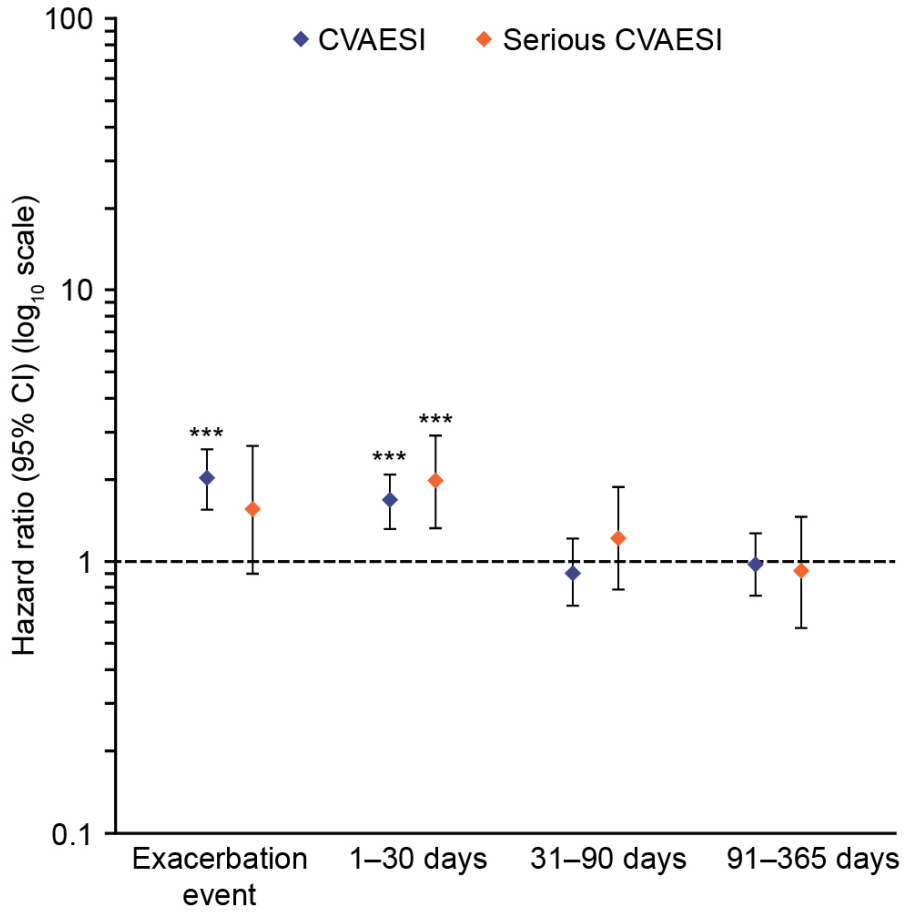
SUPPLEMENTAL MATERIAL

Table S1. Breakdown of CVAESI event types by time period and exacerbation type (primary analysis method)

	Time period								
	Exacerbation-free	Post moderate exacerbation				Post severe exacerbation			
CVAESI N (%) [#]	**'Baseline' (N=681)**	**During event (N=80)**	**1–30 days (N=74)**	**31–90 days (N=49)**	**91–365 days (N=61)**	**During event (N=124)**	**1–30 days (N=12)**	**31–90 days (N=13)**	**91–365 days (N=10)**
Any event	681 (100) [711]	80 (100) [83]	74 (100) [79]	49 (100) [52]	61 (100) [67]	124 (100) [136]	12 (100) [12]	13 (100) [13]	10 (100) [12]
Cardiac arrhythmia	207 (30) [213]	26 (33) [27]	26 (35) [27]	13 (27) [13]	23 (38) [26]	44 (35) [45]	5 (42) [5]	4 (31) [4]	3 (30) [4]
Cardiac failure (SMQ)	162 (24) [167]	26 (33) [27]	24 (32) [24]	14 (29) [15]	15 (25) [15]	45 (36) [46]	4 (33) [4]	6 (46) [6]	2 (20) [2]
CNS hemorrhages and cerebrovascular conditions (SMQ)	47 (7) [49]	4 (5) [4]	4 (5) [4]	3 (6) [3]	5 (8) [5]	3 (2) [3]	0	1 (8) [1]	2 (20) [2]
Hypertension (SMQ)	174 (26) [175]	14 (18) [14]	16 (22) [16]	15 (31) [15]	14 (23) [14]	25 (20) [25]	1 (8) [1]	1 (8) [1]	1 (10) [1]
Ischemic heart disease (SMQ)	103 (15) [108]	11 (14) [11]	8 (11) [8]	6 (12) [6]	7 (11) [7]	17 (14) [17]	2 (17) [2]	1 (8) [1]	3 (30) [3]

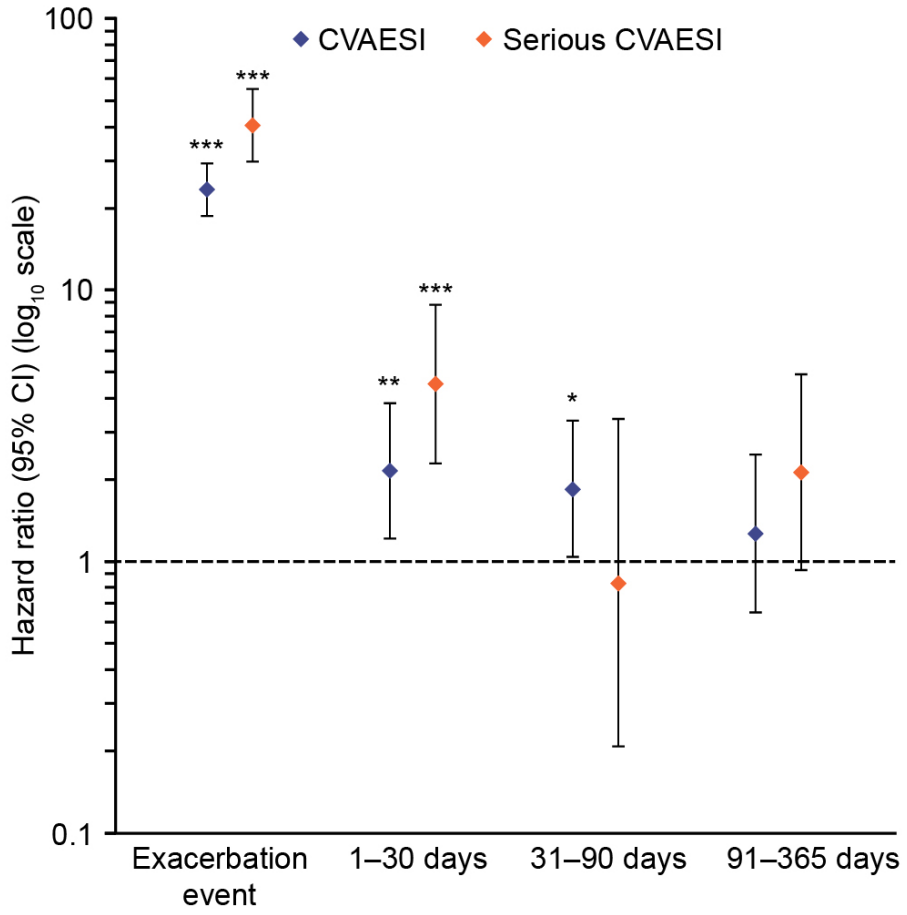
All CVAESIs are included, even if a patient had more than one CVAESI occur on the same day as their first CVAESI following exacerbation event. N (%) refers to the number (%) of patients, # refers to number of events. CVAESI, cardiovascular adverse events of special interest; CNS, central nervous system; SMQ, standardized Medical Dictionary for Regulatory Activities query.

Figure S1. Risk of a first CV event (excluding hypertension) during and following a moderate exacerbation (sensitivity analysis; primary analysis method)



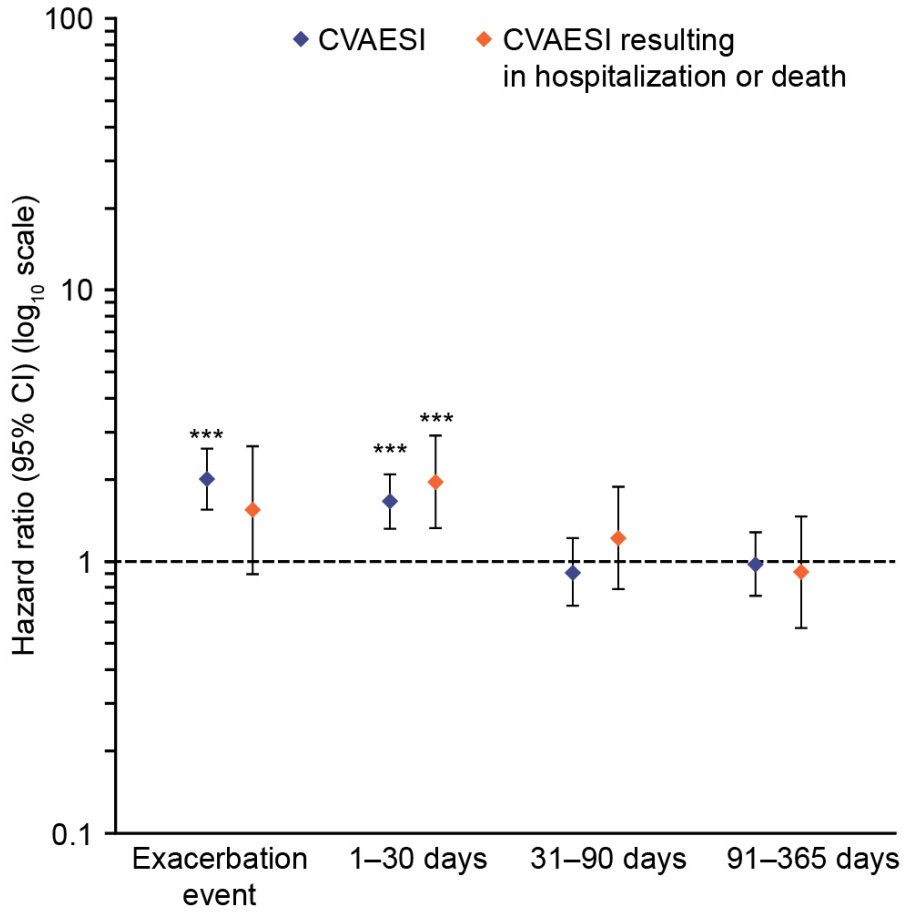
****P*<0.001 versus exacerbation-free 'baseline' period. Sensitivity analysis of CVAESI risk excluding hypertention events. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the exacerbation occurred first. Serious CVAESI are CVAESI resulting in or prolonging hospitalization or resulting in death. CI, confidence interval; CV, cardiovascular; CVAESI, cardiovascular adverse events of special interest.

Figure S2. Risk of a first CV event (excluding hypertension) during and following a severe exacerbation (sensitivity analysis; primary analysis method)



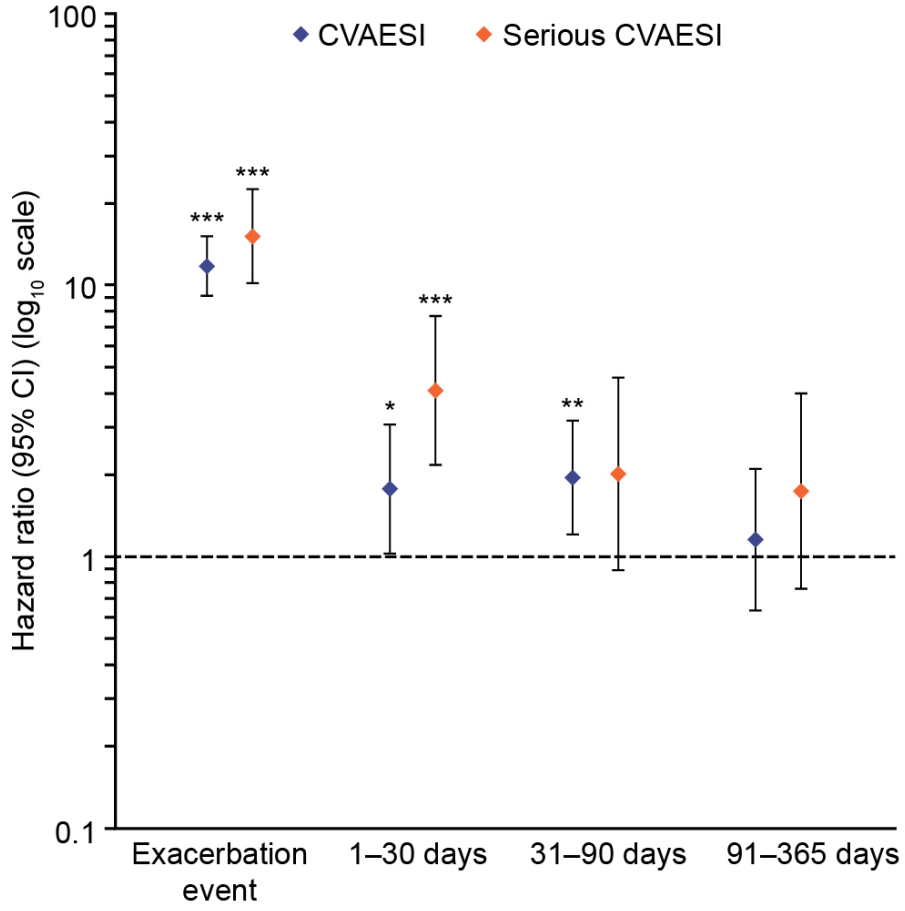
*P<0.05; **P<0.01; ***P<0.001 versus exacerbation-free 'baseline' period. Sensitivity analysis of CVAESI risk excluding hypertention events. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the exacerbation occurred first. Serious CVAESI are CVAESI resulting in or prolonging hospitalization or resulting in death. CI, confidence interval; CV, cardiovascular; CVAESI, cardiovascular adverse events of special interest.

Figure S3. Risk of a first CV event during and following a moderate exacerbation (secondary analysis method)



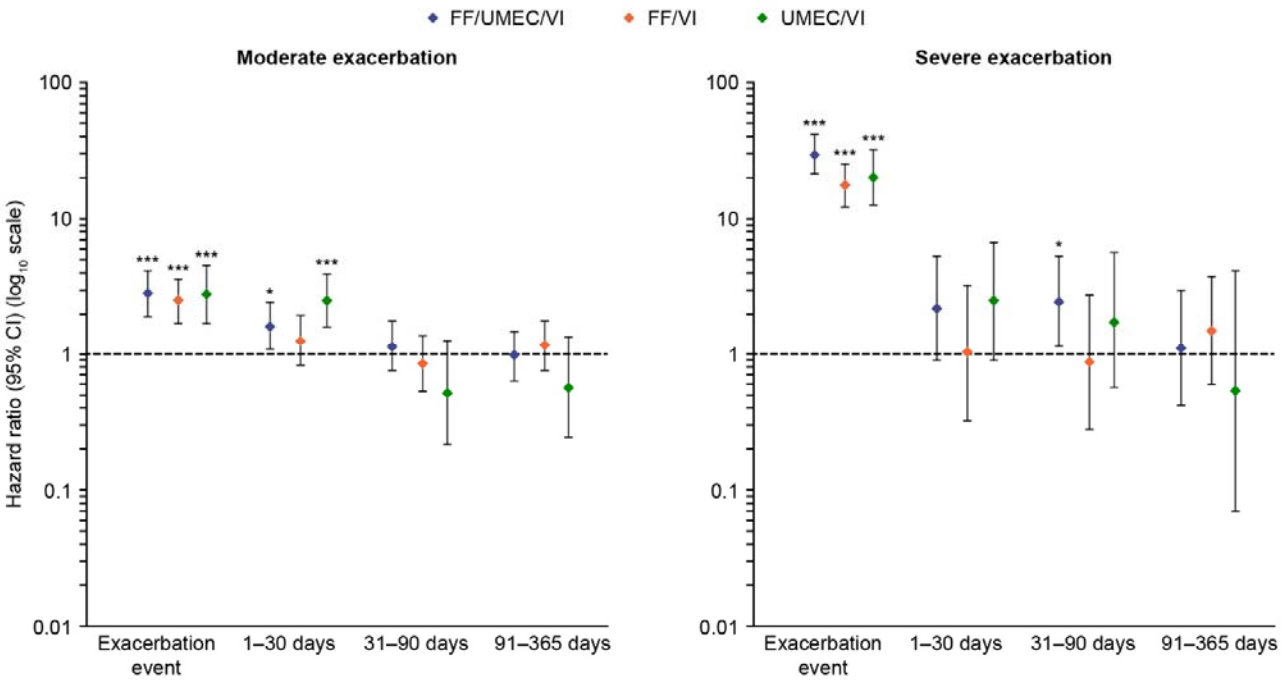
****P*<0.001 versus exacerbation-free 'baseline' period. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the CVAESI occurred first. Serious CVAESI are CVAESI resulting in or prolonging hospitalization or resulting in death. CI, confidence interval; CV, cardiovascular; CVAESI, cardiovascular adverse events of special interest.

Figure S4. Risk of a first CV event during and following a severe exacerbation (secondary analysis method)



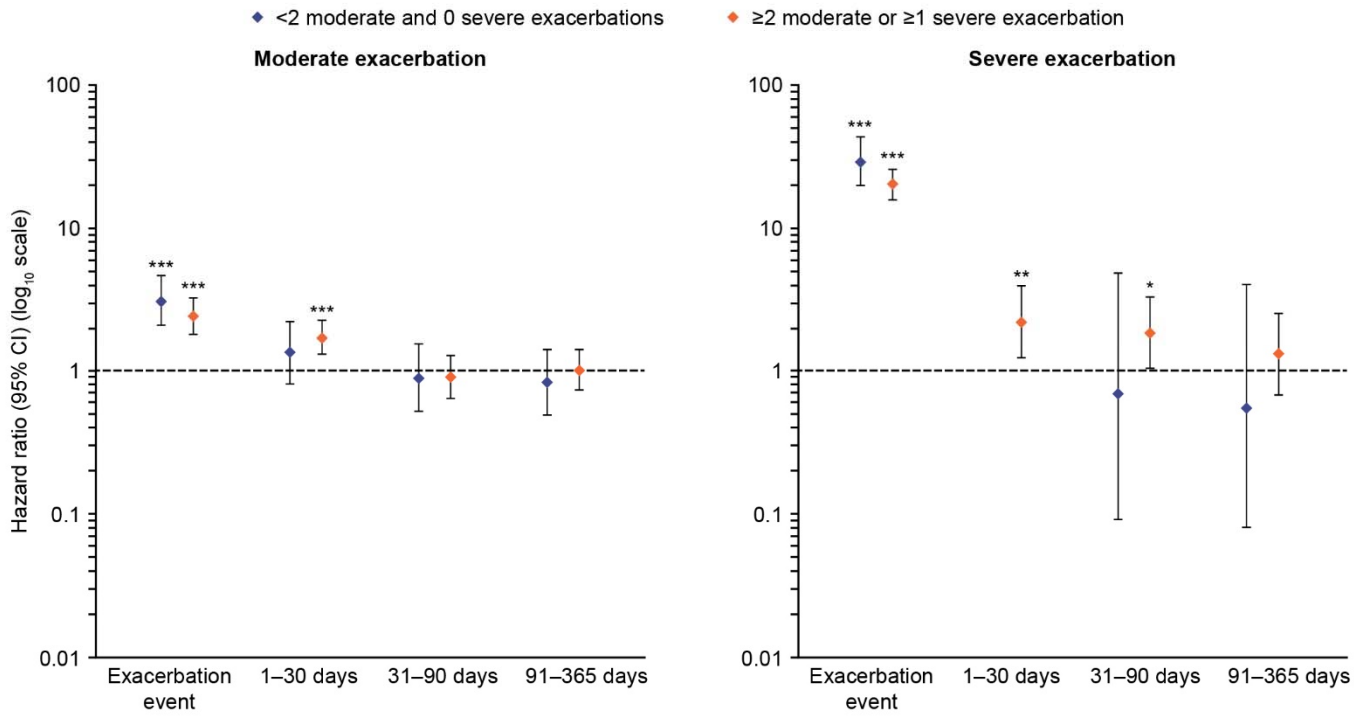
*P<0.05; **P<0.01; ***P<0.001 versus exacerbation-free 'baseline' period. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the CVAESI occurred first. Serious CVAESI are CVAESI resulting in or prolonging hospitalization or resulting in death. CI, confidence interval; CV, cardiovascular; CVAESI, cardiovascular adverse events of special interest.

Figure S5. Risk of a first CVAESI during and following a moderate or severe exacerbation by study treatment (primary analysis method)



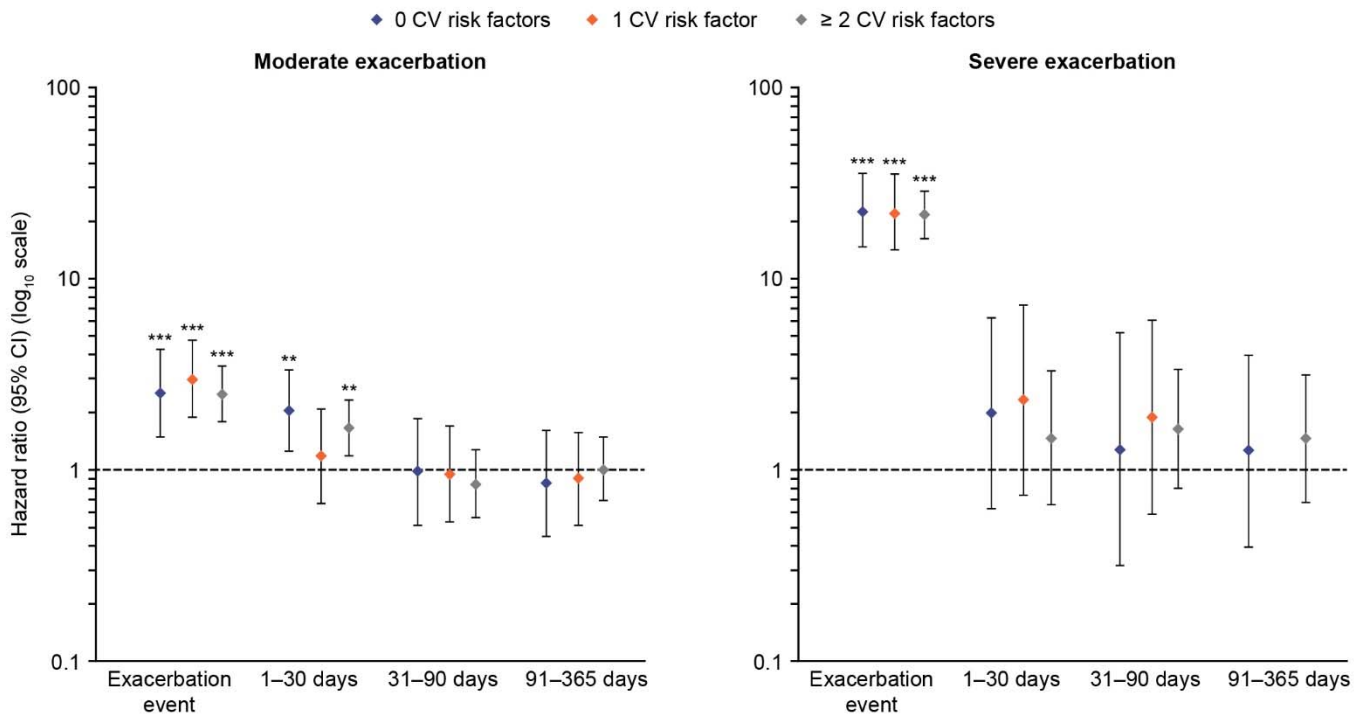
*P<0.05; **P<0.01; ***P<0.001 versus exacerbation-free 'baseline' period. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the exacerbation occurred first. CI, confidence interval; CVAESI, cardiovascular adverse events of special interest; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

Figure S6. Risk of a first CVAESI during and following a moderate or severe exacerbation by exacerbation history in the previous year (primary analysis method)



*P<0.05; **P<0.01; ***P<0.001 versus exacerbation-free 'baseline' period. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the exacerbation occurred first. Note: no events were recorded within 1–30 days post severe exacerbation in the <2 moderate and 0 severe exacerbations subgroup. CI, confidence interval; CVAESI, cardiovascular adverse events of special interest.

Figure S7. Risk of a first CVAESI during and following a moderate or severe exacerbation by CV risk factors at baseline (primary analysis method)



*P<0.05; **P<0.01; ***P<0.001 versus exacerbation-free 'baseline' period. The hazard for a CVAESI was compared assuming that for exacerbations and CVAESIs that occurred on the same day, the exacerbation occurred first. Note: no events were recorded within 91–365 days post severe exacerbation in the 1 CV risk factor subgroup. CI, confidence interval; CV, cardiovascular; CVAE, cardiovascular adverse events of special interest.