

e-Table 1: Inclusion and exclusion criteria of the TIOSPIR trial

	Category	Explicit criterion	Code /Unit	Category	Explicit Threshold	Code/ Applicable in KVB	Code Unit used in KVB	Category/ Explicit used in KVB	Code/ Threshold
Inclusion Criteria	Sex	Sex	Male/Female		Male/Female	Yes	Male/Female	Male/Female	
	Age	Age	Years		≥40	Yes	Years	40	
	Lifestyle	Current or Ex-Smokers	Pack-years		≥10	No ¹	-	-	
	Clinical diagnosis	COPD	Yes		Yes	Yes	ICD-10-GM	J44.-	
	Post-bronchodilator spirometry	FEV1/FVC ratio	NA		0.70	No	-	-	
	Post-bronchodilator spirometry	FEV1 % of predicted	NA		≤70	No ²	-	-	
	Study ability	Ability to use both the HandiHaler® and Respimat® devices	Yes / no		Yes	No	-	-	
Exclusion criteria	Co-morbidities	Significant diseases other than COPD that put the patient at risk for participation in the study or that might interfere with participation in the study	Yes / No		No	No	-	-	
	Concomitant cardiovascular disease	Myocardial infarction within the last 6 months	Yes / No		No	Yes	ICD-10-GM	I21, I22, I25.20	
		Hospitalization for cardiac failure (NYHA Class III or IV) during the last year	Yes / No		No	Yes ³	ICD-10-GM	I50.14	
		Unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year	Yes/No		No	Yes ⁴	ICD-10-GM	I44.2, I45.9, I46, I47.0, I47.2, I49.0	
	Other significant lung diseases	Known active tuberculosis	Yes/No		No	Yes	ICD-10-GM	A15, A16, A17, A18, A19	
		Asthma	Yes/No		No	Yes	ICD-10-GM	J45, J46	
		Cystic fibrosis	Yes/No		No	Yes	ICD-10-GM	E84	
		Clinically evident bronchiectasis (not excluded for radiographic evidence of bronchiectasis if they were not being treated for this condition)	Yes/No		No	Yes	ICD-10-GM	J47	
		Interstitial lung disease	Yes/No		No	Yes	ICD-10-GM	J60-J70, J80, J82, J84	
		Resectional lung surgery	Yes/No		No	No	-	-	
		Pulmonary thromboembolic disease	Yes/No		No	Yes	ICD-10-GM	I26	
	Cancer	Malignancies (other than treated basal cell carcinoma) requiring therapy within the last 5 years (resection, radiation, chemotherapy, or biological treatments)	Yes/No		No	Yes ⁵	ICD-10-GM	C00-C97 except C44	
	Others	Known moderate to severe renal impairment (as judged by the investigator)	Yes/No		No	Yes	ICD-10-GM	N18.0, N18.83, N18.84	
		Drug abuse within the past 12 months	Yes/No		No	Yes	ICD-10-GM	F11.2, F12.2, F13.2, F19.0	
		Significant alcohol abuse within the past 12 months	Yes/No		No	Yes	ICD-10-GM	F10, K70, Z72.0	
Known hypersensitivity to anticholinergic		Yes/No		No	(Yes)	ICD-10-GM	E73.-		

Category	Explicit criterion	Code /Unit	Category	Explicit Threshold	Code/ Applicable in KVB	Code Unit used in KVB	Category/ Explicit used in KVB	Code/ Threshold
	drugs, lactose, or other components of the HandiHaler® or Respimat® inhalation solution delivery system							
	Known narrow angle glaucoma	Yes/No	No		Yes	ICD-10-GM	H40.2	
	Known significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Subjects whose symptoms were controlled on treatment may have been included.	Yes/No	No		Yes	ICD-10-GM	N32.0	
	Pregnancy	Yes/No	No		No	-	-	
	Lactation	Yes/No	No		No	-	-	
	Child-bearing potential not on contraceptives	Yes/No	No		Yes	ATC	No G03A	
						Age	≤ 45 years	
Unstable COPD								
	Plans for lung transplantation or lung volume reduction surgery	Yes/No	No		No	-	Z94.2, Z94.3, T86.3, T86.81, U55.2, U55.3	
	Use of supplemental oxygen for more than 12 hours per day	Yes/No	No		No	-	-	
	Completion of a pulmonary rehabilitation program in the 6 weeks prior to the screening visit or subjects who were currently in a pulmonary rehabilitation program that was not maintained throughout the duration of the study	Yes/No	No		No	-	-	
	Unstable dose of systemic corticosteroid medication (i.e. less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisolone per day	Yes/No	No		No ⁶	-	-	
Others								
	Current participation in an interventional study	Yes/No	No		No	-	-	
	Intake of an investigational drug within 30 days prior to the Screening visit	Yes/No	No		No	-	-	
	Previous participation in this study (receipt of randomised treatment)	Yes/No	No		No	-	-	

Legend: NA, not applicable; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICD-10-GM, International Statistical Classification of Diseases and Related Health Problems – Version 10 (German modification); KVB, Association of Statutory Health Insurance Physicians, Bavaria, Germany. ¹ In a pilot analysis, only a small number of patients (<0.01%) was documented with smoking-related ICD codes (T65.2, F17.2). ² In a pilot study, only a small number of patients (<0.01%) was documented with FEV-1-related ICD codes (J44.- (5th digit: 0, 1 or 2). Most patients were coded with J44.9 (Chronic obstructive pulmonary disease, unspecified). ³ As a surrogate for heart failure-related hospital admissions (New York Heart Association (NYHA) Class III or IV), ICD code I50.14 (Left ventricular failure, NYHA stage IV) was used. ⁴ Since for several drugs, not only arrhythmias but other indications might be present (e.g., beta-blockers might be prescribed for atrial fibrillation or hypertension), a unique linkage between drugs and arrhythmias or other indications was not possible. Hence, several ICD codes were used for defining life-threatening arrhythmia. ⁵ As surrogate for malignancies requiring therapy, ICD codes C00–C97 (Malignant neoplasms) are used (except basal cell carcinoma, C44). ⁶ Since the prescribed daily dose was unavailable, no dose-related analyses could be conducted.

e-Table 2: Period prevalence per 10,000 persons for stratified by age group and inhaler device

	HandiHaler® period prevalence rate per 10,000 persons						Respimat® period prevalence rate per 10,000 persons		
	2004	2005	2006	2007	2008	Change [%] (2004–2008)	2007	2008	Change [%] (2007– 2008)
20–29	2.3	2.1	2.0	1.9	1.6	-29.9	0.1	0.4	325.5
30–39	4.5	5.1	4.9	5.1	4.1	-7.4	0.1	0.9	737.8
40–49	14.1	16.7	15.8	16.9	15.6	10.6	0.5	2.5	454.7
50–59	50.1	62.3	62.8	64.8	61.5	22.8	1.5	9.0	521.2
60–69	97.9	123.9	134.7	147.6	147.3	50.5	3.2	19.4	501.9
70–79	155.1	207.4	209.6	225.1	219.7	41.7	3.8	24.8	555.7
80–89	122.3	181.0	198.7	230.3	241.7	97.7	4.4	25.9	490.8
90+	49.5	78.3	91.1	115.5	125.7	154.1	1.5	19.3	1,217.2

e-Table 3: Number and proportion of off-label indications (year 2008, multiple counting of off-label indications per prescription)

	HandiHaler® (n, %)	Respimat® (n, %)
Asthma	2,674 (37.4%)	438 (40.3%)
Acute bronchitis	1,030 (14.4%)	208 (19.2%)
Acute upper respiratory infections	1,297 (18.1%)	271 (25.0%)
Chronic bronchitis	195 (18.0%)	141 (13.0%)
Emphysema	421 (5.9%)	80 (7.4%)
Influenza and pneumonia	628 (8.8%)	120 (11.0%)
Other diseases of the respiratory system	1,080 (15.1%)	188 (17.3%)
Other diseases of upper respiratory tract	1,387 (19.4%)	243 (22.4%)
Unspecified acute lower respiratory infection	1,022 (14.3%)	868 (12.1%)
Missing or other diagnoses	1,766 (24.7%)	207 (19.1%)

e-Table 4: Characteristics of patients potentially excluded / not included in the TIOSPIR trial

	HandiHaler®			Respimat®		
	Excluded	Included	p-value	Excluded	Included	p-value
Age [years] (mean±SD)	69.0±12.1	70.5±10.1	<0.0001	67.3±13.0	69.3±10.4	<0.0001
Female (n (%))	18,886 (44.8%)	8,755 (44.0%)	0.069	2,556 (47.0%)	1,093 (46.8%)	0.929