

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093-103.

SUPPLEMENTARY APPENDIX

Supplement to: Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of COPD exacerbations

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Section 2: Secondary and safety endpoints

Secondary Endpoints	<ul style="list-style-type: none">• Time to event:<ul style="list-style-type: none">○ Time to first COPD exacerbation leading to hospitalization (i.e. severe COPD exacerbation)○ Time to first moderate COPD exacerbation○ Time to premature discontinuation of trial medication○ Time to first COPD exacerbation or time to discontinuation of study medication because of worsening of underlying disease (whichever came first)○ Time to first exacerbation treated with systemic steroids○ Time to first exacerbation treated with antibiotics○ Time to first exacerbation treated with systemic steroids and antibiotics• Number of patients with events:<ul style="list-style-type: none">○ Occurrence of at least 1 COPD exacerbation○ Occurrence of at least 1 COPD exacerbation leading to hospitalization○ Occurrence of premature discontinuation of trial medication• Number of events:<ul style="list-style-type: none">○ Number of COPD exacerbations○ Number of COPD exacerbations leading to hospitalization (i.e. severe COPD exacerbations)○ Number of moderate COPD exacerbations○ Number of exacerbations treated with systemic steroids
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	<ul style="list-style-type: none"> ○ Number of exacerbations treated with antibiotics ○ Number of exacerbations treated with systemic steroids and antibiotics ● Pre-dose morning Peak Expiratory Flow Rate (PEFR) measured by patients at home during the first 4 months of randomized treatment (weekly means were calculated)
Safety Endpoints	<ul style="list-style-type: none"> ● Serious adverse events ● Adverse events leading to treatment discontinuation ● Treatment-related adverse events ● Major adverse cardiovascular events (MACE) during treatment* ● All-cause mortality with onset of fatal AE during treatment with study medication + 30 days ● All-cause mortality including follow-up of vital status from patients who prematurely discontinued treatment and date of death within 360 days

*Included fatal cardiac disorders, fatal vascular disorders, sudden death, cardiac death, sudden cardiac death, serious adverse events (fatal and non-fatal) from myocardial infarction, and stroke.

Section 3: Analysis of exacerbations by exacerbation severity and by treatment with systemic steroids and/or antibiotics

	Tiotropium (N=3707)	Salmeterol (N=3669)	Ratio (95% CI)	P-value
Moderate/severe exacerbation				
Patients with ≥1 moderate/severe exacerbation, n (%)	1277 (34.4)	1414 (38.5)	0.83* (0.77–0.90)	<0.001
Number of moderate/severe exacerbations	2114	2297	--	--
Rate of moderate/severe exacerbations per patient year	0.64	0.72	0.89 [†] (0.83–0.96)	0.002
Moderate exacerbation				
Patients with ≥1 moderate exacerbation, n (%)	1114 (30.1)	1206 (32.9)	0.86* (0.79–0.93)	<0.001
Number of moderate exacerbations	1802	1884	--	--
Rate of moderate exacerbations per patient year	0.54	0.59	0.93 [†] (0.86–1.00)	0.048
Severe exacerbation				
Patients with ≥1 severe exacerbation, n (%)	262 (7.1)	336 (9.2)	0.72* (0.61–0.85)	<0.001
Number of severe exacerbations	312	413	--	--
Rate of severe exacerbations per patient year	0.09	0.13	0.73 [†] (0.66–0.82)	<0.001
Exacerbations treated with systemic steroids				

Patients with ≥ 1 systemic steroid-treated exacerbation, n (%)	715 (19.3)	852 (23.2)	0.77* (0.69–0.85)	<0.001
Number of systemic steroid-treated exacerbations	1106	1302	--	--
Rate of systemic steroid-treated exacerbations per patient year	0.33	0.41	0.82 [†] (0.76–0.90)	<0.001
Exacerbations treated with antibiotics				
Patients with ≥ 1 antibiotics-treated exacerbation, n (%)	1154 (31.1)	1259 (34.3)	0.85* (0.78–0.92)	<0.001
Number of antibiotics-treated exacerbations	1753	1894	--	--
Rate of antibiotics-treated exacerbations per patient year	0.53	0.59	0.90 [†] (0.84–0.97)	0.004
Exacerbations treated with systemic steroids and antibiotics				
Patients with ≥ 1 systemic steroid- and antibiotics-treated exacerbation, n (%)	562 (15.2)	671 (18.3)	0.76* (0.68–0.86)	<0.001
Number of systemic steroid- and antibiotics-treated exacerbations	749	906	--	--
Rate of systemic steroid- and antibiotics-treated exacerbations per patient year	0.23	0.28	0.80 [†] (0.73–0.88)	<0.001

*Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.

†Number of event analysis was done using Poisson regression correcting for overdispersion and adjusting for treatment exposure; ratio refers to rate ratio. Findings of this analysis were supported by negative binomial regression analysis (not shown).

Section 4A: Subgroup analysis of primary endpoint for pulmonary medication subgroups

Pulmonary medication use at baseline	Tiotropium n/N	Salmeterol n/N	Hazard Ratio* (95% CI) Tiotropium vs. Salmeterol	Subgroup by treatment interaction P-value
Maintenance naïve [†]				0.48
Yes	167/672	202/671	0.79 (0.65, 0.97)	
No	1110/3035	1212/2998	0.86 (0.79, 0.93)	
LABA				0.84
Yes	740/1910	807/1891	0.86 (0.78, 0.95)	
No	537/1797	607/1778	0.84 (0.75, 0.95)	
Tiotropium				0.11
Yes	478/1131	490/1110	0.93 (0.82, 1.05)	
No	799/2576	924/2559	0.81 (0.74, 0.89)	
Anticholinergics [‡]				0.41
Yes	770/2002	826/1985	0.88 (0.79, 0.97)	
No	507/1705	588/1684	0.82 (0.73, 0.92)	
Tiotropium + LABA				0.19
Yes	308/676	310/656	0.94 (0.80, 1.10)	
No	969/3031	1104/3013	0.83 (0.76, 0.90)	
LABA + ICS				0.62
Yes	648/1606	700/1597	0.87 (0.78, 0.97)	
No	629/2101	714/2072	0.84 (0.75, 0.93)	

Tiotropium + LABA + ICS				0.22
Yes	277/602	274/578	0.94 (0.80, 1.11)	
No	1000/3105	1140/3091	0.83 (0.76, 0.90)	

n=number of patients with at least one exacerbation (onset during actual treatment); N=total number of patients.

*Based on subgroup-wise Cox regression with treatment as covariate.

†Maintenance naïve means that patients were not receiving any of the following treatments at baseline: ICS, systemic corticosteroids, xanthines, anticholinergics (short- or long-acting), LABA.

‡Short- or long-acting anticholinergics.

LABA=long-acting beta-agonist; ICS=inhaled corticosteroid.

Section 4B: Post-hoc subgroup analysis by geographical region – time to first COPD exacerbation

Region**	Tiotropium		Salmeterol		Hazard ratio* (95% CI) Tiotropium vs. Salmeterol
	N	n (%)	N	n (%)	
Eastern Europe	2449	801 (32.7)	2412	878 (36.4)	0.87 (0.79, 0.95)
Mediterranean countries	263	110 (41.8)	256	127 (49.6)	0.81 (0.62, 1.04)
Nordic countries	70	34 (48.6)	75	37 (49.3)	0.81 (0.51, 1.29)
Western Europe	925	332 (35.9)	926	372 (40.2)	0.83 (0.72, 0.97)

n=number of patients with at least one exacerbation (onset during actual treatment); N=total number of patients.

Subgroup-by-treatment interaction P-value 0.92 (Cox regression).

*Based on subgroup-wise Cox regression with treatment as covariate.

****Eastern Europe:** Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia, Ukraine; **Mediterranean countries:** Israel, Italy, Portugal, Spain, Turkey; **Nordic Countries:** Denmark, Finland, Norway; **Western Europe:** Austria, Belgium, France, Germany, Netherlands, United Kingdom.

Section 4C: Post-hoc subgroup analysis by geographical region – number of COPD exacerbations

Region*	Tiotropium		Salmeterol		Rate ratio (95% CI) Tiotropium vs. Salmeterol
	N	Rate [†] (95% CI)	N	Rate [†] (95% CI)	
Eastern Europe	2449	0.54 (0.51, 0.58)	2412	0.62 (0.58, 0.66)	0.88 (0.80, 0.96)
Mediterranean countries	263	1.02 (0.87, 1.18)	256	1.12 (0.96, 1.30)	0.91 (0.74, 1.13)
Nordic countries	70	1.38 (1.06, 1.79)	75	1.43 (1.09, 1.86)	0.97 (0.67, 1.41)
Western Europe	925	0.76 (0.69, 0.84)	926	0.84 (0.77, 0.93)	0.90 (0.79, 1.03)

Poisson regression correcting for overdispersion and adjusted for treatment exposure (treated set); events with onset during actual treatment. Subgroup-by-treatment interaction P-value 0.95.

***Eastern Europe:** Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia, Ukraine; **Mediterranean countries:** Israel, Italy, Portugal, Spain, Turkey; **Nordic Countries:** Denmark, Finland, Norway; **Western Europe:** Austria, Belgium, France, Germany, Netherlands, United Kingdom.

[†]Mean adjusted rate of exacerbations per patient year.

Section 5: Genotyping and daily peak flow

Genotyping

Genotyping of two genetic polymorphisms B16 (ARG16GLY) and B27 (GLN27GLU) was performed in patients (tiotropium arm n=2564; salmeterol arm n=2561) who gave informed consent for genotyping. The results of the genotyping substudy will be reported separately.

Daily Peak Flow

Patient recorded once daily peak flow measurements throughout the 2-week run-in period, and during the first 4 months of the randomized treatment period. Morning measurements were performed immediately upon arising after the patient had cleared out mucus and prior to administration of trial and/or rescue medication. The best of 3 readings for each measurement was recorded. The results will be reported separately.

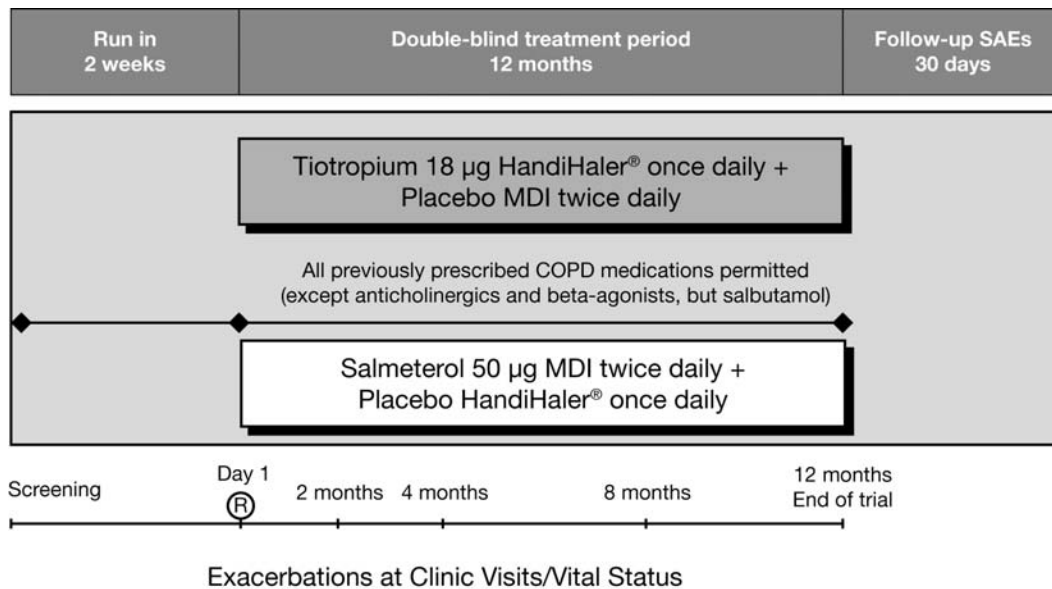
Section 6: Patient exclusion criteria

- Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may have put the patient at risk because of participation in the study or may have influenced either the results of the study or the patients' ability to participate in the study
- Patients with a diagnosis of asthma
- Patients with a life-threatening pulmonary obstruction, or a history of cystic fibrosis
- Patients with known active tuberculosis
- Patients with a known symptomatic prostatic hyperplasia or bladder neck obstruction
- Patients with symptomatically-controlled prostatic hyperplasia on medication might have been included and should have continued their medication.
- Patients with known narrow-angle glaucoma
- Patients with a history of myocardial infarction within the year prior to Visit 1
- Patients with a history of hospital admission for heart failure within the year prior to Visit 1
- Patients with cardiac arrhythmia that required medical or surgical treatment
- Patients with severe cardiovascular disorders

- Patients with a known hypersensitivity to anticholinergic drugs, beta-adrenergics, lactose or any other component of the medication delivery system
- Patients with known moderate or severe renal insufficiency (known creatinine clearance of ≤ 50 mL/min)
- Patients with untreated known hypokalaemia
- Patients with untreated known thyrotoxicosis
- Patients with brittle/unstable diabetes mellitus
- Patients with a history of and/or active significant alcohol or drug abuse. See exclusion criterion 1
- Patients who had taken an investigational drug within 30 days or 6 half-lives (whichever is greater) prior to Visit 1
- Use of systemic corticosteroid medication at unstable doses (i.e., less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisolone per day or 20 mg every other day
- Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm or subdermal implants such as Norplant) for at least 3 months prior to, and for the duration of the trial
- Previous participation (receipt of randomized treatment) in this study
- Patients who were participating at the same time in another study

- Patients with any respiratory infection or COPD exacerbation in the 4 weeks prior to Visit 1 or during the run-in period should have been postponed. In the case of a respiratory infection or COPD exacerbation during the run-in period, the run-in period could have been extended up to 4 weeks

Section 7: Trial design



R=randomization; SAEs=serious adverse events; MDI=metered-dose inhaler; COPD=chronic obstructive pulmonary disease.

Section 8: Randomization and blinding procedures

A randomization list was generated by the sponsor using a validated system involving a pseudo-random number generator. Patients were randomized to treatment via an Interactive Voice Response System (Perceptive Informatics Inc., Berlin, Germany). Patients were randomized in a 1:1 ratio in blocks of four, with equal allocation of treatment within each block per country site.

Blinding was maintained by allocation of a dummy placebo MDI to those randomized to the tiotropium arm and a dummy placebo HandiHaler to those in the salmeterol arm. Tiotropium and placebo capsules were identical in size and colour and were therefore indistinguishable.

Section 9: Statistical analysis – sample size determination

Sample size was based on meta-analyses of previous clinical studies. To derive an assumption about the proportion of patients treated with tiotropium who had at least one exacerbation after 12 months, nine trials using the same definition of an exacerbation as POET-COPD and with durations of between 6 months and one year (Boehringer Ingelheim clinical trial reference numbers 114/117,¹ 115/128,¹ 130,² 137,² 214,³ 259,⁴ 266,⁵ 256,⁶ 270⁷) were analyzed. This resulted in a Kaplan-Meier estimate at week 46 of 0.421 with a 95% confidence interval of (40.015%, 44.159%). Thus it was reasonable to assume that the percentage of patients treated with tiotropium and experiencing at least one COPD exacerbation within 52 weeks would be at least 40%.

Three previous head-to-head comparisons available at the time of the planning of POET-COPD between tiotropium and salmeterol of 3–6 months duration^{1,8} were used to substantiate the choice of a hazard ratio between tiotropium and salmeterol of 0.9 for sample size calculations.

One blinded interim analysis was planned in the POET-COPD protocol to assess event rates during the conduct of the study and to increase the sample size when the overall event rate turns out to be too small. The results of the conducted interim analysis indicated an event rate to experience at least one exacerbation within 12 months about 2% lower than assumed. This led to the decision to increase the total sample size from 6,800 to 7,350.

References:

1. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217-224.
2. Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;58:399-404.
3. Dusser D, Bravo M-L, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J* 2006;27:547-555.
4. Chan CKN, Maltais F, Sigouin C, Haddon JM, Ford GT. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. *Can Respir J* 2007;14:465-472.
5. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143:317-326.
6. Tonnel AB, Perez T, Grosbois J-M, Verkindre C, Bravo M-L, Brun M on behalf of the TIPHON study group. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. *Int J Chron Obstruct Pulmon Dis* 2008;3:301-310.
7. Powrie DJ, Wilkinson TM, Donaldson GC, Jones P, Scrine K, Viel K, Kesten S, Wedzicha JA. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in chronic obstructive pulmonary disease. *Eur Respir J* 2007;30:472-478.

8. Briggs DD, Covelli H, Lapidus R, et al. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulm Pharmacol Ther* 2005;18:397-404.

Section 10: Committees

Name of Committee	Purpose	Members
Data Safety Monitoring Board	Evaluate accrued data and determine, based on safety data, whether study should continue	Paul Corris, MD Department of Respiratory Medicine, Freeman Hospital Newcastle upon Tyne, United Kingdom Frans Van de Werf, MD Cardiology Division, U.Z. Gasthuisberg Leuven, Belgium Stephen Senn, Ph.D. Department of Statistics, University of Glasgow Glasgow, United Kingdom Michael Rudolf, MD Department of Respiratory Medicine, Ealing Hospital Southall, United Kingdom
Mortality Adjudication Committee	Provide consistent, systematic, and independent assessment of the primary cause of death (blinded to treatment group) by	Norbert Krug, MD Fraunhofer Institute for Toxicology and Experimental Medicine Hannover, Germany

reviewing the information provided in the Council for International Organisation of Medical Sciences (CIOMS) form for each patient.

Two adjudication meetings were held.

F Joachim Meyer, MD
Heidelberg University Hospital
Heidelberg, Germany

Matthias John, MD
Medical practice at Asklepios Hospital Uckermark
Schwedt/Oder, Germany

Steering Committee Advise on protocol amendments, interim analyses, subgroup analyses, health economic analysis, publication of trial design, and publication of primary publication

Claus Vogelmeier, MD
Hospital of the Universities of Giessen and Marburg
Marburg, Germany

Kai-Michael Beeh, MD
insaf Respiratory Research Institute
Wiesbaden, Germany

Maureen Rutten-van Mólken, PhD
Institute for Medical Technology Assessment, Erasmus
Medical Centre
Rotterdam, The Netherlands

Section 11: Coexisting conditions at baseline in ≥5% patients (in any treatment group) by MedDRA system organ class

System Organ Class	Tiotropium (N = 3707) n (%)	Salmeterol (N = 3669) n (%)	Total (N = 7376) n (%)
Total with any comorbid condition	3003 (81.0)	2982 (81.3)	5985 (81.1)
Vascular disorders*	1880 (50.7)	1890 (51.5)	3770 (51.1)
Cardiac disorders	979 (26.4)	941 (25.6)	1920 (26.0)
Metabolism and nutrition disorders	905 (24.4)	847 (23.1)	1752 (23.8)
Musculoskeletal and connective tissue disorders	707 (19.1)	673 (18.3)	1380 (18.7)
Gastrointestinal disorders	647 (17.5)	592 (16.1)	1239 (16.8)
Respiratory, thoracic and mediastinal disorders	516 (13.9)	556 (15.2)	1072 (14.5)
Nervous system disorders	342 (9.2)	340 (9.3)	682 (9.2)
Infections and infestations	353 (9.5)	321 (8.7)	674 (9.1)
Surgical and medical procedures	242 (6.5)	260 (7.1)	502 (6.8)
Reproductive system and breast disorders	228 (6.2)	265 (7.2)	493 (6.7)
Psychiatric disorders	209 (5.6)	187 (5.1)	396 (5.4)
Hepatobiliary disorders	201 (5.4)	170 (4.6)	371 (5.0)

*Predominantly hypertension.

MedDRA= Medical Dictionary for Regulatory Activities.

Section 12: Incidence rates and incidence rate ratios (95% confidence intervals) for serious adverse events in $\geq 0.5\%$ of the population by preferred term*

Preferred Term	Tiotropium (N = 3707)		Salmeterol (N = 3669)		Rate ratio (95% CI) Tiotropium vs. Salmeterol
	N (%)	Rate [†]	N (%)	Rate [†]	
COPD	270 (7.3)	7.77	335 (9.1)	10.03	0.77 (0.66, 0.91)
Pneumonia	54 (1.5)	1.50	64 (1.7)	1.84	0.82 (0.57, 1.18)
Cardiac failure	17 (0.5)	0.47	21 (0.6)	0.60	0.79 (0.41, 1.49)
Myocardial infarction	20 (0.5)	0.55	13 (0.4)	0.37	1.50 (0.74, 3.02)
Respiratory failure	16 (0.4)	0.44	20 (0.5)	0.57	0.78 (0.40, 1.50)

*Preferred term (PT) according to the Medical Dictionary for Regulatory Affairs. Listed are PTs that were reported by $\geq 0.5\%$ of patients in either study group with onset during the on treatment period plus 30 days after last dose of treatment.

[†]Incidence rate (per 100 patient-years).

COPD=chronic obstructive pulmonary disease.

Section 13A: Mortality – all-cause

Patients, n (%)	Tiotropium (N=3707)	Salmeterol (N=3669)	Hazard Ratio* (95% CI)	P value†
On treatment + 30 days	66 (1.8)	73 (2.0)	0.85 (0.61, 1.19)	0.35
Planned treatment (date of death ≤360 days)	64 (1.7)	78 (2.1)	0.81 (0.58, 1.13)	0.21

On treatment + 30 days: Number of deaths with onset during on treatment + 30 days.

Planned treatment: Date of death ≤day 360 (includes vital status collection of prematurely discontinued patients).

*Hazard ratio (tiotropium/salmeterol) calculated using Cox regression with treatment as a covariate.

†Based on Wald's chi-square test.

Section 13B: Mortality – fatal events by MedDRA system organ class (planned treatment)

Patients, n (%)	Tiotropium (N=3707)	Salmeterol (N=3669)
Total with fatal events	64 (1.7)	78 (2.1)
Cardiac	8 (0.2)	6 (0.2)
Gastrointestinal	2 (0.1)	2 (0.1)
General*	16 (0.4)	25 (0.7)
Infections	7 (0.2)	5 (0.1)
Injury, poisoning and procedural complications	1 (0.0)	1 (0.0)
Neoplasm	12 (0.3)	13 (0.4)
Nervous system	2 (0.1)	3 (0.1)
Psychiatric	1 (0.0)	2 (0.1)
Respiratory	13 (0.4)	20 (0.5)
Surgical and medical procedures	1 (0.0)	0 (0.0)
Vascular disorders	1 (0.0)	1 (0.0)

Planned treatment: Date of death prior to day 360 (includes vital status collection of prematurely discontinued patients, adjudicated primary cause of death.

MedDRA= Medical Dictionary for Regulatory Activities.

*Including death of unknown cause, sudden death and sudden cardiac death.

Section 13C: Mortality – fatal events by MedDRA system organ class (on treatment + 30 days)

Patients, n (%)	Tiotropium (N=3707)	Salmeterol (N=3669)
Total with fatal events	66 (1.8)	73 (2.0)
Cardiac	8 (0.2)	6 (0.2)
Gastrointestinal	2 (0.1)	2 (0.1)
General*	14 (0.4)	20 (0.5)
Infections	8 (0.2)	5 (0.1)
Injury, poisoning and procedural complications	1 (0.0)	1 (0.0)
Neoplasm	14 (0.4)	16 (0.4)
Nervous system	2 (0.1)	2 (0.1)
Psychiatric	1 (0.0)	1 (0.0)
Respiratory	15 (0.4)	19 (0.5)
Vascular disorders	1 (0.0)	1 (0.0)

On treatment + 30 days: Number of deaths with onset during on treatment + 30 days, adjudicated primary cause of death.

MedDRA= Medical Dictionary for Regulatory Activities.

*Including death of unknown cause, sudden death and sudden cardiac death.