

Supplementary material

Table S1 Demographic and baseline patient characteristics for the Japanese sub-population (treated population, combined studies)

	O 5 µg (n=108)	T 2.5 µg (n=72)	T 5 µg (n=76)	T+O 2.5/5 µg (n=78)	T+O 5/5 µg (n=79)
Male, n (%)	101 (93.5)	70 (97.2)	70 (92.1)	71 (91.0)	74 (93.7)
Mean (SD) age, years	68.4 (6.6)	70.4 (8.1)	68.7 (6.6)	69.0 (7.1)	69.3 (6.9)
Mean (SD) body mass index, kg/m ²	22.5 (3.8)	22.8 (3.8)	22.4 (3.1)	22.1 (3.9)	22.3 (3.4)
Smoking status, n (%)					
Ex-smoker	87 (80.6)	60 (83.3)	65 (85.5)	66 (84.6)	61 (77.2)
Current smoker	21 (19.4)	12 (16.7)	11 (14.5)	12 (15.4)	18 (22.8)
Mean (SD) smoking history, pack-years	65.9 (31.5)	62.9 (30.2)	66.5 (36.3)	63.0 (32.2)	60.0 (36.4)
Mean (SD) duration of diagnosis, years	4.3 (3.8)	4.8 (3.5)	4.5 (4.1)	4.8 (5.0)	5.4 (4.7)

Co-morbidities, n (%)	98 (90.7)	65 (90.3)	73 (96.1)	72 (92.3)	73 (92.4)
Cardiac	17 (15.7)	11 (15.3)	11 (14.5)	17 (21.8)	9 (11.4)
Vascular	47 (43.5)	31 (43.1)	45 (59.2)	33 (42.3)	36 (45.6)
Mean (SD) pre-bronchodilator screening					
FEV ₁ , L	1.188 (0.437)	1.175 (0.412)	1.172 (0.500)	1.158 (0.440)	1.153 (0.493)
Mean (SD) post-bronchodilator screening					
FEV ₁ , L	1.348 (0.460)	1.345 (0.411)	1.331 (0.473)	1.319 (0.445)	1.325 (0.475)
Change from pre- to post-bronchodilator					
FEV ₁ , mL	160 (127)	170 (129)	158 (118)	162 (95)	172 (154)
FEV ₁ /FVC, %	42.6 (11.3)	45.0 (10.2)	42.7 (11.6)	42.3 (11.7)	42.7 (11.6)
% of predicted normal FEV ₁	53.2 (14.9)	54.9 (14.3)	52.3 (16.2)	52.8 (15.0)	53.0 (14.4)
GOLD, n (%) ^a					
2 (50–<80%)	62 (57.4)	47 (65.3)	43 (56.6)	46 (59.0)	49 (62.0)
3 (30–<50%)	38 (35.2)	21 (29.2)	26 (34.2)	29 (37.2)	25 (31.6)
4 (<30%)	8 (7.4)	4 (5.6)	7 (9.2)	3 (3.8)	5 (6.3)

Baseline pulmonary medication, n (%)	82 (75.9)	60 (83.3)	64 (84.2)	66 (84.6)	70 (88.6)
SAMA ^b	3 (2.8)	1 (1.4)	2 (2.6)	0 (0.0)	2 (2.5)
LAMA ^c	63 (58.3)	47 (65.3)	48 (63.2)	54 (69.2)	55 (69.6)
SABA ^d	4 (3.7)	8 (11.1)	3 (3.9)	10 (12.8)	7 (8.9)
LABA ^e	27 (25.0)	22 (30.6)	19 (25.0)	24 (30.8)	20 (25.3)
ICS ^f	28 (25.9)	13 (18.1)	22 (28.9)	23 (29.5)	24 (30.4)
Xanthine ^g	12 (11.1)	10 (13.9)	15 (19.7)	9 (11.5)	11 (13.9)

Note: ^aBased on post-bronchodilator FEV₁ percentage predicted; ^bipratropium, oxitropium; ^ctiotropium; ^dincluding salbutamol and procaterol; ^eincluding formoterol/budesonide, indacaterol, salmeterol, salmeterol/fluticasone; ^fincluding beclomethasone, budesonide, ciclesonide, fluticasone, mometasone, formoterol/budesonide, salmeterol/fluticasone; ^gtheophylline.

Abbreviations: T, tiotropium; O, olodaterol; SD, standard deviation; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β -agonist; LABA, long-acting β ₂-agonist; ICS, inhaled corticosteroid.

Table S2 FEV₁ AUC₀₋₃ and trough FEV₁ (change from baseline) at Week 24 for the Japanese sub-population (full analysis set, combined studies)

Treatment	n	FEV₁ AUC₀₋₃, mL	n	Trough FEV₁, mL
Common baseline mean		1120 (23)		1120 (23)
Olodaterol 5 µg	107	143 (16)	107	75 (15)
Tiotropium 2.5 µg	72	160 (19)	72	87 (18)
Tiotropium 5 µg	75	160 (18)	75	98 (18)
Tiotropium + olodaterol 2.5/5 µg	78	230 (18)	78	134 (17)
Tiotropium + olodaterol 5/5 µg	79	294 (18)	79	205 (18)

Note: Data are presented as adjusted mean (standard error) unless otherwise stated.

Adjusted mean (standard error) obtained from fitting a mixed-effect model for repeated measures including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Abbreviations: FEV₁, forced expiratory volume in 1 second; AUC₀₋₃, area under the curve from 0–3 hours.

Table S3 Change from baseline in treatment comparisons for FEV₁ AUC₀₋₃ and trough FEV₁ at Week 24 for the Japanese sub-population (full analysis set, combined studies)

Treatment comparison	Treatment difference in FEV₁ AUC₀₋₃, mL	95% CI	Treatment difference in trough FEV₁, mL	95% CI
Common baseline mean	1120 (23)		1120 (23)	
Tiotropium + olodaterol 5/5 µg				
vs olodaterol 5 µg	151 (24)***	104, 198	131 (23)***	85, 176
vs tiotropium 5 µg	134 (26)***	83, 185	108 (25)***	59, 156
Tiotropium + olodaterol 2.5/5 µg				
vs olodaterol 5 µg	87 (24)**	39, 134	60 (23)**	14, 105
vs tiotropium 2.5 µg	70 (26)**	18, 122	47 (25)	-3, 97

Note: Data are presented as adjusted mean (standard error) unless otherwise stated.

*** $P < 0.0001$; ** $P < 0.01$ (nominal P values).

Abbreviations: FEV₁, forced expiratory volume in 1 second; AUC₀₋₃, area under the curve from 0–3 hours; CI, confidence interval.

Table S4 Change from baseline in lung-function end points at Week 52 for the Japanese sub-population (full analysis set; combined studies)

Treatment	n	FEV ₁	FEV ₁	Trough	FVC	Trough	FVC
		peak ₀₋₃ , mL	AUC ₀₋₃ , mL	FEV ₁ , mL	peak ₀₋₃ , mL	FVC, mL	AUC ₀₋₃ , mL
Common baseline			1120 (23)			2727 (37)	
Olodaterol 5 µg	107	143 (17)	92 (16)	9 (16)	331 (41)	46 (40)	186 (38)
Tiotropium 2.5 µg	72	172 (21)	125 (20)	55 (19)	443 (50)	243 (49)	313 (46)
Tiotropium 5 µg	75	199 (20)	139 (19)	51 (19)	365 (49)	91 (47)	238 (44)
Tiotropium + olodaterol 2.5/5 µg	78	239 (20)	188 (19)	87 (18)	526 (48)	246 (47)	380 (43)
Tiotropium + olodaterol 5/5 µg	79	307 (20)	255 (19)	151 (19)	546 (49)	289 (47)	419 (44)

Note: Data are presented as adjusted mean (standard error) unless otherwise stated.

Adjusted mean (standard error) obtained from fitting a mixed-effect model for repeated measures including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Abbreviations: FEV₁, forced expiratory volume in 1 second; peak₀₋₃, peak value from 0–3 hours; FVC, forced vital capacity; AUC₀₋₃, area under the curve from 0–3 hours.

Table S5 Treatment comparisons for change from baseline in lung-function end points at Week 52 for the Japanese sub-population (full analysis set; combined studies)

Treatment comparison	FEV₁ peak₀₋₃, mL	FEV₁ AUC₀₋₃, mL	Trough FEV₁, mL	FVC peak₀₋₃, mL	Trough FVC, mL	FVC AUC₀₋₃, mL
T+O 5/5 µg						
vs O 5 µg	164 ± 26 (112, 216)***	163 ± 25 (114, 213)***	142 ± 25 (94, 190)***	215 ± 64 (89, 341)**	243 ± 62 (121, 366)***	233 ± 58 (119, 347)***
vs T 5 µg	108 ± 28 (52, 163)**	116 ± 27 (64, 169)***	100 ± 26 (48, 152)**	181 ± 69 (46, 316)**	198 ± 67 (67, 329)**	182 ± 62 (60, 304)**
T+O 2.5/5 µg						
vs O 5 µg	96 ± 26 (45, 148)**	96 ± 25 (47, 144)***	78 ± 24 (30, 126)**	196 ± 63 (72, 320)**	200 ± 62 (79, 320)**	193 ± 57 (81, 306)**
vs T 2.5 µg	67 ± 29 (11, 124)*	62 ± 27 (9, 116)	32 ± 27 (-20, 85)	83 ± 70 (-53, 220)	3 ± 68 (-130, 136)	67 ± 63 (-57, 191)

Note: Data are presented as adjusted mean \pm standard error (95% confidence interval) unless otherwise stated.

*** $P \leq 0.0001$; ** $P < 0.01$; * $P < 0.05$ (nominal P values).

Abbreviations: FEV₁, forced expiratory volume in 1 second; peak₀₋₃, peak value from 0–3 hours; FVC, forced vital capacity; AUC₀₋₃, area under the curve from 0–3 hours; T, tiotropium; O, olodaterol.

Table S6 Patients' Global Rating at Week 24 for Japanese and overall populations (full analysis set, combined studies)

Treatment	Japanese population		Overall population	
	n	Patient's Global Rating	n	Patient's Global Rating
Olodaterol 5 µg	106	3.51 (0.09)	1011	3.22 (0.03)
Tiotropium 2.5 µg	72	3.35 (0.11)	1005	3.19 (0.03)
Tiotropium 5 µg	76	3.37 (0.11)	1008	3.22 (0.03)
Tiotropium + olodaterol 2.5/5 µg	78	3.03 (0.11)	1017	3.05 (0.03)
Tiotropium + olodaterol 5/5 µg	78	3.01 (0.11)	1007	2.99 (0.03)

Note: Data are presented as adjusted mean (standard error) unless otherwise stated.

Adjusted mean (standard error) obtained from fitting a mixed-effect model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Table S7 Treatment differences for Patients' Global Rating at Week 24 for Japanese and overall populations (full analysis set, combined studies)

Treatment differences	Japanese population			Overall population		
	Adjusted mean (SE)	95% CI	Nominal <i>P</i> value	Adjusted mean (SE)	95% CI	Nominal <i>P</i> value
Tiotropium + olodaterol 5/5 µg						
vs olodaterol 5 µg	-0.49 (0.15)	-0.78, -0.21	0.0007	-0.23 (0.05)	-0.33, -0.14	<0.0001
vs tiotropium 5 µg	-0.35 (0.16)	-0.66, -0.05	0.0233	-0.22 (0.05)	-0.32, -0.13	<0.0001
Tiotropium + olodaterol 2.5/5 µg						
vs olodaterol 5 µg	-0.48 (0.14)	-0.76, -0.20	0.0009	-0.17 (0.05)	-0.27, -0.08	0.0003
vs tiotropium 2.5 µg	-0.32 (0.16)	-0.63, -0.01	0.0415	-0.14 (0.05)	-0.24, -0.05	0.0029

Note: Adjusted mean (SE) obtained from fitting a mixed-effect model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Abbreviations: SE, standard error; CI, confidence interval.

Figure S1. FEV₁ AUC₀₋₃ response (a) and trough FEV₁ response (b) at Week 24 for the Japanese and overall populations.

Note: *** $P < 0.0001$ vs O 5 μg ; ** $P < 0.001$ vs O 5 μg ; * $P < 0.01$ vs O 5 μg ;

††† $P < 0.0001$ vs T 5 μg , ††† $P < 0.0001$ vs T 2.5 μg ; †† $P < 0.01$ vs T 2.5 μg (nominal

P values for the Japanese population).

Abbreviations: FEV₁, forced expiratory volume in 1 second; AUC₀₋₃, area under the curve from 0–3 hours; SE, standard error; O, olodaterol; T, tiotropium.

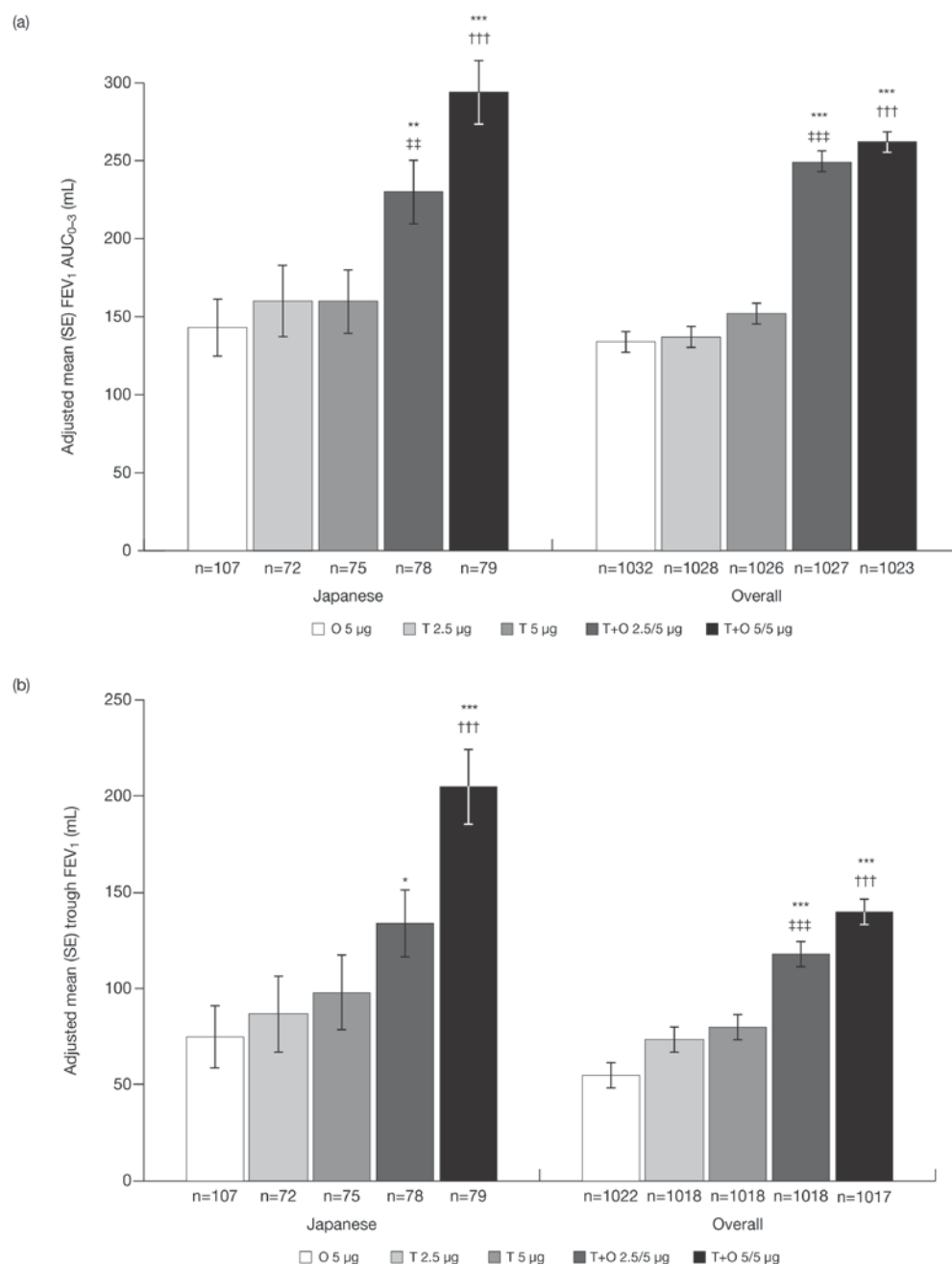


Figure S2. Weekly mean morning PEFr (a) and evening PEFr (b) for the Japanese sub-population (full analysis set, combined data).

Note: Morning PEFr common baseline mean (standard error), L/min: 194.26 (4.343);

evening PEFr common baseline mean (standard error), L/min: 203.50 (4.440).

Abbreviations: PEFr, peak expiratory flow rate; T, tiotropium; O, olodaterol.

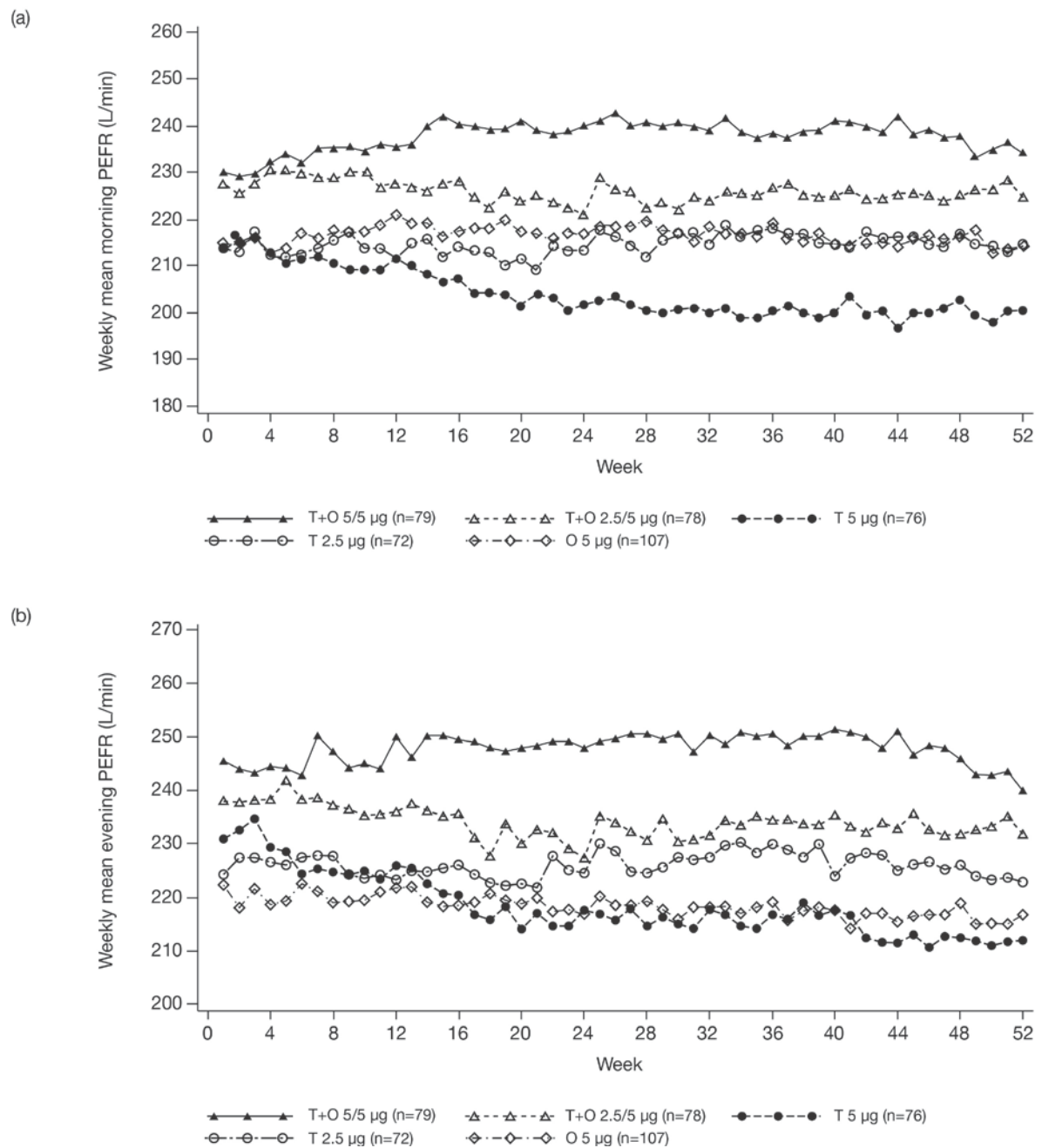


Figure S3. SGRQ component scores (change from baseline) at Week 24 for the Japanese sub-population (full analysis set, combined data).

Note: Common baseline mean (SE): symptom score 46.67 (1.15), activity score 48.71 (0.99), impact score 21.16 (0.79).

* $P < 0.05$; ** $P \leq 0.01$ (nominal P values).

Abbreviations: SGRQ, St. George's Respiratory Questionnaire; SE, standard error;

T, tiotropium; O, olodaterol.

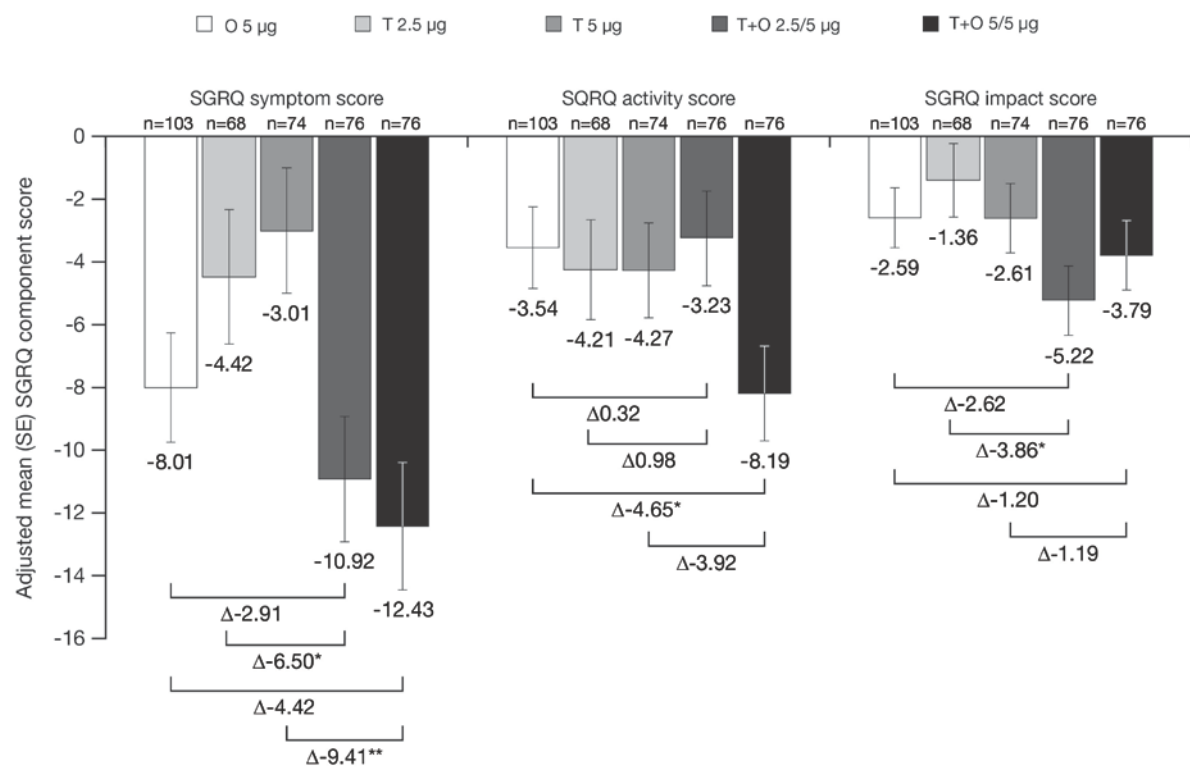


Figure S4. Daytime rescue medication use for the Japanese sub-population (full analysis set, combined population).

Note: Common baseline mean (standard error), puffs/day: 0.41 (0.045).

Abbreviations: T, tiotropium; O, olodaterol.

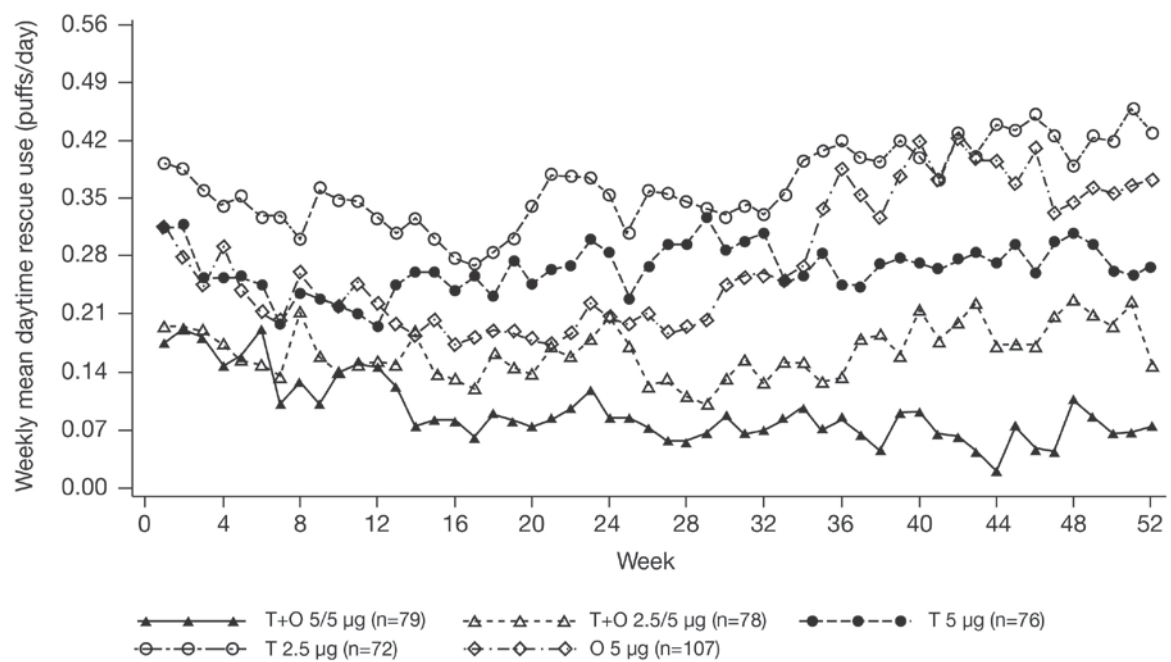
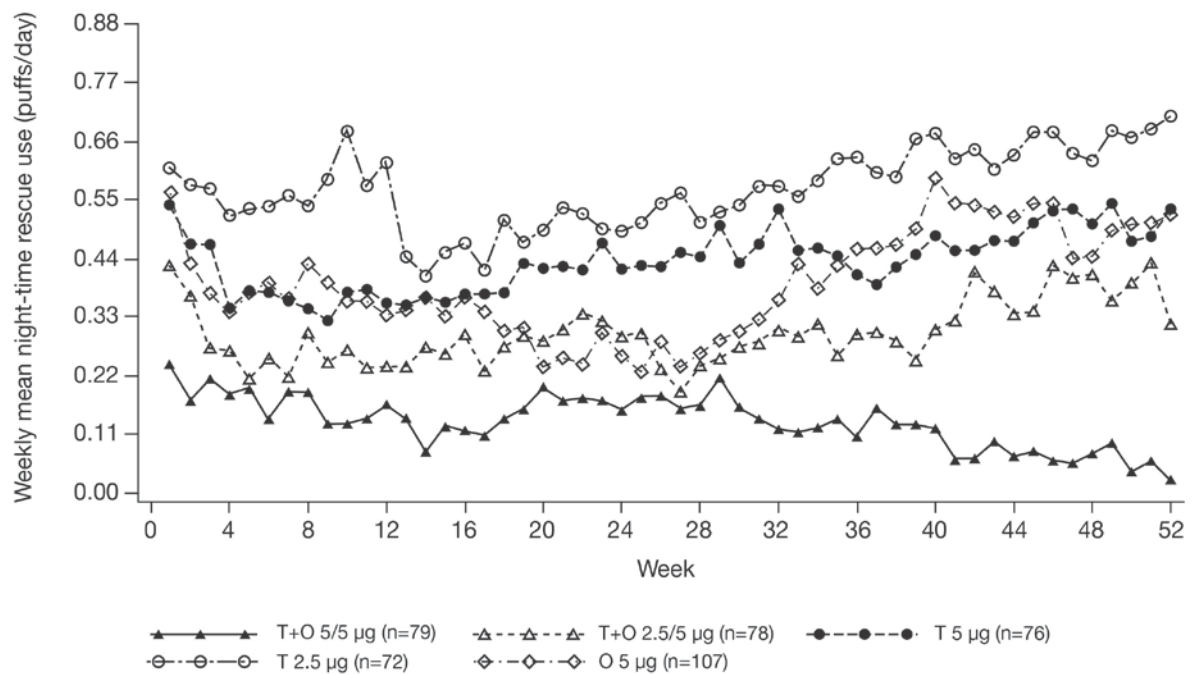


Figure S5. Night-time rescue medication use for the Japanese sub-population (full analysis set, combined studies).

Note: Common baseline mean (standard error), puffs/day: 0.68 (0.070).

Abbreviations: T, tiotropium; O, olodaterol.



Institutional review board approval

The protocols for TONADO[®] 1 and 2 were approved by the individual Institutional Review Boards (IRBs) for each trial center. These trial centers (all based in Japan) are listed as follows: National Hospital Organization, Asahikawa Medical Center, 7-4048, Hanasaki-cho, Asahikawa, Hokkaido; Iwate Medical University Hospital, 19-1, Uchimarui, Morioka, Iwate; National University Corporation, Tohoku University Hospital, 1-1, Seiryomachi, Aoba-ku, Sendai, Miyagi; National Hospital Organization, Ibaraki Higashi National Hospital, 825, Terunuma, Tokai-mura, Naga-gun, Ibaraki; Kameda Clinic, 1344, Higashi-cho, Kamogawa, Chiba; Juntendo University Hospital, 3-1-3, Hongo, Bunkyo-ku, Tokyo; Tokyo Medical University Hospital, 6-7-1, Nishishinjyuku Shinjyuku-ku, Tokyo; Nihon University Itabashi Hospital, 30-1, Oyaguchikami-cho, Itabashi-ku, Tokyo; Tosei General Hospital, 160, Nishioiwake-cho, Seto, Aichi; Matsusaka City Hospital, 1550, Tonomachi, Matsusaka, Mie; Kishiwada City Hospital, 1001, Gakuhara-cho, Kishiwada, Osaka; Kinki University Hospital, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka; Wakayama Medical University Hospital, 811-1, Kimiidera, Wakayama, Wakayama; National Hospital Organization, Himeji Medical Center, 68, Hommachi, Himeji, Hyogo; Kurume University Hospital, 67, Asahi-machi, Kurume, Fukuoka; Fukuoka University Hospital, 7-45-1, Nanakuma, Jonan-ku, Fukuoka; Harasanshin Hospital, 1-8, Taihaku-machi, Hakata-ku, Fukuoka; K-YOU HEALTH CARE Co. KIRIGAOKA TSUDA HOSPITAL, 3-9-20, Kirigaoka, Kokurakita-ku, Kitakyusyu, Fukuoka; Kumamoto Saishunso National Hospital, 2659, Suya, Koshi, Kumamoto; General Hospital Kagoshima Co-op Hospital, 5-20-10, Taniyamacyuo, Kagoshima; Kagoshima University Medical And Dental Hospital, 8-35-1, Sakuragaoka, Kagoshima; Okinawa Medical Association, 218-9, Arakawa, Minamihaebarucho,

Shimajiri-gun, Okinawa; Tokyo Medical University Ibaraki Medical Center, 3-20-1, Chuo, Ami-machi Inashiki-gun, Ibaraki; Social Welfare Organization Saiseikai Imperial Gift Foundation Incorporation, Saiseikai Kurihashi Hospital, 714-6, Koemon, Kuki, Saitama; Sakayori Clinic, 2-26-3, Higashi-oi, Shinagawa, Tokyo; Koto Hospital, 6-8-5, Ojima, Koto-ku, Tokyo; Kanagawa Cardiovascular and Respiratory Center, 6-16-1, Timiokahigashi; Shinshu University Hospital, 3-1-1, Asahi, Matsumoto-city, Nagano; National Hospital Organization, Matsumoto Medical Center, 811, Kotobuki-oyooka, Oaza Matsumoto, Nagano; National Hospital Organization, Tenryu National Hospital, 4201-2, Oro, Hamakitaku Hamamatsushi, Shizuoka; Komaki City Hospital, 1-20, Jobushi, Komaki, Aichi; Kobori Clinic, 5-11-8, Nishi-Nippori, Arakawa-ku, Tokyo; Chubu Rosai Hospital, 1-10-6, Komei, Minato-ku, Nagoya, Aichi; Gifu Prefectural General Medical Center, 4-6-1, Noisshiki, Gifu, Gifu; Daido Hospital, 9, Hakusuicho, Minamiku, Nagoya, Aichi; Nara Hospital Kinki University Faculty of Medicine, 1248-1, Otodacho, Ikoma, Nara; National Public Service Personnel Mutual Aid Associations, Kure Kyosai Hospital, 2-3-28, Nishichuoh Kure, Hiroshima; Takamatsu Municipal Hospital, 2-36-1, Miyawakicho, Takamatsu, Kagawa; KKR Takamatsu Hospital, 4-18, Tenjinmae, Takamatsu, Kagawa; Fukuoka National Hospital, 4-39-1, Yakatabaru Minami-ku, Fukuoka; National Hospital Organization, Fukuoka-Higashi Medical Center, 1-1-1, Chidori, Koga, Fukuoka; Seiwakai Medical Corporation, Nagata Hospital, 523-1, Shimomiyanaga-machi, Yanagawa-shi, Fukuoka; Kuwamizu Hospital, 1-14-41, Kuwamizu, Chuo-ku, Kumamoto, Kumamoto; Japan Labour Health and Welfare Organization, Tohoku Rosai Hospital, 4-3-21, Dainohara, Aoba-ku, Sendai, Miyagi.