

Online Supplement.

Table 1S. Baseline characteristics of underweight participants: sensitivity analysis

	Underweight II <18.5 kg/m ² (n=534)	Underweight I 18.5-<20 kg/m ² (n=577)	Underweight <20 kg/m ² (n=1111)
Demographics			
Body-mass index (kg/m ²)	17.2 (1.1)	19.3 (0.4)	18.3 (1.3)
Age (years)	65.7 (7.9)	65.1 (8.7)	65.4 (8.4)
Women	99 (19%)	130 (23%)	229 (21%)
Race			
White	184 (34%)	284 (49%)	468 (42%)
Asian	341 (64%)	284 (49%)	625 (56%)
Other	9 (2%)	9 (2%)	18 (2%)
Region			
United States	36 (7%)	39 (7%)	75 (7%)
Europe	125 (23%)	215 (37%)	340 (31%)
Asia	341 (64%)	284 (49%)	625 (56%)
Rest of World	32 (6%)	39 (7%)	71 (6%)
Current Smokers	308 (58%)	309 (54%)	617 (56%)
Smoking history (pack-years)	38.1 (22.6)	40.1 (24.5)	39.1 (23.6)
Lung Function			
Post-bronchodilator FEV ₁ (L) at Screening	1.5 (0.4)	1.6 (0.4)	1.5 (0.4)
% Predicted post-bronchodilator FEV ₁ at Screening	59.7 (6.6)	60.2 (6.1)	60.0 (6.3)
FEV ₁ reversibility (as a % of pre-bronchodilator FEV ₁) at Screening	7.7 (13.5)	7.6 (10.9)	7.6 (12.2)
Pre-study COPD exacerbations in 12 months before study			
0	355 (66%)	362 (63%)	717 (65%)
1	103 (19%)	130 (23%)	233 (21%)
2+	76 (14%)	85 (15%)	161 (14%)
Cardiovascular inclusion criteria*			
Manifest disease			
Coronary artery disease	192 (36%)	253 (44%)	445 (40%)
Peripheral arterial disease	99 (19%)	146 (25%)	245 (22%)
Previous stroke	61 (11%)	86 (15%)	147 (13%)
Previous myocardial infarction	74 (14%)	70 (12%)	144 (13%)
Diabetes with target organ disease	24 (4%)	34 (6%)	58 (5%)
At risk			
Hypercholesterolaemia	263 (49%)	284 (49%)	547 (49%)
Hypertension	412 (77%)	421 (73%)	833 (75%)
Diabetes mellitus	98 (18%)	102 (18%)	200 (18%)
Peripheral arterial disease	49 (9%)	81 (14%)	130 (12%)
Pre-study COPD therapy			
Long-acting β agonist	151 (28%)	182 (32%)	333 (30%)
Long-acting muscarinic agonist	63 (12%)	66 (11%)	129 (12%)
Inhaled corticosteroids	152 (28%)	167 (29%)	319 (29%)
Concomitant cardiovascular therapy			
Any medication	500 (94%)	538 (93%)	1038 (93%)
Anti-thrombotic medication	237 (44%)	297 (51%)	534 (48%)
Lipid-lowering medication	319 (60%)	335 (58%)	654 (59%)
Renin-angiotensin aldosterone inhibitor therapy	244 (46%)	305 (53%)	549 (49%)
B blockers	102 (19%)	111 (19%)	213 (19%)
Calcium channel blockers	250 (47%)	246 (43%)	496 (45%)
Nitrates	70 (13%)	101 (18%)	171 (15%)
Diuretics	118 (22%)	132 (23%)	250 (23%)
SUMMIT treatment assignment			
Fluticasone furoate	142 (27%)	156 (27%)	298 (27%)
Vilanterol	131 (25%)	149 (26%)	280 (25%)
Fluticasone furoate/vilanterol	133 (25%)	147 (25%)	280 (25%)
Placebo	128 (24%)	125 (22%)	253 (23%)

Data are mean (SD) or n (%). FEV₁=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease. *Patients could have several cardiovascular diseases or risks at study entry.

Table 2S. Baseline therapy of study participants by BMI category

	Underweight <20 kg/m ² (n=1111)	Normal 20-<25 kg/m ² (n=4306)	Overweight 25-<30 kg/m ² (n=5662)	Class I Obesity 30-<35 kg/m ² (n=3452)	Class II Obesity 35-<40 kg/m ² (n=1367)	Class III Obesity ≥40 kg/m ² (n=587)
Pre-Study COPD Therapy						
Long-acting β agonist	333 (30%)	1425 (33%)	2100 (37%)	1378 (40%)	557 (41%)	240 (41%)
Long-acting muscarinic agonist	129 (12%)	647 (15%)	967 (17%)	692 (20%)	286 (21%)	134 (23%)
Inhaled corticosteroids	319 (29%)	1377 (32%)	1978 (35%)	1326 (38%)	517 (38%)	251 (43%)
Concomitant cardiovascular therapy						
Any medication	1038 (93%)	4099 (95%)	5526 (98%)	3410 (99%)	1357 (99%)	581 (99%)
Anti-thrombotic medication	534 (48%)	2400 (56%)	3320 (59%)	2232 (65%)	896 (66%)	379 (65%)
Lipid-lowering medication	654 (59%)	2794 (65%)	3880 (69%)	2496 (72%)	974 (71%)	411 (70%)
Renin-angiotensin aldosterone inhibitor therapy	549 (49%)	2700 (63%)	4083 (72%)	2767 (80%)	1129 (83%)	484 (82%)
β blockers	213 (19%)	1279 (30%)	2020 (36%)	1417 (41%)	617 (45%)	264 (45%)
Calcium channel blockers	496 (45%)	1708 (40%)	2177 (38%)	1319 (38%)	592 (43%)	234 (40%)
Nitrates	171 (15%)	659 (15%)	873 (15%)	520 (15%)	222 (16%)	79 (13%)
Diuretics	250 (23%)	1268 (29%)	2101 (37%)	1695 (49%)	771 (56%)	396 (67%)

Data are mean (SD) or n (%).

Table 4S. Total On- and Post-treatment Mortality by BMI Category in Underweight, Sensitivity Analysis

	Underweight II <18.5 kg/m ² (n=534)	Underweight I 18.5-<20 kg/m ² (n=577)	Underweight <20 kg/m ² (n=1111)
All-Cause Mortality			
Deaths (%)	54 (10.1%)	51 (8.8%)	105 (9.5%)
Hazard Ratio (95% CI)	1.42 (1.05, 1.91)	1.22 (0.90, 1.64)	1.31 (1.04, 1.64)
Respiratory Mortality			
Deaths (%)	15 (2.8%)	9 (1.6%)	24 (2.2%)
Hazard Ratio (95% CI)	1.70 (0.93, 3.11)	1.16 (0.55, 2.41)	1.44 (0.86, 2.41)
Cardiovascular Mortality			
Deaths (%)	22 (4.1%)	19 (3.3%)	41 (3.7%)
Hazard Ratio (95% CI)	1.51 (0.94, 2.42)	1.12 (0.69, 1.83)	1.30 (0.90, 1.87)

The category of Underweight (<20 kg/m²) has been split into two new categories: Underweight II (<18.5 kg/m²) and Underweight I (18.5-<20 kg/m²). The Hazard ratios shown are in comparison to the reference category of Normal (20-<25 kg/m²). For clarity, Underweight (<20 kg/m²) has been shown again in this table from Figure 1 and Table 2. Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, , cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV₁ treatment arm, BMI

Table 5S. On-treatment System-Specific Morbidity by BMI Categories in Underweight, Sensitivity Analysis

	Underweight II <18.5 kg/m ² (n=534)	Underweight I 18.5-<20 kg/m ² (n=577)	Underweight <20 kg/m ² (n=1111)
Moderate/Severe COPD Exacerbation			
Events (%)	158 (29.6%)	167 (28.9%)	325 (29.3%)
Hazard Ratio (95% CI)	1.00 (0.85, 1.19)	1.01 (0.86, 1.19)	1.01 (0.89, 1.14)
Severe COPD Exacerbation			
Events (%)	64 (12.0%)	64 (11.1%)	128 (11.5%)
Hazard Ratio (95% CI)	1.18 (0.90, 1.54)	1.19 (0.91, 1.56)	1.18 (0.96, 1.46)
Pneumonia			
Events (%)	57 (10.7%)	49 (8.5%)	106 (9.5%)
Hazard Ratio (95% CI)	1.39 (1.03, 1.87)	1.26 (0.92, 1.72)	1.33 (1.05, 1.67)
Composite Cardiovascular Events			
Events (%)	22 (4.1%)	24 (4.2%)	46 (4.1%)
Hazard Ratio (95% CI)	1.02 (0.65, 1.59)	1.00 (0.65, 1.54)	1.01 (0.73, 1.40)

The category of Underweight (<20 kg/m²) has been split into two new categories: Underweight II (<18.5 kg/m²) and Underweight I (18.5-<20 kg/m²). The Hazard ratios shown are in comparison to the reference category of Normal (20-<25 kg/m²). For clarity, Underweight (<20 kg/m²) has been shown again in this table from Table 3.

Hazard ratio (95% confidence interval) per Cox-proportional hazards. Adjusted model accounts for age, sex, region, race, ischemic heart disease indicator, vascular disease indicator, smoking status, cardiovascular entry criteria (history and risk by age), previous COPD exacerbations, % predicted FEV₁, treatment arm, BMI

Moderate COPD exacerbation: exacerbation treated with antibiotics and/or systemic corticosteroids

Severe COPD exacerbation: required hospitalization

Pneumonia: pre-defined MedDRA preferred terms applied to investigator-reported adverse events

Composite Cardiovascular Events: pre-defined secondary endpoint contains myocardial infarction, stroke, transient ischemic attack, unstable angina, and on-treatment cardiovascular death