

## Tiotropium Respimat (Spiriva Respimat) Abbreviated Review

VA Pharmacy Benefits Management Services,  
Medical Advisory Panel, and VISN Pharmacist Executives

*The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.*

### Introduction

Tiotropium Respimat is a propellant-free, multi-dose hand-held inhaler soft mist inhaler (SMI). The SMIs provide multi-dose medication using liquid formulations similar to that used in nebulizers and are propellant-free. The only other commercially available SMI at this time are ipratropium/albuterol (Combivent) and olodaterol.

Concern regarding the safety of tiotropium Respimat was raised when meta-analyses of clinical trials showed that tiotropium Respimat was associated with increased mortality relative to placebo. As a result of these concerns, the manufacturer conducted long-term safety trial (mean follow-up 2.3 years) comparing tiotropium Respimat 2.5mcg and 5mcg to tiotropium HandiHaler 18mcg in more than 17,000 patients. The primary focus of this review is to compare tiotropium Respimat to the Handihaler with a particular emphasis on safety.

### Pharmacokinetics

A dedicated pharmacokinetic study in patients with COPD comparing tiotropium Respimat 5mcg once daily and tiotropium HandiHaler 18mcg once daily found similar systemic exposure between the 2 products.

### FDA Approved Indication(s)

Tiotropium Respimat is approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD.

Do not use for relief of acute symptoms (i.e., rescue therapy for acute episodes of bronchospasm)

### Dosing/Administration

- Two inhalations once daily; total daily dose 5mcg
- Do not exceed more than 1 dose (2 inhalations) in 24 hours
- See package insert for instructions on preparing the inhaler prior to first use and after periods of non-use.
- No dosage adjustments needed for hepatic or renal impairment or geriatric patients. However, patients with moderate-severe renal impairment (creatinine clearance < 60mL/min) should be monitored closely for anticholinergic effects.
- After assembly, tiotropium Respimat should be discarded at the latest 3 months after first use or when the clicking mechanism is engaged, whichever occurs first.

### Dosage Form/Strengths and Handling

Tiotropium Respimat: 2.5mcg tiotropium per actuation

### Efficacy

The efficacy review is limited to the three 1-year trials comparing tiotropium Respimat to placebo and the head-to-head trial comparing tiotropium via Respimat vs. HandiHaler.

The 1-year trials were similar in design. Patients were required to be  $\geq 40$  years old, have a post bronchodilator FEV1/FVC ratio  $\leq 0.70$ , pre-bronchodilator FEV1  $\leq 60\%$  predicted, and  $\geq 10$  pack-year smoking history. Rescue albuterol and stable doses of concomitant medications as shown in **Table 1** were allowed.

The mean demographic and baseline characteristics of patients in the 1-year trials include: 64 years old, 77% male, 36% current smokers, 45 pack-years smoking history, FEV1 1.1L, pre-albuterol FEV1 39% of predicted, FEV1/FVC 0.47, and 15-20% reversibility.

Entry criteria and patient demographics for the TIOSPIR trial are described in the ADVERSE EVENTS section.

**Table 1: Clinical Trials**

Study	n	Duration	Treatment Arms	Concomitant medications
Bateman 2010a*	1990	1-year	TIO Respimat 5mcg, 10mcg, placebo	ICS, theophylline, mucolytics, antileukotrienes
Bateman 2010b	3991	1-year	TIO Respimat 5mcg, placebo	All respiratory medications other than inhaled anticholinergics
Wise 2013 (TIOSPIR)	17,135	2-3 years Mean 2.3	TIO Respimat 2.5mcg, 5mcg, TIO HandiHaler 18mcg	LABA, ICS

\*Combination of 2 identically designed studies

#### Pulmonary Function, Dyspnea, Quality of Life

Trough FEV1 was used to evaluate pulmonary function. Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). The SGRQ is widely used in clinical trials to measure symptoms, activities, and impact of COPD on daily life as reported by patients. An improvement in score of  $\geq 4$  units is considered to be clinically meaningful. The transitional dyspnea index (TDI) score is used to assess dyspnea. For the TDI, a difference in score of  $\geq 1$  unit is considered to be clinically meaningful. There was significantly greater improvement in pulmonary function, quality of life, dyspnea, and need for rescue inhaler use with tiotropium Respimat relative to placebo (**Table 2**).

A substudy of 1370 patients in the TIOSPIR trial showed that trough FEV1 with tiotropium Respimat was noninferior to tiotropium Handihaler (difference -10mL; 95%CI -38 to 18mL).

**Table 2: Efficacy**

Treatment Arms	N	Treatment Difference vs. Placebo			
		Trough FEV1 (ml)	SGRQ	Dyspnea	Rescue albuterol (puffs/day)
Bateman 2010a*					
TIO RESP 5mcg	670	127 $\pm$ 13 <sup>^</sup>	-3.5 $\pm$ 0.7 <sup>^</sup>	1.05 $\pm$ 0.17 <sup>^</sup>	-0.6 $\pm$ 0.1 <sup>^</sup>
TIO RESP 10mcg	667	150 $\pm$ 13 <sup>^</sup>	-3.8 $\pm$ 0.7 <sup>^</sup>	1.08 $\pm$ 0.17 <sup>^</sup>	-0.7 $\pm$ 0.1 <sup>^</sup>
Placebo	653				
Bateman 2010b					
TIO RESP 5mcg	1889	168 [141, 196] <sup>^</sup>	-2.9 [-3.9, -2.0] <sup>^</sup>	N/A	N/A
Placebo	1870				

\*Combined results of 2 identically designed studies

<sup>^</sup>Significant vs. placebo

Abbreviations: SGRQ=St. George's Respiratory Questionnaire; TIO RESP=tiotropium Respimat

#### COPD Exacerbations

COPD exacerbations were evaluated in the 1-year and TIOSPIR trials. A recent history of COPD exacerbation was not required as an entry criterion. Relative to placebo, there were significantly fewer exacerbations and a longer time to first exacerbation in patients receiving tiotropium (**Table 3**). In the TIOSPIR trial, there was no difference in COPD exacerbations between tiotropium Respimat and HandiHaler (**Table 4**).

**Table 3: COPD Exacerbations in 1-year Trials**

	Bateman 2010a			Bateman 2010b	
	TIO RESP 5mcg	TIO RESP 10mcg	Placebo	TIO RESP 5mcg	Placebo
≥1 exacerbation (%)	37.2	36.9	44.1	35.3	43.1
HR or OR [95%CI] relative to PBO	OR=0.75[0.60, 0.93]		-	HR=0.693[0.625, 0.769]	
Time to first exacerbation (days)	160	178	86	169	119
Exacerbation rate (per pt-yr)	0.93	1.02	1.91	0.69	0.87
RR [95%CI] relative to PBO	-	-	-	0.79[0.72, 0.87]	
Exacerbations requiring hospitalization (per pt-yr)	0.12	0.16	0.20	0.12	0.15
RR [95%CI] relative to PBO	-	-	-	0.81[0.70, 0.93]	

**Table 4: Risk of COPD Exacerbation in TIOSPIR Trial**

	TIO Respimat 2.5mcg (n=5724)	TIO Respimat 5mcg (n=5705)	TIO HandiHaler 18mcg (n=5687)
<b>Any exacerbation</b>			
Patients with event n(%)	2827 (49.4)	2733 (47.9)	2782 (48.9)
Number of events	6565	6425	6504
Rate (E per pt-yr) [95%CI]	0.59 [0.57, 0.62]	0.59 [0.56, 0.61]	0.59 [0.57, 0.61]
HR [95%CI] vs. HandiHaler	1.02 [0.96, 1.07]	0.98 [0.93, 1.03]	-
<b>Moderate or severe exacerbation</b>			
Patients with event n(%)	2769 (48.4)	2694 (47.2)	2732 (48)
Number of events	6423	6308	6362
Rate (E per pt-yr) [95%CI]	0.58 [0.56, 0.61]	0.58 [0.55, 0.60]	0.58 [0.55, 0.60]
HR [95%CI] vs. HandiHaler	1.01 [0.96, 1.07]	0.98 [0.93, 1.04]	-
<b>Severe exacerbation</b>			
Patients with event n(%)	869 (15.2)	826 (14.5)	811 (14.3)
Number of events	1316	1284	1216
Rate (E per pt-yr) [95%CI]	0.12 [0.11, 0.13]	0.12 [0.11, 0.13]	0.11 [0.10, 0.12]
HR [95%CI] vs. HandiHaler	1.07 [0.97, 1.18]	1.02 [0.93, 1.13]	-

### Patient Satisfaction

The Patient Satisfaction and Preference Questionnaire (PASAPQ) is a validated tool for evaluating inhaler satisfaction. The questionnaire is comprised of 3 sections; total PASAPQ score, preference, and willingness to continue. The total PASAPQ score has 2 domains; performance and convenience. A 10-point difference in the total PASAPQ score between devices is considered to be the minimum important difference (MID).

There are 2 comparative studies (active drugs ipratropium/fenoterol and budesonide) that used PASAPQ to evaluate inhaler satisfaction with Respimat versus other delivery devices in patients with COPD or asthma. The PASAPQ scores were higher for Respimat (MID met in Schurmann study) and more patients preferred and were willing to continue treatment with Respimat.

**Table 2: Patient Satisfaction**

Design	Disease	Treatment Arms	Duration	n	Total PASAPQ score	Preference	Willingness to continue <sup>§</sup>
Schurmann 2005 CO, OL	Asthma/ COPD	IPR+FEN via Respimat IPR+FEN via HFA-MDI	7 weeks per arm	224	83.7±14.6 (Respimat) 72.9±15.7 (HFA-MDI)	80.6% (Respimat) 19.4% (HFA-MDI)	85% (Respimat) 50% (HFA-MDI)
Hodder 2009 R, DB, DD	Asthma	BUD via Respimat BUD via Tubuhaler	12 weeks	153	85.5(Respimat) 76.9 (Turbuhaler)	73.7% (Respimat) 17.1% (Turbuhaler) 9.2% (no preference)	80 (Respimat) 62(Turbuhaler)

BUD=budesonide; CO=cross-over; DB=double-blind; DD=double-dummy; IPR+FEN=ipratropium + fenoterol; OL=open-label; R=randomized

<sup>§</sup>For Schurmann, % of patients willing to continue on each device is shown; for Hodder, a score for willingness to continue is shown

A small study conducted in Japanese patients with COPD evaluated switching from tiotropium HandiHaler to tiotropium Respimat (n=34). Four patients dropped out after the switch; 2 because of difficulty handling Respimat and 1 each for cough and feeling of discomfort. Among the remaining patients, 11 found Respimat much easier to use, 10 found it easier to use, and 8 felt it was the same as HandiHaler. When asked how they felt about switching

January 2015

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from HandiHaler to Respimat, 2 felt it was much better, 14 said it was better, and 13 said it was the same. There was no significant difference in FEV1, quality of life, or dyspnea. More patients reported cough initially after switching; however, this improved as patients became accustomed to the different inhalation technique.

### Adverse Events (Safety Data)

The UPLIFT trial did not show increased mortality with tiotropium HandiHaler compared to placebo (HR=0.87; 95% CI 0.76-0.99). However, a meta-analysis of 5 clinical trials (3 one-year and 2 twelve-week) by Singh et al., showed an increased risk of mortality associated with tiotropium Respimat compared to placebo in patients with COPD. In the overall group, deaths occurred in 90/3686 (2.4%) versus 47/2836 (1.7%) receiving tiotropium Respimat and placebo respectively [RR=1.52; 95% CI 1.06 to 2.16; p=0.02]. The 10mcg dose was associated with a higher risk than the 5mcg dose. The FDA review included 4 trials (3 one-year and 1 twenty-four week). There was a numerically higher risk with Respimat compared to placebo [HR=1.33; 95% CI 0.93 to 1.92]. **Table 5**

**Table 5: Mortality Risk of Tiotropium Respimat (Meta-analysis)**

			Overall	TIO10mcg	TIO5mcg
Singh	3 (1-year) trials 2 (12-week) trials	Relative Risk [95%CI]; p-value	1.52; [1.06 to 2.16]; p=0.02	2.15 [1.03 to 4.51]; p=0.04	1.46 [ 1.01 to 2.10]; p=0.04
FDA review	3 (1-year) trials 1 (24-week) trial	Hazard ratio[95%C]	-	-	1.33 [0.93, 1.92]

Risks are relative to placebo

The FDA analysis also looked at cause of death and found an excess of cardiovascular-related deaths with tiotropium Respimat [26 (0.9%) vs. 13 (0.4%) HR=2.00; 95% CI 1.03, 3.89] and those that were due to MI [9 (0.4%) vs 2 (0.1%) IRR=4.49; 95% CI 0.96, 20.96]. There were also more deaths due to neoplasm (10 vs. 3 IRR=3.32; 95% CI 0.92, 12.02). However, note the small number of patients with events and the wide confidence intervals for these outcomes. The risk for respiratory-related deaths was lower for tiotropium than placebo. (**Appendix**)

### Observational Study

A Dutch observational cohort study compared the risk of death in patients with COPD between tiotropium HandiHaler (n=9226) and Respimat (n=2827). Patients with baseline cardiovascular disease and renal failure were included; however, statistically more patients in the Respimat group had these comorbidities. The model was adjusted for several covariates (e.g., age, smoking, recent pneumonia, systemic steroid use, hospitalization for COPD, and physician visits in the previous year), but not for underlying cardiovascular disease. Use of Respimat was associated with an increased risk of death (HR=1.27; 95% CI 1.03, 1.57). The most common reason for death was cardiovascular-related followed by pulmonary-related. A sensitivity analysis found that those with coexisting cardiovascular disease had a higher risk of death (HR=1.36; 1.07, 1.73) than those who did not (HR=1.02; 1.06, 2.40).

### TIOSPIR Trial

In order to better understand the potential for risk, the TIOSPIR trial was conducted. This was a large (n=17,135) randomized, double-blind study comparing tiotropium Respimat 2.5mcg and 5mcg, and tiotropium HandiHaler 18mcg administered once daily. The primary safety endpoint was all-cause mortality using a non-inferiority analysis. The primary efficacy endpoint was risk of first COPD exacerbation using a superiority analysis. Cardiovascular safety was also assessed noting that patients with concomitant cardiac disease were included in the trial; however, those with a MI within the previous 6 months, hospitalized for class III or IV heart failure, or had unstable or life-threatening arrhythmia requiring new treatment within the previous 12 months were excluded. Additionally, patients with moderate-severe renal disease were excluded. This latter exclusion is important to note because including this population could potentially increase systemic exposure of tiotropium 5mcg via Respimat to that observed with the riskier 10mcg dose.

Approximately 71% of patients were males, mean age 65 years, current smoker 38%, and had a mean FEV1 48% of predicted value. Approximately 11% of patients had prior cardiac arrhythmia, 5.9% prior MI, 2.3% prior stroke, and 15% prior ischemic heart disease or coronary artery disease. Concomitant medications for COPD that were used during the trial were long-acting beta-agonists (68%) and inhaled steroids (68%).

The median duration of treatment for all 3 study groups was 835 days and the mean follow-up time was 2.3 years. Study drug exposure was similar for the 3 groups; 11,405, 11,343, and 11,337 patient-years for Respimat 2.5mcg, 5mcg, and HandiHaler 18mcg respectively.

Tiotropium Respimat was found to be noninferior to tiotropium HandiHaler regarding all-cause mortality. There were numerically more cardiovascular deaths with Respimat but the study was not powered to look at death due to specific causes. The risk of death was not increased in those with a cardiac history or a history of cardiac arrhythmias (**Table 6**). These findings cannot be extended to patients with more severe underlying cardiac disease as these patients were excluded from the trial.

**Table 6: Deaths (TIOSPIR trial)**

	TIO Respimat 2.5mcg (n=5730)	TIO Respimat 5mcg (n=5711)	TIO HandiHaler 18mcg (n=5694)
Death n(%)	440 (7.7)	423 (7.4)	439 (7.7)
HR [95%CI] vs. HandiHaler	1.00 [0.87, 1.14]	0.96 [0.84, 1.09]	-
Rate of death per 100 patient-years	3.35	3.22	3.36
Cardiovascular cause of death n(%)	119 (2.1)	113 (2.0)	101 (1.8)
HR [95%CI] vs. HandiHaler	1.17 [0.90, 1.53]	1.11 [0.85, 1.45]	-
Myocardial infarction n(%)	10 (0.2)	11 (0.2)	3 (0.1)
Sudden death n(%)	82 (1.4)	67 (1.2)	68 (1.2)
Stroke n(%)	10 (0.2)	14 (0.2)	11 (0.2)
Other CV cause n(%)	17 (0.3)	21 (0.4)	19 (0.3)
Death in those with previous cardiac arrhythmia n/N(%)	79/604 (13.1)	65/614 (10.6)	78/607 (12.9)
HR [95%CI] vs. HandiHaler	1.02 [0.74, 1.39]	0.81 [0.58, 1.12]	-
Respiratory cause n(%)	143 (2.5)	148 (2.6)	155 (2.7)
Neoplasm n(%)	110 (1.9)	100 (1.8)	95 (1.7)
Undetermined/unknown n(%)	35 (0.6)	27 (0.5)	37 (0.6)
Other cause n(%)	33 (0.6)	35 (0.6)	51 (0.9)

It is not clear why there were differences in mortality risk in the meta-analysis of Respimat placebo-controlled trials and TIOSPIR and UPLIFT trials. Study design, entry criteria, patient demographics, lack of patient level data may explain the difference (**Appendix**). For example, moderate-severe renal impairment was an exclusion criterion for the TIOSPIR and UPLIFT trials whereas the placebo-controlled tiotropium Respimat trials allowed inclusion. Tiotropium is renally eliminated and those with renal impairment may have had increased drug exposure, potentially putting them at greater risk for events. There were also slightly more patients with GOLD stage IV COPD and history of cardiac arrhythmias in the Respimat placebo-controlled trials; however, there were more patients with a history of MI in the TIOSPIR trial.

#### Major Adverse Cardiovascular Events (MACE)

MACE was defined as the composite of any MI, stroke or TIA event, and any cardiovascular death. Based on the FDA meta-analysis and TIOSPIR, there was no increased risk of MACE with tiotropium Respimat (**Appendix**).

#### Other Cardiovascular Events

The FDA meta-analysis showed a numerically a higher incidence of fatal and nonfatal arrhythmias with tiotropium Respimat relative to placebo; bradyarrhythmias were more common. In TIOSPIR, there was no increased risk of arrhythmias (including bradyarrhythmias) with Respimat versus HandiHaler. Similar results were observed for tiotropium HandiHaler and placebo in UPLIFT (**Appendix**).

The incidence rates for fatal and nonfatal ischemic heart disease were similar for tiotropium Respimat and placebo and Respimat and Handihaler (**Appendix**).

#### Contraindications

Hypersensitivity to tiotropium or ipratropium, or any component of this product

## Summary

Compared to placebo, tiotropium Respimat improved pulmonary function, dyspnea, quality of life, and reduced the need for rescue albuterol and rate of COPD exacerbations. The TIOSPIR trial showed comparable improvement in pulmonary function and no difference in risk for COPD exacerbations between tiotropium Respimat and HandiHaler.

However, meta-analyses indicate a greater mortality risk with tiotropium Respimat relative to placebo and an observational trial found greater risk with tiotropium Respimat relative to HandiHaler. In contrast, the large, blinded and randomized TIOSPIR trial showed that the risk of all-cause mortality was comparable between tiotropium Respimat and tiotropium HandiHaler.

A greater risk for cardiovascular mortality was observed with tiotropium Respimat vs. placebo in the FDA meta-analysis; in TIOSPIR, there were numerically more CV deaths with Respimat. Both the FDA meta-analysis and TIOSPIR trial showed more deaths due to MI with tiotropium Respimat. The overall number of events in these secondary analyses was small and the confidence intervals for the risks were wide, and none of these trials were powered to look at specific causes of mortality.

In the TIOSPIR and UPLIFT trials, patients with significant cardiovascular disease and/or moderate-severe renal impairment were excluded and the results cannot be generalized to this population.

**Table 7: Summary of Deaths among Studies**

	FDA vital status database meta-analysis*	Singh meta-analysis <sup>^</sup>	TIOSPIR	UPLIFT
	Respimat 5mcg vs. PBO	Respimat 5mcg vs. PBO	Respimat 5mcg vs. HandiHaler 18mcg	HandiHaler 18mcg vs. PBO
All-Cause Mortality	68 (2.2%) vs. 51 (1.7%) HR=1.33 [0.93-1.92]	RR=1.46 [1.01, 2.10]	423 (7.4%) vs. 439 (7.7%) HR=0.96 [0.84-1.09]	430 (14.4%) vs. 491 (16.3%) HR=0.87 [0.76-0.99]
CV Mortality	26 (0.9%) vs. 13 (0.4%) HR=2.00 [1.03-3.89]	N/A	113 (2%) vs. 101 (1.8%) HR=1.11 [0.85-1.45]	70 (2.5%) vs. 101 (3.4%) HR=0.75 [0.56-1.01]
Deaths due to MI	9 (0.35%) vs. 2(0.08%) IRR=4.49 [0.96-20.96]	N/A	11 (0.2%) vs. 3 (0.1%) IRR=3.64 [1.02-13.06]	11 (0.10%) vs. 14 (0.13%) IRR=0.78 [0.35-1.72]

\*FDA vital status database: 3 one-year trials (Bateman) + 24-week trial

<sup>^</sup>Singh: 3 one-year trials (Bateman) + 2 twelve-week trials (Voshaar)

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FDA Advisory Committee Briefing Document TIOTROPIUM RESPIMAT

<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm409201.pdf>

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January 2015**

**Appendix: Comparison of Meta-analysis, TIOSPIR and UPLIFT trials**

	<b>Respirat PC trials (FDA analysis) (Respirat 5mcg/Placebo)</b>	<b>TIOSPIR (Respirat 5mcg/HandiHaler)</b>	<b>UPLIFT (HandiHaler/Placebo)</b>
COPD duration (yrs)	8.4/8.5	7.5/7.4	9.9/9.7
GOLD stage II (%)	37/38	48/48	46/45
GOLD stage III (%)	46/46	40/40	43/44
GOLD stage IV (%)	14/14	10/11	8/8.5
<b>Baseline cardiac history</b>			
Myocardial infarction	3.2/3.3	5.9/6.1	3.2/2.5
Stroke/TIA	5.7/5.4	3.9/3.4	5.3/4.8
Cardiac arrhythmia	13.3/10.5	10.8/10.7	7.1/6.5
Conduction disorders	4.7/3.2	5.0/5.1	0.5/0.7
Heart failure	3.5/3.1	7.8/7.6	4.8/4.6
IHD/CAD	13.8/14.4	15/15.7	17/16.3
Renal function	^^Pts. with mild (46%), moderate (20.2%), and severe renal impairment (0.6%)	Patients with moderate-severe renal impairment excluded	Patients with moderate-severe renal impairment excluded
Deaths	68 (2.2%) vs. 51 (1.7%) HR=1.33 [0.93-1.92] 2.63 vs. 1.98 E/100 pt-yrs	423 (7.4%) vs. 439 (7.7%) HR=0.96 [0.84-1.09]	430 (14.4%) vs. 491 (16.3%) HR=0.87 [0.76-0.99]
	Excess mortality in those with known rhythm disorder	No mortality difference between groups for those with cardiac rhythm disorders	No mortality difference between groups for those with cardiac rhythm disorders
CV deaths	26 (0.9%) vs. 13 (0.4%) HR=2.00 [1.03-3.89]	113 (2%) vs. 101 (1.8%) HR=1.11 [0.85-1.45]	70 (2.5%) vs. 101 (3.4%) HR=0.75 [0.56-1.01]
Fatal MI	9 (0.35%) vs. 2(0.08%) IRR=4.49 [0.96-20.96]	11 (0.2%) vs. 3 (0.1%) IRR=3.64 [1.02-13.06]	11 (0.10%) vs. 14 (0.13%) IRR=0.78 [0.35-1.72]
MACE	^^IRR=0.90 [0.60-1.34] ^^IRR=0.73 [0.38-1.39]	HR=1.10 [0.91-1.33] Time to first MI HR=1.40 [0.98-2.00]	**IRR=0.86[0.74, 1.01] **IRR=0.87 [0.67-1.14]
MI (fatal + nonfatal)		MI per standard AE reporting HR=1.02 [0.85-1.23]	
	Incidence less for TIO vs. PBO	Time to first stroke similar for Respirat and HandiHaler	**Incidence similar between HandiHaler and PBO
Stroke (fatal + nonfatal)		Time to first TIA HR=1.50 [0.85-2.64]	
		Stroke per standard AE reporting: no difference between groups	
Arrhythmias (fatal + non-fatal)	^^SAE: IRR=1.52 [0.87-2.66] ^^Any: IRR=1.20 [0.94, 1.52]	SAE: IRR=0.97 [0.75-1.25] Any: IRR= 1.00 [0.81, 1.24]	**SAE: IRR=0.84 [0.69-1.02] **Any: 0.92 [0.81, 1.24]
	^^Bradycardias more common IRR=1.82[1.04-3.16]	No differences in incidence of bradycardias	**No differences in incidence of bradycardias
IHD (fatal + nonfatal)	^^IRR=1.18 [0.73, 1.92]	IRR=1.15 [0.91, 1.47]	IRR=0.82 [0.67, 0.99]
Neoplasm deaths	IRR=3.32[0.92-12.02] 10 vs. 3 deaths	IRR=1.05 [0.79-1.38]	IRR=0.97 [0.75-1.25]
Neoplasms	IRR=1.42 [0.97-2.07]	IRR=1.10 [0.93-1.30]	IRR=0.99 [0.85-1.15]
Respiratory deaths	IRR=0.85 [0.39-1.85]	IRR=0.94 [0.73-1.20]	IRR=0.76[0.6-0.97]

^^Based on FDA on-treatment database of 7 trials (includes the 4 trials used in the mortality analysis + 2 twelve-week and 1 four week trial)

\*\*Data obtained from meta-analysis of 28 HandiHaler placebo-controlled trials including the UPLIFT trial