A new class of bronchodilator improves lung function in COPD: A trial with GSK961081

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ONLINE SUPPLEMENT 1

Sample size assumptions

Sample size calculations were based on the primary efficacy endpoint. A 2-sided, 5% significance level was considered acceptable for this study. A separate closed step-down testing procedure was used for the once-daily and twice-daily dosing intervals and was apportioned 2.5% for each dosing interval. Forty-two evaluable patients per active arm, and 63 evaluable placebo patients would provide greater than 90% power to detect a difference between a GSK961081 dose regimen and placebo of 150 mL, assuming a standard deviation of 200 mL. Allowing for 15% withdrawal, 425 patients (50 per active arm, 75 placebo) were planned to be randomized.

ONLINE SUPPLEMENT 2

Inclusion criteria continued

Patients were excluded if they were pregnant or had a body mass index (BMI) ≥35 kg/m^2. Patients were excluded if they were previously hospitalised for an acute COPD exacerbation or pneumonia within 12 weeks of study start, had lung resection surgery, or clinically significant abnormalities on X-ray taken within the previous 6 months. Patients were excluded if they had electrocardiogram (ECG) abnormalities, a pacemaker, a current cancer malignancy liver disease, hepatitis antigens or a history of drug allergies or hypersensitivity to cholinergic, beta agonists or milk proteins. Patients could not use LAMA or LABAs alone or in combination, or had oxygen therapy greater than 12h per day, or have taken part in a pulmonary rehabilitation program within 4 weeks of the screening visit. Patients also needed to be able to withhold their rescue medication for a 4 hr period prior to spirometry testing.

ONLINE SUPPLEMENT 3

Efficacy assessments continued

Spirometry was carried out using standardised spirometry equipment (Vitalograph) from Biomedical Systems (BMS) according to American Thoracic Society (ATS) guidelines [21] at all clinic visits. Over-reading of the spirometry efforts was carried out centrally by BMS. Serial spirometry over 12 hours was carried out at on treatment days 1 and 28 at all sites. At sites which were able to accommodate patients overnight for 24h at visit 6. Subject diaries were filled in by the patients to collect rescue medicine use, any untoward medical problem, any medications used and the time of dosing for day 13 and day 27.

ONLINE SUPPLEMENT 4

Safety assessments

The incidence and severity of adverse events (AEs) were collected. Vital signs, pulse rate, systolic and diastolic blood pressure were carried out at each clinic visit except the final clinic visit day 29 (Visit7) or early withdrawal. 12 lead ECGs were carried out at the screening visit, treatment days 1, 14 and 28 and for early withdrawal. ECG over reading was carried out by Biomedical Systems (BMS) a centralised vendor. Further safety assessments included clinical laboratory tests (QUEST), chemistry including glucose and potassium at visits 1, 5, 6, early withdrawal and urinalysis at screening and on day 28. Urine pregnancy tests were carried out at visits 1, 2, 7 and early withdrawal. COPD exacerbations were defined as a worsening of COPD symptoms that require treatment over and above salbutamol, including antibiotics or oral corticosteroids or hospitalisation, and severity was also collected and reported.

ONLINE SUPPLEMENT TABLE 1

Data subset splits of the primary endpoint (LS mean change from baseline trough FEV_1 on day 29 compared to placebo)

	Reversible to salbutamol		Not reversible to salbutamol		Concurrent ICS use		No concurrent ICS use	
	n	Difference (95% CI)	n	Difference (95% CI)	n	Difference (95% CI)	n	Difference (95% CI)
SAL	16	109 (-21, 238)	27	82 (-10, 174)	24	21 (-79, 121)	19	158 (40, 278)
100 BD	16	203 (76, 330)	31	157 (69, 245)	28	109 (12, 205)	19	256 (138, 374)
200 BD	17	280 (151, 409)	29	225 (135, 315)	27	217 (120, 313)	19	286 (166, 405)
400 BD	16	290 (165, 415)	33	237 (150, 324)	27	227 (131, 323)	22	293 (179, 407)
100 OD	13	306 (172, 441)	32	91 (3, 179)	29	136 (40, 231)	16	165 (39, 291)
400 OD	12	232 (87, 378)	29	224 (135, 313)	21	199 (96, 302)	20	244 (127, 362)
800 OD	13	257 (125, 390)	35	290 (204, 376)	26	224 (127, 321)	22	350 (237, 463)

LS mean differences are compared to placebo.

BD: twice daily; CI: confidence interval; ICS: inhaled corticosteroid; LS: least squares; OD: once daily; SAL: salmeterol.

LS means adjusted for age, sex, smoking status, reversibility stratum, overnight site stratum, concurrent ICS use, baseline and treatment.

ONLINE SUPPLEMENT TABLE 2

Trough FEV1 changes during the study.

Trough FEV_1, LS mean chg (mL)	Placebo	SAL 50 BD	081 100 BD	081 200 BD	081 400 BD	081 100 OD	081 400 OD	081 800 OD
Day 2	16	94	155	239	261	111	162	189
Day 14	-6	45	176	227	228	93	177	271
Day 28	-17	38	143	253	230	85	223	257
Day 29	-7	71	167	243	251	148	209	270

Trough FEV_1, LS mean diffs (mL)		SAL 50 BD	081 100 BD	081 200 BD	081 400 BD	081 100 OD	081 400 OD	081 800 OD
Day 2		78	139	223	245	96	146	173
Day 14		51	182	233	234	99	183	277
Day 28		55	160	270	247	102	240	274
Day 29		77	173	249	258	155	215	277

BD: twice daily; FEV_1: forced; LS: least squares; OD: once daily; SAL: salmeterol.