

Supplementary table 1 Baseline biomarker tertile groupings

Biomarker	Tertile grouping	Values
CRP (mg/L)	Lowest tertile (N=553)	<2.14
	Middle tertile (N=552)	≥2.14 to <5.26
	Highest tertile (N=553)	≥5.26
sRAGE (ng/L)	Lowest tertile (N=550)	<571
	Middle tertile (N=550)	≥571 to <790
	Highest tertile (N=549)	≥790
SPD (μg/L)	Lowest tertile (N=553)	<168
	Middle tertile (N=552)	168 ≤ to <286
	Highest tertile (N=551)	≥ 286
Fibrinogen (mg/dL)	Lowest tertile (N=538)	<292
	Middle tertile (N=532)	≥292 to <366
	Highest tertile (N=530)	≥366
CC-16 (μg/L)	Lowest tertile (N=552)	<0.00691
	Middle tertile (N=552)	≥0.00691 to <0.0117
	Highest tertile (N=552)	≥0.0117

CC-16, club cell protein 16; CRP, C-reactive protein; SPD, surfactant protein D; sRAGE, soluble receptor of activated glycogen end-product.

Supplementary table 2 Effect of inhaled therapy on CC-16 at 3 months

	Placebo (N=439)	FF 100 (N=415)	VI 25 (N=416)	FF/VI 100/25 (N=403)
Number of patients with baseline and 3-month CC-16	337	341	343	334
Baseline CC-16, geometric mean, µg/L	0.0088	0.0089	0.0087	0.0087
CC-16 at 3 months, adjusted geometric mean, µg/L	0.0091	0.0085	0.0085	0.0083
Adjusted ratio to baseline	1.043	0.967	0.975	0.953
Ratio of 3-month CC-16 in active treatment vs placebo (95% CI)		0.927 (0.885 to 0.972)	0.935 (0.893 to 0.979)	0.914 (0.872 to 0.957)
P value		0.001	0.005	<0.001

Model is ANCOVA of log transformed CC-16, adjusted for baseline CC-16, age and gender. Note that due to log transformation, SE are not displayed.

ANCOVA, analysis of covariance; CC-16, club cell protein 16; CI, confidence interval; FF, fluticasone furoate; VI, vilanterol.

Supplementary table 3 Effect of the inhaled therapy on systemic levels of CRP, sRAGE, SPD and fibrinogen versus placebo

	Placebo (N=439)	FF 100 (N=415)	VI 25 (N=416)	FF/VI 100/25 (N=403)
Baseline CRP, geometric mean, mg/L	3.21	3.61	3.52	3.46
CRP at 3 months, adjusted geometric mean, mg/L	3.52	3.54	3.34	3.72
Adjusted ratio to baseline	1.020	1.026	0.969	1.080
Ratio of 3-month CRP in active treatment vs placebo (95% CI)		1.006 (0.887 to 1.141)	0.950 (0.838 to 1.078)	1.059 (0.933 to 1.202)
Baseline sRAGE, geometric mean, ng/L	706	716	717	680
sRAGE at 3 months, adjusted geometric mean, ng/L	697	679	699	685
Adjusted ratio to baseline	0.989	0.964	0.992	0.973
Ratio of 3-month sRAGE in active treatment vs placebo (95% CI)		0.975 (0.944 to 1.007)	1.003 (0.971 to 1.035)	0.983 (0.952 to 1.015)
Baseline SPD, geometric mean, µg/L	204	212	218	200
SPD at 3 months, adjusted geometric mean, µg/L	207	205	197	196
Adjusted ratio to baseline	0.994	0.982	0.946	0.938
Ratio of 3-month SPD in active treatment vs placebo (95% CI)		0.988 (0.925 to 1.055)	0.952 (0.891 to 1.017)	0.944 (0.883 to 1.009)

Baseline Fibrinogen, mean, mg/dL (SD)	331.5 (88.6)	333.7 (88.7)	326.3 (91.0)	327.1 (86.9)
Fibrinogen* at 3 months, adjusted mean, mg/dL (SE)	329.7 (5.0)	327.1 (4.9)	324.3 (4.9)	334.3 (5.0)
Adjusted mean change from baseline (SE)	0.0 (5.0)	-2.5 (4.9)	-5.4 (4.9)	4.7 (5.0)
Difference in Fibrinogen in active treatment vs placebo (95% CI)		-2.5 (-16.3 to 11.2)	-5.4 (-19.1 to 8.3)	4.6 (-9.2 to 18.4)

Models are ANCOVA of log transformed* biomarker, adjusted for baseline biomarker, age and gender, (*Except Fibrinogen which was not log transformed as this marker was Normally distributed on natural scale). Note that due to log transformation, SE are not displayed.

ANCOVA, analysis of covariance; CC-16, club cell protein 16; CI, confidence interval; FF, fluticasone furoate; VI, vilanterol.

SUPPLEMENTARY FIGURE LEGENDS

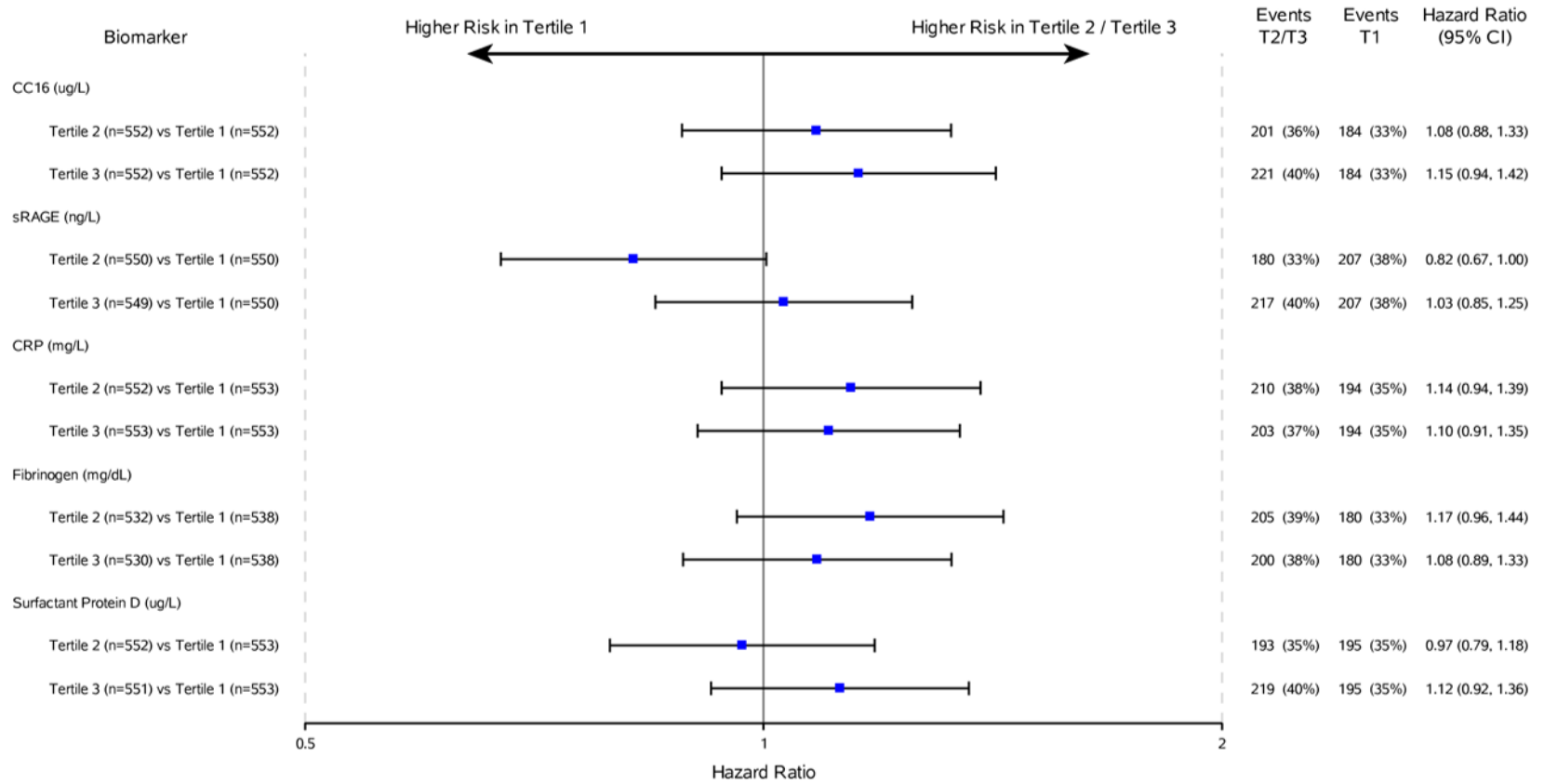
Supplementary figure 1 Hazard ratios for time to first moderate or severe COPD exacerbation by biomarker tertile groups. CC-16, club cell protein 16; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; sRAGE, soluble receptor of activated glycogen end-product.

Supplementary figure 2 Hazard ratios for time to first hospitalised COPD exacerbation by biomarker tertile groups. CC-16, club cell protein 16; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; sRAGE, soluble receptor of activated glycogen end-product.

Supplementary figure 3 Hazard ratios for time to death from any cause by biomarker tertile groups. CC-16, club cell protein 16; CI, confidence interval; CRP, C-reactive protein; sRAGE, soluble receptor of activated glycogen end-product.

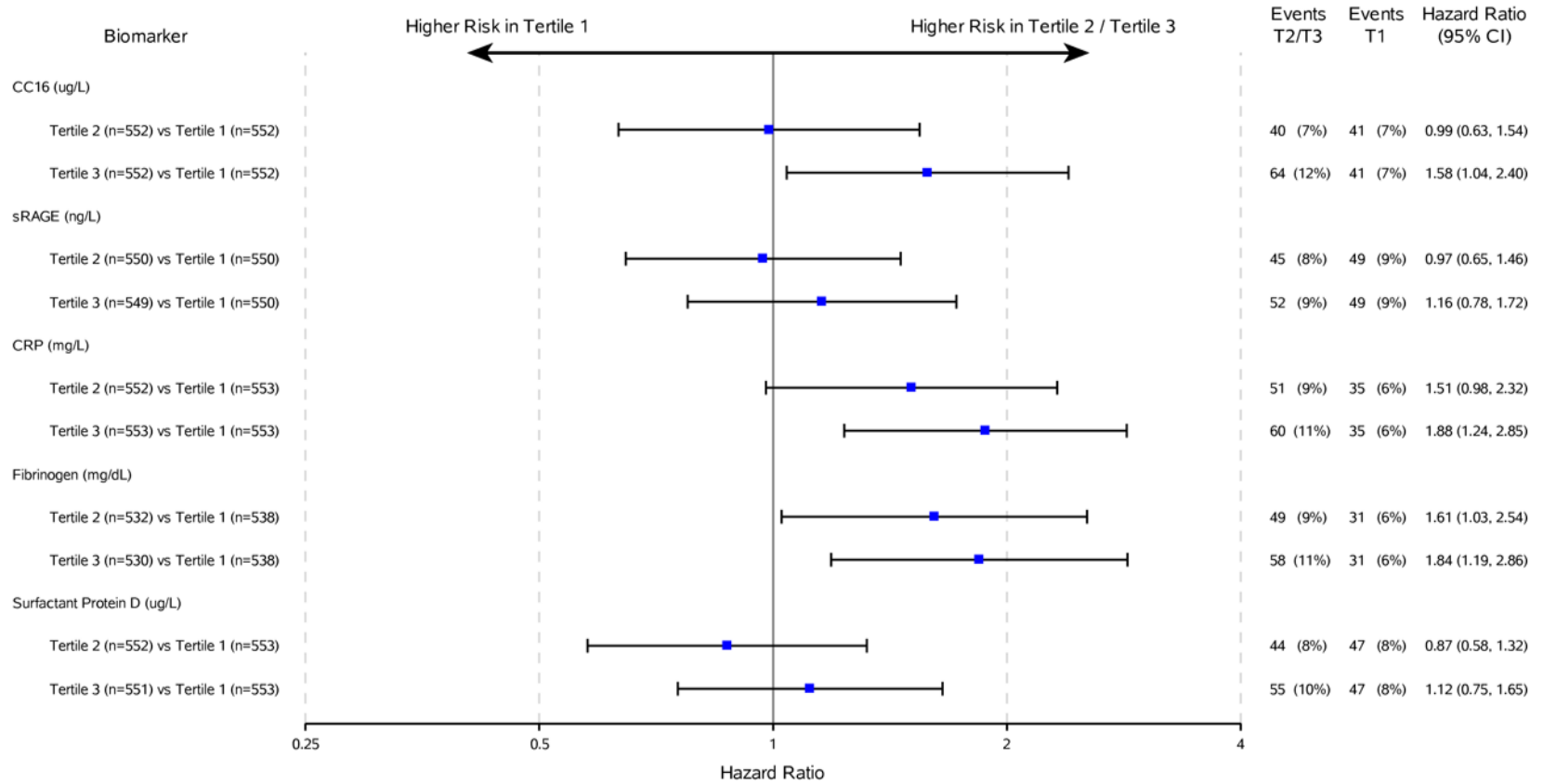
Supplementary figure 4 Hazard ratios for time to cardiovascular death by biomarker tertile groups. CC-16, club cell protein 16; CI, confidence interval; CRP, C-reactive protein; sRAGE, soluble receptor of activated glycogen end-product.

Supplementary figure 1 Hazard ratios for time to first moderate or severe COPD exacerbation by biomarker tertile groups.



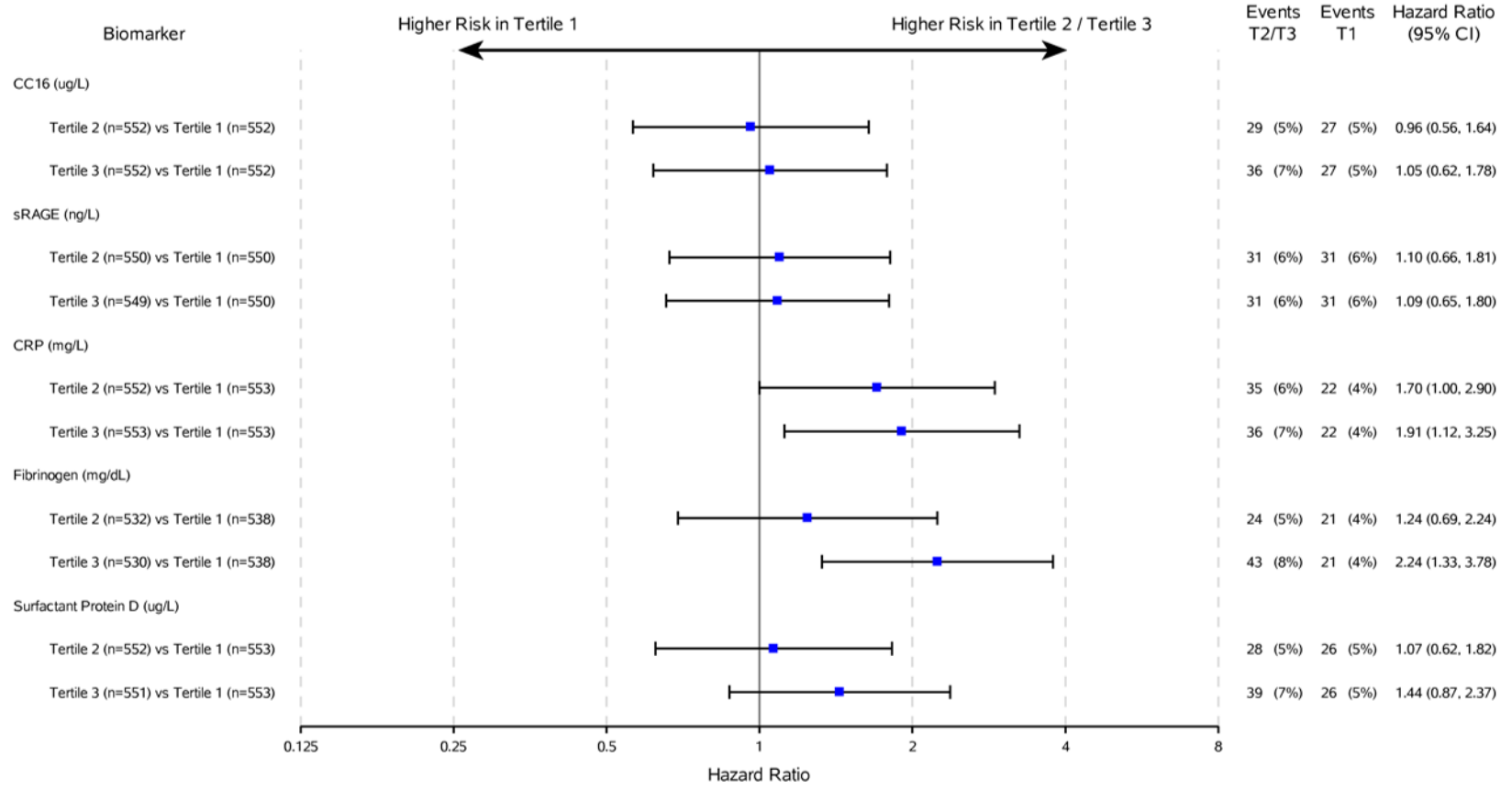
Hazard Ratios from Cox Proportional Hazard model adjusted for treatment, age and gender and number of moderate/severe COPD exacerbations in 12 months prior to screening

Supplementary figure 2 Hazard ratios for time to first hospitalised COPD exacerbation by biomarker tertile groups.



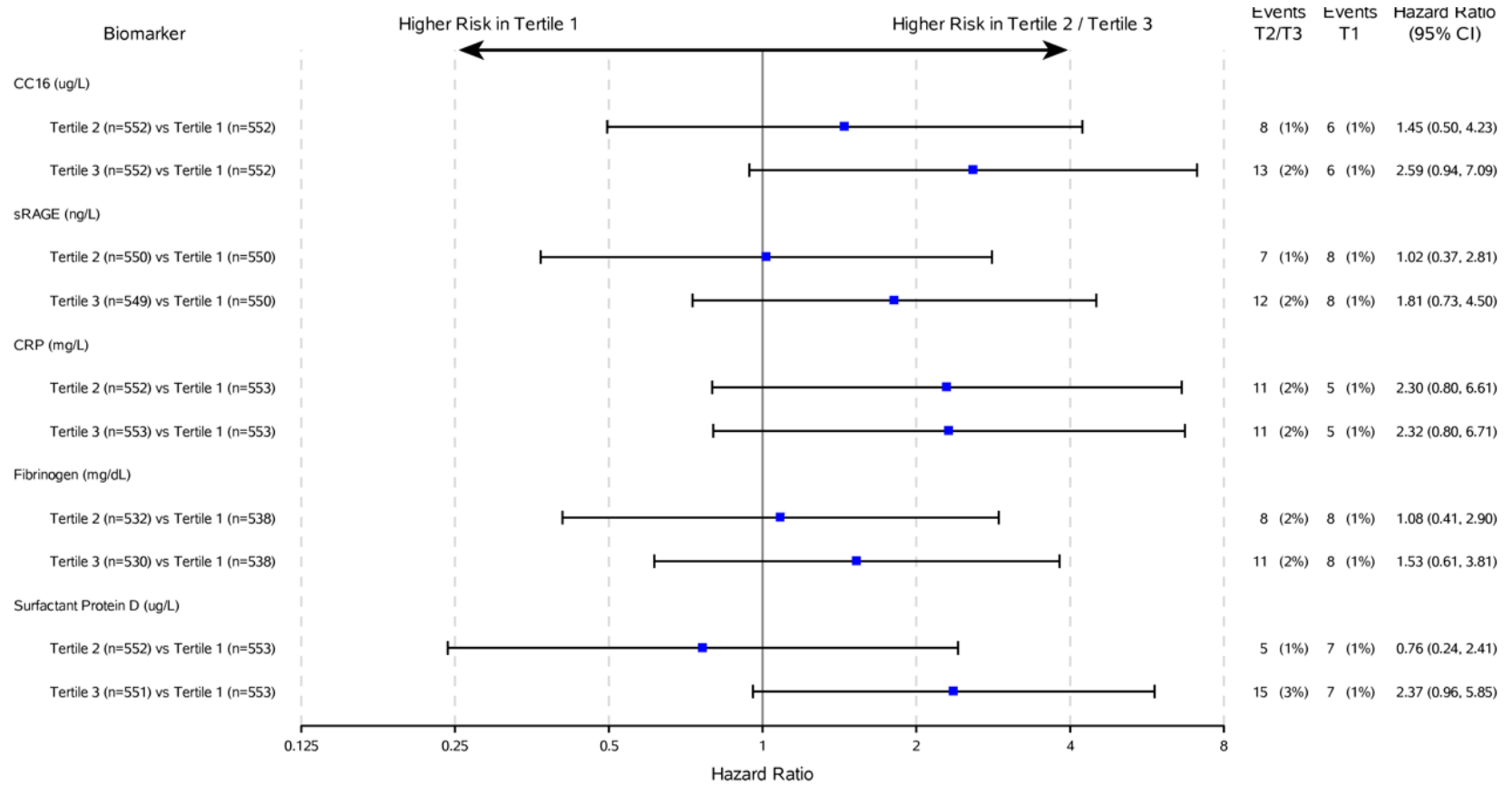
Hazard Ratios from Cox Proportional Hazard model adjusted for treatment, age and gender and number of moderate/severe COPD exacerbations in 12 months prior to screening

Supplementary figure 3 Hazard ratios for time to death from any cause by biomarker tertile groups.



Hazard Ratios from Cox Proportional Hazard model adjusted for treatment, age and gender.

Supplementary figure 4 Hazard ratios for time to cardiovascular death by biomarker tertile groups.



Hazard Ratios from Cox Proportional Hazard model adjusted for treatment, age and gender