Supplementary materials

Table S1 GSK R&D or local GSK sponsored Phase II–IV randomized clinical trials included in the analysis

Study name	ClinicalTrials.gov identifier	Principal inclusion/exclusion criteria*
Japan-only studies		
SCO100646	NCT00269126	Inclusion: Diagnosis of COPD; Both genders; Age 40–80 years. Exclusion: Diagnosis of asthma or an uncontrolled medical condition or respiratory disorder other than COPD.
SCO100648	NCT00269087	Inclusion: Diagnosis of COPD; Both genders; Age 40–80 years. Exclusion: Diagnosis of asthma or an uncontrolled medical condition or respiratory disorder other than COPD.
HZC114156	NCT01192191	Inclusion: Outpatient at least 40 years of age; Both genders (females of childbearing potential must be willing to use birth control method); Diagnosis of COPD at screening; Subjects with a current or prior history of at least 10 pack-years of cigarette smoking at screening; Post-bronchodilator FEV_1/FVC ratio of less than 70%; Post-bronchodilator FEV_1 of less than 80%. Exclusion: Current diagnosis of asthma; Respiratory disorders other than COPD; Upper or lower respiratory infection or exacerbation of COPD within 4 weeks prior to screening; Concurrent other disease that would confound study participation or affect subject safety; Allergies to study drugs, study drugs' excipients, medications related to study drugs; Taking another investigational medication or medication prohibited for use during this study.

DB2115362	NCT01376388	Inclusion: Outpatient; A signed and dated written informed consent prior to study participation; Japanese subjects 40 years of age or older at screening; Male or female subjects (female subjects who have childbearing potential have a negative pregnancy test at screening, and agree to one of the acceptable contraceptive methods used consistently and correctly); Diagnosis of COPD; 10 pack-year or greater history of cigarette smoking. Exclusion: Women who are pregnant or lactating or are planning on becoming pregnant during the study; A current diagnosis of asthma; Respiratory disorders other than COPD; Clinically significant non-respiratory diseases or abnormalities that are not adequately controlled; A chest X-ray or CT scan that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD; A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, $beta_2$-agonist, lactose/milk protein or magnesium stearate or a medical condition; Hospitalization for COPD or pneumonia within 12 weeks prior to screening.
AC4115361	NCT01702363	Inclusion: Outpatient; A signed and dated written informed consent prior to study participation; Japanese subjects 40 years of age or older at Visit 1; Male or female subjects (a female is eligible if she is of: Non-childbearing potential or childbearing potential and agrees to one of the contraceptive methods); Subjects with a clinical history of COPD in accordance with the definition by COPD domestic guideline; Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Visit 1. Exclusion: Women who are pregnant or lactating or are planning on becoming pregnant during the study; A current diagnosis of asthma; Known respiratory disorders other than COPD; Subjects with historical or current evidence of clinically significant abnormalities that are uncontrolled; A chest X-ray or CT scan that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD; Allergy or hypersensitivity to muscarinics, $beta_2$-

		agonists, lactose/milk protein or magnesium stearate or a condition that contraindicates participation.
SCO116571	NCT01607398[1]	Inclusion: Japanese (male or female) outpatients aged 40–80 years inclusive at Visit 1 (Female patients may be enrolled only if they are not of childbearing potential, or are of childbearing potential who agree to properly use protocol-specified contraceptive measures); Have a diagnosis of COPD (defined as per the COPD guideline); Have a FEV_1/FVC ratio <0.70 at 15–60 minutes following use of SALTANOL® inhaler; Have a FEV_1 of ≥40% to <80% of the predicted normal value at 15–60 minutes following use of SALTANOL® inhaler; Current or ex-smokers with a smoking history of at least 10 pack-years; Able to use the DISKUS inhaler and the short-acting inhaled anticholinergic drug. Exclusion: Diagnosed by the investigator (or sub-investigator) as having bronchial asthma; Have any respiratory disorder other than COPD (eg, lung cancer, sarcoidosis, tuberculosis [including old tuberculosis], pulmonary fibrosis); Have a chest X-ray (or CT scan) indicating a diagnosis other than COPD that might interfere with assessments in the study (This must be assessed using last imaging study performed within 6 months prior to Visit 1, or, a chest X-ray must be obtained at Visit 1); Have chronic respiratory failure; Have undergone lung volume reduction and/or lung transplant; Have had a COPD exacerbation or respiratory infection requiring systemic corticosteroid or microbial therapy or hospitalization, within 6 weeks prior to Visit 1.
SCO116717 (COSMOS-J)†	NCT01762800[2]	Inclusion: Male or female aged 40–80 years inclusive; Has an established clinical history of COPD (defined as per the GOLD definition); The subject achieves a grade of ≥1 on mMRC at Visit 1; A signed and dated written informed consent is obtained from the subject prior to study participation; The subject has a post-bronchodilator FEV_1 of ≥30% to ≤80% of predicted normal; The subject has a post-bronchodilator FEV_1/FVC ratio <70%.

		Exclusion: Has a predominant asthma (comorbid asthma is not an exclusion criterion); Has a medical diagnosis of narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction that in the opinion of the investigator should prevent them from entering the study (Note: As with other anticholinergic drugs, subjects with narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction should only be entered into the study at the investigator's discretion); Has known respiratory disorders other than COPD (eg, lung cancer, sarcoidosis, tuberculosis, or lung fibrosis); Has undergone lung surgery eg, lung transplant and/or lung volume reduction; Had a chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken at Visit 1, if subject has not had one and/or CT image taken within 3 months of Visit 1); Requires regular (daily) or long term oxygen therapy (LTOT). (LTOT is defined as ≥12 hours oxygen use per day).
Multi-country studies		
HZC112206	NCT01053988[3]	Inclusion: Outpatient; Subjects must give their signed and dated written informed consent to participate; Male or female subjects (A female is eligible to enter and participate in the study if she is of: Non-childbearing potential OR Childbearing potential, has a negative pregnancy test at screening, and agrees to one of the acceptable contraceptive methods defined in the protocol); ≥40 years of age at screening (Visit 1); Subjects with a clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society; Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening (Visit 1). Exclusion: Women who are pregnant or lactating or are planning on becoming pregnant during the study; Subjects with a current diagnosis of asthma; Subjects with α1-antitrypsin deficiency as the underlying cause of COPD; Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary

		hypertension, interstitial lung diseases, or other active pulmonary diseases; Subjects with lung volume reduction surgery within the 12 months prior to screening (Visit 1); Subjects with a chest X-ray (or CT scan) that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD.
HZC112207	NCT01054885[3]	Inclusion: Outpatient; Subjects must give their signed and dated written informed consent to participate; Male or female subjects (a female is eligible to enter and participate in the study if she is of: Non-childbearing potential OR Childbearing potential, has a negative pregnancy test at screening, and agrees to one of the acceptable contraceptive methods defined in the protocol); ≥40 years of age at screening (Visit 1); Subjects with a clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society;[4] Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening (Visit 1). Exclusion: Women who are pregnant or lactating or are planning on becoming pregnant during the study; Subjects with a current diagnosis of asthma; Subjects with α1-antitrypsin deficiency as the underlying cause of COPD; Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases; Subjects with lung volume reduction surgery within the 12 months prior to screening (Visit 1); Subjects with a chest X-ray (or CT scan) that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD.
DB2113361	NCT01313637[4]	Inclusion: Diagnosis of COPD; 10 pack-year or greater history of cigarette smoking; Post-bronchodilator FEV_1/FVC of <0.7; Predicted FEV_1 of 70% of normal or less; mMRC dyspnea score of 2 or greater. Exclusion: Women who are pregnant, lactating, or planning to become pregnant; Respiratory disorders other than COPD, including a current diagnosis of asthma; Clinically significant non-respiratory

		diseases or abnormalities that are not adequately controlled; Significant allergy or hypersensitivity to anticholinergics, beta$_2$-agonists, or the excipients of magnesium stearate or lactose used in the inhaler delivery device; Hospitalization for COPD or pneumonia within 12 weeks prior to screening; Lung volume reduction surgery within 12 weeks prior to screening.
DB2113373	NCT01313650[5]	Inclusion: Diagnosis of COPD; 10 pack-year or greater history of cigarette smoking; Post-bronchodilator FEV_1/FVC of <0.7; Predicted FEV_1 of 70% of normal or less; mMRC dyspnea score of 2 or greater. Exclusion: Women who are pregnant, lactating, or planning to become pregnant; Respiratory disorders other than COPD, including a current diagnosis of asthma; Clinically significant non-respiratory diseases or abnormalities that are not adequately controlled; Significant allergy or hypersensitivity to anticholinergics, beta-agonist, or the excipients of magnesium stearate or lactose used in the inhaler delivery device; Hospitalization for COPD or pneumonia within 12 weeks prior to screening; Lung volume reduction surgery within 12 weeks prior to screening.
AC4115408	NCT01387230[6]	Inclusion: Diagnosis of COPD; 10 pack-year or greater history of cigarette smoking; Post-bronchodilator FEV_1/FVC of <0.7; Predicted FEV_1 of 70% of normal or less; mMRC dyspnea score of 2 or greater. Exclusion: Women who are pregnant, lactating, or planning to become pregnant; Respiratory disorders other than COPD, including a current diagnosis of asthma; Clinically significant non-respiratory diseases or abnormalities that are not adequately controlled; Significant allergy or hypersensitivity to anticholinergics, beta$_2$-agonists, or the excipients of magnesium stearate or lactose used in the inhaler delivery device; Hospitalization for COPD or pneumonia within 12 weeks prior to screening; Lung volume reduction surgery within 12 weeks prior to screening.

Notes: *The first six inclusion and exclusion criteria, as cited on clinicaltrials.gov, are given (accessed February 2017); †Did not exclude patients with asthma overlap.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CT, computed tomography; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

References:

1. Asai K, Kobayashi A, Makihara Y, Johnson M. *Int J Chron Obstruct Pulmon Dis.* 2015;10:803–811.
2. Betsuyaku T, Kato M, Fujimoto K, et al. *Int J Chron Obstruct Pulmon Dis.* 2013;8:453–459.
3. Svedsater H, Dale P, Garrill K, Walker R, Woepse MW. *BMC Pulm Med.* 2013;13:72.
4. Celli B, Crater G, Kilbride S, et al. *Chest.* 2014;145(5):981–991.
5. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. *Respir Med.* 2013;107(10):1538–1546.
6. Trivedi R, Richard N, Mehta R, Church A. *Eur Respir J.* 2014;43(1):72–81.

Table S2 Patient demographics by percentage blood eosinophils

Characteristic	**All studies, Japanese patients**			**Multi-country studies, non-Japanese patients**		
	<2% EOS (N=402)	≥2% EOS (N=902)	Total (N=1,304)	<2% EOS (N=2,218)	≥2% EOS (N=2,937)	Total (N=5,155)
Age (years), n (%)						
<65	97 (24)	206 (23)	303 (23)	1,336 (60)	1,697 (58)	3,033 (59)
≥65	305 (76)	696 (77)	1,001 (77)	882 (40)	1,240 (42)	2,122 (41)
Male, n (%)	377 (94)	861 (95)	1,238 (95)	1,420 (64)	2,038 (69)	3,458 (67)
GOLD stage, n (%)						
n	393	859	1,252[a]	2,205	2,927	5,132
I: FEV_1≥80% predicted	2 (<1)	2 (<1)	4 (<1)	1 (<1)	1 (<1)	2 (<1)
II: 50%≤FEV_1<80% predicted	224 (57)	513 (60)	737 (59)	1,002 (45)	1,369 (47)	2,371 (46)
III: 30%≤FEV_1<50% predicted	146 (37)	317 (37)	463 (37)	985 (45)	1,279 (44)	2,264 (44)
IV: FEV_1<30% predicted	21 (5)	27 (3)	48 (4)	217 (10)	278 (9)	495 (10)

SGRQ Total score						
n	85	71	156[b]	1,344	1,561	2,905[b]
Mean (SD)	37.80 (16.66)	41.25 (14.22)	39.37 (15.64)	50.35 (17.61)	47.70 (17.61)	48.92 (17.66)
Number of patients with COPD exacerbations managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) in the past 12 months, n (%)						
n	227	520	747[c]	820	1,323	2,143[d]
0	222 (98)	505 (97)	727 (97)	728 (89)	1,175 (89)	1,903 (89)
1	5 (2)	15 (3)	20 (3)	80 (10)	129 (10)	209 (10)
2	0	0	0	11 (1)	14 (1)	25 (1)
>2	0	0	0	1 (<1)	5 (<1)	6 (<1)
Number of patients with COPD exacerbations requiring						

oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) in the past 12 months, n (%)	313	591	904[e]	2,218	2,937	5,155
n	274 (88)	522 (88)	796 (88)	1,662 (75)	2,164 (74)	3,826 (74)
0	29 (9)	50 (8)	79 (9)	434 (20)	600 (20)	1,034 (20)
1	7 (2)	13 (2)	20 (2)	84 (4)	115 (4)	199 (4)
2	3 (<1)	6 (1)	9 (<1)	38 (2)	58 (2)	96 (2)
>2						
Number of patients with COPD exacerbations requiring hospitalization in the past 12 months, n (%)						
n	393	860	1,253[a]	2,218	2,937	5,155
0	375 (95)	831 (97)	1,206 (96)	2,003 (90)	2,665 (91)	4,668 (91)
1	18 (5)	26 (3)	44 (4)	188 (8)	249 (8)	437 (8)

2	0	3 (<1)	3 (<1)	23 (1)	20 (<1)	43 (<1)
>2	0	0	0	4 (<1)	3 (<1)	7 (<1)

Notes: [a]Not available for study SCO116571; [b]Available for studies AC4115408, DB2113361, and DB2113373 only; [c]Available for studies AC4115361, DB2115362, HZC112206, HZC112207, HZC114156, and SCO116717 only; [d]Available for studies HZC112206 and HZC112207 only; [e]Not available for studies SCO100646, SCO100648, and SCO116571.

Abbreviations: EOS, eosinophil; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

Table S3 Patient demographics in Japan studies by absolute eosinophils

		Japan studies		
Characteristic		<150cells/mm^3 EOS (N=343)	≥150cells/mm^3 EOS (N=505)	Total (N=848)
Age (years), n (%)				
<65		68 (20)	121 (24)	189 (22)
≥65		275 (80)	384 (76)	659 (78)
Male, n (%)		321 (94)	482 (95)	803 (95)
GOLD stage, n (%)				
n		329	468	797
I:	FEV_1≥80% predicted	1 (<1)	0	1 (<1)
II:	50%≤FEV_1<80% predicted	173 (53)	272 (58)	445 (56)
III:	30%≤FEV_1<50% predicted	144 (44)	180 (38)	324 (41)
IV:	FEV_1<30% predicted	11 (3)	16 (3)	27 (3)
Number of patients with COPD exacerbations managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) in the past 12 months, n (%)				
n		177	271	448[a]
0		175 (99)	262 (97)	437 (98)
1		2 (1)	9 (3)	11 (2)
2		0	0	0
>2		0	0	0

Number of patients with COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) in the past 12 months, n (%)			
n	177	271	448[a]
0	159 (90)	236 (87)	395 (88)
1	13 (7)	26 (10)	39 (9)
2	4 (2)	7 (3)	11 (2)
>2	1 (<1)	2 (<1)	3 (<1)
Number of patients with COPD exacerbations requiring hospitalization in the past 12 months, n (%)			
n	329	468	797[b]
0	313 (95)	456 (97)	769 (96)
1	14 (4)	12 (3)	26 (3)
2	2 (<1)	0	2 (<1)
>2	0	0	0

Notes: Studies AC4115361, DB2115362, HZC114156, SCO100646, SCO100648, and SCO116571 are included; For studies SCO100646, SCO100658, and SCO116571, patients in the full analysis set population are included; [a]Not available for studies SCO100646, SCO100648, and SCO116571; [b]Not available for study SCO116571.

Abbreviations: EOS, eosinophil; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease.