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COPD

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

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ABSTRACT GSK961081 is a bifunctional molecule demonstrating both muscarinic antagonist and β-agonist activities.

This was a 4-week, multicentre, randomised, double-blind, double-dummy, placebo and salmeterol controlled parallel group study. Doses ranging across three twice-daily doses and three once-daily doses were assessed in moderate and severe chronic obstructive pulmonary disease (COPD) patients. Trough forced expiratory volume in 1 s ($FEV_1$) at day 29 was the primary end-point. At days 1 and 28, 12-h $FEV_1$ spirometry was performed in all patients. A subset of patients underwent complete 24-h spirometry at day 28.

The study recruited 436 patients. GSK961081 showed statistically and clinically significant differences from placebo in all doses and regimens for trough $FEV_1$ on day 29 (155–277 mL). The optimal total daily dose was 400 μg, either as 400 μg once daily or as 200 μg twice daily, with an improvement in day 29 trough $FEV_1$ of 215 mL and 249 mL, respectively. Other efficacy end-points also showed improvement. No effects were observed on glucose, potassium, heart rate, blood pressure and no dose–response effect was seen on corrected QT elongation.

This study showed that GSK961081 is an effective bronchodilator in COPD and appeared to be safe and well tolerated.

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## Introduction

Pharmacological management of chronic, stable chronic obstructive pulmonary disease (COPD) is primarily aimed at improving symptoms and quality of life, optimising lung function, reducing exacerbations and improving exercise tolerance [1, 2]. Inhaled bronchodilators, including $\beta_2$-agonists and antimuscarinics, are the mainstays of therapy in patients diagnosed with COPD [1].

While the mechanism of dual bronchodilators is not fully understood, addition of a $\beta_2$- agonist to an antimuscarinic results in greater bronchodilation in the airways than either component alone. Mechanistically it is thought that the addition of a $\beta_2$-agonist decreases the release of acetylcholine (ACh) through the modulation of cholinergic neurotransmission by pre-junctional $\beta_2$-adrenergic receptors ($\beta_2$-ARs), amplifying the bronchial smooth muscle relaxation induced by the muscarinic antagonist. Secondly, the addition of a muscarinic antagonist reduces the bronchoconstrictor effects of ACh, whose release has been modified by the $\beta_2$-agonist, and thereby amplifies the bronchodilation elicited by the $\beta_2$-agonist through the direct stimulation of smooth muscle $\beta_2$-ARs [3].

Clinical research confirms that addition of $\beta_2$-agonist to a muscarinic antagonist is more effective at improving lung function and patient-centred outcomes than either of the components alone and that there are no untoward safety issues [4–9]. In studies evaluating the combined use of tiotropium with formoterol or salmeterol, the number and type of reported adverse events were similar when comparing co-administration of monotherapies with individual treatments for up to 1 year [6–10].

As of 2012 there is currently no licensed combination of long-acting β-agonist/long-acting muscarinic antagonist, either as two separate drugs in the same device or as a single molecule. Compounds with both muscarinic antagonist and β-agonist activity offer a single pharmacokinetic profile for both pharmacological activities, potential for maximising the synergy between the two mechanisms, and a simpler technical and clinical development pathway compared to coformulation of two compounds [11]. GSK961081 is a bifunctional molecule and has muscarinic antagonist activity at one end of the molecule, separated from $\beta_2$-agonist activity by an inert linker portion. The bifunctional nature of GSK961081 has been demonstrated *in vitro* [12] and *in vivo* in a guinea pig bronchoprotection model [13]. In a study in healthy volunteers with and without propranolol ($\beta_2$-adrenergic receptor blockade) GSK961081 showed activity at both receptors, with the $\beta_2$-agonist effect being longer lasting than the antimuscarinic activity [14]. In a small, 14-day crossover study in 50 moderate COPD patients, GSK961081 was found to be safe and well tolerated and showed bronchodilation *versus* placebo that was comparable to tiotropium plus salmeterol [15].

This study was designed to determine the bronchodilator effects of GSK961081, the dose and dosing interval (using trough $FEV_1$ at day 29 as the primary outcome), as well as safety and tolerability in moderate and severe COPD patients. The study evaluated three once-daily doses and three twice-daily doses, a placebo arm and an active comparator, salmeterol.

## Methods

### Study design

This was a 4-week, phase IIb, multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled, parallel-group, dose-interval and dose-ranging study. After the screening visit and a 7-day run-in period, eligible patients were randomised and entered a 28-day treatment period. Clinic visits were on days 1, 2, 14, 28 and 29, plus two telephone contacts on day 7 and 7 days after the last clinic visit.

Patients enrolled at centres with overnight accommodation had 24-h serial spirometry assessed on day 28.

### Sample size calculations

Sample size calculations were based on the primary efficacy end-point and the assumptions are shown in the online supplementary material S1. Eligible patients were randomised to one of eight arms, with once-daily doses of 100 μg, 400 μg or 800 μg or twice-daily doses of 100 μg, 200 μg or 400 μg of GSK961081, 50 μg salmeterol twice daily or placebo (table 1), in a ratio of 2:2:2:2:2:2:2:3. Patients were provided with two Diskus inhalers (GlaxoSmithKline, Ware, UK and Stevenage, UK), one for morning use and one for evening use. For the once-daily regimen the evening inhaler was a placebo. The study was stratified by reversibility to salbutamol and inhaled corticosteroid (ICS) use.

### Study patients

This study included both current and former smokers aged $\geqslant$40 years, who had a smoking history of $\geqslant$10 pack-years. Patients had a clinical diagnosis of moderate-to-severe stable COPD (post-bronchodilator forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity (FVC) $<$70% and $FEV_1$ $\geqslant$30% and $\leqslant$70%

TABLE 1 Patient demographics and clinical characteristics at screening

| | Placebo | Salmeterol | GSK961081 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Twice daily | | | Once daily | | |
| | | | 100 μg | 200 μg | 400 μg | 100 μg | 400 μg | 800 μg |
| **ITT subjects n** | 81 | 47 | 52 | 50 | 54 | 50 | 50 | 52 |
| **Age years** | 63±7 | 61±7 | 62±9 | 61±9 | 63±8 | 63±9 | 62±8 | 61±9 |
| **Male %** | 70 | 62 | 71 | 64 | 70 | 64 | 52 | 67 |
| **BMI kg·m$^{-2}$** | 26±4 | 26±4 | 26±4 | 26±4 | 26±4 | 26±4 | 27±4 | 26±4 |
| **Current smoker %** | 44 | 62 | 54 | 66 | 46 | 40 | 54 | 48 |
| **Concurrent ICS use %** | 59 | 55 | 58 | 60 | 56 | 60 | 54 | 56 |
| **Reversible to salbutamol[#] %** | 33 | 36 | 33 | 34 | 37 | 32 | 26 | 31 |
| **FEV1 L[¶]** | 1.56±0.53 | 1.48±0.47 | 1.55±0.50 | 1.59±0.46 | 1.62±0.47 | 1.63±0.49 | 1.53±0.45 | 1.56±0.42 |
| **FEV1 % pred[¶]** | 49±11 | 48±10 | 50±10 | 51±10 | 51±10 | 53±10 | 52±10 | 51±10 |
| **FEV1 % reversibility** | 12±11 | 12±16 | 12±14 | 13±13 | 14±11 | 11±12 | 12±12 | 13±13 |
| **FEV1/FVC ratio[¶]** | 0.49±0.10 | 0.50±0.10 | 0.51±0.09 | 0.50±0.09 | 0.50±0.10 | 0.50±0.10 | 0.52±0.10 | 0.51±0.09 |

Data are presented as mean±SD, unless otherwise stated. ITT: intent-to-treat; BMI: body mass index; ICS: inhaled corticosteroid; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. [#]: reversibility to salbutamol defined as increase in FEV1 of 200 mL and 12% following salbutamol administration; [¶]: post-salbutamol measurements.

predicted), according to the National Health and Nutrition Examination Survey III [16]. Patients on a stable dose of ICS were allowed to participate in the study.

A current diagnosis of asthma was exclusionary. Due to the presence of vocal fold erosions in dogs given high doses of GSK961081, patients who were symptomatic (or had a documented history of) laryngopharyngeal reflux, extraoesophageal reflux, posterior laryngitis or laryngopharyngeal ulcerations and erosions were also excluded. This was to ensure that patients with pre-existing throat problems would not confound the potential to identify any new instances of throat irritation during the study. Further characteristics of the COPD population are shown in the online supplementary material (S2).

The study was approved by the medical ethical committees of the participating centres, and all patients gave their written informed consent. The study was conducted according to the declaration of Helsinki using Good Clinical Practice.

### *Study assessments*

#### *Efficacy*

Spirometry was carried out using the Vitalograph (Biomedical Systems (BMS), Brussels, Belgium) (online supplementary material (S3)). Over-reading of traces was also performed by BMS. A subject was reversible if they increased their pre-salbutamol FEV1 by $\geqslant$200 mL and $\geqslant$12% 15 min after the administration of 400 μg of salbutamol at the screening visit.

#### *Safety assessments*

The incidence and severity of all adverse events was recorded in the electronic case report form. Details for ECGs, blood chemistry and vital signs are in the online supplementary material (S4). Data were collected for any patients who reported throat symptoms for 7 days or longer, including hoarseness of voice, sore throat, lump in throat, difficulty in swallowing or any abnormal sensations in the throat. These patients also underwent a protocol-defined flexible laryngoscopy examination by a specialist.

#### *End-points*

The primary end-point for the study was the change from baseline in trough FEV1 at day 29. Trough was defined as the mean of 11- and 12-h measurement after the evening dosing on day 28.

Secondary end-points included the weighted mean for 0–24-h serial FEV1 measurements in the subset of patients with overnight spirometry, serial FEV1 on day 28 at each time-point up to 24 h post-dose in the subgroup of patients undergoing overnight spirometry and serial morning post-dose FEV1 0–12 h on day 1 and day 28 in the whole cohort.


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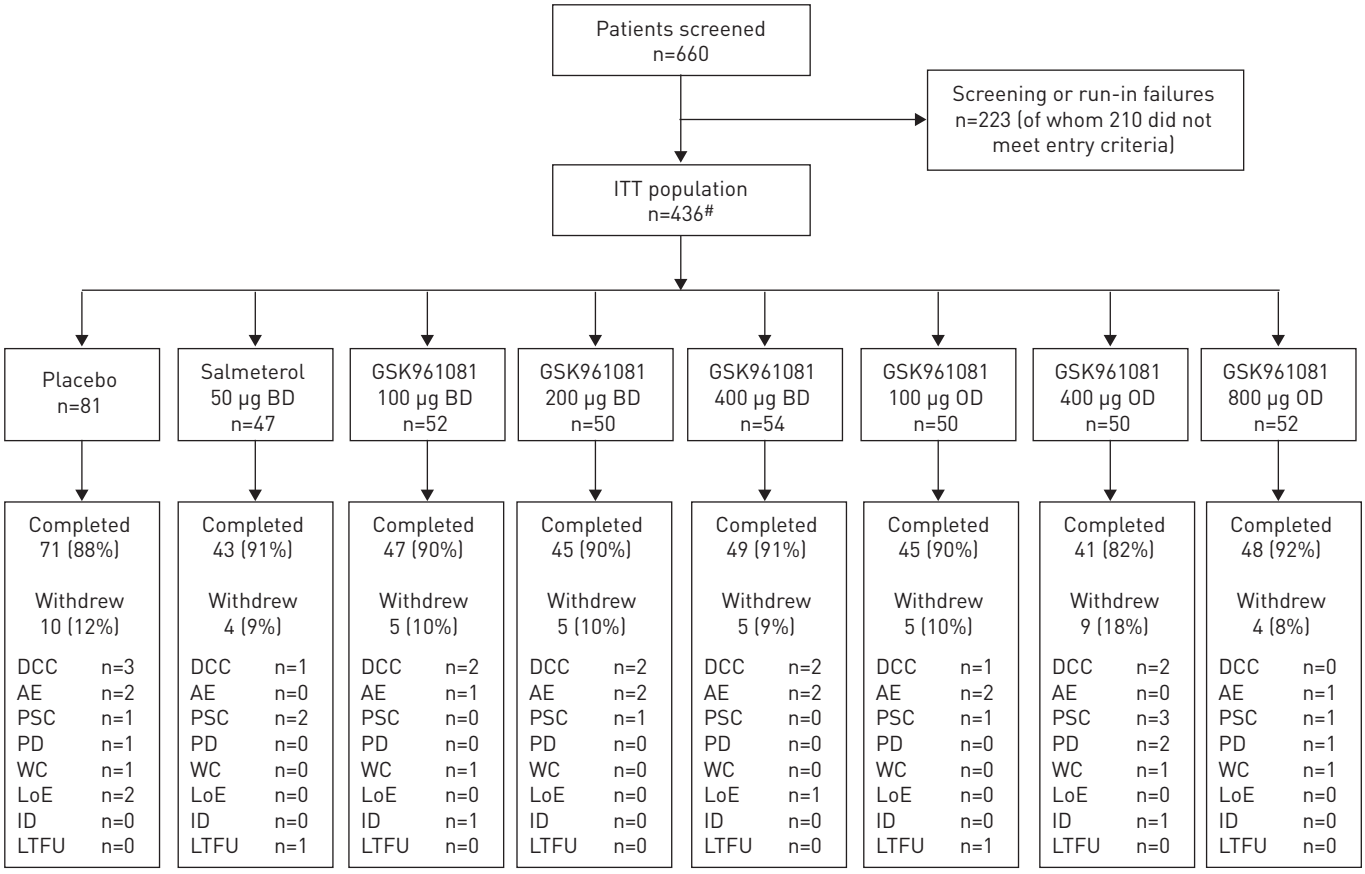


FIGURE 1 Subject disposition consort diagram. ITT: intent-to-treat; BD: twice daily; OD: once daily; DCC: did not meet continuation criteria; AE: adverse event; PSC: protocol-defined stopping criteria; PD: protocol deviation; WC: withdrew consent; LoE: lack of efficacy; ID: investigator discretion; LTFU: lost to follow-up. #: 437 subjects were randomised, but one subject did not receive any randomised medication, leaving 436 for the ITT population.

### *Statistical analysis*

The primary end-point was analysed using a repeated measures model, with fixed effects for baseline $FEV_1$, reversibility, concurrent ICS use, sex, age, smoking status (at screening), treatment, study day, treatment by study day interaction and whether or not the patient participated in 24-h spirometry assessments. In order

TABLE 2 Results for least squares mean change from baseline trough forced expiratory volume in 1 s on day 29

| Treatment | Subjects n | Change from baseline mL | Difference from placebo mL | p-value *versus* placebo | Difference from salmeterol mL# | p-value *versus* salmeterol# |
|---|---|---|---|---|---|---|
| **Placebo** | 71 | -7 | | | | |
| **Salmeterol** | 43 | 71 | 77 (1–153) | 0.046# | | |
| **GSK961081** | | | | | | |
| Twice daily | | | | | | |
| 100 µg | 47 | 167 | 173 (100–247) | <0.001 | 96 (14–179) | 0.023 |
| 200 µg | 46 | 243 | 249 (175–323) | <0.001 | 172 (89–255) | <0.001 |
| 400 µg | 49 | 251 | 258 (185–330) | <0.001 | 181 (98–263) | <0.001 |
| Once daily | | | | | | |
| 100 µg | 45 | 148 | 155 (80–229) | <0.001 | 78 (-7–162) | 0.071 |
| 400 µg | 41 | 209 | 215 (139–291) | <0.001 | 138 (53–223) | 0.002 |
| 800 µg | 48 | 270 | 277 (204–350) | <0.001 | 200 (117–282) | <0.001 |

Data are presented as least squares mean or least squares mean (95% CI), unless otherwise stated. For the primary end-point, p-values for GSK961081 doses were compared to placebo at $\alpha$=0.025 due to separate closed step-down procedures. Least squares means were adjusted for age, sex, smoking status, reversibility stratum, overnight site stratum, concurrent inhaled corticosteroid use, baseline and treatment. #: inferences involving salmeterol were *post hoc* analyses.

TABLE 3 Weighted mean 0–24-h forced expiratory volume in 1 s ($FEV_1$) on day 28, trough forced vital capacity (FVC) on day 29 and salbutamol use during the study

| | Weighted mean $FEV_1$ (0–24 h) on day 28 | | Trough FVC on day 29 | | Salbutamol use | |
|---|---|---|---|---|---|---|
| | Subjects | Difference mL | Subjects | Difference mL | Subjects | Difference mL |
| **Placebo** | 34 | | 71 | | 78 | |
| **Salmeterol** | 19 | 85 (-21–191)$^{\#}$ | 43 | 120 (-3–244)$^{\#}$ | 43 | -0.39 (-0.73– -0.05)* |
| **GSK961081** | | | | | | |
| Twice daily | | | | | | |
| 100 µg | 22 | 226 (125–327)*** | 47 | 310 (190–430)*** | 50 | -0.57 (-0.89– -0.25)*** |
| 200 µg | 21 | 325 (222–428)*** | 46 | 374 (253–496)*** | 48 | -0.56 (-0.88– -0.23)*** |
| 400 µg | 24 | 307 (209–405)*** | 49 | 328 (210–446)*** | 52 | -0.74 (-1.05– -0.42)*** |
| Once daily | | | | | | |
| 100 µg | 18 | 246 (139–353)*** | 45 | 153 (31–275)* | 48 | -0.45 (-0.78– -0.12)** |
| 400 µg | 18 | 300 (192–407)*** | 41 | 310 (185–435)*** | 45 | -0.65 (-0.99– -0.32)*** |
| 800 µg | 23 | 335 (236–434)*** | 48 | 381 (261–500)*** | 51 | -0.62 (-0.94– -0.30)*** |

Data are presented as n or least squares mean (95% CI). Inference between salmeterol and placebo was part of a *post hoc* analysis. Least squares means were adjusted for age, sex, smoking status, reversibility stratum, overnight site stratum, concurrent inhaled corticosteroid use, baseline and treatment. $^{\#}$: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

to preserve an overall $\alpha$ level of 5% inference *versus* placebo a closed sequential testing procedure was used within each dosing regimen at a significance level of 2.5%, initially comparing the highest dose with placebo. Subsequent comparisons at lower doses continued in a step-down manner only if the preceding comparison was significant. Inferences for secondary end-points were not adjusted for multiplicity. A *post hoc* analysis was carried out to provide inferences between all groups and salmeterol.

## Results

### *Cohort characteristics*

437 patients were randomised into the study. One patient received no investigational product and was withdrawn, giving a modified intent-to-treat population of 436 patients from nine countries and 49 sites, with 46% of patients in the overnight cohort. Demographic characteristics of the study population can be found in table 1 and the disposition of patients in figure 1.

For the primary end-point (morning trough $FEV_1$ at day 29), GSK961081 at all doses was significantly different from placebo ($p<0.001$) (table 2). Differences for the once daily doses ranged from 155 mL (100 µg) to 277 mL (800 µg) and differences for the twice daily doses ranged from 173 mL (100 µg) to 258 mL (400 µg). When looking at treatment effects *versus* placebo within the pre-defined strata, $FEV_1$ improvements were generally greater for patients who were reversible to salbutamol and greater for patients who were not concurrent ICS users (online supplementary table S1). During the study the trough $FEV_1$ increased over the first 14 days and remained constant to 28 days (online supplementary table S2).

The active comparator salmeterol was compared against all treatments in a *post hoc* analysis. In this analysis, there was a nominal statistical difference in favour of salmeterol compared to placebo (77 mL difference, $p=0.046$). Differences between GSK961081 doses and salmeterol ranged from 78 mL (100 µg once daily) to 200 mL (800 µg once daily), with statistically significant differences in favour of GSK961081 for all doses except 100 µg once daily (table 2).

### *Secondary end-points*

For the subset of overnight patients (n=18–23), the 24-h weighted mean $FEV_1$ differences from baseline at day 28 were statistically significant compared to placebo ($p<0.001$) for all doses and regimens over the 24-h time period, ranging from 226 mL (100 µg twice daily) to 335 mL (800 µg once daily) (table 3). Salmeterol had a weighted mean improvement of 85 mL, but the difference from placebo was not statistically significant.

The 0–24-h $FEV_1$ profile on day 28 (n=18–23) indicated that patients on placebo showed a reduction in $FEV_1$ following their evening dose from 11 h onwards (fig. 2). Salmeterol also mirrored the evening drop in $FEV_1$, as did the GSK961081 once daily doses of 100 µg and 400 µg, dropping the mean change from baseline <200 mL by the following morning. The twice daily doses of 200 µg and 400 µg induced the extra


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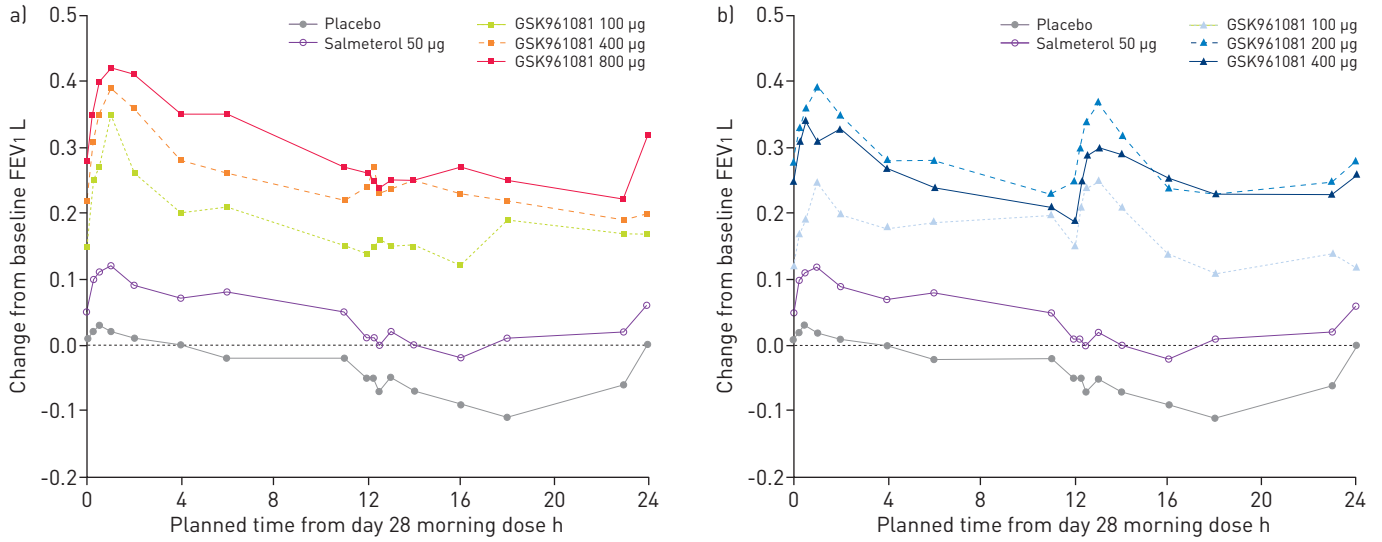


FIGURE 2 Serial forced expiratory volume in 1 s ($FEV_1$) profile over 0–24 h on day 28 in the subset of overnight subjects. a) Once daily dosage regimen; b) twice daily dosage regimen.

peak at 12–14 h, which ensured that the mean change from baseline remained >200 mL overnight until the following morning.

On day 1, all GSK961081 treatments gave differences over placebo which exceeded 100 mL at all time-points from 0 h to 12 h post-morning dose, with the exception of 100 µg twice daily and 100 µg once daily at 11 h and 12 h post-dose (fig. 3a). On day 28, the 200 µg twice daily, 400 µg twice daily, 400 µg once daily and 800 µg once daily GSK961081 treatments had differences over placebo which exceeded 200 mL at all time-points from 0 h to 12 h post-morning dose (fig. 3b).

### *Other end-points*

The proportion of patients showing an improvement of 100 mL within 15 min on day 1 was between 60% and 81% for GSK961081 doses (table 4), compared with 43% of patients who were treated with salmeterol. The peak $FEV_1$ response increased from day 1 to day 28 for all doses of GSK961081, except the 100 µg once daily dose, as shown in table 4.

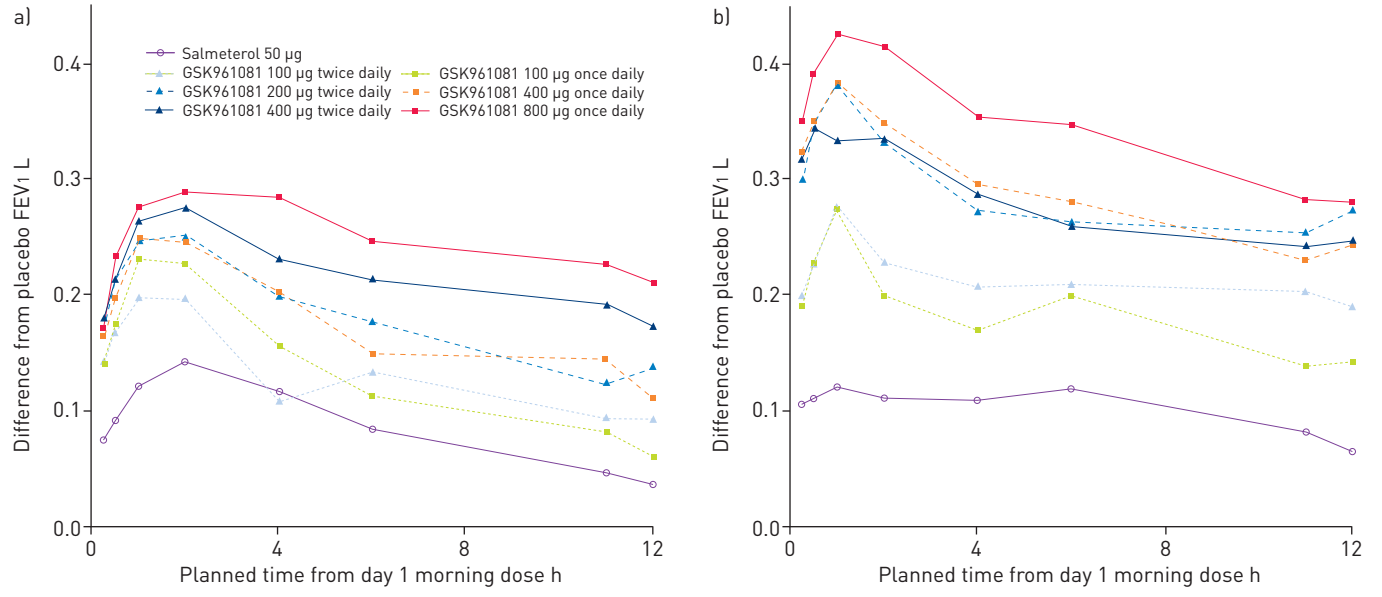


FIGURE 3 Serial forced expiratory volume in 1 s ($FEV_1$) profile over 0–12 h on a) day 1 and b) day 28, in all subjects.

TABLE 4 Summary of onset of effect and peak forced expiratory volume in 1 s ($FEV_1$)

| | Subjects | 15-min onset# | Peak $FEV_1$¶ mL | |
|---|---|---|---|---|
| | | | Day 1 | Day 28 |
| **Placebo** | 81 | 11 (14) | 117±117 | 73±200 |
| **Salmeterol** | 47 | 20 (43) | 229±134 | 170±170 |
| **GSK961081** | | | | |
| Twice daily | | | | |
| 100 µg | 52 | 34 (65) | 281±159 | 317±221 |
| 200 µg | 50 | 34 (68) | 339±188 | 399±239 |
| 400 µg | 54 | 44 (81) | 344±144 | 384±205 |
| Once daily | | | | |
| 100 µg | 50 | 30 (60) | 293±176 | 279±229 |
| 400 µg | 50 | 34 (68) | 295±161 | 368±201 |
| 800 µg | 52 | 34 (65) | 392±250 | 436±300 |

Data are presented as n, n (%) or mean±SD. #: defined as achieving a 100-mL improvement from pre-dose trough to the first post-dose measurement; ¶: defined as the highest $FEV_1$ value from 0 h to 6 h post-dose.

Trough FVC measurements for all doses of GSK961081 showed nominal statistical differences compared to placebo ($p=0.014$ for 100 µg once daily and $p<0.001$ for all other GSK961081 doses) and varied from 153 mL for GSK961081 100 µg once daily to 381 mL for the 800-µg once daily dose (table 3). Salmeterol (120 mL difference from placebo on day 29) was not statistically different from placebo.

The mean number of occasions per day of salbutamol use prior to treatment was 1.49. During the study, there was a nominal statistical difference ($p<0.01$) for the reduction in the number of occasions per day for the GSK961081 doses, ranging from 0.45 occasions for the 100-µg once daily dose to 0.74 for the 400-µg twice daily dose (table 3). Salmeterol showed a nominal statistical difference ($p=0.026$) with a reduction of 0.39 occasions per day over the study period.

### *Safety*

One nonfatal serious adverse event was reported during treatment and required hospitalisation. This was an incident of biliary colic which was reported in a patient with a suspected past history of gallstones, in the 400-µg once daily GSK961081 treatment group, and was not considered to be related to the study drug. The incidence of adverse events is shown in table 5. GSK961081 was well tolerated, with headache, cough, dysgeusia (bad taste) and nasopharyngitis being the most common adverse events. Drug-related adverse events were reported more frequently in the GSK961081 groups than in the placebo or salmeterol arms. The most frequently reported events were cough and dysgeusia. Six exacerbations of COPD occurred during the study: four in the placebo group, and one each in the 100-µg once daily and twice daily GSK961081 groups; none required hospitalisation. There were four post-dose ECG abnormalities. One was a tachycardia in the 100-µg twice daily group, which was judged to be unrelated to the study drug by the investigator and did not lead to withdrawal. The other three were deemed treatment-related and led to withdrawal of GSK961081. A left bundle branch block and a case of Wolff–Parkinson–White syndrome were diagnosed on day 1 post-dose ECGs, although review of ECGs indicated that both these abnormalities were present on ECGs obtained before dosing. In addition, a patient was withdrawn for first-degree atrioventricular block (PR 244 ms) and had a normal ECG at screening (PR 177 ms) but had a day-1, pre-dose PR interval of 215 ms.

Heart rate and systolic and diastolic blood pressure showed little response to GSK961081. Changes in glucose and potassium were also minimal when on treatment with GSK961081. There was a pharmacological effect with GSK961081 on QT interval corrected for heart rate (QTc(F)) with a 3–4-ms increase compared to placebo on day 28. However, no dose–response relationship was apparent.

## Discussion

This study was designed to assess the efficacy and safety of the novel dual bronchodilator GSK961081, in moderate and severe COPD patients. The study showed robust clinically and statistically significant improvements in trough $FEV_1$ after 28 days of treatment and reduced the use of rescue medication. A comparison of the dosing intervals with the same total daily dose of GSK961081 at 400 µg and 800 µg demonstrated that there were no significant differences between once-daily and twice-daily dosing with respect to trough $FEV_1$, FVC trough, rescue medication usage and safety parameters. There was a small


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TABLE 5 Most common on-treatment adverse events (⩾3% incidence in any treatment group)

| | Placebo | Salmeterol | GSK961081 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Twice daily | | | Once daily | | |
| | | | 100 μg | 200 μg | 400 μg | 100 μg | 400 μg | 800 μg |
| **Subjects** | 81 | 47 | 52 | 50 | 54 | 50 | 50 | 52 |
| **Any adverse event** | 20 (25) | 8 (17) | 12 (23) | 12 (24) | 16 (30) | 16 (32) | 15 (30) | 13 (25) |
| **Headache** | 5 (6) | 2 (4) | 2 (4) | | 5 (9) | 5 (10) | 5 (10) | 2 (4) |
| **Cough** | 2 (2) | | 2 (4) | 4 (8) | 1 (2) | 5 (10) | 5 (10) | 4 (8) |
| **Dysgeusia** | | | 2 (4) | 3 (6) | 3 (6) | 2 (4) | 1 (2) | |
| **Nasopharyngitis** | 3 (4) | | 1 (2) | 3 (6) | | 3 (6) | 1 (2) | |
| **Back pain** | 2 (2) | | 1 (2) | | | | 2 (4) | |
| **Dysphonia** | 2 (2) | | | | | | 1 (2) | 2 (4) |
| **Muscle spasms** | | 1 (2) | 1 (2) | | 2 (4) | | | 1 (2) |
| **Nausea** | 2 (2) | | | | | 1 (2) | 2 (4) | |
| **Myalgia** | 1 (1) | 1 (2) | | | | | 2 (4) | |
| **Palpitations** | | 1 (2) | | | 2 (4) | | | |

Data are presented as n or n (%).

increase in trough $FEV_1$ as the total daily dose increased from 400 μg to 800 μg. Increases in trough $FEV_1$ greater than the widely accepted minimal clinically important difference of 100 mL [17] for a single bronchodilator were observed for doses of 100 μg once daily and 100 μg twice daily; however, increases in trough $FEV_1$ >200 mL (as expected for a dual bronchodilator) were not observed for these doses. Therefore, compared with a total daily dose of 400 μg, the lower daily doses would be considered as suboptimal. Using the safety data there was no clear increase in safety parameters of concern as the dose increased. Therefore we conclude that the optimum total daily dose would be 400 μg, either as a 200-μg twice-daily dose or a 400-μg once-daily dose in moderate-to-severe COPD patients.

Over the 28 days of the study, a *post hoc* analysis showed that GSK961081 was consistently better in improving lung function than the active comparator salmeterol. GSK961081 produced improvements of trough $FEV_1$ by day 29, with mean differences (compared to placebo) which exceeded 150 mL for all doses, and specifically exceeded 200 mL at total daily doses ⩾400 μg.

The 24-h spirometric profiles at day 28 in the subset of patients at overnight sites showed in the placebo-treated patients a diurnal variation, with a $FEV_1$ decrease of approximately 100 mL overnight. Despite the fluctuations due to diurnal effect, all active treatment arms at least tracked the changes and maintained the differences achieved in lung function compared to placebo. There is a suggestion that doses of GSK961081 ⩾200 μg twice daily or ⩾400 μg once daily had a reduced diurnal variation, resulting in greater differences in mean lung function compared to placebo during the evening period. Patients showed sustained bronchodilation over the 24-h period with all doses of GSK961081, although less so with the 100 μg once daily or the 100 μg twice daily doses.

The 12-h spirometric profiles of all patients showed that there was an increase in improvement of trough $FEV_1$ *versus* placebo from day 1 to day 28. The trough $FEV_1$ increased up to day 14 and then remained constant for the remainder of the study (online supplementary table S1).

GSK961081 onset was rapid, with ⩾60% of patients across all GSK961081 doses reaching 100-mL improvement in $FEV_1$ by the first post-dose assessment (15 min), with the majority of patients reaching peak bronchodilation between 1 h and 2 h. GSK961081 also showed nominal statistical improvements compared to placebo for trough FVC and rescue medication use.

In general, GSK961081 was well tolerated. The most common adverse events were headache, cough, dysgeusia and nasopharyngitis. Treatment with GSK961081 was associated with prolongation of various QTc intervals ranging from 3 to 5 ms more compared to placebo or salmeterol. However, there was no apparent dose–response relationship, and in a previous study [15], where a dose of 1200 μg once daily was used, there was no prolongation of the QT interval seen. In pre-clinical studies in dogs, high doses of GSK961081 showed the development of vocal fold erosions in the larynx. Two patients were excluded at screening due to pre-existing laryngopharyngeal reflux or oesophageal reflux. Throat symptoms were

monitored throughout the study. On treatment there were two reported incidents of throat symptoms lasting longer than 7 days, but laryngoscopy showed no evidence of vocal fold erosions.

The main limitation of this phase IIb study was that it used a selected population of moderate and severe COPD patients. Whether the effect sizes seen in this study would be maintained for a longer period of time in a broader COPD population will need to be addressed in future studies.

COPD treatment guidelines recommend the use of a single bronchodilator initially. Single bronchodilators such as salmeterol, in moderate or severe COPD patients provide ~80 mL improvement in trough $FEV_1$ *versus* placebo whereas tiotropium and indacaterol show ~100 mL improvement [18–20]. If patients remain symptomatic, guidelines suggest adding a bronchodilator with a different mechanism [1]. Clinical studies provide the evidence for this [3–10]. When tiotropium was added to indacaterol in a moderate-to-severe COPD population in two separate studies an improvement of 60–90 mL *versus* tiotropium alone was seen [21]. In a double-blind 26-week study with moderate-to-severe COPD patients taking the fixed dose dual bronchodilator QVA149, there was a 200-mL ($p<0.001$) improvement *versus* placebo [20]. Therefore, the expectation was that a bronchodilator with two mechanisms of action would provide a trough improvement of ~200 mL. The improvement in trough $FEV_1$ of $\geqslant$200 mL was achieved by the 800-μg once-daily, 400-μg once-daily, 200-μg twice-daily and 400-μg twice-daily GSK961081 regimens *versus* placebo. The 100-μg once-daily and 100-μg twice-daily regimens, while an improvement over single bronchodilators, are sub-optimal in terms of the 200 mL trough $FEV_1$ expectation for a bronchodilator with two mechanisms. Although the improvements in lung function at total daily doses $\geqslant$400 μg for GSK961081 appear similar to current combinations, direct comparisons need to be carried out in randomised controlled trials.

In conclusion, GSK961081 is bifunctional, having both muscarinic antagonist and $\beta_2$-agonist activities in the same molecule. This study showed that a total daily dose of 400 μg GSK961081 was optimal given either as 400 μg once daily or 200 μg twice daily. GSK961081 had a rapid onset of action, was a potent bronchodilator in moderate and severe COPD patients and appeared to be safe and well tolerated.

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