Table S1. Patient Demographics and Baseline Characteristics among Subjects with High CV Risk, Excluding Those with Hypertension Only

	Placebo-Controlled Studies (12-Week Treatment Period)			Active-Controlled Study (48-Week Treatment Period)	
	Placebo (n=94)	GLY 25mcg BID (n=95)	GLY 50mcg BID (n=81)	GLY 50mcg BID (n=138)	TIO 18mcg QD (n=87)
Mean (SD) Age, years	66.6 (8.3)	66.7 (7.9)	65.9 (8.9)	66.6 (7.6)	65.3 (8.3)
Gender, n (%)					
Female	35 (37.2)	36 (37.9)	26 (32.1)	39 (28.3)	23 (26.4)
Male	59 (62.8)	59 (62.1)	55 (67.9)	99 (71.7)	64 (73.6)
Race, n (%)					
Caucasian	80 (85.1)	87 (91.6)	73 (90.1)	135 (97.8)	86 (98.9)
Black/African American	12 (12.8)	7 (7.4)	7 (8.6)	3 (2.2)	1 (1.1)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (2.2)	1 (1.1)	1 (1.2)	0 (0.0)	0 (0.0)
Background LABA Use, n (%)					
Yes	26 (27.7)	31 (32.6)	27 (33.3)	57 (41.3)	40 (46.0)
No	68 (72.3)	64 (67.4)	54 (66.7)	81 (58.7)	47 (54.0)
ICS Use, n (%)					
Yes	25 (26.6)	29 (30.5)	26 (32.1)	49 (35.5)	36 (41.4)
No	69 (73.4)	66 (69.5)	55 (67.9)	89 (64.5)	51 (58.6)

BID=twice daily; CV=cardiovascular; GLY=glycopyrrolate; ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-agonist; QD=once daily; SD=standard deviation; TIO=tiotropium

Table S2. TEAEs Occurring in ≥ Two Percent of Participants in Any Treatment Group and Overall Serious TEAEs Among Participants with High CV Risk, Excluding Those with Hypertension Only

System Organ Class Preferred Term, %	Placebo-Controlled Studies (12-Week Treatment Period)			Active-Controlled Study (48-Week Treatment Period)	
	Placebo (n=94)	GLY 25mcg BID (n=95)	GLY 50mcg BID (n=81)	GLY 50mcg BID (n=138)	TIO 18mcg QD (n=87)
TEAEs					
Overall	47.9	41.1	58.0	68.8	62.1
Respiratory, Thoracic and Mediastinal Disorders	19.1	16.8	29.6	34.8	25.3
Cough	5.3	6.3	16.0	8.7	5.7
COPD Exacerbation	6.4	4.2	8.6	16.7	16.1
Dyspnea	2.1	4.2	4.9	5.8	1.1
Oropharyngeal Pain	0.0	3.2	0.0	3.6	1.1
Wheezing	2.1	1.1	1.2	0.7	1.1
Infections and Infestations	11.7	11.6	19.8	31.9	27.6
Upper Respiratory Tract Infection	1.1	3.2	3.7	3.6	5.7
Urinary Tract Infection	1.1	3.2	3.7	3.6	3.4
Bronchitis	1.1	1.1	1.2	8.0	4.6
Gastroenteritis Viral	0.0	0.0	2.5	0.0	1.1
Sinusitis	1.1	2.1	0.0	3.6	3.4
Influenza	0.0	0.0	1.2	0.0	2.3
Pneumonia	3.2	0.0	1.2	3.6	1.1
Nasopharyngitis	0.0	0.0	0.0	5.1	1.1
Tooth Abscess	0.0	0.0	1.2	0.0	2.3

Cellulitis	2.1	0.0	0.0	0.0	3.4
Nail Infection	0.0	0.0	0.0	0.0	2.3
Nervous System Disorders	2.1	9.5	7.4	5.1	5.7
Headache	1.1	5.3	2.5	0.7	0.0
Carotid Artery Stenosis	0.0	2.1	0.0	0.7	0.0
Tremor	0.0	0.0	2.5	0.0	0.0
General Disorders and Administration Site Conditions	5.3	8.4	6.2	5.8	10.3
Chest Discomfort	2.1	2.1	2.5	0.0	2.3
Fatigue	0.0	2.1	1.2	0.7	0.0
Asthenia	0.0	2.1	0.0	0.0	0.0
Edema Peripheral	2.1	1.1	1.2	2.2	0.0
Pyrexia	0.0	0.0	1.2	0.0	5.7
Non-Cardiac Chest Pain	0.0	0.0	0.0	0.0	2.3
Gastrointestinal Disorders	7.4	7.4	6.2	14.5	12.6
Dry Mouth	1.1	2.1	2.5	0.0	3.4
Nausea	0.0	1.1	2.5	1.4	3.4
Constipation	1.1	0.0	2.5	2.2	2.3
Vomiting	1.1	0.0	2.5	0.0	2.3
Oral Pain	2.1	0.0	0.0	0.0	0.0
Abdominal Pain Upper	0.0	0.0	0.0	0.7	2.3
Dental Caries	1.1	0.0	0.0	0.0	2.3
Diarrhea	1.1	0.0	1.2	2.9	2.3
Musculoskeletal and Connective Tissue Disorders	2.1	4.2	7.4	8.0	8.0
Back Pain	0.0	1.1	2.5	1.4	0.0

Arthralgia	2.1	1.1	1.2	0.0	1.1
Osteoarthritis	1.1	0.0	2.5	0.0	0.0
Muscle Spasms	0.0	1.1	0.0	0.0	2.3
Injury, Poisoning and Procedural Complications	4.3	2.1	6.2	8.7	11.5
Contusion	0.0	0.0	2.5	0.7	0.0
Laceration	0.0	0.0	1.2	0.7	2.3
Periorbital Hemorrhage	0.0	0.0	0.0	0.0	2.3
Procedural Pain	0.0	0.0	0.0	2.2	0.0
Metabolism and Nutrition Disorders	2.1	3.2	3.7	4.3	8.0
Dehydration	0.0	0.0	2.5	0.0	1.1
Diabetes Mellitus	0.0	0.0	0.0	1.4	2.3
Hypoglycemia	0.0	0.0	0.0	0.7	2.3
Cardiac Disorders	5.3	2.1	3.7	8.0	5.7
Angina Pectoris	0.0	2.1	0.0	0.7	0.0
Atrial Fibrillation	2.1	0.0	0.0	2.2	0.0
Cardiac Failure Congestive	0.0	0.0	0.0	0.7	2.3
Tachycardia	0.0	0.0	0.0	1.4	2.3
Vascular Disorders	2.1	1.1	1.2	5.1	5.7

Hypertension	1.1	1.1	0.0	2.2	3.4
Renal and Urinary Disorders	3.2	1.1	4.9	5.1	5.7
Hematuria	2.1	0.0	1.2	0.7	1.1
Urinary Retention	0.0	0.0	0.0	0.0	2.3
Hepatobiliary Disorders	0.0	0.0	1.2	1.4	3.4
Hepatic Steatosis	0.0	0.0	0.0	0.7	2.3
Eye Disorders	1.1	2.1	0.0	3.6	2.3
Cataract	0.0	0.0	0.0	2.2	0.0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	2.1	0.0	0.0	5.8	1.1
Basal Cell Carcinoma	0.0	0.0	0.0	2.2	0.0
Psychiatric Disorders	4.3	0.0	1.2	4.3	3.4
Depression	2.1	0.0	1.2	1.4	0.0
Anxiety	2.1	0.0	0.0	0.7	1.1
Serious TEAEs					
Overall	9.6	4.2	8.6	14.5	18.4

BID=twice daily; COPD=chronic obstructive pulmonary disease; CV=cardiovascular; GLY=glycopyrrolate; QD=once daily;

TEAE=treatment-emergent adverse event; TIO=tiotropium

Table S3. Cardiovascular Events of Special Interest and Major Adverse Cardiovascular Events by Cardiovascular Risk Status and Background Long-acting Beta2-Agonists Use

	Placebo-Controlled Studies (12-Week Treatment Period)												Active-Controlled Study (48-Week Treatment Period)							
	Placebo				GLY 25mcg BID				GLY 50mcg BID				GLY 50mcg BID				TIO 18mcg QD			
CV Risk	High (n=278)		Low (n=152)		High (n=275)		Low (n=156)		High (n=275)		Low (n=157)		High (n=401)		Low (n=219)		High (n=297)		Low (n=169)	
LABA Use (Yes/No)	LABA Yes (n=95)	LABA No (n=183)	LABA Yes (n=37)	LABA No (n=115)	LABA Yes (n=88)	LABA No (n=187)	LABA Yes (n=47)	LABA No (n=109)	LABA Yes (n=91)	LABA No (n=184)	LABA Yes (n=44)	LABA No (n=113)	LABA Yes (n=175)	LABA No (n=226)	LABA Yes (n=92)	LABA No (n=127)	LABA Yes (n=132)	LABA No (n=165)	LABA Yes (n=60)	LABA No (n=109)
Any CV Event of Special Interest, n (%)	1 (1.1)	9 (4.9)	1 (2.7)	0 (0.0)	0 (0.0)	3 (1.6)	1 (2.1)	3 (2.8)	2 (2.2)	4 (2.2)	2 (4.5)	1 (0.9)	8 (4.6)	12 (5.3)	2 (2.2)	3 (2.4)	4 (3.0)	11 (6.7)	2 (3.3)	5 (4.6)
MACE, n (%) [IR]	0 (0.0) [0.0]	2 (1.1) [37.9]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	2 (1.1) [36.0]	0 (0.0) [0.0]	1 (0.9) [30.5]	0 (0.0) [0.0]	2 (0.9) [11.7]	0 (0.0) [0.0]	1 (0.8) [10.5]	4 (3.0) [36.6]	2 (1.2) [14.6]	0 (0.0) [0.0]	2 (1.8) [21.4]

BID=twice daily; CV=cardiovascular; GLY=glycopyrrolate; IR=incidence rate; LABA=long-acting beta2-agonist; MACE=major adverse cardiovascular event; QD=once daily; TIO=tiotropium