing at least one exacerbation and improvement of QoL as measured by the CFQ-R. This indicates a limited efficacy.

- **Supportive studies**

Respimat handling by paediatric patients was studied in two trials. In these studies no lung function parameters were measured.
From the results of the handling studies and the *in vitro* study it was concluded that children ≥ 5 years of age demonstrate adequate performance, while children below 5 years should use the Respimat inhaler with spacer.

III.3.2 Clinical safety

Risks
More patients on Tio R5 experienced a serious adverse event: Tio R5 (n=56 (12%)) compared with placebo (n=34 (11%)). The stratified incidence rate ratio did not demonstrate a statistical difference.

The system organ classes related to manifestations of CF are in disfavour (although not statistically significant) for tiotropium.
However, an increased incidence of serious adverse events categorised as 'respiratory disorder, lower' was observed for Tio R (N=38 (8.2%) compared to placebo (n=13 (4.2%)); stratified incidence rate ratio Tio R5/placebo 2.07 (95% CI 1.09-3.96) was observed. As this AE is considered to reflect exacerbations of CF, an increased incidence of serious pulmonary exacerbations related to Tio R5 seems likely.

The system organ classes related to manifestations of CF congenital, familial and genetic disorders (Tio R5 9.5%, placebo 8.4%), gastrointestinal disorders (Tio R5 18.1%, placebo 15.4%), infections (Tio R5 41.1%, placebo 38.3%), and respiratory, thoracic and mediastinal disorders (Tio R5 41.3%, placebo 39.5%) had a higher incidence on Tio R5 than on placebo. The stratified risk ratio of these System-Organ Classes (SOC) is larger than 1, but the 95% CI interval includes 1 indicating that the difference is not significant.

Six adverse events were identified with an incidence for Tio R5 over 5% in either 205.339 and/or 205 438 and also a higher incidence compared to placebo. These adverse events were cough, cystic fibrosis, bronchitis, upper respiratory tract infections, nasal congestion and sputum increased. Only cough was statistically significantly increased (stratified incidence ration 1.42 (1.01,1.99)). The incidence of cough increases over exposure time.

Numerically more patients using tiotropium experienced a respiratory tract infection as assessed by the respiratory infections pooled incidence classified according to Higher Level Group terms: placebo 30.2%, Tio R5 31.2%, stratified incidence ration rate 1.12 (95% CI 0.86-1.46), but the difference was not statistically significant.

Also, numerically more patients using tiotropium experienced an exacerbation not treated with I.V. antibiotics as assessed by the RSSQ symptom score (placebo n=67 (25%), tiotropium R5 N=112 (28.9%), odds ratio 1.16 (95% CI 0.81-1.67, p=0.41)).
Numerically more patients using tiotropium started with oral antibiotics during the trial (placebo 42.1%, Tio R5 49.1%).

In patients ≤ 11 years, the system organ classes in favour of placebo were those related to signs and symptoms of CF. They appear to be based upon infectious conditions and on signs and symptoms that are the result of an infection. The adverse event profile seems comparable to adults.

The reported incidence on gastrointestinal side effects is low; although constipation is more frequently observed in patients using tiotropium.

Uncertainties
No new safety events emerged regarding the cardiac safety, but the ECG were performed in a sub-selection of patients (103 patients).
An increased incidence of the AE cystic fibrosis, bronchitis and upper respiratory tract infection was observed in a study of relatively short duration. The difference was not statistically significantly different, however, the numbers are relatively small and consequently, the 95% CI is wide. The combination of the increased incidence of these AEs might be a reason for concern, as this might indicate that the sputum is less well cleared.

Overall there seems to be a tendency that the incidence of respiratory infection and/or manifestation of CF is increased with the use of Tio R5, but up until now, no differences in the System-Organ Classes or subclasses have been observed. This might become of clinical importance when the number of exacerbations increases. However, the observation period is relatively short and the incidence/amount of pulmonary exacerbations is difficult to establish.

IV. UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

In the clinical documentation for this variation application the MAH provided four studies which investigated use of tiotropium in patients with cystic fibrosis.

The dose finding study demonstrated a statistical improvement in lung function (change in baseline FEV_1 AUC_{0-4H}, trough FEV_1) after 12 weeks of treatment, but the effect is small (< 5%, < 100 ml). No statistical benefit was observed in the confirmatory phase III study. No significant difference between treatments was observed in the proportion of patients experiencing at least one exacerbation or in quality of life as measured according to the CFQ-R. The effect in lung function is not supported by symptomatic and health related improvements.

In the pivotal phase III study in patients with CF, tiotropium provides a marginal, not statistically significant bronchodilation. In the patient group ≤ 11 years no improvement was observed. No improvement in quality of life was provided either.

Based on the provided efficacy and safety data, use of tiotropium in patients with CF cannot be recommended. Unlike in COPD, tiotropium does not provide a clinically significant improvement in FEV_1 and a protection against exacerbations, including severe pulmonary exacerbations. Signs and symptoms considered to be manifestations of cystic fibrosis increased numerically, although not statistically significantly, with tiotropium, especially in patients ≤11 years old.

One of the CMS proposed a contraindication due to a concern that tiotropium may cause dryness of the sputum and a reduced mucociliary cleaning leading to more infections. No direct proof for this hypothesis can be derived from a clinical study, i.e. where the mucociliary cleaning in patients with CF is assessed in the presence or absence of tiotropium. From literature it appeared that quaternary ammonium ions like tiotropium do not impair mucociliary cleaning, in contrast to tertiary ammonium anions like atropine. Tiotropium also does not alter the composition of the sputum, while dry mucus or mucus impaction has not been mentioned in the current SmPC. In absence of the clear underlined pathophysiological mechanism it is difficult to apply a contraindication if no statistical difference in the burden due to respiratory infections has been observed.

However, indirect evidence of the decreased mucociliary cleaning may be derived from the increased respiratory tract infection incidence, numerically more serious adverse events and/or other complications or manifestations of CF as observed in disfavour for tiotropium. An absolute contraindication would imply that anticholinergics could also be withheld from patients with CF for whom tiotropium could be beneficial, e.g. those who suffer concomitantly from COPD or severe asthma, and is therefore not appropriate.

In conclusion, based on the review of the data on safety and efficacy, the use of tiotropium in patients with CF is not recommended, especially in patients ≤ 11 years old.

The member states consider that the update of SmPC sections 4.2, 4.4, 5.1, 5.2 and 5.3 with the results of the paediatric studies in cystic fibrosis is approvable.

The variation was completed on 16 May 2013.

V. CHANGES IN PRODUCT INFORMATION

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

- SmPC

4.2 Posology and method of administration

Paediatric population
COPD
There is no relevant use of Spiriva Respimat ~~is not recommended for use~~ in children and adolescents below 18 years ~~due to lack of data on safety and efficacy (see 5.1 and 5.2)~~.

Cystic fibrosis
The efficacy and safety of Spiriva Respimat has not been established (see sections 4.4 and 5.1).

4.4 Special warnings and precautions for use

Spiriva Respimat is not recommended in cystic fibrosis (CF). If used in patients with CF, Spiriva Respimat may increase the signs and symptoms of CF (e.g. serious adverse events, pulmonary exacerbations, respiratory tract infections).

5.1 Pharmacodynamic properties

Paediatric population
~~No data in paediatric population were established (see 4.2~~).

COPD
The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

Clinical efficacy and safety in cystic fibrosis (CF):

The clinical development programme in CF included 3 multicentre studies in 959 patients aged 5 months and above. Patients below 5 years used a spacer (AeroChamber Plus®) with face mask and were included for safety assessment only. The two pivotal studies (a dose finding Phase II study and a confirmatory Phase III study) compared lung function effects (percent predicted FEV_1 AUC_{0-4h} and trough FEV_1) of Spiriva Respimat (tiotropium 5 µg: 469 patients) versus placebo (315 patients) in 12-weeks randomised, double-blind periods; the Phase III study also included a long term open label extension, up to 12 months. In these studies, all respiratory medications, except anticholinergics, were allowed as concomitant treatment, e.g. long acting beta agonists, mucolytics and antibiotics.

Effects on lung function are displayed in Table 2. No significant improvement in symptoms and health status (exacerbations by Respiratory and Systemic Symptoms Questionnaire and quality of life by Cystic Fibrosis Questionnaire) have been observed.

Table 2: Adjusted mean difference from placebo for absolute changes from baseline after 12 weeks

	Phase II		**Phase III**			
	All patients ($N_{Spiriva}$ = 176, $N_{placebo}$ = 168)		All patients ($N_{Spiriva}$ = 293, $N_{placebo}$ = 147)		≤11 years ($N_{Spiriva}$ = 95, $N_{placebo}$ = 47)	≥12 years ($N_{Spiriva}$ = 198, $N_{placebo}$ = 100)
	mean (95% CI)	p-value	**mean** (95% CI)	p-value	**mean** (95% CI)	**mean** (95% CI)

	Phase II		**Phase III**			
	All patients ($N_{Spiriva}$ = 176, $N_{placebo}$ = 168)		All patients ($N_{Spiriva}$ = 293, $N_{placebo}$ = 147)		≤11 years ($N_{Spiriva}$ = 95, $N_{placebo}$ = 47)	≥12 years ($N_{Spiriva}$ = 198, $N_{placebo}$ = 100)
	mean (95% CI)	p-value	**mean** (95% CI)	p-value	**mean** (95% CI)	**mean** (95% CI)
FEV_1AUC_{0-4h} (% predicted) [a] *absolute changes*	**3.39** (1.67, 5.12)	<0.001	**1.64** (-0.27, 3.55)	0.092	**-0.63** (-4.58, 3.32)	**2.58** (0.50, 4.65)
FEV_1AUC_{0-4h} (litres) *absolute changes*	**0.09** (0.05, 0.14)	<0.001	**0.07** (0.02, 0.12)	0.010	**0.01** (-0.07, 0.08)	**0.10** (0.03, 0.17)
Trough FEV_1 (% predicted) [a] *absolute changes*	**2.22** (0.38, 4.06)	0.018	**1.40** -0.50, 3.30	0.150	**-1.24** (-5.20, - 271)	**2.56** (0.49, 4.62)
Trough FEV_1 (litres) *absolute changes*	**0.06** (0.01, 0.11)	0.028	**0.07** (0.02, 0.12)	0.012	**-0.01** (-0.08, 0.06)	**0.10** (0.03, 0.17)

[a] Co-primary endpoints

All Adverse Drug Reactions (ADRs) observed in the CF studies are known undesirable effects of tiotropium (see 4.8). The most commonly observed adverse events considered related during the 12 week double blind period were cough (4.1%) and dry mouth (2.8%).

The number and percentage of patients reporting adverse events (AEs) of special interest in cystic fibrosis irrespective of relatedness are shown in Table 3. Signs and symptoms considered to be manifestations of cystic fibrosis increased numerically, although not statistically significantly, with tiotropium, especially in patients ≤11 years old.

Table 3: Percentage of patients with AEs of special interest in cystic fibrosis by age group over 12 weeks of treatment irrespective of relatedness (pooled Phase II and Phase III)

	≤11 years		≥12 years	
	$N_{placebo}$ = 96	$N_{Spiriva}$ = 158	$N_{placebo}$ = 215	$N_{Spiriva}$ = 307
Abdominal pain	7.3	7.0	5.1	6.2
Constipation	1.0	1.9	2.3	2.6
Distal intestinal obstruction syndrome	0.0	0.0	1.4	1.3
Respiratory tract infections	34.4	36.7	28.4	28.3
Sputum increased	1.0	5.1	5.6	6.2
Exacerbations	10.4	14.6	18.6	17.9

"Distal intestinal obstruction syndrome" and "Sputum increased" are MedDRA preferred terms. "Respiratory tract infections" is the MedDRA higher level group term. "Abdominal pain", "Constipation" and "Exacerbations" are collections of MedDRA preferred terms.

Thirty-four (10.9 %) patients randomised to placebo and 56 (12.0%) patients randomised to Spiriva Respimat experienced a serious adverse event.

The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in the subset of paediatric patients below 1 year of age.

5.2 Pharmacokinetic properties

Paediatric Patients: ~~See 4.2~~

There were no paediatric patients in the COPD programme (see 4.2). Paediatric patients were studied as part of the CF clinical programme also covering adults.

Following inhalation of 5 µg tiotropium, the tiotropium plasma level in CF patients ≥5 years was 10.1 pg/ml 5 minutes post-dosing at steady-state and decreased rapidly thereafter. The fraction of the dose available in CF patients <5 years old who used the spacer and mask was approximately 3- to 4-fold lower than that observed in CF patients 5 years and older. Tiotropium exposure was related to body-weight in CF patients <5 years.

5.3 Preclinical safety data

In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key developmental parameters, tracheal or key organ development were seen.

- Package leaflet

2. What you need to know before you take Spiriva Respimat

If you have cystic fibrosis, tell your doctor because Spiriva Respimat could make your cystic fibrosis symptoms worse.

Annex V – Extension of the indication (NL/H/0718/001/II/009)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the member states consider that the variation for Spiriva Respimat (tiotropium bromide), for the proposed extension of the indication is approvable.

The extension of the indication is marked in **bold**:

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

Asthma
Spiriva Respimat is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting β2 agonists and who experienced one or more severe exacerbations in the previous year.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

Spiriva is a long-acting muscarinic antagonist. Tiotropium's main mode of action is the blockage of the M3 receptor, which results in prolonged bronchodilation. It is administered by inhalation through the Respimat inhaler device.
Spiriva Respimat is already registered for maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD). The recommended dose in COPD is 5 µg tiotropium, given as two consecutive doses from the Respimat inhaler once daily.

The scope of this variation was to obtain approval for the addition of the proposed indication *add-on maintenance bronchodilator treatment in adult patients with asthma who remain symptomatic on at least inhaled corticosteroids (ICS).*

The proposed posology for adults is 5 microgram tiotropium given as two puffs from the Respimat inhaler once daily, at the same time of the day.

Scientific advice
The MAH was given scientific advice for the clinical development in a meeting with the MEB in 2009.

Paediatric development
The inhaler can be used with the valved holding chamber, AeroChamber Plus®, and the formulation is suitable for the entire age range of patients with asthma. The paediatric development is currently ongoing and a separate paediatric submission is envisaged in the Paediatric Investigational Plan. This application was therefore submitted for an indication for adult asthma patients only.

II.2 Tiotropium in the treatment of asthma

The role of tiotropium as a long-acting bronchodilator in the treatment of COPD has been well established in clinical guidelines, but its role in the treatment in asthma has not been defined.
Tiotropium has been considered as an option in the management of asthma, based on the fact that a substantial proportion of patients do not achieve symptom control with current controller options,

including the combination of a long-acting β_2 agonist (LABA) with even a high dose of ICS[2,3]. Up until now, the sustained prolonged bronchodilator effect can only be provided with one therapy class (β_2 adrenergic), although asthmatics might also be responsive to anticholinergics.

The reasons for the limited use of anti-cholinergic therapy in asthmatic patients include its slower onset of action and the generally inferior bronchodilator responses observed comparing short-acting anticholinergic with short acting β_2 agonists. The combined use of short acting anti-cholinergic with short acting β_2 agonists is a well-accepted treatment for acute exacerbations of severe asthma requiring hospitalisation. Patients with more severe asthma were thought to have a better response to anti-cholinergic compared to those with mild disease.

The clinical dossier is divided into two main parts. The first part is the addition of tiotropium on top of a maintenance treatment of inhaled corticosteroids. The principal comparator for tiotropium is the class of long-acting β_2 agonists.
The second part is the addition of tiotropium on top of a high maintenance dose of ICS + LABA, where further treatment options are limited.
In the clinical programme two doses of Spiriva Respimat were investigated: 2.5 µg once daily and 5 µg once daily. The MAH applied for approval of the Spiriva Respimat 5 µg dose.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

III.1.1 Pharmacokinetics

The pharmacokinetic (PK) profile of tiotropium inhaled via the Respimat inhaler was previously addressed in the clinical development programme for Spiriva Respimat in the COPD indication. In support of the sought extension of the indication, additional PK parameters of tiotropium in patients with asthma have been assessed in 2 Phase II trials in adults, 4 Phase III studies in adults, and 1 Phase II trial in adolescents (12 to 17 year-olds).

Pharmacokinetics of tiotropium following inhalation of Spiriva Respimat has been characterised sufficiently in adults with asthma. At steady-state, a peak tiotropium plasma concentration of 5.15 pg/mL was attained 5 min after inhalation of 5 µg tiotropium in patients with asthma. Dose proportionality was observed based on urinary excretion over 24 h and Cmax at steady state. The effective half-life of tiotropium was 34 h (geometric mean; 80% CV) in patients with asthma and approximately 11.9% (0.595 µg, range 0.7%-48%) of the dose was excreted unchanged in the urine over 24 h post-dose at steady-state.

Systemic exposure to tiotropium was found to be lower for patients with asthma than for patients with COPD: Cmax was 42 to 53% lower and the fraction of the dose excreted unchanged in the urine over 6 h post-dose at steady-state was 52% lower in patients with asthma. The lower systemic exposure of tiotropium in asthma patients as compared to COPD patients is not a concern with efficacy, because dose finding for Spiriva Respimat in asthma has been based on clinical efficacy.
No additional intrinsic factors impacting the pharmacokinetics of tiotropium were identified from the new pharmacological data submitted. Renal function is the most important factor affecting the clearance of tiotropium, though no dose adjustment is considered necessary in patients with reduced renal function.

[2] Bateman et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controL (GOAL) study Allergy 2008; 63: 932-8.
[3] Chanez P et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol 2007; 119:1997-48

III.1.2 Clinical efficacy

Tiotropium will present a new treatment modality in asthma because it is the first long-acting muscarinic antagonist for which approval is sought. Currently, the only approved long-acting bronchodilators in the treatment of asthma are the long-acting β_2 agonists. Their main mode of action is to stimulate the β_2-receptor. The role of LABA in the treatment of asthma has been well established. Monotherapy with LABA is not recommended because it is associated with increased asthma mortality. However, if combined with inhaled glucocorticosteroids, they provide several beneficial effects like lung function improvement, symptom control, and reduction of exacerbations. The combination of LABA and ICS is the preferred treatment according to the leading GINA (Global Initiative for Asthma) guidelines It is still a matter of debate if the observed effect is due to the additional bronchodilating effect of LABA on top of ICS or may be caused by synergism between LABA and ICS.

The clinical package in support of the asthma indication for Spiriva Respimat included 4 phase II studies and 5 pivotal phase III studies with one additional supportive phase III trial in Japanese patients to establish the role of tiotropium in asthma in adults (study 205.464).

- **Phase II studies**

One parallel group Phase II study (205.342) was performed in patients homozygous for B16-Arg/Arg with moderate persistent asthma, and three crossover Phase II studies were conducted in patients with moderate (205.420, 205.380) or severe (205.341) persistent asthma. These were well designed crossover studies, although the treatment periods in studies 205.380 and 205.420 were of relatively short duration (4-8 weeks).

Two doses of tiotropium were examined: Tio R2.5 and Tio R5. The tiotropium R2.5 dose was not examined in a very severe patient population in the phase II program. The study in severe patients was conducted with 5 µg and 10 µg, based on the experience in the COPD programme.
Considering a comparable efficacy but better safety profile, the MAH chose to continue with the 5 µg o.i.d. dose in the clinical phase III program as this dose was still on the steep part of the dose response.

In the meantime, the clinical development was started for patients with less severe asthma (GINA 2-4). In this patient group, additional dose finding studies were conducted in order to explore the lower part of the dose responses curve. In the phase II crossover study of 4 week treatment periods (205.420), the effect of tiotropium 2.5 µg and tiotropium 5 µg was investigated in patients GINA 2-4, mainly GINA 3. The efficacy was numerically in favour of tiotropium 5 µg, while the safety profile between tiotropium 2.5 µg and tiotropium 5 µg was comparable. The MAH decided to proceed with tiotropium 2.5 µg once daily and tiotropium 5 µg once daily.

- **Phase III studies**

The clinical phase III programme to establish the role of tiotropium in asthma can be divided in two main parts:

- The first part consists of the studies 205.442 and the twin studies 205.418/419. Tiotropium's role as add-on therapy to maintenance monotherapy ICS was investigated. This is the comparable position of LABA according the current guidelines.
  Trial 205.442 was designed to support the indication as add-on to a low dose ICS (GINA 2), and the trials 205.418/419 to support the indication on a medium dose of ICS (GINA 3).
  In these trials, two doses of tiotropium, tiotropium Respimat 2.5 µg (Tio R2.5) and tiotropium Respimat 5 µg are compared with placebo and salmeterol (trials 205.418/419 only).

- The second part consists of the studies 205.416/417. In these studies, tiotropium is added on top of a high dose of ICS (≥ 800 µg budesonide/day or equivalent) and LABA. For these patient groups (Gina ≥ 4), additional treatment options are limited if a patient remains symptomatic.
  In these trials tiotropium R5 was compared to placebo.

Table 1 Tabular overview of the pivotal clinical studies Phase III

Study	No of study centres/location	First patient in	Last patient out	Design[1]	Run-in period	Duration	Posology[2]	Randomised/completed (N, %)	Gender M/F, median age	Primary endpoint[9]
Severe Asthma[3]										
205.416[4]	75 centres/15 countries: DK, DE, IT, NL, RU, RS, TR, UA, UK, AU, CA, JP, ZA, US	3/10/08	22/07/11	PG	4 w	48 w[6,7]	Tio R5 Placebo	237/211 (89%) 222/202 (91%)	170M /289 F 55 (18-75)	FEV_1Peak_{0-3h}; trough FEV_1
205.417[4]	73 centres/14 countries: DK, DE, NL, IT, RS, TR, UA, UK AU, CA, JP, ZA, US.	3/11/08	22/7/11	PG	4 w	48 w[6,7]	Tio R5 Placebo	219/198 (90%) 234/203 (87%)	191 M /262F 54 (19-75)y	FEV_1Peak_{0-3h}; trough FEV_1
Pooled 416/417	148 sites, 15 countries	3/10/08	22/7/11		4 w		Tio R5 Placebo	456/409 (90%) 456/405 (88%)	361M /155F 54 (18-75)y	Time to first asthma exacerbation
Moderate asthma[5]										
205.418[4]	114 centres/ 11 countries: LV, PL, RU, BR, CN, GT, IN, JP, MX, PE, US.	07/09/10	13/11/12	PG, DD	4 w	24 w	Tio R2.5 qd Tio R5 qd Sal 50 bid Placebo	262/249 (95%) 264/241 (91%) 275/260 (94%) 269/248 (92%)	435 M /635F 43 (18-75)y	FEV_1Peak_{0-3h}; trough FEV_1
205.419[4]	124 centres/ 11 countries: PL, RO, DE, BR, CN, C0, IN, JP, MX, PE, US	24/08/10	07/11/12	PG, DD	4 w	24 w	Tio R2.5 qd Tio R5 qd Sal 50 bid Placebo	257/ 245 (95%) 253/240 (95%) 266/249 (94%) 254/240 (95%)	426 M /604F 43 (18-75)	FEV_1Peak_{0-3h}; trough FEV_1
Pooled 418/419	273 sites, 14 countries	24/08/10	13/11/12				Tio R2.5 qd Tio R5 qd Sal 50 bid Placebo	519/509 (94%) 517/481 (93%) 541/494 (95%) 523/488 (93%)	861 M /1239F 43 (18-75)y	ACQ total responder rate[10]
Mild asthma[8]										
205.442[4]	65 centres/12 countries: AT, HR, EE, HU, IT, LV, PL, SK; AR, GT, IN, KP	7/04/11	19/4/12	PG		12 w	Tio R2.5 qd Tio R5 qd Placebo qd	154/149 (97%) 155/152 (98%) 155/154 (99%)	183 M/ 281 F 44 (18.74)	FEV_1Peak_{0-3h}; Key secondary endpoint trough FEV1

Tio R 1.25, Tio R2.5 Tio R10 = 1.25 µg, 5 µg and 10 µg tiotropium respectively, administered via the Respimat; Sal 50 = salmeterol 50 µg via a hydrofluoralkane [HFA] metered dose inhaler {MDI}; qd quaque die (once daily); bid = bis in die (twice daily); PG = parallel-group; CO = crossover; w = weeks

1 all trials were conducted in a randomised double blind and placebo controlled manner

2 all treatments were given in addition to stable minimum maintenance therapy in the evening, except for trials 205.416/417 (morning administration)

3 Symptomatic despite treatment with at least high dose inhaled corticosteroid (ICS) + long-acing β_2 adrenergic agonist (LABA)

4 Confirmatory, efficacy, safety and PK (no PK for 205.442)

5 Symptomatic despite treatment with at least minimum medium dose ICS maintenance therapy

6. Evaluation of first co/primary endpoints took place at week 24 for the individual trials, and the third cop/primary endpoint was assessed over 48 weeks for the pooled analysis.

7. Patients had to have a history of at least 1 asthma exacerbation per year

8. Symptomatic treatment despite maintenance treatment with at least low dose ICS

9 for the clinical pulmonary function tests (FEV_1 Peak $_{0\text{-}3h}$; trough FEV_1), change from study baseline

10 ACQ: asthma control questionnaire. A responder is defined as an improvement ≥ 0.5 from baseline.

In the second round of this type II variation, an additional supportive study (205.464) was submitted. The objective of this trial was to establish the long-term safety of the two tiotropium doses in approximately 100 Japanese asthma patients for each dose. Tiotropium (Tio R2.5 and Tio R5) was administered on top of low to medium maintenance dose ICS ± LABA (GINA 2-4) and compared to placebo.

CHMP guidelines

The clinical study designs are based on the requirements of the current Note for Guidance on the clinical investigation of medicinal products in the treatment of Asthma (CHMP/EWP/2933/01), as the studies were initiated in 2008 (trials 205.416/417; severe population), 2010 (trials 205.418/419; moderate population) and 2011 (mild population).
According to the previous NfG, equal emphasis should be placed on lung function and a symptom based endpoint. For patients with mild asthma, a symptom based endpoint might be considered. For moderate and severe persistent asthma, symptom based endpoints are particularly important. These endpoints may include the frequency of exacerbations and an assessment of asthma control.

The revised draft note for guidance (NfG) on clinical investigation of medicinal products for treatment of asthma (CHMP/EWP/2922/01-Rev1) was published in June 2013. This new NfG puts emphasis on the reduction of exacerbations, and recommends that separate studies must be carried out for each grade of asthma severity of asthma for which the new product is intended to be used. For a new bronchodilator, used as concomitant medication with inhaled corticosteroids, an effect on lung function and exacerbation should be demonstrated. Exacerbations have, however, low frequency in patients with mild asthma. Therefore, in mild asthma a symptomatic endpoint can be used to assess the efficacy.
Both guidelines recommend two co-primary endpoints for the grade of asthma severity for which the product is developed; a lung function measurement and a symptomatic outcome. According to this new NfG, the symptomatic co-primary endpoints for a new bronchodilator are for the mild population a symptom based outcome, and for both the moderate and severe population an exacerbation outcome.

The study design of study 205.442 (mild asthma population) does not meet the requirements of both NfGs because only one primary endpoint was included.
The studies intended for the moderate population (205.418/419) were designed with a co-primary endpoint to show symptomatic improvements, in accordance with the former NfG. Secondary endpoints included exacerbation parameters.

Symptomatic improvements are associated with a reduction in exacerbations, though it is nowadays recognized that the association is less clear with combination therapy ICS/LABA than with monotherapy ICS (GINA 2014).

The RMS considered that if the secondary endpoints related to exacerbations point towards an improvement, and if also further evidence for the beneficial effect of tiotropium on severe exacerbations has been provided, no long-term efficacy studies for assessing the effect on exacerbations would be required.

The study design of trials 205.416/417 (intended for the severe population) meets the requirement of both the new and old NfG: their co-primary endpoints were lung function improvements (trough FEV_1 and $FEV_1Peak_{0\text{-}3h}$) and the co-primary endpoint 'time to the first severe exacerbation' is related to exacerbations.

III.1.2.1 The addition of Tiotropium Respimat to a maintenance dose ICS (Studies 205.442, 205.418/419)

Introduction
The studies 205.442 and 205.418/419 were designed to support the use of tiotropium in the stepwise approach in asthma treatment. Study 205.442 included patients on a low maintenance dose ICS (GINA 2), while in the twin studies 205.418/419 mainly patients on a medium maintenance dose ICS were included (GINA 3). During the run-in period, patients were homogenized and stabilized on monotherapy ICS.
In these studies, two doses of tiotropium (Tio R2.5 and Tio R5) were compared to placebo. In study 205.418/419 the active comparator salmeterol was included to allow a descriptive statistical comparison with a well established maintenance bronchodilator.

Endpoints of the studies
In study 205.442 the two co-primary endpoints were lung function parameters. Functional parameters were included as secondary parameters. In studies 205.418/419 the co-primary endpoints were lung function parameters while a third co-primary endpoint included the combined results of a symptomatic improvement measured by the Asthma Control Questionnaire (ACQ).

- Study 205.442 (low maintenance dose ICS, GINA step 2)

Outcomes
Lung function
This study demonstrated a statistically significant improvement in the lung function compared to placebo for $FEV_1Peak_{0\text{-}3h}$ and trough FEV_1 when tiotropium was added to low dose maintenance inhaled corticosteroid.
However, the improvements in lung function are less than observed in historical controls with long-acting β_2[4] [5]agonists, and lower than the MCID of 150-200 mL or 5% improvement of FEV_1 predicted.
No dose response was observed between tiotropium 2.5 µg and tiotropium 5 µg when the results were displayed in mL; a dose response between tiotropium 2.5 µg and tiotropium 5 µg became apparent for the FEV_1 displayed as % improvement from predicted (post hoc).

Symptomatic improvement
In the studies, no significant improvement of a symptomatic endpoint compared to placebo was observed.

Exacerbations
The study was of too short duration (12 weeks) to determine a beneficial effect on the severe exacerbation rate. Based on the limited data, no differences in exacerbation rate between the active treatment and placebo was observed.

- Study 205.418/419

Patient population
Study 205.418/419 was aimed to be performed in a homogenous patient population using a higher maintenance dose of inhaled corticosteroids than in study 205.442. Indeed, the mean ICS (SD) daily dose budesonide or equivalent 660 (212) µg, was higher than in study 205.442: 381 (78) µg. The inclusion criteria excluded patients on a high maintenance dose of monotherapy inhaled corticosteroid, although these patients can be considered as GINA 3 as well. The concomitant use of a leukotriene modifier was allowed, probably resulting in an additional 9% of patients being treated

[4] Kelsen et al J. Asthma 1999; 36(8):703-715
[5] Juniper. Eur Respir Journal 1999;14:1038-43.

according to GINA step 4. After screening, during the run-in period patients received maintenance monotherapy corticosteroids. At randomisation, at least 25% of patients were on a low maintenance dose of ICS (400 µg budesonide or equivalent i.e. GINA step 2), which overlaps with the patient population included in study 205.442. After the run-in period, patients were classified according the GINA guidelines. The GINA does not clearly classify patients with a maintenance ICS > 400 µg budesonide + leukotriene modifier. It was considered that if patients with a low dose ICS + leukotriene modifier are classified as GINA 3, it can be agreed that patients with a medium ICS dose + leukotriene modifier are classified as GINA 4.

Outcome measurements

Lung function

The clinical studies included two co-primary endpoints for lung function improvement: the FEV_1Peak_{0-3h} and trough FEV_1. In the clinical studies, the improvements were statistically significant.
The trough FEV_1, the prebronchodilator FEV_1, provides information for the sustained bronchodilation effects.

The clinical studies 205.418/419 included the active comparator salmeterol to provide internal assay sensitivity. Both tiotropium doses showed a comparable improvement in FEV_1 as salmeterol when added to a maintenance dose ICS. Salmeterol showed a mean (SE) improvement in trough FEV_1 of 0.114 (0.21)L, tiotriopium R5 showed an improvement of 0.146 (0.021)L, and Tio R2.5 an improvement of 0.180L (combined analysis study 205.418/419).

Maintenance of lung function

In trial 205.418, initially the observed effect of the tiotropium 5 µg was numerically higher than for tiotropium 2.5 µg, similar to what was observed in the phase II studies, when the effect was measured after 4 weeks treatment. However, in study 205.418 a small deterioration in trough FEV_1, was observed from week 8 onwards. Also at week 24, in the 24 h pulmonary lung function tests, the sustained bronchodilation was not maintained with tiotropium 5 µg, in contrast to tiotropium 2.5 µg. In analogy to the long-acting β_2 agonist, this might be due to tachyphylaxis, or to the transient loss of maintenance of bronchodilation and symptom control in the face of a worsening asthma inflammation.

Symptomatic improvement

The trials used the Asthma Control Questionnaire (ACQ) responder rate to assess the symptomatic improvement. The co-primary symptomatic endpoint was the responder rate compared to placebo of the combined analyses. A responder was defined as a patient with an improvement ≥ 0.5 compared with baseline.
An improvement of ≥ 0.5 in the ACQ is considered clinically relevant on the individual level. It is however not meant to be used for comparisons between groups. Therefore, the responder rate, defined as an improvement in minimal clinically important difference ≥ 0.5, is considered to be a better reflection of demonstrating the clinical relevance of the observed improvements. The responder rate was included as a co-primary endpoint.
In the prespecified combined analyses, ACQ responder rate demonstrated statistically significant improvements for the active treatments (both tiotropium doses 65%) compared with placebo (58%). The results appeared to be mainly driven by study 205.418, which showed highly significant results while no such results were observed in study 205.419. However, in both trials the mean value was higher for the active treatments than for placebo. For this reason, it is acceptable to combine the studies.
In the combined analyses, the study met its primary endpoint because a statistical significant improvement in the ACQ responder rate compared with placebo was shown, and a symptomatic improvement appeared to be shown.

However, the ACQ includes a lung function measurement and therefore, might not purely reflect the symptomatic improvement. The ACQ6 is the same as the ACQ, but without the assessment of lung function and might therefore be a better instrument to show a symptomatic improvement.

Tio R5 and salmeterol, showed statistically significant improvements in the ACQ-6 responder rate, (p=0.04 and p=0.002 respectively), indicating that a significant symptomatic improvement was observed. No statistically significant difference between placebo and TioR2.5 was observed.

Exacerbations
Severe exacerbations and asthma exacerbations were included as secondary parameters. The incidence of severe exacerbations was low, but numerically improvements with placebo were observed.
The patient population of trial 205.419 appeared not sensitive for the outcome "severe exacerbation" because the salmeterol outcome measures (hazard/odds/rate ratio) were numerically close to 1.
Nevertheless, both tiotropium doses showed improvements in the severe exacerbations outcome measures compared to placebo in both trials (Hazard/odds/rate ratio <1). This indicates that tiotropium may have a beneficial effect in this patient population on the exacerbation outcome. Tiotropium R5 showed the most consistent improvements in both trials, although the improvements were numerically in favour of Tio R2.5.

All active treatments showed improvements in the asthma exacerbations outcomes (time to first asthma exacerbation, number of patients with at least one exacerbation, number of asthma exacerbations per patient per year) compared with placebo. In the pooled analyses, tiotropium R2.5, like salmeterol reached statistical significance for all asthma exacerbations outcome measures. Tiotropium R5 showed numerical improvements, but failed to show statistical significance. However, the confidence intervals between Tio R5, salmeterol and Tio R2.5 were overlapping, showing no statistical difference between the treatments.

III.1.2.2 The addition of Tiotropium Respimat on top of maintenance dose ICS + LABA

- Study 205.416/417

Design
The studies 205.416/417 were performed in patients GINA ≥4 with at least one severe exacerbation in the previous year. Both studies were placebo controlled which is considered adequate due to the limited additional treatment options for this patient population.
The primary endpoints were lung function improvement and an exacerbation parameter. The reduction of exacerbations is an important goal for this patient group. The outcome measures are considered adequate.

Patient population
The percentage of patients using anti-IgE treatment and oral steroids was 5% and 4% respectively. Therewith approximately 9% of the included patient population was treated according to GINA step 5.
In this trial, the MAH limited the inclusion of patients on a baseline treatment of a medium ICS dose to the upper limit of 800 µg budesonide or equivalent, although patients on a medium dose of ICS + LABA can also be considered being treated according to GINA step 4.

Reversibility criteria
In these trials, asthma was not confirmed with a reversibility test at screening. A positive reversibility test is difficult to obtain in patients on controller therapy. The MAH used GINA's recommended criteria like the hyper-responsiveness, a positive glucocorticosteroids trial, PEF reversibility or a positive exercise challenge to confirm the diagnosis of asthma.

Severe asthma
In studies 205.416/417 the post bronchodilator FEV_1 (<80%) and the FEV_1/FVC ratio (<0.7) were used as inclusion criteria. These criteria are also used to define patients with COPD GOLD II.

The post bronchodilator criterion FEV_1 <80% is used to define severe asthma in previous guidelines, but the inclusion criterion FEV_1/FVC <0.7 lacks external validity. It is not inconceivable that the beneficial effects are obtained in non-smoking COPD look alike patients with asthma.
At request, the MAH performed a subgroup analysis in 130 patients with a post bronchodilatory FEV_1 > 80% and/or FEV_1/FVC > 0.7. These patients showed improvement in the peak FEV1 0.201 (0.098)L and trough $FEV_1$of 0.105 (0.061)L confirming the observed improvement in the studies 205.416/417, i.e. $FEV_1Peak_{0\text{-}3h}$0.110 (0.024) L and trough FEV1 0.093 (0.022). Thus it can be concluded that also in patients GINA Step 4 with FEV_1/FVC > 0.7 a potential benefit for tiotropium can be shown.

Study 205.416/417 outcomes

Lung function

The addition of tiotropium 5 µg demonstrated statistically significant improvements in lung function: mean (SD) improvement trough FEV_1 0.093 (0.022) (95% CI 0.50-0.137) on top of high dose ICS + LABA (≥800 µg budesonide/day or equivalent). The improvements in trough FEV_1 remained stable during the treatment periods.

The observed improvements were on top of high dose ICS + LABA, when there is less room for improvement. The MAH conducted a post-hoc analysis, displaying the improvements as % predicted from baseline. The percent change from baseline for all time points up to and including the primary time point for trials improved from 4.1% to 9.7% for trough FEV_1 response.
In a recent procedure (EMEA/H/C/002673), the CHMP considered an improvement of trough FEV_1 of 0.091 (95% CI 0.053-0.129) L clinically relevant when an LABA was added to monotherapy ICS. The observed improvements with tiotropium (combined analyses adjusted mean (SE) 0.093 (0.022) 95% CI 0.050-0.137) are comparable and therefore considered clinically relevant.

Exacerbations

Tiotropium Respimat 5 µg delayed the time to the first severe exacerbation on top of high dose inhaled ICS + LABA (≥ 800 µg budesonide/day or equivalent) (Hazard ratio 0.79, 95% CI 0.062, 1.00, p=0.03), showing a risk reduction of 21%. It also showed a trend to an improvement in the number of patients experiencing a severe exacerbation (27-33% is 6%). The primary outcome was supported by an additional sensitivity analysis for the time to the first severe asthma exacerbation and/or withdrawal due to lack of efficacy/worsening asthma. In addition, the outcome is supported by improvements in the asthma exacerbations, observed in both trials.

Symptomatic improvement

Secondary parameters of the trial included the use of the ACQ and AQLQ to measure symptomatic improvements. The patient population of trial 205.416 appeared insensitive to show symptomatic improvement: the patient population showed an almost similar ACQ responder rate for placebo (53.6%) compared to tiotropium (55.3%), and a reverse responder rate for the AQLQ (placebo 44.1%), tiotropium R5 41.4%. Pooling of the results is therefore not possible.

III.1.2.3 Summary of main efficacy results of the pivotal phase III trials

An overview of the primary endpoint parameters (and key secondary parameter of study 205.442) is provided in Table 2.

Table 2 Overview of the primary outcomes (and key secondary outcome trial 205.442 only) of the pivotal phase III studies – Mixed effects model with repeated measures – Full analyses set

Trial		**205.442 (at week 12)**			
Endpoint	Treatment	Adjusted mean (SE) difference to placebo [L] (at week 12)	P-value	Adjusted mean difference to placebo (% predicted)	P-value
FEV_1Peak_{0-3h}	Placebo				
	TioR2.5	0.159 (0.036)	<0.0001	4.206 (1.105)	0.0002
	TioR5	0.128 (0.036)	0.0005	4.678 (1.104)	<0.0001
Through FEV_1	Placebo				
	TioR2.5	0.110 (0.037)	0.003	2.597 (1.155)	0.0249
	TioR5	0.122 (0.037)	0.001	4.414 (1.156)	0.0001

Trial		**205.418 (at week 24)**		**205.419 (at week 24)**		**Combined analyses 205.418/419 (at week 24)**		
Primary endpoint	Treatment	Adjusted mean (SE) difference to placebo [L]	P-value	Adjusted mean (SE) difference to placebo [L]	P-value	N	Adjusted mean difference (SE)	P-value
FEV_1Peak_{0-3h}	Placebo					492		
	TioR2.5	0.236 (0.028)	<0.0001	0.211 (0.027)	<0.0001	492	0.223 (0.020)	<0.0001
	TioR5	0.198 (0.028)	<0.0001	0.169 (0.027)	<0.0001	481	0.185 (0.020)	<0.0001
	Salmeterol	0.213 (0.028)	<0.0001	0.176 (0.027)	<0.0001	510	0.196 (0.019)	<0.0001
Trough FEV_1	Placebo					492		
	TioR2.5	0.185 (0.030)	<0.0001	0.176 (0.029)	<0.0001	492	0.180 (0.021)	<0.0001
	TioR5	0.152 (0.030)	<0.0001	0.133 (0.029)	<0.0001	481	0.146 (0.021)	<0.0001
	Salmeterol	0.123 (0.030)	<0.0001	0.106 (0.029)	0.0002	510	0.114 (0.021)	<0.0001

		Combined endpoint: Responder rate (combined analyses)		**Odds ratio**	**P-value**
ACQ	Placebo	299/518 (58%)			
	TioR2.5	332/515 (65%)		1.33	0.03
	TioR5	330/513 (64%)		1.32	0.03
	Salmeterol	356/535 (67%)		1.46	0.004

Trial		**205.416 (at week 24)**		**205.417 (at week 24)**		**Combined analyses 205.416/417 (at week 48)**		
Primary endpoint		**Adjusted mean (SE) difference to placebo** [L]	**P-value**	**Adjusted mean (SE)difference to placebo** [L]	**P-value**	**N**	**Adjusted mean difference (SE)**	**P-value**
FEV_1Peak_{0-3h}	Placebo					429		

	TioR5	0.086 (0.034)	0.01	0.154 (0.032)	<0.0001	422	0.110 (0.024)	<0.0001
Through FEV_1	Placebo					429		
	TioR5	0.088 (0.031)	0.005	0.111 (0.030)	0.0002	422	0.093 (0.022)	<0.001
		Combined endpoint Median (95% CI) Q1, Q3 (in days) [1]				**N**	**Hazard ratio[2] (95%CI)**	**P-value**
Time to first severe exacerbation	Placebo	nc (nc,226, nc)				454		
	TioR5	nc (nc, 282,nc)				453	0.79 (0.62,1.00)	0.03[3]

nc = not calculable (i.e. for median time to exacerbation: less than 59% of patients for experience exacerbations; for Q1 and Q3 time to exacerbation: less than 25% and 75% of patients, respectively experienced exacerbations.
1Median 95% CI 25th Q1 and 75th (Q3) percentile are calculated from an unadjusted Kaplan –Meier curve for each treatment
2 Hazard ratio, confidence interval p-value obtained from a proportional hazards model with only treatment as effects
3.Using method of Cui Hung and Wang.

- Supportive study 205.464

In the second round, the MAH submitted an additional supportive study, study 205.464. This study was conducted to meet the requirements of the Japanese Regulatory Authorities. Trial 205.464 was a Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of Tio R5 and Tio R2.5 compared with placebo over 52 weeks.

285 patients with moderate to severe persistent asthma on a medium dose of inhaled corticosteroid, with or without the concomitant use of LABA were included.
The primary objective of this trial was to evaluate the long-term (52-week) safety of 2 doses (2.5 µg and 5 µg) of tiotropium inhalation solution (administered once daily in the evening delivered by the Respimat inhaler) compared with placebo on top of maintenance therapy with ICS controller medication in at least 100 Japanese patients with moderate to severe persistent asthma per dose. The secondary objective of this trial was to evaluate the long-term efficacy.

In this supportive study a statistically significant effect compared to placebo was observed after 52 weeks of treatment for Tio R5, but not for Tio R2.5 in trough FEV_1 response (Tio R5: 0.112 L; Tio R2.5: 0.012 L for all study time points) and trough PEF response (Tio R5: 34.176 L/min; Tio R2.5: 0.498 L/min for all study time points). Furthermore, Tio R5 provided sustained bronchodilation over the 52 week treatment period. The study provides limited evidence for the use of tiotropium on top of maintenance (low to) medium dose ICS + LABA (≥400 µg - ≤800 µg budesonide/day or equivalent), as 67% of patients concomitantly used a LABA. Overall, the numbers are considered too small to be conclusive, and were obtained in the Japanese population only.

III.1.3 Clinical safety

The active substance tiotropium has a well-established role in the treatment of COPD, but its beneficial effects are unknown in the treatment of asthma. Bronchodilators are considered to be the corner stone in the treatment of COPD, whereas in asthma treatment anti-inflammatory treatment is known to be crucial. Monotherapy with LABA is contra-indicated in asthma since it contributes only to symptom relief without impact on the underlying inflammation. Therefore, in asthma, the long-acting bronchodilators should be combined with anti-inflammatory treatment.

Since the pathogenesis of COPD and asthma are different, efficacy and safety of Spiriva could not be extrapolated from COPD studies. The long-term experience with tiotropium in asthma is limited. The long-term safety for Tio R2.5 and Tio R5 has not been established for at least 1000 patients for one year for this therapeutic indication. The exposure to Tio R2.5 is limited to 343 patients for 6 months. The treatment with tiotropium was well tolerated. Most commonly reported adverse events (AE) were

anti-cholinergic side effects like dry mouth and obstipation. This adverse event profile is different from the long-acting β_2 agonists where the main adverse events are tremor and palpitations. Both long-acting β_2 agonists and tiotropium were well tolerated. Tiotropium showed numerically lower AE, drug related AE, and SAE compared with salmeterol, but slightly more discontinuations were observed due to adverse events.
In the clinical data submitted, only two patients discontinued due to AEs which might be related to salmeterol use (tachycardia and chest pain). None of the patients discontinued due to tremor.

Bronchitis was consistently observed at a higher frequency in the tiotropium group than in the placebo treatment groups in the asthma clinical program. However, in the COPD clinical program, bronchitis (and related terms) was reported at a lower frequency for patients in the Tio R5 group compared to those in the placebo treatment group. Considering that the profile of symptoms for asthma compared to bronchitis are difficult to distinguish, it is agreed that bronchitis is not identified as an adverse drug reaction.

In the PK studies, the systemic exposure was lower in the asthmatic population than seen in the COPD population. Due to the long-term experience with tiotropium in COPD it appears to be unlikely that imbalance in malignancies observed with Tio R5 compared with placebo is treatment related.
The lower systemic exposure observed in asthma may improve the systemic safety profile of tiotropium in asthma compared with COPD.

In trial 205.416/417, tiotropium was added to a maintenance dose ICS + LABA. Both muscarinic antagonists and β_2 agonists may affect the cardiovascular system, due to the systemic exposure. The systemic safety profile in asthma is limited, but some supportive evidence for the systemic safety might come from the COPD population. Generally, the population with asthma is younger and with less cardiovascular co-morbidity compared to COPD. In this trial, no new safety signals emerged.

Insufficient evidence has been provided by a subgroup of supportive study 205.464. In this subgroup (N=158, Tio R2.5 n=61; Tio R5 N=62, placebo N=35) tiotropium was added on a low to medium dose ICS + LABA. The incidence of the adverse event 'worsening of asthma' was comparable between the tiotropium groups and placebo. The incidence of severe exacerbations was numerically higher with tiotropium (both doses 13%) than with placebo (9%). However, the number of included patients is too low to be conclusive, and limited to Japanese patients. No comparison with currently approved treatment is made.

III.1.4 Risk management plan

The MAH has submitted an updated version of the 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 Spiriva Respimat.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	• All-cause mortality • Cardiac mortality (for Respimat only) • Sudden death and unspecified death • 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
Missing information	Pregnant and breast-feeding women

As it might be related to interaction between tiotropium and the disease under investigation, there is no need to update the RMP with this information for the moment. No further indication-specific risks for the use of Spiriva Respimat in asthma were identified.
The Member States considered that use in children should be addressed as missing information in the next updated RMP. In addition, the MAH committed to discuss cases of tiotropium use for more than 1 year in the asthma indication in future PSURs.

IV. UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

In the clinical documentation for this variation application the MAH provided studies which investigated use of tiotropium on top of a maintenance treatment of inhaled corticosteroids (ICS), and the addition of tiotropium on top of a high maintenance dose of ICS + long-acting β_2 agonist (LABA).

The MAH proposed a broad indication: 'add-on maintenance bronchodilator treatment in adult patients with asthma who remain symptomatic on at least inhaled corticosteroids'.

For patients GINA 2 (study 205.442), tiotropium demonstrated a statistically significant improvement in lung function when added to a low dose maintenance ICS, but the clinical relevance of the lung function improvement needs to be further determined The observed improvement in lung function is also not supported with a statistical improvement in symptoms, quality of life or exacerbation parameter compared with placebo.
The study lacked the comparison with an active control. It is therefore difficult to determine whether tiotropium indeed provided insufficient symptomatic improvement or that the patient population was not sensitive. In conclusion, the place of tiotropium in asthma GINA step 2 is difficult to determine.

The studies 205.418/419 were designed to show a clinically relevant improvement in lung function and symptomatic improvement compared to placebo in patients GINA 3. Salmeterol was included which allowed a descriptive statistical comparison of tiotropium's effect size with that of a well established comparator. Tiotropium showed a larger improvement in lung function than salmeterol, showing the clinical relevance of the observed lung function improvements.
The combined study results showed also a symptomatic improvement as measured by the Asthma Control Questionnaire. However, the ACQ could be driven by the lung function measurements and therefore, the ACQ-6 might be a better instrument to show symptomatic improvements as required by the guideline.. Both tiotropium R5 and salmeterol showed a statistically significant improvement in the ACQ-6 responder rate. The observed symptomatic improvements were less robust with tiotropium than with salmeterol.
The studies 205.418/419 were not designed to measure the effect of tiotropium on the reduction of severe exacerbations. The limited provided evidence demonstrated that the low dose tiotropium had a comparable effect on the reduction of exacerbations to salmeterol, but that the effect of the high dose was numerically worse than salmeterol. The studies are of too short duration (<12 months) to be conclusive, therefore, it is difficult to determine if tiotriopium is a controller, like salmeterol.

Studies 205.416/417 included patients with severe asthma (GINA 4/5), who experienced ≥1 severe exacerbation in the past year. Tiotropium showed a reduction in exacerbations when added on top of maintenance dose ICS equivalent to ≥ 800 µg budesonide + LABA. It also showed an additional improvement in lung function.
Since the addition of tiotropium on top of low to medium ICS + LABA has not been investigated, the indication was limited to those with at least 800 mcg budesonide + LABA.

The MAH provided an appropriate updated Risk Management Plan. Additional warnings in the SmPC are not considered necessary, but the indication should be limited in order to reflect the investigated patient population for which the benefit has been shown: patients using inhaled corticosteroids (≥800 µg budesonide/day or equivalent), and long-acting β_2 agonists (see section V).

In the Board meetings of 9 January 2014 and 3 July 2014 the submitted dossier in support of the asthma indication was discussed. The addition of tiotropium to inhaled corticosteroids for the treatment of asthma was considered not justified. Regarding the addition of tiotropium on top of ICS and LABA the Board came to a positive decision, provided that the indication would be restricted.

Overall, based on the review of the data on safety and efficacy, the RMS and Concerned Member States consider that the proposed extension of the indication to include asthma, is approvable.

The variation for extension of the indication was approved on 7 August 2014.

V. CHANGES IN PRODUCT INFORMATION

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

- SmPC

4.1 Therapeutic indications

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

Asthma
Spiriva Respimat is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥800 µg budesonide/day or equivalent) and long-acting ß$_2$ agonists and who experienced one or more severe exacerbations in the previous year.

4.2 Posology and method of administration

In the treatment of asthma the full benefit will be apparent after several doses of the medicinal product.

Asthma
The efficacy and safety of Spiriva Respimat in children and adolescents has not yet been established.

4.4 Special warnings and precautions for use

Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, ~~i.e. rescue therapy~~ or for the relief of acute symptoms. In the event of an acute attack a rapid-acting beta-2-agonist should be used.

Spiriva Respimat should not be used as (first-line) monotherapy for asthma. Asthma patients must be advised to continue taking anti-inflammatory therapy, i.e. inhaled corticosteroids, unchanged after the introduction of Spiriva Respimat, even when their symptoms improve.

4.5 Interaction with other medicinal products and other forms of interaction

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, anti-IgE treatment without clinical evidence of drug interactions.
The co-administration of tiotropium bromide with other anticholinergic containing drugs has not been studied and therefore is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 Spiriva Respimat during pregnancy.
~~For tiotropium bromide, no clinical data on exposed pregnancies are available. Animal studies have shown reproductive toxicity associated with maternal toxicity (see 5.3).~~
~~The potential risk for humans is unknown. Spiriva Respimat should therefore only be used during pregnancy when clearly indicated.~~

4.8 Undesirable effects

Tabulated summary of adverse reactions
The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group ~~(2,802 patients)~~ pooled from 5 placebo-controlled clinical trials in COPD (2,802 patients) and 6 placebo-controlled clinical trials in asthma (1,256 patients) with treatment periods ranging from twelve weeks to one year.

System Organ Class / MedDRA Preferred Term	**Frequency COPD**	**Frequency Asthma**
Metabolism and nutrition disorders		
Dehydration	Not known	Not known
Nervous system disorders		
Dizziness	Uncommon	Uncommon
Headache	Uncommon	Uncommon
Insomnia	Not known	Uncommon
Eye disorders		
Glaucoma	Rare	Not known

System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
Intraocular pressure increased	Rare	Not known
Vision blurred	Rare	Not known
Cardiac disorders		
Atrial fibrillation	Uncommon	Not known
Palpitations	Uncommon	Uncommon
Supraventricular tachycardia	Uncommon	Not known
Tachycardia	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders		
Cough	Uncommon	Uncommon
Epistaxis	Uncommon	Not known
Pharyngitis	Uncommon	Uncommon
Dysphonia	Uncommon	Uncommon
Bronchospasm	Rare	Uncommon
Laryngitis	Rare	Not known
Sinusitis	Not known	Not known
Gastrointestinal disorders		
Dry Mouth	Common	Common
Constipation	Uncommon	Rare
Oropharyngeal candidiasis	Uncommon	Uncommon
Dysphagia	Uncommon	Not known
Gastrooesophageal reflux disease	Rare	Not known
Dental caries	Rare	Not known
Gingivitis	Rare	Rare
Glossitis	Rare	Not known
Stomatitis	Rare	Rare
Intestinal obstruction, including ileus paralytic	Not known	Not known
Nausea	Not known	Not known
Skin and subcutaneous tissue disorders, immune system disorders		
Rash	Uncommon	Rare
Pruritus	Uncommon	Rare
Angioneurotic oedema	Rare	Rare
Urticaria	Rare	Rare
Skin infection/skin ulcer	Rare	Not known
Dry skin	Rare	Not known
Hypersensitivity (including immediate reactions)	Not known	Rare
Anaphylactic reaction	Not known	Not known
Musculoskeletal and connective tissue disorders		
Joint swelling	Not known	Not known
Renal and urinary disorders		
Urinary retention	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Not known

Description of selected adverse reactions
In controlled clinical studies in COPD, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 3.2% of patients. In asthma the incidence of dry mouth was 1.2%.

In 5 clinical trials in COPD, dry mouth led to discontinuation in 3 of 2,802 tiotropium treated patients (0.1 %). No discontinuations due to dry mouth were reported in 6 clinical trials in asthma (1,256 patients).

5.1 Pharmacodynamic properties

Clinical efficacy and safety in asthma
The clinical Phase III programme for persistent asthma included two 1-year randomised, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving Spiriva Respimat) on a combination of ICS (≥800 µg budesonide/day or equivalent) with a LABA. The studies included lung function measurements and severe exacerbations as primary endpoints.

PrimoTinA-asthma studies
In the two 1-year studies in patients who were symptomatic on maintenance treatment of at least ICS (≥800 µg budesonide/day or equivalent) plus LABA, Spiriva Respimat showed clinically relevant improvements in lung function over placebo when used as add-on to background treatment.

At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively. The improvement of lung function compared to placebo was maintained for 24 hours.

In the PrimoTinA-asthma studies, treatment of symptomatic patients (N=453) with ICS plus LABA plus tiotropium reduced the risk of severe asthma exacerbations by 21% as compared to treatment of symptomatic patients (N=454) with ICS plus LABA plus placebo. The risk reduction in the mean number of severe asthma exacerbations/patient year was 20%.

This was supported by a reduction of 31% in risk for asthma worsening and 24% risk reduction in the mean number of asthma worsenings/patient year (see Table 2).

Table 2: Exacerbations in Patients Symptomatic on ICS (≥800 µg budesonide/day or equivalent) plus LABA (PrimoTinA-asthma studies)

Study	Endpoint	Spiriva Respimat, added-on to at least ICS[a]/LABA (N=453)	Placebo, added-on to at least ICS[a]/LABA (N=454)	% Risk Reduction (95% CI)	p-value
two 1-year Phase III studies, pooled analysis	Days to 1st severe asthma exacerbation	282[c]	226[c]	21[b] (0, 38)	0.0343
	Mean number of severe asthma exacerbations/ patient year	0.530	0.663	20[d] (0, 36)	0.0458
	Days to 1st worsening of asthma	315[c]	181[c]	31[b] (18, 42)	<0.0001
	Mean number of asthma worsenings/ patient year	2.145	2.835	24[d] (9, 37)	0.0031

[a] ≥800 µg budesonide/day or equivalent
[b] Hazard ratio, confidence interval and p-value obtained from a Cox proportional hazards model with only treatment as effect. The percentage risk reduction is 100(1 - hazard ratio).
[c] Time to first event: days on treatment by when 25%/50% of patients had at least one severe asthma exacerbation/worsening of asthma
[d] The rate ratio was obtained from a Poisson regression with log exposure (in years) as offset. The percentage risk reduction is 100 (1-rate ratio).

Asthma
The European Medicines Agency has deferred the obligation to submit the results of studies with Spiriva Respimat in one or more subsets of the paediatric population in the treatment of asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption: Following inhalation of the solution by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reach the systemic circulation. 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%. Food is not expected to influence the absorption of this quaternary ammonium compound.

At steady state, tiotropium bromide plasma levels in COPD patients at peak were 10.5-11.7 pg/ml when measured 10 minutes after administration of a 5 microgram dose delivered by the Respimat inhaler and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.49-1.68 pg/ml. A steady state tiotropium peak plasma concentration of 5.15 pg/ml was attained 5 minutes after the administration of the same dose to patients with asthma. ~~Food is not expected to influence the absorption of this quaternary ammonium compound.~~

Elimination: The terminal elimination half-life of tiotropium bromide is between 5 and 6 days following inhalation by healthy volunteers and COPD patients. The effective half-life was 34 hours in patients with asthma. 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 inhalation of the solution by healthy volunteers urinary excretion is 20.1-29.4 % of the dose, the remainder being mainly non-absorbed drug in gut that is

eliminated via the faeces. In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state. The renal clearance of tiotropium bromide exceeds the creatinine clearance, indicating secretion into the urine.

Geriatric Patients: As expected for all predominantly renally excreted drugs, advanced age was associated with a decrease of tiotropium bromide renal clearance (326 ml/min in COPD patients < 58 years to 163 ml/min in COPD patients > 70years) 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 did not change significantly with advancing age within COPD patients if compared to inter- and intraindividual variability (43 % increase in AUC_{0-4h} after dry powder inhalation). Exposure to tiotropium was not found to differ with age in patients with asthma.

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 inhalation. Mild renal impairment (CLCR50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC0-4h after intravenous infusion). In COPD patients with moderate to severe renal impairment (CLCR < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the plasma concentrations (82% increase in AUC0-4h), which was confirmed by plasma concentrations after dry powder inhalation and also by inhalation of the solution via the Respimat inhaler. In asthma patients with mild renal impairment (CLCR 50-80 ml/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.

- PACKAGE LEAFLET

1. What Spiriva Respimat is and what it is used for

Spiriva Respimat helps people who have chronic obstructive pulmonary disease (COPD) or asthma to breathe more easily. COPD is a long-term lung disease that causes shortness of breath and coughing. The term COPD is associated with the conditions chronic bronchitis and emphysema. Asthma is a long-term disease characterised by airway inflammation and narrowing of the airways.
As COPD and asthma are ~~is a~~ long-term diseases you should take Spiriva Respimat every day and not only when you have breathing problems or other symptoms ~~of COPD~~. ~~When used to treat asthma you should use Spiriva Respimat in addition to so-called inhaled corticosteroids and long-acting ß$_2$ agonists.~~

3. What you need to know before you take Spiriva Respimat

Spiriva Respimat is indicated for the maintenance treatment of your chronic obstructive pul**m**onary disease or asthma. Do not use this medicine ~~It should not be used~~ to treat a sudden attack of breathlessness or wheezing. Your doctor should have given you another inhaler ("rescue medication") for this. Please follow the instructions you doctor has given you.

If you have been prescribed Spiriva Respimat for your asthma it should be added on to inhaled corticosteroids and long-acting ß2 agonists. Continue taking the inhaled corticosteroids as prescribed by your doctor, even if you feel better.

No interaction side effects have been reported when Spiriva Respimat has been taken with other products used to treat COPD such as reliever inhalers (e.g. salbutamol), methylxanthines (e.g. theophylline), antihistamines, mucolytics (e.g. ambroxol), leukotriene modifiers (e.g. montelukast), cromones, anti-IgE treatment (e.g. omalizumab) and/or inhaled or oral steroids (e.g. budesonide, prednisolone).

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. ~~If you are pregnant or believe you are pregnant, or if you are breast-feeding, you~~ You should not use this medicine unless specifically recommended by your doctor.

4. How to take Spiriva Respimat

The ~~usual~~ recommended dose for adults is:

Spiriva Respimat is effective for 24 hours so you will need to use Spiriva Respimat only **ONCE A DAY**, if possible at the same time of the day. Each time you use it take TWO PUFFS.

As COPD and asthma are ~~is a~~ long-term diseases take Spiriva Respimat every day and not only when you experience breathing problems. Do not take more than the recommended dose.

4. Possible side effects

Side effect	**Frequency COPD**	**Frequency Asthma**
Dry mouth: this is usually mild	Common	Common
Dizziness	Uncommon	Uncommon
Headache	Uncommon	Uncommon
Difficulty in sleeping (insomnia)	Not known	Uncommon
Irregular heart beat (atrial fibrillation, supraventricular tachycardia)	Uncommon	Not known
Feeling your heartbeat (palpitations)	Uncommon	Uncommon
Faster heart beat (tachycardia)	Uncommon	Not known
Cough	Uncommon	Uncommon
Nosebleed (epistaxis)	Uncommon	Not known
Inflammation of the throat (pharyngitis)	Uncommon	Uncommon
Hoarseness (dysphonia)	Uncommon	Uncommon
Tightness of the chest, associated with coughing, wheezing or breathlessness immediately after inhalation (bronchospasm)	Rare	Uncommon
Constipation	Uncommon	Rare
Fungal infections of the oral cavity and throat (oropharyngeal candidiasis)	Uncommon	Uncommon
Difficulties swallowing (dysphagia)	Uncommon	Not known
Rash	Uncommon	Rare
Itching (pruritus)	Uncommon	Rare
Difficulties passing urine (urinary retention)	Uncommon	Not known
Painful urination (dysuria)	Uncommon	Not known
Seeing halos around lights or coloured images in association with red eyes (glaucoma)	Rare	Not known
Increase of the measured eye pressure	Rare	Not known
Blurred vision	Rare	Not known
Inflammation of the larynx (laryngitis)	Rare	Not known
Heart burn (gastrooesophageal reflux disease)	Rare	Not known
Dental caries	Rare	Not known
Inflammation of the gums (gingivitis)	Rare	Rare
Inflammation of the tongue (glossitis)	Rare	Not known
Inflammation of the mouth (stomatitis)	Rare	Rare

Side effect	Frequency COPD	Frequency Asthma
Serious allergic reaction which causes swelling of the mouth and face or throat (angioneurotic oedema)	Rare	Rare
Nettle rash (urticaria)	Rare	Rare
Infections or ulcerations of the skin	Rare	Not known
Dryness of the skin	Rare	Not known
Hypersensitivity, including immediate reactions	Not known	Rare
Infections of the urinary tract	Rare	Not known
Depletion of body water (dehydration)	Not known	Not known
Inflammation in sinuses (sinusitis)	Not known	Not known
Blockage of intestines or absence of bowel movements (intestinal obstruction, including ileus paralytic)	Not known	Not known
Feeling sick (nausea)	Not known	Not known
Severe allergic reaction (anaphylactic reaction)	Not known	Not known
Swelling of joint	Not known	Not known

Annex VI – Update of the SmPC with the results of Tiospir study 205.452 and with PK/PD study 205.458 (NL/H/0718/001/II/011/G)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the member states consider that the variation for Spiriva Respimat (tiotropium bromide), for the proposed changes to the SmPC, Package Leaflet and labelling is approvable.

The changes are specified in section V of this annex.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

The scope of this variation is to update the SmPC driven by the results of the TioSpir™ study. The main proposed changes were:

- to add the key outcome results of the TioSpir (205.452) to SmPC section 5.1
- to delete the remark on the imbalance in mortality information (section 5.1).
- to delete the precautionary statement (SmPC section 4.4./Package Leaflet section 2) *Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders.*
- to update section 5.2 with the new pharmacokinetic/pharmacodynamic data (study 205.452).

In addition, updates have been made for SmPC sections 4.5, 4.8 and 4.9:

- In section 4.5 (interaction), a statement is added on the use of common concomitant medications in COPD.
- In section 4.8 (undesirable effects), the frequencies categories of some adverse events have been altered due to the inclusion of the safety profile of two additional double-blinded, placebo-controlled trials. These trials were performed indifferent development program.
- In section 4.9 (overdose), the statement of inadvertent oral ingestion has been deleted.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

The MAH submitted three clinical studies to support this variation for the changes in the SmPC: two phase II studies, study 205.291 and study 205.458; and the Post authorisation safety study 205.452. The mortality data obtained in study 205.452 will be put into the context of the mortality and safety data from the placebo/controlled pooled Tio R5 and Tio Handihaler (HH) database.

The studies **205.291** and **205.458** compare the systemic exposure of Tio R5 and Tio HH 18 µg in Japanese (205.291) and European (205.458) patients.
Study 205.458 included also a comparison with placebo and lower doses of TioR (Tio R1.25 µg, Tio R2.5 µg). Additional efficacy (lung function) and safety assessments (ECG Holter monitoring) were conducted in a subset of patients of preselected sites.

III.1.1 Pharmacokinetics

A PK meta-analysis using data from the previously submitted studies 205.249, 205.250, and the two new studies 205.458 and 205.291 was conducted to:
• Compare the systemic exposure of Tio R5 and Tio HH18 based on pooled PK data.
• Evaluate dose proportionality of tiotropium following inhalation via the Respimat inhaler.
• describe the effect of the intrinsic and extrinsic factors.

Based on the pooled PK analysis of the four cross-over studies, the exposure to tiotropium following the inhalation of Tio R5 was comparable to the Tio HH 18 (

Table 3).

Table 3 Comparison of pharmacokinetic parameters of tiotropium following inhalation using Tio R5 once daily with Tio HH 18 once daily (study 205.291)

	Tio R 5			Tio HH 18		
	N	gMean	gCV [%]	N	gMean	gCV [%]
$Ae_{0\text{-}4,ss}$ [µg]*	122	0.342	57.1	122	0.341	69.1
$AUC_{0\text{-}4,ss}$ [pg·h/mL]*	128	30.2	61.5	128	29.4	65.0
$AUC_{0\text{-}\tau,ss}$ [pg·h/mL]*	128	94.4	57.7	128	89.6	52.6
$C_{0.167,ss}$ [pg/mL]	139	17.7	57.8	135	17.9	57.3

*Patients with PK parameters calculated in both treatment periods

The pooled PK data from all four studies show dose proportionality for tiotropium administered from the Respimat inhaler over the range 1.25 to 10 µg. This has been described adequately in SmPC section 5.2.
Of the various intrinsic and extrinsic factors tested for an effect on the PK of tiotropium, renal function appeared to have a slight impact: 2-30% higher AUC0-6,ss values in COPD patients with mild renal impairment compared to patients with normal renal function. No systemic exposure data were available in patients with moderate and severe renal impairment. Therefore, data in moderate or severe renal impairment obtained after IV administration will be used for the label.
Plasma exposure of tiotropium appeared to be higher in Japanese compared to Caucasian patients, although a high variability in data was observed and the results overlap. This observation is considered useful information and is therefore included in SmPC section 5.2 under 'Special populations'.

Co-medication with either the LABA or ICS appeared not to affect the pharmacokinetics of tiotropium. The absence of effect has been reported in section 4.5 of the SmPC.

III.1.2 Clinical efficacy

Study 205.458 was a multicentre, randomised, placebo- and active-controlled, 5-way crossover trial to compare the systemic absorption (PK blood sampling) at steady state of tiotropium Handihaler (open label) and tiotropium Respimat at different strengths (1.25, 2.5, 5 µg or placebo). The study was conducted in Europe. At the end of each treatment period the dose ranging efficacy (FEV_1, FVC) was evaluated, and two Holter monitoring periods were included.

The TioSpir study (205.452) was an event driven (i.e. death), multinational, randomized, double-blind, double-dummy, parallel group study making a head-to-head comparison between the tiotropium Respimat 5 µg and tiotropium Handihaler® possible. The TioSpir study included an additional tiotropium Respimat 2.5 µg (2 puffs of 1.25 µg once daily) arm as part of the development plan for

tiotropium Respimat including use in combination products. Lung function was evaluated in a subset of 1370 patients over a long term period.

The results of the TioSpir trial (205.452) have been discussed in the PRAC committee (EMA/PRAC/735657 /2013), with the main focus on the different safety profile of Spiriva Respimat (Tio R5 µg) and Handihaler (Tio HH 18 µg). On 8 May 2014 the PRAC issued the following recommendation (EMA/PRAC/265397/2014 ADOPTED):
"The PRAC has considered the available evidence from the Tiotropium Safety and Performance in Respimat (TIOSPIR) trial showing no difference in the overall or cardiovascular mortality between tiotropium Respimat and Handihaler in patients with and without baseline cardiac disorders or cardiac arrhythmia, as well as the additional analysis carried out by the MAH in response to PRAC requests. The MAH of tiotropium has submitted a variation to update the SmPC of tiotropium Respimat with the results of the TioSpir trial."

- **Main study 205.452**

Study 205.452 (TioSpir) was an event driven, multinational, randomized, double-blind, double-dummy, parallel group study comparing the safety and efficacy of two doses of tiotropium (Tio R5 and Tio R2.5) to Tio HH 18 µg.
The two aims of this study were: to demonstrate non-inferiority between all-cause mortality between Tio R5 and Tio HH 18 µg and to demonstrate the superiority of Tio R5 over tiotropium Handihaler for the time to the first COPD exacerbation.

Methods
Patient population
Male and female outpatients with a diagnosis of at least moderate COPD (post-bronchodilator forced expiratory volume in 1 second [FEV1] ≤ 70%, predicted FEV1/ forced vital capacity [FVC] ≤ 70%) aged 40 years or older and smoking history of ≥ 10 pack years were included.

Patients with a medical history, including myocardial infarction, cardiac arrhythmia, or cardiac failure were generally included. They were excluded if they had a myocardial infarction (MI) within 6 months, hospitalization for heart failure within 12 months, or unstable or life-threatening arrhythmia that required intervention or change in drug therapy within 12 months of Visit 1 (randomization).
Patients with asthma or a significant other disease than COPD that put the patient at risk for participation at the study were also excluded.

Treatments
Patients were treated with tiotropium Respimat 2.5 µg, tiotropium Respimat 5 µg or tiotropium HH 18 µg. During the randomized treatment, patients were not allowed to use of inhaled short- and long-acting anticholinergic medications.

Duration of treatment
The event-driven trial (i.e. mortality) had a recruitment period of 11 months and was to end when approximately 1,266 fatal adverse events were reported. The actual number of deaths was 1302. During the trial, all subjects were to be followed for vital status every 12 weeks, regardless of premature discontinuation of study medication, until study closeout. The actual duration of the trial was approximately 3 years. Vital status was confirmed for 99.7% of all eligible randomized subjects at the end of the trial.

Endpoints
The primary safety endpoint was time to death (all-cause mortality). The primary efficacy endpoint was time to first COPD exacerbation.

Secondary efficacy endpoints were number of COPD exacerbations, time to first COPD exacerbation associated with hospitalization, number of COPD exacerbations associated with hospitalization, time to first moderate to severe COPD exacerbation.
A COPD exacerbation was defined as "a complex of lower respiratory events/symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a change in treatment".
The "complex of lower respiratory events/symptoms" was defined by having at least two of the following: shortness of breath, increase in sputum production, occurrence of purulent sputum, cough, wheezing, and chest tightness.
"A required change in treatment" was defined by a prescription of antibiotics and/or systemic steroids and/or a newly prescribed maintenance respiratory medication (i.e. bronchodilators including theophyllines).
Exacerbations were classified as mild (a new prescription of maintenance bronchodilator only), moderate (antibiotics or systemic steroids without hospitalization) or severe (hospitalization).
Although it is possible that fewer exacerbations were recorded given the criteria for a minimum of 3 days duration, it is considered unlikely that patients with an exacerbation requiring antibiotics and steroids would have symptoms for less than 3 days. Moreover, it is not likely, considering the active treatments in all treatment arms, that a difference would be present in exacerbation < 3 days.

In a pulmonary function subset study (PFT substudy), additional pulmonary lung function tests were performed in selected sites. For inclusion, more main requirements were added like additional pulmonary function test (PFT) and additional restrictions on concomitant therapies.
The endpoint in the pulmonary function test was the trough FEV_1 (key secondary endpoint) averaged over week 24 to week 120. Trough FEV_1 was defined as the FEV_1 measured at the -10 minute time point at the end of the dosing interval (24 hours post drug administration).
Lung function was assessed through pulmonary function testing (FEV_1 and FVC) every 24 weeks.

Statistical methods
The primary analysis of time to death from any cause was based on all subjects included in the death analysis set (DAS). The primary analysis of time to first COPD exacerbation was based on all subjects included in the treated set (TS). A subgroup participated in the pulmonary function testing (PFT) substudy.

Primary analyses
Three tests were conducted in hierarchical order.
Non-inferiority of time to death from any cause was tested on the two Respimat doses (Tio R5 first, followed by Tio R2.5 if non-inferiority was achieved with Tio R5) versus Tio HH 18. Additionally, if non-inferiority was also shown with Tio R2.5, the Respimat dose of 5 µg (Tio R5) was to be tested for superiority over Tio HH 18 for time to first COPD exacerbation.

The statistical methods are considered appropriate. The applied non-inferiority delta of 1.25 of hazard ratio (HR) of time to death from any cause is agreed.

Efficacy results
1202 centers actively enrolled subjects in a total of 50 countries. Overall, 20313 subjects were enrolled in the study. A total of 17116 subjects received at least one dose of study drug;
Tiotropium Respimat® 2.5 µg (Tio R2.5): DAS 5730 patients, treated patients 5724
Tiotropium Respimat® 5 µg (Tio R5): DAS 5711 patients, treated patients 5705
Tiotropium HandiHaler® 18 µg (Tio HH 18): DAS 5694 patients, treated patients 5687

A total of 1370 randomized subjects participated in the pulmonary function testing (PFT) substudy.

A total of 3917 subjects (22.9%) prematurely discontinued study medication. The incidence of premature discontinuation from trial medication was comparable across the three treatment groups:

23.1% in the Tio R2.5 group, 22.9% in the Tio R5 group, and 22.6% in the Tio HH 18 group. The three most common reasons for discontinuation were occurrence of AEs (10.8%), subject refusal to continue taking trial medication (5.8%), and 'other' (3.3%).

The three most common reasons for discontinuation in the PFT substudy were occurrence of AEs (9.1%), 'other' (3.1%), and subject refusal to continue taking trial medication (2.2%). The incidence of all other reasons for premature discontinuation was less than 2%.

Most subjects eligible for follow up of vital status were followed for 24 to 36 months: 62.1% of subjects were followed for 24 to 30 months and an additional 27.1% were followed for 30 to 36 months. The mean observation time was 838.2 days in the total population and balanced within the three tiotropium treatment groups.

Included population
The mean age of subjects was 65.0 years and the majority of subjects were male (71.5%). 38.1% of patients were current smokers, the mean duration of COPD was 7.4 years, and mean % predicted FEV1 at baseline was 48.3%. The baseline characteristics for the COPD GOLD classification and the number of COPD exacerbations were comparable among the groups at baseline.

Cardiac history and use of all classes of cardiac medications was balanced at baseline and during treatment. Overall, 10.7% of all treated subjects had a history of cardiac arrhythmias at baseline, and 15.2% of all treated subjects had a history of ischaemic heart disease/coronary artery disease. The incidence of subjects who reported a medical history of stroke, TIA, or MI was 2.3%, 1.4%, and 6.0%, respectively. Medical history, including history of cardiovascular and COPD events, was generally similar across the three treatment groups at baseline. Approximately 50% of subjects (51.1%) were receiving cardiovascular medications (other than statins). Cardiac medication use was balanced at baseline and during treatment.

Pulmonary medication use at baseline
The majority of all treated subjects (90.6%) were receiving pulmonary medications at baseline. The overall incidence of pulmonary medication use at baseline was balanced across treatments. Use of all classes (including the combination) of pulmonary medications at baseline was balanced across treatment groups.

Primary endpoint
All analyses of the primary endpoint of 'time to first COPD exacerbation' are based on the treated set (TS).

The median time to first COPD exacerbation was longer in the Tio R5 group compared to the Tio HH 18 group (756 days and 719 days, respectively). The HR for Tio R5 versus Tio HH 18 was 0.978 [95% CI: (0.928, 1.032), p=0.4194]. The difference was not statistically significant: superiority of Tio R5 over Tio HH 18 was not achieved.
There were no meaningful differences between either Tio R5 compared to Tio HH 18 in predefined subgroup analyses for time to first COPD exacerbation.

The incidence of COPD exacerbations was comparable: 49.4% in the Tio R2.5 group, 47.9% in the Tio R5 group, and 48.9% in the Tio HH 18 group.

Table 4: Analysis of time to first COPD exacerbation by treatment (TS,on-treatment only)

	Tio R 2.5		Tio R 5		Tio HH 18	
	N	(%)	N	(%)	N	(%)
Number of patients	5724	(100.0)	5705	(100.0)	5687	(100.0)
Patients with COPD exacerbations [N (%)]	2827	(49.4)	2733	(47.9)	2782	(48.9)
Median time to event (95% CI) [days]	707	(662, 750)	756	(692, 816)	719	(672, 777)
(Q1)		(195)		(202)		(197)
Comparison versus Tio HH 18						
Hazard ratio		1.016		0.978		
95% CI		(0.964,1.070)		(0.928, 1.032)		
p-value		0.5593		0.4194		
Comparison versus Tio R 5						
Hazard ratio		1.038				
95% CI		(0.985, 1.094)				
p-value		0.1639				

Because of the study design, i.e. an event driven study that was to be stopped when a certain number of deaths were observed, only a small number of patients were observed for the maximum duration of the study.

As 62.1% of subjects were followed for 24 to 30 months and an additional 27.1% were followed for 30 to 36 months and balanced within the three tiotropium treatment groups, it is not likely that the comparison between the treatments has been influenced for this endpoint.

Pulmonary Function Test results
The adjusted mean trough FEV1 over 120 weeks was 1.285 L for the Tio R5 group and 1.295 L for the Tio HH 18 group.

The adjusted difference between Tio R5 and Tio HH 18 was -0.010 L [95% CI: (-0.038 to 0.018)]. Because the lower bound of the confidence interval was greater than the pre-defined non-inferiority delta of -50 mL (-0.050 L), it was demonstrated that Tio R5 is non-inferior to Tio HH 18 for FEV_1.

The adjusted difference between Tio R2.5 and Tio HH 18 was -0.037 L [95% CI: (-0.065 to -0.009)]. Because the lower bound of the confidence interval was less than the pre-defined non-inferiority delta of -50 mL (-0.050 L), Tio R2.5 did not achieve non-inferiority compared to Tio HH 18 for FEV1. In addition, the upper bound of the confidence interval was less than 0, indicating that Tio R2.5 is inferior to Tio HH 18 for FEV_1.

The following table presents the results of adjusted trough FEV_1.

Table 5: Trough FEV1 [L] MMRM treatment comparisons by sub−study visit (SSS)

					Comparison vs Tio HH 18		
Visit	Treatment	N	Adjusted* mean (L)	SE	Adjusted* mean of difference (L)	SE	95% CI
Week 24	Tio R 2.5	464	1.297	0.013	-.027	0.017	(-.060,0.006)
	Tio R 5	461	1.306	0.014	-.018	0.017	(-.051,0.015)
	Tio HH 18	445	1.324	0.014			
Week 48	Tio R 2.5	464	1.274	0.014	-.053	0.017	(-.086,-.019)
	Tio R 5	461	1.306	0.014	-.021	0.017	(-.055,0.012)
	Tio HH 18	445	1.327	0.014			
Week 72	Tio R 2.5	464	1.252	0.014	-.028	0.017	(-.061,0.006)
	Tio R 5	461	1.278	0.014	-.001	0.017	(-.035,0.033)
	Tio HH 18	445	1.279	0.014			
Week 96	Tio R 2.5	464	1.242	0.014	-.036	0.018	(-.071,-.002)
	Tio R 5	461	1.274	0.014	-.004	0.017	(-.038,0.031)
	Tio HH 18	445	1.278	0.014			
Week 120	Tio R 2.5	464	1.224	0.014	-.041	0.018	(-.076,-.005)
	Tio R 5	461	1.261	0.014	-.004	0.018	(-.039,0.031)
	Tio HH 18	445	1.265	0.015			

The criterion for non-inferiority of Spiriva Respimat to Spiriva Handihaler was met on the predefined endpoint trough FEV_1 through 120 weeks. Moreover, the results of additional sensitivity analyses using the last observation carried forward (LOCF) and using 30% of the patient's predicted normal for missing data confirm the results of the primary analysis and show that Tio R5 is non inferior to Tio HH 18.

III.1.3 Clinical safety

- **TioSpir study 205.452**

In trial 205.452 the collection of adverse events was limited to all fatal adverse events (FAEs), all serious adverse events (SAEs), all AEs leading to discontinuation of study medication, and all AEs considered by the investigator to be drug-related. The following other AEs were assessed as protocol-defined outcome events: all COPD exacerbations, all pneumonias, all myocardial infarctions (MIs), all strokes, and all transient ischemic attacks (TIAs). Other non-serious, non-related AEs were not routinely collected.

The data of the active controlled study 205.452 is put into context with the mortality from the placebo-controlled pooled Tio R5 and Tio HH 18 databases. For the placebo-controlled pooled trials two different safety databases are defined:

The safety database: consisting of seven placebo-controlled studies with Tio R; and 28 placebo controlled studies of at least four weeks treatment duration with Tio HH.
The vital status database consisting of a subgroup of the previous database; this database includes studies in which deaths were collected throughout the vital status period (i.e., all deaths up to the planned end of treatment for each study, including patients with premature discontinuations followed until study close-out). The vital database consisted of 4 studies with Tio R5: three 1-years randomised, double-blind, placebo controlled trials (trials 205.254/255 and 205.372) one 6-month trial (trial 1205.14); the vital database for the Handihaler consisted of one large randomised, double-blind placebo-controlled trial of 4 years duration, the Uplift trial (study 205.235).
The table below represents of the number of the studies and exposure to randomised treatment in study 205.452 and in the safety database:

Table 6 Exposure to randomised treatment in the different databases.

	Study 205.452		Vital studies database				Safety database			
	Tio R	Tio HH	Plac R	Tio R	Plac HH	Tio HH	Plac R	Tio R	Plac HH	Tio HH
Number of studies	1		4		1		7		28	
Number of patients	5705	5687	3047	3049	3006	2986	3283	3282	8343	9647

The key inclusion criteria for the studies were a diagnosis of COPD, a ratio of FEV1/FVC <0.7, an age > 40 years and a smoking history of ≥10 pack years.

Key exclusion criteria for the studies included a history of asthma, a history of renal impairment and a history of recent cardiac disorders (including MI, unstable cardiac arrhythmias and hospitalisation due to cardiac failure) or use of systemic corticosteroid medication at unstable dose of ≥10 mg/day.

The baseline demographics are balanced between the treatment groups within each database. The majority of patients were male, white, >60 years old (median: 65 years), and considered overweight (BMI ≥25 kg/m2. Most patients are classified as COPD GOLD II or COPD GOLD III. In the TioSpir vital database 14% patients were of Asian origin; this was 20% in the Tio R5 vital database and 6% in the Tio HH vital database.

Deaths
The mortality analyses are based on the vital status database. In the event-driven, active-controlled study 205.452, deaths were counted on-treatment through study closeout with a sensitivity analysis conducted on end of treatment + 30 days (EOT+30 days). Vital status results (i.e., dead or alive) at the end of the planned treatment period were obtained for almost all patients in study 205.452 and the Tio R5 vital status database, and >94% of patients in the Tio HH 18 vital status database.

Table 7 Summary of vital status

	Study 205.452		Tio R 5 (4 studies) Day 169 or Day 337		Tio HH 18 (Study 205.235) Day 1440	
Percentage of treated patients	Tio R 5 N=5711	Tio HH 18 N=5694	Plac R N=3047	Tio R 5 N=3049	Plac HH N=3006	Tio HH 18 N=2986
Vital status complete (%)	99.8	99.7	98.2	98.8	94.5	95.4
Alive (%)	92.3	92.0	96.6	96.6	78.2	81.0
Died (%)	7.4	7.7	1.7	2.2	16.3	14.4
Lost to follow-up (%)	0.2	0.3	1.8	1.2	5.5	4.6

The Tio R5 vital status database included shorter duration studies (six months and one year) than either Study 205.452 (2 to 3 years) or the Tio HH 18 vital status database (4 years). Accordingly, the number of deaths in the Tio R5 vital status database was fewer than in Study 205.452 and the Tio HH 18 vital status databases.
Tio R5 achieved non-inferiority to Tio HH 18 for all-cause mortality in Study 205.452 (7.4% vs. 7.7%, respectively; HR=0.96 [95% CI 0.84, 1.09]). The incidence rate (IR) per 100 patient years was 3.22 for Tio R5 and 3.36 for Tio HH 18.
A sensitivity analysis for on treatment (EOT+30) showed similar results: 5.7% and 6.3% for Tio R5 and Tio HH 18, respectively (HR=0.913 [95% CI 0.785, 1.060]).
Mortality with Tio R5 was higher than with Plac R in the smaller Tio R5 vital status database (HR=1.33 [95% CI 0.93, 1.92]). In contrast, in Study 205.235, Tio HH 18 was associated with lower mortality compared with Plac HH, Day 1440 including vital status (HR=0.87 [95% CI 0.76, 0.99]).

Table 8 All-cause mortality in study 205.452 and the vital databases: N (%) of deaths, incidence rates, hazard ratios, and rate differences.

	Study 205.452, Day 663 to 1094		RESPIMAT (4 studies) Day 169* or Day 337		HANDIHALER (Study 205.235) Day 1440	
	Tio R 5	Tio HH 18	Plac R	Tio R 5	Plac HH	Tio HH 18
Number of patients treated	5711	5694	3047	3049	3006	2986
Number of deaths	423	439	51	68	491	430
Percentage of patients dying	7.4	7.7	1.7	2.2	16.3	14.4
Total years at risk	13135	13050	2571	2574	10872	10927
Incidence rate per hundred patient years	3.22	3.36	1.98	2.64	4.52	3.94
Treatment comparison	**Tio R 5/Tio HH 18**		**Tio R 5/Plac R**		**Tio HH 18/Plac HH**	
Hazard ratio (95% CI)[1]	0.96 (0.84, 1.09)		1.33 (0.93, 1.92)[2]		0.87 (0.76, 0.99)[3]	
Rate difference (95% CI)[4]	-0.14 (-0.58, 0.30)		0.66 (-0.17, 1.49)[2]		-0.58 (-1.13, -0.04)	

* Day 169: Plac R, n=429 patients; Tio R 5, n=427 patients
** Day 337: Plac R, n=2618 patients; Tio R 5, n=2622 patients
1 Time to death analyzed using a Cox proportional hazards model with treatment fitted as an explanatory variable.
2 Stratified by study protocol
3 Day 1440 is a post-hoc analysis used for comparison across databases. The HR (95% CI) for the analysis defined prior to unblinding (Day 1470) was 0.89 (0.79, 1.02).
4 Incidence rate differences were estimated based on the method described by Greenland and Robins.

The results of the TioSpir study show non-inferiority of Respimat to Handihaler for death from any cause (7.4% and 7.7% for Respimat and Handihaler, respectively; HR=0.957 [0.837-1.094]). There is no numerically increased risk of mortality observed for Respimat compared to Handihaler. This is supported by the findings of PK trials showing that the exposure to tiotropium following the use of Tio R5 was comparable, even lower, than that for Tio HH 18. The observed mortality is also in the range of reported fatal incidence rates in the literature among COPD patients (which varies between 1.5-6.1 per 100 person years).
An important difference between Respimat pooled studies and the other two studies is the duration of the treatment. The vital database for Tio R5 consist of three 1-years placebo controlled trials and one 6-month trial, which is shorter than that of TioSpir study (2 to 3 years), and Uplift trial (4 years). This can explain the lower rate of mortality in Respimat pooled analysis.

Overall mortality by primary SOC
The frequencies of adjudicated causes of death were, generally, similar across treatment groups by SOC. However, under SOC cardiac disorder, there was a numerically higher incidence of death in Tio R5 compared to Tio HH 18 in Study 205.452 (IRR=1.58 [95% CI 0.86, 2.89]) and Plac R in the Tio R5 vital status database (IRR=2.28 [95% CI 0.94, 5.55]). Conversely, there were a comparable (lower) number of deaths in Tio HH 18 compared to Plac HH (IRR=0.80 [95% CI 0.47, 1.36]).

Table 9 All-cause mortality in study 205.452 and the vital databases: N (%) of deaths, incidence rate ratio by SOC cardiac disorder

	Study 205.452			Tio R vital status (4 studies)			Tio HH18 vital status (1 study)		
	Tio R5 N=5711 N (%)	Tio HH N=5694 N (%)	IRR (95% CI)	Plac R N=3047 N (%)	Tio R5 N=3049 N (%)	IRR (95% CI)	Plac HH N=3006 N (%)	Tio HH N=2986 N (%)	IRR (95% CI)
SOC Cardiac disorders (fatal)	27 (0.5)	17 (0.3)	1.58 (0.86, 2.89)	7 (0.2)	16 (0.5)	2.28 (0.94, 5.55)	31 (1.0)	25 (0.8)	0.80 (0.47, 1.36)

Deaths due to MACE
The composite outcome of MACE (major cardiovascular event) and death due to MACE was evaluated in all databases.
Additional analysis of death due to MACE included: "death unknown" i.e. any fatal event with an unknown code was coded as PT death, which is contained within the SOC General Disorders and administration site conditions.

Table 10 Fatal MACE in study 205.452 and the vital databases: N (%) of deaths and Hazard ratios

	Study 205.452			Tio R vital status (4 studies)			Tio HH18 vital status (1 study)		
	Tio R5 N=5711 N (%)	Tio HH N=5694 N (%)	HR (95% CI)	Plac R N=3047 N (%)	Tio R5 N=3049 N (%)	HR (95% CI)	Plac HH N=3006 N (%)	Tio HH 18 N=2986 N (%)	HR (95% CI)
Fatal MACE	113 (2.0)	101 (1.8)	1.11 (0.85, 1.45)	13 (0.4)	26 (0.9)	2.00 (1.03, 3.89)	101 (3.4)	76 (2.5)	0.75 (0.56, 1.01)

The risk on fatal MACE between the Respimat and Handihaler is comparable; however, this risk is higher for Tio R5 compared to placebo, and lower with Handihaler in comparison to placebo.

Deaths due to SMQ ischemic heart disease
Fatal MI is significantly higher for Respimat in the TioSpir study in the vital status database. The comparison to placebo, although numerically higher for Respimat, is not statistically significant. For Handihaler, the risk of fatal MI is not statistically significant in comparison to placebo.

Table 11 Deaths due to SMQ ischemic heart disease in study 205.452 and the vital databases: N (%) of deaths and incidence rate ratio

	Study 205.452			Tio R vital status (4 studies)			Tio HH18 vital status (1 study)		
	Tio R5 N=5711 N (%)	Tio HH 18 N=5694 N (%)	IRR (95% CI)	Plac R N=3047 N (%)	Tio R5 N=3049 N (%)	IRR (95% CI)	Plac HH N=3006 N (%)	Tio HH 18 N=2986 N (%)	IRR (95% CI)
SMQ Ischaemic heart disease (fatal)	14 (0.2)	4 (0.1)	3.48 (1.14, 10.56)	2 (0.1)	9 (0.3)	4.49 (0.96, 20.96)	15 (0.5)	11 (0.4)	0.73 (0.34, 1.59)
SMQ Ischaemic heart disease sub-SMQ MI (broad) (fatal)	11 (0.2)	3 (0.1)	3.64 (1.02,13.06)	2 (0.1)	9 (0.3)	4.49 (0.96, 20.96)	14 (0.5)	11 (0.4)	0.78 (0.35, 1.72)

Deaths due to cardiac arrhythmias 'SMQ cardiac arrhythmias'
Tio R5 and Tio HH 18 showed identical incidences in the SMQ cardiac arrhythmias in study 205.452 (IRR=1.01 [95% CI 0.72, 1.41]). In comparison with Plac R, Tio R5 had a higher incidence of deaths due to cardiac arrhythmias (IRR=1.58 [0.61, 4.07]), albeit insubstantially lower number of events than study 205.452. Pooled trials for Tio HH showed a numerically lower incidence of deaths due to cardiac arrhythmias for Tio HH 18 compared to Plac HH (IRR=0.76 [0.49, 1.20]).

By PT, sudden cardiac death and sudden death comprised the majority of fatal events in the SMQ cardiac arrhythmias. The incidence of stroke was balanced across databases and between treatment groups. SMQ cardiac failure showed similar between-treatment rates in each database.

Analysis of selected AEs by organ system or syndrome

On SOC level, SAEs were similar between treatment groups in each of the safety databases in the SOC Cardiac disorders. The majority of SAEs and AEs in the SOC Cardiac disorders were due to cardiac arrhythmias, ischemic heart disease and cardiac failure.
For MACE, both vital data databases do not show a statistically significant difference with placebo; the difference between Tio R5 and Tio HH is also not significant.
The incidence of cardiac arrhythmia is low but comparable with placebo in the vital status database of Tio R5 and Tio HH. No difference between Tio R5 and Tio HH is observed in the TioSpir study.
The reporting rate of MI for HH in the TioSpir trial (investigator reports) is consistent with the rates from pooled placebo trials (1.2% each). The risk of MI does not reach statistical significance in any of the databases.

All cause mortality subgroup analyses
Patients with baseline cardiac disorder in the Tiospir study
In the TioSpir study a separate analysis for sub-population with cardiac disorder at baseline in each treatment arm with respect to cardiac mortality, fatal arrhythmia, fatal ischemic heart disease and MI (both fatal and non-fatal, serious and non-serious) was performed (Table 12,

Table 13).

Table 12 Number of patients in study 205,452 by treatment group and subgroup cardiac disorder at baseline (death analysis set)

Treatment group (Total N)	Subgroup cardiac disorder at baseline	Patients per subgroup N (%)
Tio R 2.5 (Total N = 5730)	Yes	1510 (26.4%)
	No	4220 (73.6%)
Tio R 5 (Total N = 5711)	Yes	1459 (25.5%)
	No	4252 (74.5%)
Tio HH 18 (Total N = 5694)	Yes	1508 (26.5%)
	No	4186 (73.5%)

Patients in the TioSpir study with a history of cardiac disorder at baseline present had a similar hazard ratio (HR) for mortality on Tio R5 compared to Tio HH 18. Similarly, patients with history of cardiac disorder at baseline not present had a comparable HR for mortality on Tio R5 vs. Tio HH 18.

Table 13 All cause mortality for patients with baseline cardiac disorder in the Tiospir study

Cardiac disorder at baseline	All cause mortality (%)				
	Tio R2.5 N=5730	Tio R5 N=5711	Tio H 18 N=5694	Tio R2.5/Tio HH 18 HR (95% CI)	Tio R5/Tio HH 18 HR (95% CI)
Not present*	6.4	6.3	6.4	1.00 (0.81, 1.24)	0.94 (0.76, 1.17)
Present*	11.2	10.6	10.2	1.00 (0.84, 1.18)	0.97 (0.82, 1.15)
Total*	7.7**	7.4**	7.7**	1.0 0.87, 1.14)	0.96 (0.84, 1.09)

* Total number of patients per subgroup/group: Tio R2.5, Present = 1510, Not present= 4220, Total = 5730; Tio R5, Present=1459, Not present=4252, Total=5711; Tio HH 18, Present=1508, Not present=4186, Total=5694
** n=440,423,439 for Tio R2.5, Tio R5 and Tio HH 18 respectively

Fatal cardiac events
These concern fatal events in SOC Cardiac disorders, SMQ Cardiac arrhythmias, SMQ Ischaemic heart disease and SMQ Ischaemic heart disease sub-SMQ Myocardial infarction. IRRs for Tio R5 versus Tio HH 18 for fatal cardiovascular events were, in general, similar irrespective of whether patients had cardiac disorder at baseline present or not. There were numerical differences for some of the outcomes (e.g. fatal ischaemic heart disease [IHD]); however, the number of these events was low and the results most likely reflect variability of rare events. No subgroup was at greater risk of a fatal cardiovascular event with any of the treatments investigated.

Endpoints including non-fatal events
These events were myocardial infarction (MI) including fatal and non-fatal, serious and non-serious. Overall MI (all events irrespective of severity) showed a similar event rate between Tio R5 and Tio HH 18 with or without presence of cardiac disorder at baseline. This result was replicated for MIs reported as serious. The rate ratios were comparable for both subgroups to that of the overall population, suggesting that no subgroup was at greater risk of a myocardial infarction. The MAH therefore concluded that a history of cardiac disorder is not a predictive factor for future MI in patients treated with Respimat compared with Tio HH.

Patients with baseline cardiac disorder/cardiac arrhythmia: comparison between the databases
The MAH performed a subgroup analysis of the TioSpir study and pooled placebo controlled studies according to the baseline characteristic 'cardiac disorder at baseline and cardiac arrhythmia at baseline'.
A comparable risk of mortality was observed in the head-to-head comparison of Tio R5 to Tio HH in the sub-population with cardiac disorder, or arrhythmic disorders at baseline.

In section 4.4 of the SmPC for Respimat, a warning is included that Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders. The results of the large Uplift study (205.235) showed a positive safety profile regarding mortality of Handihaler. Considering that the results of the well designed TioSpir trial, it is agreed that the warning regarding risk of mortality can be tempered.

Analysis by race
The assessment of the results of the pooled PK data suggested a higher systemic exposure of tiotropium (both formulations) in the Asian population. More Asian patients were included in the Tio R5 vital database which showed imbalance in mortality. In the Holter studies a possible dose response of ventricular tachycardia was observed. The submitted additional data showed no statistical difference for Asians population with respect to all-cause mortality, MACE mortality, SMQ IHC mortality and SMQ Cardiac arrhythmia mortality. The databases did not reveal a higher mortality for the Asian population.

- **Post-marketing data**

In addition to the data from clinical trials, the MAH provided post-marketing data on reporting rate of AEs per SOC as well as MACE of interest for Respimat and Handihaler. For SOC 'cardiac disorder' the reporting rate of AEs is comparable between two formulations (67.6 for HH vs. 66.7 for TioR). There was no significant increase in the reporting rate of cardiovascular topics of interest (including ischaemic cerebrovascular conditions (SMQ), myocardial infarction (SMQ) [broad] and Cardiac arrhythmia terms (incl. bradyarrhythmias and tachyarrhythmias) (SMQ) [broad], MACE and fatal MACE).
Although post-marketing data has its limitations, it is reassuring that the reporting rates of events from cardiac disorder (SOC) and related topics of interest remains comparable for two formulations. For the ischaemic cerebrovascular conditions and MI (SMQ) [broad] the post-marketing reporting rate is even slightly lower for the Respimat formulation.

- **Study 205.458, additional *post hoc* re-analyses of Holter registrations, reanalyses of 4 Holter studies**

Cardiac Holter monitoring of trial 205.458
A subset of 123 patients of selected sites underwent Holter monitoring: 99 males (81%) and 24 (19%) females. All patients were Caucasians. The mean (SD) age was 63.1 ± 8.1 years, with mean (SD) duration of COPD of 9.6 ± 7.1 years, a mean FEV_1 of 1.49 ± 80.54 L. Almost all patients were current smokers (82%).

At day 29, a higher number of ventricular runs were observed with the higher doses of tiotropium, but this was not confirmed with the *post hoc* analyses of day 26. Therefore, this might be a chance finding.
No clinically relevant effect on the QTc prolongation was observed, but the study lacked an active control for confirming the sensitivity of the included population.

The study did not include night time Holter analyses. One other limitation of the study is that the analyses were performed in a general COPD population. Probably a patient group with concomitant cardiovascular disease might be more sensitive to demonstrate differences.
Overall, no relevant differences between the Tio R5 Respimat and Tio HH were observed.

Additional *post hoc* re-analyses of Holter registrations performed in clinical studies
In trial 205.458, more patients experienced ventricular premature beats (VPB) run episodes on a higher dose of tiotropium on day 29. Based on these results, the MAH performed additional post-hoc analyses. It was shown that incidence of VPB and Ventricular tachycardia are generally comparable between Tio R5 and Tio HH. An imbalance in the number of ventricular tachycardia is observed for the higher doses of tiotropium; for tiotropium Respimat the number is increased with the dose suggestive for a dose response relationship.

Reanalyses of 4 Holter studies
A reanalysis of all tiotropium trials with COPD involving Holter ECG monitoring was undertaken. In these studies identical Holter monitoring analyses were applied as far as possible. The primary objective was to present a summary assessment of cardiac arrhythmia endpoints in a broad data base.

The re-analyses included all clinical trials with Holter monitoring within the development program of tiotropium Handihaler and Respimat within the last 10 years. One trial performed with Tio HH 18 µg was excluded for technical reasons (205.123). This study was performed in 1997/1998 and the technical standards for Holter monitoring and evaluation were not comparable with the other trials.

The following matching variables were included in this reanalysis: heart rate (HR), supraventricular premature beats (SVPB), ventricular premature beats (VPB) and pauses. Pauses were defined as the absence of a beat for more than 3 seconds.

Overall, 727 patients were included in this re-analysis (placebo: n=341, Tio R1.25 n=117, Tio R2.5: n=117, Tio R5: n=265, Tio R10: n=133, Tio HH 18: n=214). Age (mean ± SD) across all trials: 64.7 ± 8.7 years), BMI (mean: 26.5 ± 5.5 kg/m2), gender (male: 67.7%), racial distribution (White: 95.9 %), and duration of COPD (mean: 9.8 ± 7.7 years) were largely comparable across treatments.

The re-analysis of the Holter ECG endpoints detected increased risk of ECG endpoints following the administration of tiotropium, irrespective of dose, device or duration of treatment.
However, in trial 205.458, a tendency to the higher frequency of VPB runs was observed for the higher doses of tiotropium (Tio R5 and Tio HH) compared with the lower doses (Tio R1.25, Tio R2.5 and placebo). This was not confirmed by the trial 205.254/205.255 including the highest dose level of

Tio R10 and with the longest duration of treatment (1 year) out of the 4 trials included in this re-analysis.

In study 205.458, the external cardiology experts blinded to treatment identified higher incidences of VT for the higher doses of tiotropium Tio R5 and Tio HH compared with the lower doses of TioR. For tiotropium Respimat the incidence of VT increased with the dose, which is suggestive for a dose response relationship. This could not be shown for tiotropium 18 µg, but only one dose was included.

The Holters of 4 placebo controlled studies were reanalysed, including the crossover study 205.458. The reanalyses did not show an increased risk on the Holter ECG endpoint Heart Rate (HR), Supraventricular premature beats (SVPB), Ventricular premature beats (VPB) and pauses following the administration of tiotropium. No treatment effect was observed for the ventricular premature beats or other arrhythmia endpoints, except for the VPB runs on day 29 of trial 205.458.

The most sensitive study to demonstrate differences was the crossover study 205.458. In this study, different doses of tiotropium Respimat were included, while only one dose of Tio HH was included. For Tio R5, a possible dose dependent effect on the event VT was observed. However, the overall incidence of ECG Holter findings was comparable between Tio R5 and Tio HH. The re-analyses of the Holter studies included in the development plan of Tio R5 or Tio HH did not show an increased risk.

IV. UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

In the context of this variation application the MAH provided the results of the post-marketing TioSpir study with three doses of tiotropium: Tio Respimat 2.5 µg and 5 µg and Tio Handihaler (HH) 18 µg.
The study failed to show the superiority of Tio R5 over Tio HH to the time to the first exacerbation. Because non-inferiority margins were not predefined, only numerical results are added to the SmPC.

In a subset of patients non-inferiority between Tio R5 and Tio HH in the FEV1 at week 120 was shown. The non-inferiority of Spiriva Respimat to Spiriva Handihaler is observed from week 48 on.

For this variation the MAH has put the safety data of TioSpir trial into context with the available long-term pooled placebo controlled trials for Respimat and Handihaler.
The results of TioSpir trial demonstrated comparable mortality rates (all cause, cardiac, MACE) of Respimat vs. Handihaler. Mortality rates were also comparable in patients with cardiac disorders or arrhythmia at baseline. PK trials demonstrated a similar systemic exposure for both formulations.
In addition, Holter analyses performed in the cross-over PK studies provided a head-to-head comparison between Tio R5 and Tio HH. The arrhythmia profile was comparable. In these analyses, the additional data on risk of mortality/cardiac mortality in Asian and non-Asian population showed no statistical difference with respect to all-cause mortality, MACE mortality, SMQ IHC mortality and SMQ cardiac arrhythmia mortality. The data from post marketing also showed similar reporting rates for cardiac arrhythmia, MI, ischemic cerebrovascular conditions.

The cardiac exclusion criteria were comparable between the TioSpir study, the Uplift trial (205.235) and the largest Respimat placebo controlled trial (205.372). 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 for heart failure (NYHA Class III or IV) were excluded in all trials.

There are no data available regarding a time delay between a cardiac event and continuation of tiotropium. Therefore uncertainties exist regarding the continuation of treatment after a cardiac event. These uncertainties are covered by the warning which is added to the SmPC.

The information on placebo-controlled studies remains in section 5.1 of the SmPC to reflect the imbalance in mortality observed in patients with known cardiac rhythm disorders observed with Tio R5 in the large scale pooled placebo-controlled trials.

In conclusion, based on the review of the data on safety and efficacy, 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.

The variation was completed on 20 November 2014.

V. 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

~~Spiriva Respimat should be used with caution in patients with known cardiac rhythm disorders (see 5.1).~~
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.

4.9 Undesirable effects

Tabulated summary of adverse reactions
The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group pooled from ~~5~~7 placebo-controlled clinical trials in COPD (~~2,802~~3,282 patients) and 6 placebo-controlled clinical trials in asthma (1,256 patients) with treatment periods ranging from ~~twelve~~ four weeks to one year.

Frequency is defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
Metabolism and nutrition disorders		
Dehydration	Not known	Not known
Nervous system disorders		
Dizziness	Uncommon	Uncommon

System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
Headache	Uncommon	Uncommon
Insomnia	~~Not known~~ Rare	Uncommon
Eye disorders		
Glaucoma	Rare	Not known
Intraocular pressure increased	Rare	Not known
Vision blurred	Rare	Not known
Cardiac disorders		
Atrial fibrillation	~~Uncommon~~Rare	Not known
Palpitations	~~Uncommon~~Rare	Uncommon
Supraventricular tachycardia	~~Uncommon~~Rare	Not known
Tachycardia	~~Uncommon~~Rare	Not known
Respiratory, thoracic and mediastinal disorders		
Cough	Uncommon	Uncommon
~~Epistaxis~~	~~Uncommon~~	~~Not known~~
Pharyngitis	Uncommon	Uncommon
Dysphonia	Uncommon	Uncommon
Epistaxis	Rare	Not known
Bronchospasm	Rare	Uncommon
Laryngitis	Rare	Not known
Sinusitis	Not known	Not known
Gastrointestinal disorders		
Dry Mouth	Common	Common
Constipation	Uncommon	Rare
Oropharyngeal candidiasis	Uncommon	Uncommon
Dysphagia	~~Uncommon~~Rare	Not known
Gastrooesophageal reflux disease	Rare	Not known
Dental caries	Rare	Not known
Gingivitis	Rare	Rare
Glossitis	Rare	Not known
Stomatitis	~~Rare~~ Not known	Rare
Intestinal obstruction, including ileus paralytic	Not known	Not known
Nausea	Not known	Not known
Skin and subcutaneous tissue disorders, immune system disorders		
Rash	Uncommon	Rare
Pruritus	Uncommon	Rare
Angioneurotic oedema	Rare	Rare
Urticaria	Rare	Rare
Skin infection/skin ulcer	Rare	Not known
Dry skin	Rare	Not known
Hypersensitivity (including immediate reactions)	Not known	Rare
Anaphylactic reaction	Not known	Not known
Musculoskeletal and connective tissue disorders		
Joint swelling	Not known	Not known

System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
Renal and urinary disorders		
Urinary retention	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Not known

Description of selected adverse reactions
In controlled clinical studies in COPD, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately ~~3.2~~ 2.9 % of patients. In asthma the incidence of dry mouth was 1.2%.

In ~~5~~ 7 clinical trials in COPD, dry mouth led to discontinuation in 3 of ~~2,802~~ 3,282 tiotropium treated patients (0.1 %). No discontinuations due to dry mouth were reported in 6 clinical trials in asthma (1,256 patients).

4.10 Overdose

~~Acute intoxication by inadvertent oral ingestion of tiotropium solution for inhalation from the cartridge is unlikely due to low oral bioavailability.~~

5.1 Pharmacodynamic properties

~~In a retrospective pooled analysis of the three 1 year and one 6 month placebo controlled trials with Spiriva Respimat including 6,096 patients a numerical increase in all cause mortality was seen in patients treated with Spiriva Respimat (68; incidence rate (IR) 2.64 cases per 100 patient years) compared with placebo (51, IR 1.98) showing a rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) for the planned treatment period; the excess in mortality was observed in patients with known rhythm disorders.~~

Long-term 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 Spiriva Respimat and Spiriva HandiHaler (5,711 patients receiving Spiriva Respimat; 5,694 patients receiving Spiriva HandiHaler). 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 Spiriva Repimat and Spiriva HandiHaler (hazard ratio (Spiriva Respimat/Spiriva HandiHaler) 0.98 with a 95% CI of 0.93 to 1.03). The median number of days to the first COPD exacerbation was 756 days for Spiriva Respimat and 719 days for Spiriva HandiHaler.

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

In the post-marketing TIOSPIR study comparing Spiriva Respimat and Spiriva HandiHaler, all-cause mortality (including vital status follow up) was similar with hazard ratio (Spiriva Respimat/Spiriva HandiHaler) = 0.96 , 95% CI 0.84 -1.09). Respective treatment exposure was 13,135 and 13,050 patient-years.
In the placebo-controlled studies with vital status follow-up to the end of the intended treatment period, Spiriva Respimat showed a numerical increase in all-cause mortality compared to placebo (rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) with treatment exposure to Spiriva Respimat

of 2,574 patient years; the excess in mortality was observed in patients with known rhythm disorders. Spiriva HandiHaler showed a 13 % reduction in the risk of death ((hazard ratio including vital status follow-up (tiotropium/placebo) = 0.87; 95% CI, 0.76 to 0.99)). Treatment exposure to Spiriva HandiHaler was 10,927 patient-years. No excess mortality risk was observed in the subgroup of patients with known rhythm disorders in the placebo controlled Spiriva HandiHaler study as well as in the TIOSPIR Spiriva Respimat to HandiHaler comparison.

5.2 Pharmacokinetic properties

Absorption: Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. ~~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%. Food is not expected to influence the absorption of this quaternary ammonium compound.
Maximum tiotropium plasma cocentrations were observed 5-7 minutes after inhalation.
At steady state, peak tiotropium plasma levels in COPD patients of 10.5~~-11.7~~ pg/ml were achieved ~~when measured 10 minutes after administration of a 5 microgram dose delivered by the Respimat inhaler~~ and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were ~~1.49-1.68~~ 1.60 pg/ml. ~~Food is not expected to influence the absorption of this quaternary ammonium compound.~~
A steady state tiotropium peak plasma concentration of 5.15 pg/ml was attained 5 minutes after the administration of the same dose to patients with asthma.
Systemic exposure to tiotropium following the inhalation of tiotropium via the Respimat inhaler was similar to tiotropium inhaled via the HandiHaler device.

Elimination: The ~~terminal elimination~~ effective half-life of tiotropium ~~bromide is~~ ranges between ~~5 and 6 days~~ 27 - 45 h following inhalation by healthy volunteers and COPD patients. The effective half-life was 34 hours in patients with asthma. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers~~with an interindividual variability of 22%~~. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%).
After inhalation of the solution by COPD patients to steady-state, urinary excretion is ~~20.1-29.4 %~~18.6 % (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.
After inhalation of the solution by healthy volunteers urinary excretion is 20.1-29.4 % of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.
In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.
After chronic once daily inhalation by COPD patients, pharmacokinetic steady-state was reached by day 7 with no accumulation thereafter.

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

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, ~~advanced~~ advancing age was associated with a decrease of tiotropium renal clearance (~~326~~ 347 ml/min in COPD patients < ~~58~~65 years to ~~163~~ 275 ml/min in COPD patients ≥65~~> 70~~ 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 did not change significantly with advancing age within COPD patients if compared to inter- and intraindividual~~

~~variability (43 % increase in AUC_{0-4h} after dry powder inhalation).~~This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values. Exposure to tiotropium was not found to differ with age in patients with asthma.

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 inhalation. Mild renal impairment (CL_{CR} 50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC_{0-4h} after intravenous infusion).~~
Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50 - 80 ml/min) resulted in slightly 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 a single dose of tiotropium resulted in doubling of the total exposure (82% 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.
~~plasma concentrations (82% increase in AUC_{0-4h}), which was confirmed by plasma concentrations after dry powder inhalation and also by inhalation of the solution via the Respimat inhaler.~~ In asthma patients with mild renal impairment (CL_{CR} 50-80 ml/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.

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

5. What you need to know before you take Spiriva Respimat

If you can answer any of these questions with **`Yes`** please discuss this with your doctor **before** taking Spiriva Respimat:

- (…)
- have you suffered from a myocardial infarction during the last 6 month or from any unstable or life threatening irregular heart beat or severe heart failure within the past year?

~~Make sure your prescriber knows if you have diseases of the heart, in particular conditions affecting your heartbeat (rhythm disorders). Rhythm disorders may include irregular heartbeat, too slow heart beat (bradycardia), or too fast heartbeat (tachycardia). This is important to decide if Spiriva Respimat is the right medicine for you to take.~~
In case you have suffered from a myocardial infarction during the last 6 month 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 Spiriva is the right medicine for you to take.

4. Possible side effects

Side effect	**Frequency COPD**	**Frequency Asthma**
Difficulty in sleeping (insomnia)	~~Uncommon~~Rare	Uncommon

Side effect	**Frequency COPD**	**Frequency Asthma**
Irregular heart beat (atrial fibrillation, supraventricular tachycardia)	~~Uncommon~~Rare	Not known
Feeling your heartbeat (palpitations)	~~Uncommon~~Rare	Uncommon
Faster heart beat (tachycardia)	~~Uncommon~~Rare	Not known
Nosebleed (epistaxis)	~~Uncommon~~Rare	Not known
Difficulties swallowing (dysphagia)	~~Uncommon~~Rare	Not known
Inflammation of the mouth (stomatitis)	~~Rare~~ Not known	Rare

Annex VII – Submission of an updated Risk Management Plan (NL/H/0718/001/IB/015)

I. Recommendation

Based on the provided data the member states consider that the variation for Spiriva Respimat (tiotropium bromide), for the update of Risk Management Plan (RMP, version 7.0) is approvable.

II. Safety specification

II.1 Epidemiology of the indications and target population

Epidemiology of COPD and asthma
This section of the RMP has been updated with some additional references to studies and databases for incidence, prevalence and demographics of the target population, important comorbidities found in the target population, as well as newly available alternative treatments.

II.2 Non-clinical part of the safety specification

Non-clinical data
Under "Repeated dose studies", the following study is added:
'The MAH has extended its existing non-clinical safety database by conducting a preliminary inhalation feasibility study and a pivotal 13-week inhalation toxicity study in juvenile rats.
(…) No new toxicities and no toxicologically relevant effects on key developmental parameters and on tracheal or key organ development were observed.'

No new safety issue was identified.

II.3 Clinical trial exposure

Exposure to Spiriva Handihaler and Respimat in populations studied since the last RMP update
Patients in Trial 205.452 (TioSpir)
The updates in this section provide the clinical trial exposure during the TioSpir trial, presented pooled and by medicinal product (Spiriva Handihaler and Spiriva Respimat).
A total of 17,116 patients were treated with Spiriva Handihaler or Respimat in this trial, with a total exposure of 34,085 patient-years. Separate tables of patient exposure, duration of exposure, ethnic origin, age group and gender exposure is provided for both Spiriva Handihaler and Spiriva Respimat.

The exposure figures are updated for Spiriva Respimat trials with adolescent patients (aged 12 to 17 years) (trials 205.444, 205.456 and 205.424).
Furthermore the figures on total exposure to Spiriva Handihaler and Respimat in company sponsored clinical trials were also updated.

The MAH has provided a detailed update (patient exposure, duration of exposure, ethnic origin, age group and gender exposure etc.) of clinical trial exposure data. The updates are accepted.

II.4 Populations not studied in clinical trials

This section of the RMP is updated with detailed exclusion criteria in the clinical trials for the indication COPD and Asthma.

Safety concerns due to limitations of the clinical trial programme

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern**
Safety concern	Comment	Yes/No
Long term safety for indication asthma	In asthma trials patients were exposed to Spiriva up to 1 year.	Yes
Paediatric patients	For COPD, missing information in patients ≤18 years of age is not considered to constitute a risk as COPD does not normally occur in children. For asthma, the development programme is ongoing in the paediatric population. Adolescent patients have been exposed to Spiriva during the clinical trial programme.	Yes
Pregnant or breast-feeding women	Pregnant and nursing women were excluded from all trials and consequently.	Yes
Use in elderly	A large number of elderly patients have been exposed to Spiriva both during the clinical trial programme and post-marketing. No risk minimisation strategy is needed for the elderly population. Elderly patients can use Spiriva at the recommended dose.	No
Use in patients with hepatic impairment	Liver insufficiency is not expected to have any relevant influence on tiotropium bromide pharmacokinetics. Patients with hepatic impairment were included in the clinical trials in asthma. Hepatically impaired patients can use Spiriva at the recommended dose.	No
Use in patients with severe renal impairment	Renally impaired patients can use Spiriva at the recommended dose. However, as with all predominantly renally excreted drugs, Spiriva use should be monitored closely in patients with moderate to severe renal impairment.	No
Patients with a recent history of: • myocardial infarction • unstable or life-threatening cardiac arrhythmia • paroxysmal tachycardia • decompensated heart failure	An analysis has confirmed safety in these patient groups. Information has been provided to health authorities as part of the TioSpir trial submission.	Yes
Patients with lung diseases other than COPD or asthma	Spiriva, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. Inhaled medicines may cause inhalation-induced bronchospasm.	No
Patients with other relevant co-morbidities	It is expected that patients with other relevant comorbidities using Spiriva will be under close medical supervision.	No

Patients of different racial and/or ethnic origin	Spiriva has been shown to be efficacious in patients of a wide range of races and ethnicities.	No

II.5 Post-authorisation experience

Actions taken by regulatory authorities and/or marketing authorisation holder for safety reasons
Detailed description of action taken since last update to this module:
Safety issue: Anaphylaxis
Background: PRAC request in EU
Action taken: Update of EU regional labels and local labels
Countries affected: EU, Japan, China
Dates of action: Jan–Oct 2013

Safety issue: Postulated increased mortality from cardiovascular disease and all-cause mortality
Background: Postulated imbalance in mortality findings in clinical development trials refuted
Evidence source: TioSpir trial (205.452) and new pharmacokinetics/pharmacodynamics trial (205.458)
Action taken: Submission of label update and re-submissions
Countries affected: Worldwide
Dates of action: Label updates: Dec 2013–Mar 2014

Furthermore the table of cumulative listing of actions taken by regulatory authorities and/or the marketing authorisation holder for safety reasons is also updated.

Following the assessment of the signal on anaphylactic reactions, this ADR is added to section 4.8 of the SmPC of both formulations with frequency unknown.

The TioSpir study, showing no differences in the overall mortality or cardiovascular mortality (MACE) between Respimat and Handihaler, has been assessed in 2014. The safety profile of the two formulations of Spiriva was also comparable in patients with history of cardiac disorders. Assessment of the data led to removal of the warning “Spiriva Respimat should be used in caution in patients with known cardiac rhythm disorders.” from section 4.4 of SmPC of Respimat. However a warning was added to section 4.4 of both formulations that 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. This is appropriate, as these patients were excluded from the pivotal clinical trials and it is considered that these cardiac conditions might be affected by the anticholinergic mechanism of action of tiotropium.

As requested, in the updated RMP (version 7.0), safety in patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure is addressed as missing information.

Non-study post-authorization exposure
This section has been updated with the most recent post-marketing data.

Estimated total exposure: Spiriva 18 µg inhalation powder and Spiriva Respimat 2.5 µg solution, as of 31 Dec 2013

	Estimated number of doses sold	Estimated exposure [py]
SPIRIVA HANDIHALER 18 mcg	12.7 billion capsules	34.8 million
SPIRIVA RESPIMAT 2.5 mcg	25.7 million cartridges	2.1 million

Exposure updates per EEA, USA/Canada, Japan and other areas have been provided.

II.6 Additional EU requirements for the safety specification

Potential for harm from overdose
The updates in this section concerns 8 cases of overdose in non-placebo-controlled trials; 3 of these cases related to an overdose of a drug other than Spiriva. None of the 8 patients experienced drug-related AEs as a result of the overdose. This information does not effect the benefit risk balance of the product. The risk of over dose is currently addressed in the RMP as potential risk.

Specific paediatric issues
The efficacy and safety of Spiriva Respimat has been specifically studied in adolescent patients aged ≥12 to 17 years. The clinical programme in adolescents included 3 trials:
2 parallel-group Phase III trials of different durations in patients with moderate (Trial 205.444; 48 weeks) and severe (Trial 205.456; 12 weeks) asthma and a supportive Phase II incomplete crossover trial (Trial 205.424) in adolescent patients with moderate asthma. The exposure to Spiriva in the 2 parallel-group trials in adolescents for this clinical programme covers more than 290 person years in 516 adolescent patients. In these 2 trials, the overall frequencies of AEs, drug-related AEs, and SAEs were similar across the Spiriva and placebo treatment groups. Once daily Spiriva in adolescents also taking ICS, with or without other controllers, was safe and well tolerated.

Newly identified safety concerns
No safety concerns have been newly identified since this module was last submitted.

Recent study reports with implications for safety concerns
Following analysis of data from TioSpir trial, the MAH proposed to remove all-cause mortality, cardiac mortality (for Respimat only), sudden death and unspecified death from list of potential risks.
The results of the TioSpir study have been extensively reviewed in a separate procedure variation, which is discussed in Annex VI.
The trial was designed to study the risk of “all cause mortality” between Respimat and Handihaler (primary objective) and not “cardiac mortality”. The imbalance observed in the incidence of MI and fatal MI between Respimat and Handihaler in the TioSpir trial, even though numerically too small to be conclusive, remains a concern. Furthermore, the lack of a placebo group in this trial has implications for the interpretation of the data. It should also be noted that patients at high risk were excluded from participation (this is reflected in section 4.4 of the SmPC).
Tiotropium is an anticholinergic, and based on the mechanism of action, anticholinergics can have cardiac side effects. Concerns regarding cardiac safety profile of tiotropium and other anticholinergics have been raised repeatedly. The RMP of recently approved products of the same class also address cardiac mortality as important potential risk.
As requested, in the updated RMP (version 7.0), cardiac mortality is addressed as important potential risk.

Details of important identified and potential risks from clinical development and post-authorisation experience
There are no important identified risks for Spiriva HandiHaler and Spiriva Respimat for either COPD or asthma.

Results of the TioSpir trial are integrated in this section of the RMP. The updates concern presentation of the risks per indication. For COPD the risk is presented per formulation (pooled data) as well as combined for Respimat and HandiHaler. Post-marketing updates have also been provided.

II.7 Summary of the safety concerns

The table below presents the revised Summary of the Safety Concerns for Spiriva in COPD and asthma.

Summary of safety concerns	
Important identified risks	None
Important potential risks	~~All-cause mortality~~ ~~Cardiac mortality (for Respimat only)~~ ~~Sudden death and unspecified death~~ 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*
Missing information	Treatment of pregnant and breast-feeding women Treatment of paediatric patients Long term safety for indication asthma Safety in patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure

Conclusions on the safety specification
In the updated RMP (version 7.0), the MAH has revised the list of safety specifications. Cardiac mortality is addressed as important potential risk, and safety in patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure is listed as missing information.

III. Pharmacovigilance plan

III.1 Safety concerns and overview of planned PhV actions

The MAH proposed routine pharmacovigilance for all identified and potential risks, as well as missing information. Enhanced post-marketing pharmacovigilance including close monitoring is proposed for the following topics:

- Cardiac disorders (ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure, angina pectoris)

Post-authorisation safety study (epidemiology study):

'Combined bronchodilators in COPD and the risk of adverse cardiopulmonary events: A population-based observational study'.

Objectives:

- To determine whether adding a LABA to Spiriva use, or vice versa, increases the risk of acute myocardial infarction, stroke, heart failure, arrhythmia and community acquired pneumonia in patients with COPD, relative to monotherapy.
- To compare the incidence of these outcome events in monotherapy users of Spiriva relative to monotherapy users of LABAs.
- To assess whether Spiriva and LABAs increase the risks of these cardiovascular and respiratory events, relative to non-use.

- Treatment of paediatric patients

For asthma, a total of 7 studies were discussed and agreed with the Paediatric Committee in the context of a Paediatric Investigational procedure (EMEA-000035-PIP02-09) in January 2013.

Furthermore, this section is updated with the summary of the results of the TioSpir trial.

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Not applicable.

III.3 Studies and other activities completed since last update of PhV Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
Trial 205.452 (TioSpir)	To compare the safety and efficacy of Spiriva between the Respimat and the Handihaler device.	All-cause mortality (including subgroup analysis in patients with known rhythm disorders) and exacerbation efficacy.	Completed	22 October 2013

III.4 Summary of the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
PASS (epidemiology study 205.526): 'Combined bronchodilators in COPD and the risk of adverse cardio-pulmonary events: A population-based observational	To determine whether adding a LABA to Spiriva use, or vice versa, increases the risk of acute myocardial infarction, stroke, heart failure, arrhythmia, and community acquired pneumonia in patients with COPD, relative to monotherapy. To compare the incidence of these outcome	Cardiac disorders	Last patient entered 24 March 2014	Planned: March 2016

study'.	events in monotherapy users of Spiriva relative to monotherapy users of LABAs. To assess whether Spiriva and LABAs increase the risks of these cardiovascular and respiratory events, relative to non-use.			

IV. Applicability to patients in the target population

Patients with COPD
Exposure to Spiriva in the COPD clinical trial programme as of 31 Dec 2013 was calculated at 28,192 patient-years for Spiriva Handihaler and 27,848 patient-years for Spiriva Respimat.

Patients with asthma
As of 31 Dec 2013, 3647 patients with an exposure of 1647 person years had been treated with Spiriva in the asthma clinical development programme.
As of 31 Dec 2013, a total of 722 patients aged <18 years had been treated with Spiriva in the asthma clinical development programme. The exposure to Spiriva in these patients is calculated at 330 person years. The asthma parallel group trials (205.342, 205.416, 205.417, 205.418, 205.419, 205.442, 205.444, 205.456, and 205.464) included 462 patients with mild, 45 patients with moderate, and 18 patients with severe renal impairment in the Spiriva arms. The asthma crossover trials (205.341, 205.380, 205.420, 205.441, 205.424, and 205.425) included 164 patients with mild and 18 patients with moderate renal impairment at baseline in the Spiriva arms.

The efficacy and safety of Spiriva Respimat has been specifically studied in adolescent patients aged ≥12 to 17 years. The clinical programme in adolescents included 3 trials:
2 parallel-group Phase III trials of different durations in patients with moderate (trial 205.444; 48 weeks) and severe (trial 205.456; 12 weeks) asthma and a supportive Phase II incomplete crossover trial (trial 205.424) in adolescent patients with moderate asthma. The exposure to Spiriva in the 2 parallel-group trials in adolescents for this clinical programme covers more than 290 person years in 516 adolescent patients.

IV.1 Summary of post-authorisation efficacy development plan

There are no ongoing or completed post-authorisation efficacy studies that were either initiated by the marketing authorisation holder (MAH) or were specific obligations and/or conditions of the marketing application.

V. Risk minimisation plan

As agreed, the MAH applies only routine risk minimisation for important potential risks and the important missing information. The section on risk minimisation measures has been updated in line with the revised safety concerns listed in section II.7 of this annex.

VI. Overall conclusion

The MAH provided an appropriate updated RMP. The summaries of the safety concerns and risk minimisation measures have been adequately updated.

Cardiac mortality remains as important potential risk. Safety in patients with a recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmia, paroxysmal tachycardia and decompensated heart failure is addressed as missing information.

The member states agree that the proposed risk minimisation measures and routine pharmaco-vigilance are sufficient to minimise the risks of the product in the proposed indications. In conclusion, the update to the RMP (version 7.0) is approvable.

The variation was completed with a positive outcome on 13 April 2015.