Supplemental Material

Risk of pneumonia with budesonide-containing treatments in COPD: An individual patient-level pooled analysis of interventional studies

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Table S1: Pneumonia events identified for the pooled analysis using MedDRA (version 18.0) preferred terms

Atypical pneumonia	Pneumonia bordetella	Pneumonia necrotizing
Bronchopneumonia	Pneumonia chlamydial	Pneumonia pneumococcal
Enterobacter pneumonia	Pneumonia escherichia	Pneumonia pseudomonal
Lobar pneumonia	Pneumonia hemophilus	Pneumonia salmonella
Lung infection	Pneumonia klebsiella	Pneumonia staphylococcal
Pneumonia	Pneumonia legionella	Pneumonia streptococcal
Pneumonia anthrax	Pneumonia moraxella	Pneumonia tularemia
Pneumonia bacterial	Pneumonia mycoplasmal	Psittacosis

Table S2: Pneumonia event comparisons in the various pooled analyses by treatment arm

Comparison variable	**Budesonide-containing**	**Non-budesonide-containing**
Budesonide + formoterol vs non-budesonide-containing (7 studies)	**Budesonide + formoterol**	**Formoterol or placebo**
Safety analysis set (N)	4075	3867
Exposure (patient years)*	2453.6	2176.2
Patients with pneumonia TESAEs, n (%)	64 (1.57)	55 (1.42)
Rate/Patient year	0.026	0.025
Pneumonia TESAEs, n	67	56
Rate/Patient year	0.027	0.026
Patients with pneumonia TEAEs, n (%)	140 (3.44)	100 (2.59)
Rate/Patient year	0.057	0.046
Pneumonia TEAEs, n	155	115
Rate/Patient year	0.063	0.053
Patients with fatal pneumonia, n	4	3
Budesonide + formoterol vs formoterol (6 studies)	**Budesonide + formoterol**	**Formoterol**
Safety analysis set (N)	3746	2295
Exposure (patient years)*	2381.7	1307.0
Patients with pneumonia TESAEs, n (%)	63 (1.68)	32 (1.39)
Rate/Patient year	0.026	0.024
Pneumonia TESAEs, n	66	33
Rate/Patient year	0.028	0.025
Patients with pneumonia TEAEs, n (%)	137 (3.66)	54 (2.35)
Rate/Patient year	0.058	0.041
Pneumonia TEAEs, n	152	61
Rate/Patient year	0.064	0.047
Patients with fatal pneumonia, n	4	1
Budesonide + formoterol vs placebo (5 studies)	**Budesonide + formoterol**	**Placebo**
Safety analysis set (N)	2624	1572
Exposure (patient years)*	1649.1	869.2
Patients with pneumonia TESAEs, n (%)	35 (1.33)	23 (1.46)
Rate/Patient year	0.021	0.026
Pneumonia TESAEs, n	36	23
Rate/Patient year	0.022	0.026
Patients with pneumonia TEAEs, n (%)	81 (3.09)	46 (2.93)
Rate/Patient year	0.049	0.053
Pneumonia TEAEs, n	91	54
Rate/Patient year	0.055	0.062
Patients with fatal pneumonia, n	1	2
Budesonide vs placebo (7 studies)	**Budesonide**	**Placebo**
Safety analysis set (N)	1675	1714
Exposure (patient years)*	2673.5	2593.0
Patients with pneumonia TESAEs, n (%)	33 (1.97)	21 (1.23)
Rate/Patient year	0.012	0.008
Pneumonia TESAEs, n	43	22
Rate/Patient year	0.016	0.008
Patients with pneumonia TEAEs, n (%)	129 (7.70)	115 (6.71)
Rate/Patient year	0.048	0.044
Pneumonia TEAEs, n	228	172
Rate/Patient year	0.085	0.066

Patients with fatal pneumonia, n	2	2

*Time from date of first dose of randomized treatment to date of last dose of randomized treatment/ Incidence rates for each group are calculated as the number of patients experiencing an event divided by total exposure in years. For event rates the total number of events was used in the numerator

Table S3: Hazard ratios for the effect of budesonide on pneumonia TESAEs and TEAEs by budesonide dose

	HR (95% CI)	
	Pneumonia TESAE	**Pneumonia TEAE**
Budesonide/formoterol vs formoterol		
640/18 µg vs 18 µg[1-6]	1.22 (0.77, 1.92)	1.44 (1.03, 2.03)
320/18 µg vs 18 µg[3, 4, 6]	0.82 (0.44, 1.54)	1.32 (0.86, 2.04)
Budesonide/formoterol vs placebo		
640/18 µg vs placebo[1, 3, 5-7]	0.86 (0.49, 1.52)	0.97 (0.65, 1.43)
320/18 µg vs placebo[3, 6]	0.64 (0.29, 1.45)	0.79 (0.47, 1.33)
Budesonide vs placebo		
1280 µg vs placebo[8]	0.45 (0.08, 2.47)	0.67 (0.15, 2.98)
960 µg then 640 µg vs placebo[9]	-	0.61 (0.32, 1.14)
640 µg vs placebo[1, 5, 6, 10, 11]	1.86 (1.02, 3.40)	1.23 (0.92, 1.62)

CI, confidence interval; HR, hazard ratio; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table S4: Hazard ratios for the effect of budesonide on pneumonia TESAEs and TEAEs by treatment duration

	HR (95% CI)	
	Pneumonia TESAE	**Pneumonia TEAE**
Budesonide/formoterol vs formoterol		
3 months[2]	2.57 (0.50, 13.24)	1.17 (0.42, 3.23)
6 months[6]	0.71 (0.22, 2.32)	0.92 (0.36, 2.34)
12 months[1, 3-5]	1.05 (0.65, 1.69)	1.51 (1.05, 2.17)
Budesonide/formoterol vs placebo		
3 months[7]	0.99 (0.06, 15.88)	0.99 (0.20, 4.91)
6 months[6]	1.46 (0.32, 6.76)	1.13 (0.42, 3.06)
12 months[1, 3, 5]	0.79 (0.46, 1.35)	0.93 (0.64, 1.34)
Budesonide vs placebo		
6 months[6]	1.58 (0.26, 9.45)	1.48 (0.47, 4.65)
12 months[1, 5, 8]	0.94 (0.42, 2.09)	0.99 (0.51, 1.92)
>12 months[9-11]	2.83 (1.12, 7.14)	1.07 (0.81, 1.41)

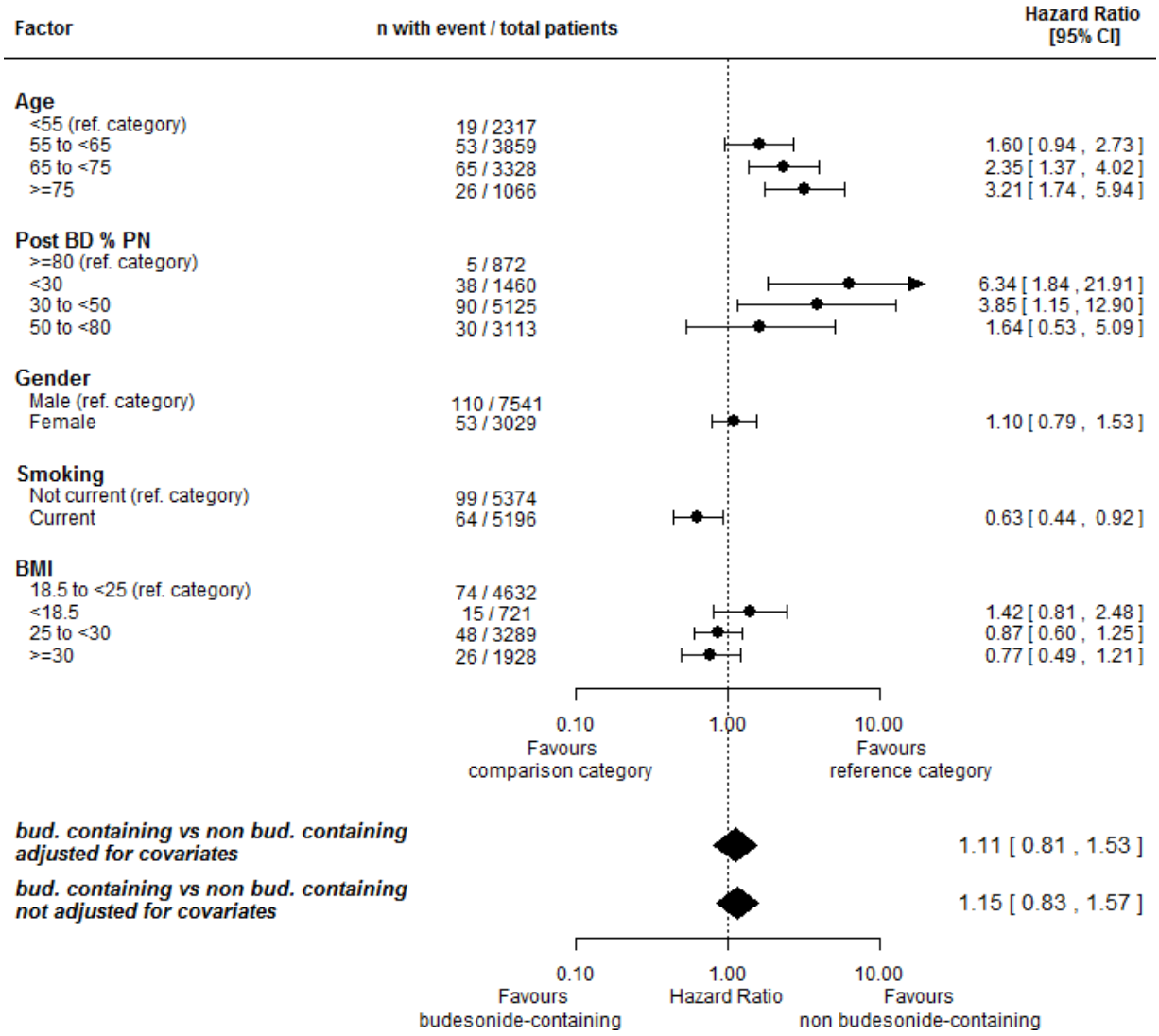
CI, confidence interval; HR, hazard ratio; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table S5: Hazard ratios for the effect of budesonide on pneumonia TESAEs and TEAEs by treatment device

	HR (95% CI)	
	Pneumonia TESAE	**Pneumonia TEAE**
Budesonide/formoterol vs formoterol		
TBH[1, 2, 5]	1.10 (0.49, 2.45)	1.46 (0.81, 2.65)
pMDI[3, 4, 6]	1.07 (0.64, 1.79)	1.40 (0.96, 2.04)
Free combination TBH + pMDI[6]	0.71 (0.16, 3.17)	0.78 (0.24, 2.57)
Budesonide/formoterol vs placebo		
TBH[1, 5, 7]	0.87 (0.35, 2.19)	1.28 (0.67, 2.42)
pMDI[3, 6]	0.74 (0.38, 1.43)	0.80 (0.51, 1.25)
Free combination TBH + pMDI[6]	1.45 (0.24, 8.68)	0.96 (0.28, 3.31)
Budesonide vs placebo		
TBH[1, 5, 8-11]	1.57 (0.87, 2.81)	1.06 (0.82, 1.37)
pMDI[6]	1.58 (0.26, 9.45)	1.48 (0.47, 4.65)

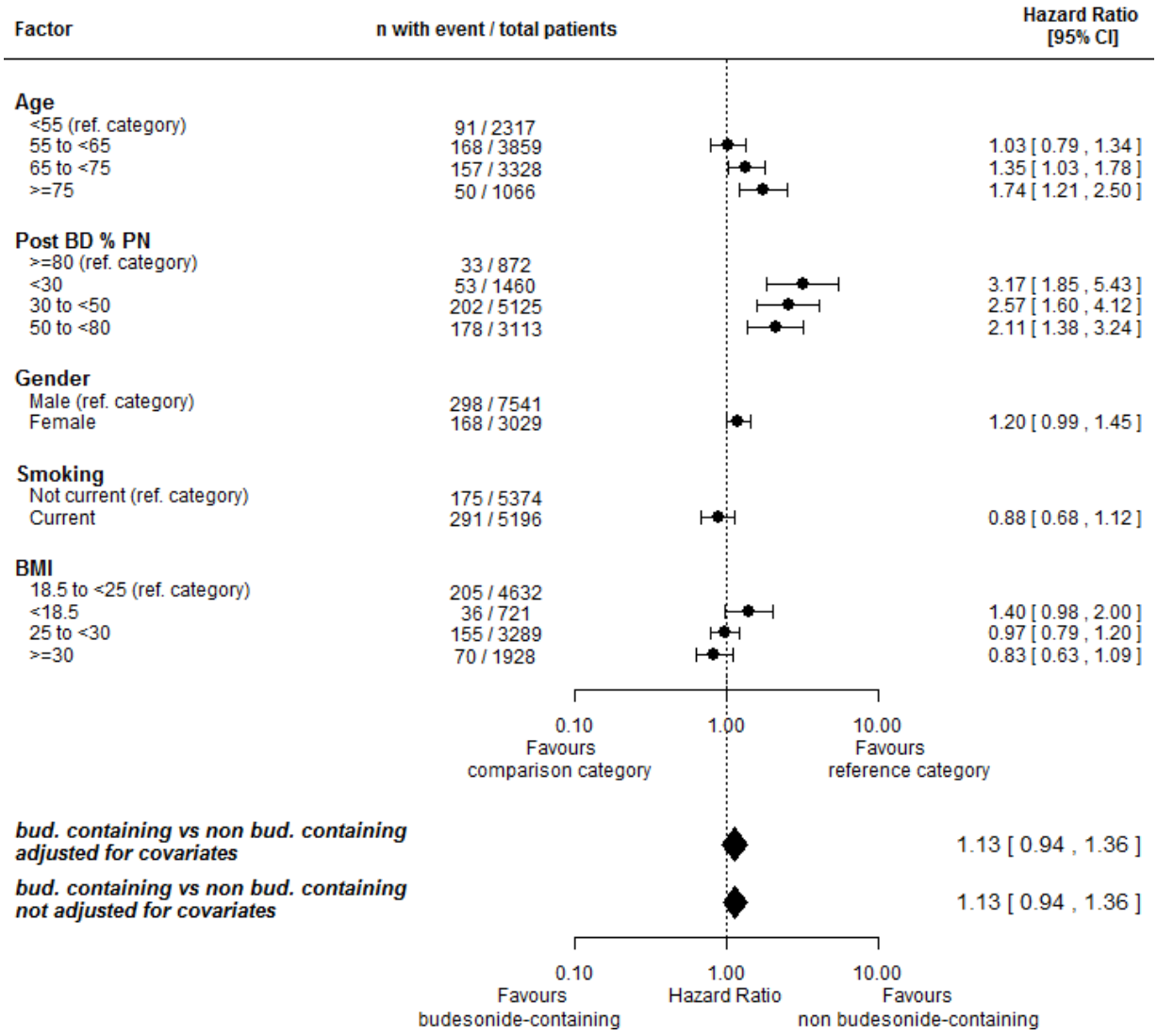
CI, confidence interval; HR, hazard ratio; TBH: Turbuhaler; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; pMDI: pressurized metered dose inhaler

Figure S1 Forest plot of hazard ratios for pneumonia TESAEs by risk factor



BD, bronchodilator; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in one second; PN, predicted normal; TESAE, treatment-emergent serious adverse event.

Figure S2. Forest plot of hazard ratios for pneumonia TEAEs by risk factor



BD, bronchodilator; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in one second; PN, predicted normal; TESAE, treatment-emergent serious adverse event.

References

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