Roflumilast with long-acting β_2 agonists for COPD: influence of exacerbation history

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Supplementary information

SUPPLEMENTARY TABLE 1 Number and percentage of patients from the various countries involved in the studies

Country pool	Roflumilast	Placebo	Total
Australia/New Zealand/UK	78 (5.1%)	81 (5.2%)	159 (5.1%)
Austria/Germany	92 (6.0%)	97 (6.2%)	189 (6.1%)
Canada	70 (4.6%)	85 (5.5%)	155 (5.0%)
France	122 (7.9%)	121 (7.8%)	243 (7.9%)
Germany	116 (7.5%)	114 (7.3%)	230 (7.4%)
Hungary/Romania	177 (11.5%)	180 (11.6%)	357 (11.5%)
India	168 (10.9%)	170 (10.9%)	338 (10.9%)
Italy/Spain	134 (8.7%)	145 (9.3%)	279 (9.0%)
Poland	75 (4.9%)	80 (5.1%)	155 (5.0%)
Russia	120 (7.8%)	121 (7.8%)	241 (7.8%)
South Africa	55 (3.6%)	59 (3.8%)	114 (3.7%)
USA	330 (21.5%)	301 (19.4%)	631 (20.4%)

SUPPLEMENTARY TABLE 2 Baseline characteristics stratified by use of short-acting muscarinic antagonist (SAMA) and previous treatment with inhaled corticosteroids (ICS)

Baseline characteristic	Concomitant treatment				Previous ICS			
	With SAMA		Without SAMA		With		Without	
	Roflumilast (n=588)	Placebo (n=616)	Roflumilast (n=949)	Placebo (n=938)	Roflumilast (n=650)	Placebo (n=657)	Roflumilast (n=887)	Placebo (n=897)
Age (years)[a]	64.1 (9.1)	64.2 (9.1)	63.5 (9.5)	63.6 (9.1)	64.1 (9.2)	64.5 (8.9)	63.4 (9.4)	63.4 (9.2)
Men, n (%)	444 (75.5)	487 (79.1)	706 (74.4)	699 (74.5)	474 (72.9)	479 (72.9)	676 (76.2)	707 (78.8)
Cigarette pack-yr[a,b]	49.6 (25.8)	47.7 (24.4)	47.6 (24.8)	46.3 (22.5)	48.3 (25.3)	46.3 (22.1)	48.4 (25.1)	47.3 (24.1)
Current smoker, n (%)[a]	244 (41.5)	257 (41.7)	391 (41.2)	386 (41.2)	244 (37.5)	238 (36.2)	391 (44.1)	405 (45.2)
Pre-bronchodilator FEV_1 (l)[c]	0.9 (0.4)	1.0 (0.3)	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	1.0 (0.3)	1.0 (0.4)	1.0 (0.4)
Post-bronchodilator FEV_1 (l)[c]	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)
Pre-bronchodilator FEV_1 (% predicted)[c]	30.9 (10.2)	31.4 (10.0)	34.3 (10.2)	34.7 (10.7)	33.2 (10.1)	33.4 (9.8)	32.9 (10.5)	33.3 (11.1)
Post-bronchodilator FEV_1 (% predicted)[c]	34.6 (10.4)	35.1 (10.5)	37.0 (10.7)	37.2 (10.8)	36.2 (10.5)	36.0 (10.2)	36.0 (10.8)	36.6 (11.1)
FEV_1 reversibility increase (%)[c]	13.7 (15.4)	13.9 (19.0)	8.8 (13.9)	8.4 (12.8)	10.3 (13.9)	9.1 (14.0)	11.0 (15.2)	11.6 (16.8)
Post-bronchodilator FEV_1/FVC (%)[c]	40.5 (11.4)	40.5 (10.6)	43.4 (10.9)	43.0 (11.0)	42.1 (11.2)	41.2 (10.7)	42.4 (11.2)	42.6 (11.0)

Body mass index (kg/m^2)[c]	25.0 (5.7)	25.4 (5.7)	26.3 (6.0)	25.8 (5.7)	26.6 (5.8)	26.4 (5.4)	25.2 (5.9)	25.1 (5.8)
COPD severity, n (%)[a,d,e]								
Severe	350 (59.5)	372 (60.4)	593 (62.5)	617 (65.8)	402 (61.8)	436 (66.4)	541 (61.0)	553 (61.6)
Very severe	201 (34.2)	200 (32.5)	262 (27.6)	240 (25.6)	194 (29.8)	179 (27.2)	269 (30.3)	261 (29.1)
Concomitant LABA, n (%)[f]	162 (27.6)	178 (28.9)	587 (61.9)	615 (65.6)	469 (72.2)	476 (72.5)	280 (31.6)	317 (35.3)
Concomitant SAMA, n (%)[f]	–	–	–	–	216 (33.2)	219 (33.3)	372 (41.9)	397 (44.3)
Prior ICS, n (%)[g]	216 (36.7)	219 (35.6)	434 (45.7)	438 (46.7)	–	–	–	–

Data shown are mean (SD) values (unless otherwise stated).

[a]Measurements were taken at the beginning of run-in period; [b]Pack-yr = duration of smoking history (years) x average number of cigarettes per day/20; [c]Measurements were taken at baseline; [d]Based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease; [e]Percentages do not add up to 100% as patients with mild or moderate COPD are not shown; [f]Based on whether the patient had used medication at least once within the start and up to the end of the treatment period inclusive; [g]Based on whether the patient had used inhaled corticosteroid therapy at least once within the period starting the day after the first visit until the day before randomization, inclusive.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC, forced vital capacity; LABA: long-acting β_2 agonist; SD: standard deviation.

SUPPLEMENTARY TABLE 3 Mean rate of moderate or severe exacerbations[a] per patient per year in patients who received and did not receive treatment with long-acting β_2 agonists (LABAs) before study start. Intention-to-treat analysis

Exacerbations/patient/year	Roflumilast	Placebo	Rate ratio (95% CI)	2-sided p-value
With LABA pre-treatment[b]	1.112	1.419	0.784	0.0006
	n=811	n=824	(0.681, 0.901)	
Without LABA pre-treatment[b]	1.104	1.290	0.856	0.0399
	n=726	n=730	(0.738, 0.993)	

Rate ratio, 95% CI and p-values are based on Poisson regression model with the following factors and covariates: treatment, age, sex, smoking status, baseline post-bronchodilator FEV_1 (% predicted) and study.

[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death;

[b]Post-hoc analyses.

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; LABA: long-acting β_2 agonist.

SUPPLEMENTARY TABLE 4 Mean rate of moderate or severe exacerbations[a] per patient per year by concomitant treatment with a short-acting muscarinic antagonist (SAMA) and treatment with inhaled corticosteroid (ICS) during run-in. Intention-to-treat analysis

Exacerbations/patient/year	**Roflumilast**	**Placebo**	**Rate ratio (95% CI)**	**2-sided p-value**
All patients	1.142	1.374	0.831	0.0003
	n=1537	n=1554	(0.752, 0.918)	
SAMA use				
With SAMA	1.670	1.922	0.869	0.0458
	n=588	n=616	(0.757, 0.997)	
Without SAMA	0.803	1.002	0.802	0.0023
	n=949	n=938	(0.696, 0.924)	
Use of ICS before the study				
With ICS	1.297	1.608	0.807	0.0038
	n=650	n=657	(0.698, 0.933)	
Without ICS	0.980	1.178	0.832	0.0102
	n=887	n=897	(0.723, 0.957)	

Rate ratio, 95% CI and p-values are based on Poisson regression model with the following factors and covariates: treatment, age, sex, smoking status, concomitant treatment with LABA, baseline post-bronchodilator FEV_1 (% predicted), study and country pool (only for the overall population).

[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death.

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; LABA: long-acting β_2 agonist.

SUPPLEMENTARY TABLE 5 Time to onset of first, second, or third moderate or severe exacerbation[a] in all patients, those receiving concomitant treatment with/without short-acting muscarinic antagonist (SAMA), and with/without treatment with inhaled corticosteroid (ICS) during run-in. Intention-to-treat analysis

	Patients with event, % (n)		Median (68% range) [days]		Hazard ratio (95% CI)	2-sided p-value
	Roflumilast	Placebo	Roflumilast	Placebo		
All patients						
First	717 (46.6)	821 (52.8)	80.0 (18.0–245.0)	71.0 (19.0–200.0)	0.886 (0.802–0.980)	0.0185
Second	329 (21.4)	430 (27.7)	177.0 (72.0–307.0)	148.0 (71.0–267.0)	0.791 (0.685–0.914)	0.0014
Third[b]	152 (9.9)	218 (14.0)	224.5 (123.0–328.0)	197.0 (114.0–308.0)	0.730 (0.593–0.899)	0.0031
With SAMA[b]						
First	334 (56.8)	392 (63.6)	68.5 (18.0–227.0)	59.0 (16.0–187.0)	0.901 (0.777–1.044)	0.1643
Second	170 (28.9)	223 (36.2)	173.0 (69.0–301.0)	141.0 (63.0–269.0)	0.797 (0.651–0.976)	0.0279
Third	87 (14.8)	115 (18.7)	226.0 (108.0–330.0)	190.0 (103.0–305.0)	0.828 (0.625–1.099)	0.1914
Without SAMA[b]						
First	383 (40.4)	429 (45.7)	87.0 (19.0–253.0)	78.0 (21.0–226.0)	0.893 (0.778–1.026)	0.1093
Second	159 (16.8)	207 (22.1)	183.0 (79.0–308.0)	159.0 (83.0–262.0)	0.780 (0.633–0.960)	0.0189
Third	65 (6.8)	103 (11.0)	221.0 (151.0–327.0)	203.0 (137.0–309.0)	0.633 (0.463–0.867)	0.0044
With ICS before the study[b]						
First	341 (52.5)	389 (59.2)	65.0 (14.0–210.0)	57.0 (17.0–186.0)	0.893 (0.771–1.034)	0.1301
Second	167 (25.7)	217 (33.0)	147.0 (62.0–294.0)	141.0 (71.0–258.0)	0.790 (0.645–0.969)	0.0234
Third	80 (12.3)	116 (17.7)	214.5 (121.0–327.0)	188.0 (112.0–299.0)	0.696 (0.522–0.928)	0.0134

Without ICS before the study[b]						
First	376 (42.4)	432 (48.2)	87.5 (25.0–266.0)	81.5 (21.0–228.0)	0.878 (0.764–1.010)	0.0681
Second	162 (18.3)	213 (23.7)	196.0 (82.0–310.0)	162.0 (75.0–274.0)	0.791 (0.644–0.971)	0.0249
Third	72 (8.1)	102 (11.4)	227.0 (123.0–332.0)	220.0 (117.0–312.0)	0.749 (0.552–1.015)	0.0622

Hazard ratio, 95% CI and p-values are based on Cox proportional hazards model with the following factors and covariates: treatment, age, sex, smoking status, concomitant treatment with LABA, and strata: study and country pool.

[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death; [b]Post-hoc analyses.

CI: confidence interval.

SUPPLEMENTARY TABLE 6 Mean change (improvement) in transitional dyspnoea index (TDI) focal score by repeated measurements analysis and also by last observation carried forward (LOCF). Intention-to-treat analysis. TDI is graded from 0 to 4, where 0 is most severe; a change in TDI score of 1.0 unit is considered clinically relevant

	Roflumilast	**Placebo**	**Difference (score, [95% CI])**	**2-sided p-value**
Repeated measurements analysis[a]	0.662 n=1470	0.409 n=1514	0.253 (0.104–0.402)	0.0009
LOCF	0.441 n=1470	0.115 n=1514	0.325 (0.101, 0.550)	0.0046

[a]Least square means, 95% CI and p-values are based on a repeated measurements analysis of covariance model with the following factors and covariates: treatment, baseline value, age, sex, smoking status, time, treatment-by-time interaction, study and country pool (only for the overall population). Concomitant treatment with LABA was also included as a factor.

CI: confidence interval.

SUPPLEMENTARY TABLE 7 Mean change in pre- and post-bronchodilator FEV_1 (least square means) according to concomitant treatment with a long-acting β_2 agonist (LABA), frequency of previous exacerbations[a], concomitant treatment with a short-acting muscarinic antagonist (SAMA) and previous treatment with inhaled corticosteroid (ICS). Intention-to-treat analysis

	Roflumilast (mL)	Placebo (mL)	Difference (mL, [95% CI])	2-sided p-value
Pre-bronchodilator				
All patients	40 n=1475	–9 n=1511	48 (35, 62)	<0.0001
LABA use				
With LABA	28 n=722	–18 n=773	46 (29, 64)	<0.0001
Without LABA	51 n=753	1 n=738	50 (29, 71)	<0.0001
By historical exacerbations[a, b]				
Frequent	36 n=400	–6 n=406	42 (14, 69)	0.0032
Infrequent	40 n=1075	–11 n=1105	51 (35, 66)	<0.0001
SAMA use				
With SAMA	30 n=560	–23 n=604	52 (30, 75)	<0.0001
Without SAMA	43 n=915	–2 n=907	46 (28, 63)	<0.0001
Use of ICS before the study				
With ICS	37 n=621	–10 n=644	47 (28, 67)	<0.0001
Without ICS	44 n=854	–5 n=867	49 (30, 68)	<0.0001
Post-bronchodilator				
All patients	50 n=1453	–4 n=1500	55 (41, 69)	<0.0001

LABA use				
With LABA	36 n=706	–10 n=766	46 (28, 64)	<0.0001
Without LABA	62 n=747	–2 n=734	64 (42, 86)	<0.0001
By historical exacerbations[a, b]				
Frequent	47 n=392	–3 n=401	49 (20, 78)	0.0009
Infrequent	51 n=1061	–6 n=1099	57 (41, 73)	<0.0001
SAMA use				
WithSAMA	31 n=551	–26 n=599	57 (34, 80)	<0.0001
Without SAMA	58 n=902	6 n=901	52 (34, 70)	<0.0001
Use of ICS before the study				
With ICS	44 n=609	0 n=636	44 (23, 66)	<0.0001
Without ICS	55 n=844	–8 n=864	63 (44, 82)	<0.0001

Least square means, 95% CI and p-values are based on a repeated measurements analysis of covariance model with the following factors and covariates: treatment, baseline value, age, sex, smoking status, time, treatment by time interaction, study and country pool (only for the overall population). For all groups apart from LABA usage, concomitant treatment with LABA was also included as a factor.

[a]COPD exacerbations in the previous year (based on patient recall). Defined as infrequent if <2 and frequent if ≥2 exacerbations per year; [b]Post-hoc analyses.

CI: confidence interval; COPD: chronic obstructive pulmonary disease.

Interaction testing

Interaction testing was performed for the different subgroups: treatment by LABA (yes/no) interaction: p=0.5382; treatment by pre-ICS (yes/no) interaction: p=0.6874; treatment by exacerbators (frequent/infrequent) interaction: p=0.6397.

SUPPLEMENTARY TABLE 8 Mean change in pre- and post bronchodilator FEV_1 by repeated measurements analysis and also by last observation carried forward (LOCF)

	Roflumilast (mL)	Placebo (mL)	Difference (mL, [95% CI])	2-sided p-value
Pre-bronchodilator				
Repeated measurements[a]	40 n=1475	–9 n=1511	48 (35, 62)	<0.0001
LOCF	21 n=1475	–14 n=1511	34 (17, 52)	<0.0001
Post-bronchodilator				
Repeated measurements[a]	50 n=1453	–4 n=1500	55 (41, 69)	<0.0001
LOCF	22 n=1453	–18 n=1500	40 (23, 58)	<0.0001

[a]Least square means, 95% CI and p-values are based on a repeated measurements analysis of covariance model with the following factors and covariates: treatment, baseline value, age, sex, smoking status, concomitant treatment with LABA, time, treatment by time interaction, study and country pool (only for the overall population).
CI: confidence interval.