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Original research

Selective androgen receptor modulation for muscle weakness in chronic obstructive pulmonary disease: a randomised control trial

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ABSTRACT

Background Selective androgen receptor modulators (SARMs) increase muscle mass via the androgen receptor. This phase 2A trial investigated the effects of a SARM, GSK2881078, in conjunction with exercise, on leg strength in patients with chronic obstructive pulmonary disease (COPD) and impaired physical function.

Methods 47 postmenopausal women and 50 men with COPD (forced expiratory volume in 1 s 30%–65% predicted; short physical performance battery score: 3–11) were enrolled into a randomised double-blind, placebo control trial. Patients were randomised 1:1 to once daily placebo or oral GSK2881078 (females: 1.0 mg; males: 2.0 mg) for 13 weeks with a concurrent home-exercise programme, involving strength training and physical activity. Primary endpoints were change from baseline in leg strength at 90 days (one-repetition maximum; absolute (kg) and relative (% change)) and multiple safety outcomes. Secondary endpoints included lean body mass, physical function and patient-reported outcomes.

Results GSK2881078 increased leg strength in men. The difference in adjusted mean change from baseline and adjusted mean percentage change from baseline between treatment and placebo were: for women, 8.0 kg (90% CI −2.5 to 18.4) and 5.2% (90% CI −4.7 to 15.0), respectively; for men, 11.8 kg (90% CI −0.5 to 24.0) and 7.0% (90% CI 0.5 to 13.6), respectively. Lean body mass increased, but no changes in patient-reported outcomes were observed. Reversible reductions in high-density lipoprotein-cholesterol and transient elevations in hepatic transaminases were the main treatment-related safety findings.

Conclusions GSK2881078 was well tolerated and short-term treatment increased leg strength, when expressed as per cent predicted, in men with COPD more than physical training alone.

Trial registration number NCT03359473.

WHAT IS ALREADY KNOWN

⇒ There are currently no pharmacological options to address muscle weakness in chronic obstructive pulmonary disease (COPD); testosterone can increase quadriceps strength in patients with COPD but has unacceptable side effects and is not commonly used.

WHAT THIS STUDY ADDS

⇒ GSK2881078, a selective androgen receptor modulator (SARM), had an acceptable safety profile. In conjunction with an exercise programme, and when compared with exercise alone, GSK2881078 improved quadriceps strength when measured as percentage predicted of the 1 repetition maximum in men but not women, at the end of 13 weeks of treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This trial showed that a SARM was well tolerated in people with COPD, increased lean body mass and has shown potential to increase leg muscle strength at least in men with COPD. Further trials with SARMs and other anabolic therapies are warranted to evaluate impact on functional endpoints and effect in women.

Linked

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INTRODUCTION

Skeletal muscle dysfunction is a common extrapulmonary manifestation of chronic obstructive pulmonary disease (COPD).[1 2] Both low lean body mass (LBM) and quadriceps weakness in COPD are independently associated with morbidity, hospitalisation[3] and mortality,[4] as are measures of function related to muscle strength.[5] Additionally, measures of quadriceps bulk[6] and lower extremity function[7] also predict readmission after acute exacerbation of COPD. Pulmonary rehabilitation (PR) is known to reduce symptom burden and increase exercise capacity in stable patients with COPD[8 9] and to reduce readmission after COPD exacerbation.[10] In both scenarios, PR is associated with increased quadriceps strength.[8 11] Thus, it seems reasonable to speculate that a medicine which improved quadriceps strength might be of benefit to patients with COPD. If so, such a medicine could be an adjunct to exercise and could be of value to patients without access to PR. Depending on jurisdiction, barriers to PR include reimbursement, accessibility, uptake and adherence, meaning that there is <5% utilisation among eligible patients in many countries.[12]

Quadriceps weakness is present in similar proportions in men and women[1] and prior studies, admittedly mostly in men, demonstrated the anabolic effects of testosterone[13] and other androgens in COPD,[14] a key finding being a synergistic effect of testosterone with resistance training.[13] However, testosterone is rarely prescribed due to its side-effect profile. Selective androgen receptor modulators (SARMs) are a novel class of compounds that bind selectively to the androgen receptor to elicit some, but not all, of the effects of testosterone; specifically SARMs increase skeletal muscle mass in both animal and human studies, while sparing prostate effects in men and virilising effects in women.[15] Identified adverse class effects of SARMs include transient elevation of hepatic transaminases and reversible lowering of high-density lipoprotein-cholesterol (HDL-C).[16] This profile makes SARMs attractive as potential anabolic medicines in conditions associated with cachexia, for example, cancer.[17]

In a previous study in healthy adult volunteers, the SARM GSK2881078 demonstrated an increase in LBM with 8 weeks of treatment, with a long half-life of 7 days and sex-related dosing differences that showed that women were more sensitive to GSK2881078 (ie, gained more muscle for the same dose) than men.[15] Here, we hypothesised that in patients with COPD and impaired physical function, GSK2881078 adjunctive to a standardised home-exercise training programme would lead to increased leg strength. We also assessed LBM, pharmacokinetics (PK), safety and efficacy of GSK2881078 in terms of functional and health-related quality of life (HRQoL) endpoints.

STUDY DESIGN AND METHODS

Study design and participants

This study (GSK study: 200182) was a randomised, placebo-controlled, double-blind, parallel-group, phase 2A trial evaluating the safety and efficacy of the SARM GSK2881078 in men and postmenopausal women with COPD.

Patients were recruited between February 2018 and June 2019 from 13 clinical sites across the USA, UK and Germany (online supplemental table S1). Patients were aged 50–75 years with confirmed diagnosis of COPD and predicted postbronchodilator forced expiratory volume in 1 s (FEV_1) between 30% and 65%. A score of 1–3 on the timed 5-repetition sit-to-stand (5STS) component of the short physical performance battery (SPPB) was used to confirm impaired physical function or muscle weakness (maximum score of 4 denotes no impairment; 0 denotes a patient unable to perform the 5STS). Patients were either current or former smokers, with a minimum of smoking history of 10 pack-year, and body mass index (BMI) of 18–32 kg/m^2. Key exclusion criteria included oral steroid use concurrently or within 4 weeks before the screening visit, COPD exacerbation requiring oral steroid treatment or hospitalisation 4 weeks before screening, score of 0 on any SPPB component or other conditions/medications that could influence muscle mass or function.

RANDOMISATION AND DOSING

Patients were randomised (1:1) to receive either GSK2881078 (women: 1 mg; men: 2 mg) or placebo once daily orally for 13 weeks. All patients undertook a concurrent standardised home-exercise programme, Respercise,[18] delivered via a smartphone app for 13 weeks from baseline. Respercise constituted daily step goals and thrice weekly sets of up to four strengthening exercises (online supplemental materials).

Procedures

Study visits were conducted at screening, day −9, baseline (day 1), day 14, day 28, day 56, day 80 and day 90, with post-treatment follow-up at day 132 (online supplemental figure S1). Patients who discontinued from the study for any reason returned for safety assessments 42 days after the last dose. The full schedule of study assessments can be found in the online supplemental table S2.

Most primary endpoints concerned safety but change from baseline at day 90 relative to placebo (absolute and percentage change) in leg strength measured by one repetition maximum (1-RM) leg press on a pneumatic instrument (A300; Keiser, Fresno, California, USA) was also a primary endpoint. Primary, secondary and exploratory endpoints are provided in online supplemental table S3.

Details of the patient experience of physical activity, disease impact and experience within the study, as well as additional procedures are given in the online supplemental material.

Statistical analysis

For all endpoints with multiple postbaseline assessment, the prespecified analysis plan was based on a mixed model repeated measures adjusted for treatment, day, treatment×day and baseline, with day as the repeated factor. Analyses were conducted separately by sex. For endpoints with a single postbaseline assessment, analysis was based on an analysis of covariance with treatment and baseline as covariate. For change and percentage change from baseline, adjusted means and corresponding SE of means and 90% CI are presented for each treatment, together with estimated treatment differences (GSK2881078—placebo) and corresponding 90% CIs. The primary efficacy analysis was based on the 'analysis population' (online supplemental table S4), which comprised all randomised patients who received ≥1 dose of study medication and had a baseline and ≥1 postbaseline assessment of 1-RM and LBM or other functional endpoints. All analyses were conducted with SAS software V.9.4. Further details of the statistical and PK analyses are given in the online supplemental material.

RESULTS

Participants

Between February 2018 and June 2019, 200 patients were screened, of whom 97 were randomised into the study. One patient was randomised in error but did not receive any treatment. Of the 96 remaining patients, 47 females and 49 males were randomised and dosed. The analysis population comprised 42 females and 46 males, with 39 females and 38 males completing the study. The primary reasons for withdrawal from the study were adverse events (AEs); 2 (8%) females and 3 (12%) males in the GSK2881078 group, and 5 (21%) males in the placebo group (figure 1). Baseline characteristics, including sex, ethnicity, BMI and FEV_1 % predicted, did not differ across treatment groups and cohorts (table 1).

Adherence to exercise

Daily compliance with Respercise, representing mean (SD (SD)) percentage of participant daily data entry for treatment duration, was similar and >90% in both the GSK2881078 treatment arms (females: 96.4% (38.2); males: 98.3% (26.5)) and placebo (females: 95.1% (28.2); males: 92.0% (27.4)).

Day 90 results

Safety

GSK2881078 was well tolerated with few patients discontinuing treatment due to AEs (table 2).

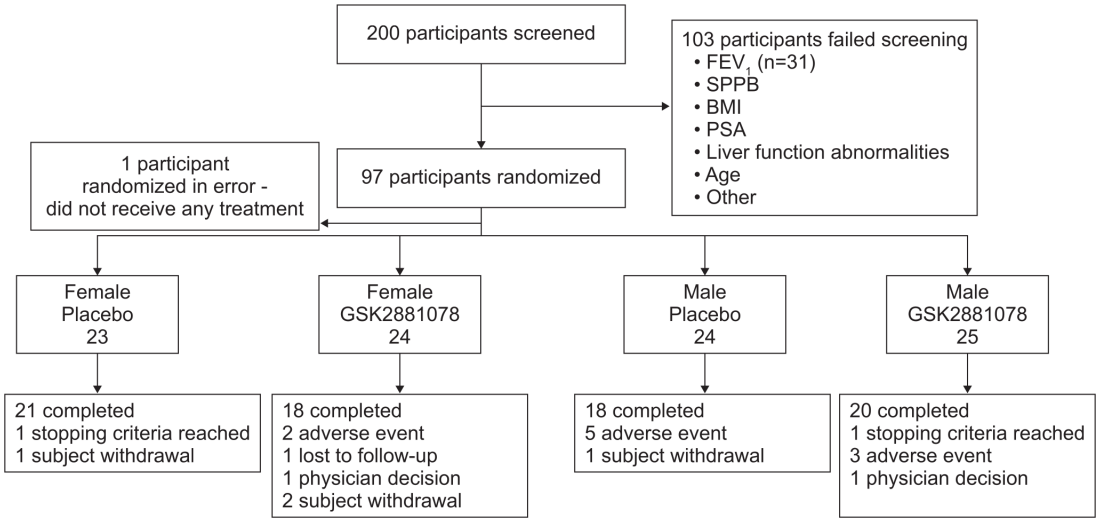

Figure 1 CONSORT diagram. BMI, body mass index; FEV_1, forced expiratory volume in 1 s; PSA, prostate-specific antigen; SPPB, short physical performance battery.

Most AEs were similar in frequency across placebo and treatment groups. AEs of special interest, such as cardiovascular effects, drug-related hepatic disorders and dyslipidaemia, were also similar across treatment groups. There was one case of benign prostatic hypertrophy in the GSK2881078 treatment group that was not deemed treatment related, and one case of acne in the female GSK2881078 cohort. Drug-related AEs for alanine aminotransferase (ALT) increase (female: 1 (4%); male: 2 (8%)) and aspartate aminotransferase increase (1 (4%) in the GSK2881078 groups of both cohorts) were observed. There were two ALT increases greater than three times upper limit of normal (ULN) (peak ALT: 7.4×ULN and 7×ULN); one male and one female on treatment with GSK2881078 withdrew from the study at day 67 and day 28, respectively, due to ALT increase and both recovered promptly after treatment discontinuation. Both cases were asymptomatic and without concurrent bilirubin or alkaline phosphatase elevation. Other reported mild increases in ALT were transient and often decreased while continuing treatment. Besides the two treatment discontinuations for elevated ALT, there were two other treatment discontinuations due to AEs that were deemed treatment-related by the investigator, and these were diarrhoea and pruritus. The main metabolic changes for patients taking GSK2881078 were reversible reductions in fasting glucose and HDL-C (both cohorts) and reversible elevations in LDL-C, mostly in females. Haematocrit was unchanged, but there was a trend toward increased platelet counts in the treatment group. No clinically significant difference in overall mean prostate-specific antigen levels between GSK2881078 and placebo were observed. There were no deaths and five serious AEs reported, but these were not considered related to treatment with GSK2882078.

Efficacy

Study results are summarised in table 3 and table 4. Expressed as per cent change from baseline, GSK2881078 increased leg strength in men by 7.0% (90% CI 0.5 to 13.6) but not women 5.2% (90% CI −4.7 to 15.0); changes when expressed as force in kg were 8.0 kg (90% CI −2.5 to 18.4) in women and 11.8 kg (90% CI −0.5 to 24.0) in men (figure 2A,B). Increases in total and appendicular LBM were observed; for total LBM (tLBM), the treatment difference in the adjusted mean change from baseline for the GSK2881078 group was 2.1 kg (90% CI 1.3 to 3.0) for females and 2.1 kg (90% CI 1.0 to 3.3) for males (figure 2C,D). No relationship between change in leg strength and LBM was observed (online supplemental figure S2).

The treatment difference in adjusted mean change from baseline in SPPB total score was 0.2 (90% CI −0.4 to 0.9) for females and 0.1 (90% CI −0.5 to 0.6) for males. In the 5STS subcomponent of the SPPB, there was a difference of −1.0 s (95% CI −2.7 to 0.8) for females and −1.9 s (95% CI –5.2 to 1.3) for males. Moreover, there was no meaningful difference between

Table 1 Baseline patient characteristics*

	Female		Male	
	Placebo (N=23)	GSK2881078 (N=24)	Placebo (N=24)	GSK2881078 (N=25)
Age, mean (SD), years	64.7 (7.16)	64.2 (7.93)	64.0 (7.27)	67.2 (6.08)
Ethnicity, n (%)				
Black or African American	0	1 (4)	2 (8)	2 (8)
White/Caucasian/European	23 (100)	23 (96)	22 (92)	23 (92)
BMI (kg/m^2), mean (SD)	23.9 (3.93)	24.2 (3.78)	25.5 (4.22)	26.0 (4.51)
Postbronchodilator FEV_1 % predicted, mean (SD)	46.2 (10.82)	49.6 (9.69)	51.2 (10.63)	48.0 (11.80)

*Baseline characteristics for the all randomised subjects who receive at least one dose of study medication.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s.;

Table 2 Safety summary (safety population)

Frequency of events (percentage of overall group)*	Female		Male	
	Placebo (N=23)	GSK2881078 (N=24)	Placebo (N=24)	GSK2881078 (N=25)
Any event	19 (83%)	20 (83%)	17 (71%)	19 (76%)
Any severe AEs	1 (4%)	3 (13%)	3 (13%)	2 (8%)
AEs leading to withdrawal	0	2 (8%)	5 (21%)	4 (16%)
Drug-related AEs leading to withdrawal	0	1 (4%)	0	3 (12%)
Drug-related AEs	1 (4%)	3 (13%)	1 (4%)	4 (16%)
Any SAEs	1 (4%)	2 (8%)	2 (8%)	0
Drug-related SAEs	0	0	0	0
Any AEs of special interest	3 (13%)	6 (25%)	5 (21%)	3 (12%)
Fatal SAEs	0	0	0	0
SAEs				
Diverticulitis	0	0	1 (4%)	0
Infective exacerbation of COPD	1 (4%)	0	0	0
Myocardial infarction	0	1 (4%)	0	0
Cholecystitis	0	1 (4%)	0	0
Adenocarcinoma of colon	0	0	1 (4%)	0
Frequent AEs*				
COPD	6 (26%)	7 (29%)	2 (8%)	3 (12%)
Nasopharyngitis	5 (22%)	2 (8%)	1 (4%)	1 (4%)
Arthralgia	0	3 (13%)	2 (8%)	2 (8%)
Muscle spasms	1 (4%)	2 (8%)	0	3 (12%)
Back pain	0	3 (13%)	0	2 (8%)
Contusion	3 (13%)	1 (4%)	0	0
Headache	0	2 (8%)	0	2 (8%)
ALT increase	0	1 (4%)	0	2 (8%)
Epistaxis	0	0	2 (8%)	1 (4%)
Hypertension	0	1 (4%)	2 (8%)	0
Musculoskeletal chest pain	0	1 (4%)	0	2 (8%)
Blood 25-hydroxycholecalciferol decreased	0	2 (8%)	0	0
Hypotension	0	0	2 (8%)	0

*Frequent AE is defined as occurring in a minimum of 2 patients of any sex for either arm.
AE, adverse event; ALT, alanine aminotransferase; COPD, chronic obstructive pulmonary disease; SAE, serious adverse events.

groups for 4-metre gait speed, incremental shuttle walking test (ISWT) or endurance shuttle walking test (ESWT). Similarly, GSK2881078 treatment did not result in increased average steps per day compared with the placebo groups: mean (SD) change from baseline was 786 (1440.0) steps per day for females, compared with −247 (756.4) steps per day with placebo and 611.4 (1499.6) steps per day for males compared with −527.1 (1077.7) steps per day with placebo (figure 3). There was no clinically relevant difference in change from baseline in respiratory measures such as FEV_1 % predicted or sniff nasal inspiratory pressure or exploratory measures of handgrip strength (table 4).

Pharmacokinetics

Following multiple dose administration, mean predose drug concentration showed time-dependent increases from day 14 through day 28 and day 90 with steady state achieved by approximately day 56. Predose drug levels on day 90 in females (mean: 134.6 ng/mL) with the 1 mg dose were marginally greater than corresponding predose drug concentration in males when dose was normalised from 2 mg to 1 mg on day 90 (online supplemental table S6).

Post-treatment follow-up period

At day 132, unadjusted mean (SD) percentage change from baseline in leg strength for the female cohort was 16.9% (17.8) for the GSK2881078 group and 19.3% (20.0) for the placebo group. In males, these changes were 8.8% (15.0) for the GSK2881078 group and 5.0% (11.0) for the placebo group. Post-treatment, at day 132, unadjusted mean change from baseline in tLBM for females was −0.9 kg (2.6) in the placebo group and 1.2 kg (1.7) in the GSK2881078 group, while for males it was −0.6 kg (1.5) for the placebo group and 0.8 kg (2.6) for the GSK2881078 group (online supplemental table S7).

DISCUSSION

The SARM, GSK2881078, combined with a home-exercise training programme, had an acceptable safety profile when

Table 3 Change in efficacy measures

Efficacy measure	Female*					Male*				
	Placebo (N=21)		GSK2881078 (N=21)			Placebo (N=23)		GSK2881078 Baseline (N=23)		
	Baseline mean (SD)†	Change at day 90 adjusted mean (90% CI)†	Baseline mean (SD)†	Change at day 90 adjusted mean (90% CI)†	Treatment difference (N=21) at day 90 (90% CI)	Baseline mean (SD)†	Change at day 90 adjusted mean (90% CI)†	Baseline mean (SD)†	Change at day 90 adjusted mean (90% CI)†	Treatment difference (N=21) at day 90 (90% CI)
1-RM (kg)	109.2 (40.12)	12.3 (5.1 to 19.6)	120.0 (45.81)	20.3 (12.8 to 27.8)	8.0 (–2.5 to 18.4)	168.8 (55.11)	14.2 (5.5 to 22.9)	202.3 (59.79)	26.0 (17.7 to 34.3)	11.8 (–0.5, 24.0)
1-RM (% change from baseline)	–	12.8 (5.9 to 19.6)	–	17.9 (10.9 to 25.0)	5.2 (–4.7, 15.0)	–	7.2 (2.5 to 11.8)	–	14.2 (9.7 to 18.6)	7.0 (0.5 to 13.6)
tLBM (kg)	36.6 (5.04)	–0.5 (–1.1 to 0.0)	36.9 (4.99)	1.6 (1.0 to 2.2)	2.1 (1.3 to 3.0)	51.4 (8.41)	–0.4 (–1.3 to 0.4)	52.4 (7.09)	1.7 (0.9 to 2.5)	2.1 (1.0 to 3.3)
SPPB score	9.5 (1.47)	0.3 (–0.2, 0.7)	9.6 (1.56)	0.5 (0.0, 1.0)	0.2 (–0.4, 0.9)	10.1 (1.20)	0.4 (0.0, 0.8)	9.9 (1.29)	0.5 (–0.5 to 0.8)	0.1 (–0.5 to 0.6)
5STS (s)	16.2 (6.51)	–1.1 (–2.2 to 0.1)	15.6 (5.14)	–2.3 (–3.3 to –0.8)	–1.0 (–2.7 to 0.8)	13.7 (2.24)	1.1 (–1.2 to 3.5)	13.9 (2.34)	–0.8 (–3.1 to 1.5)	–1.9 (–5.2 to 1.3)
4mGS (s)	4.60 (1.08)	–0.0 (–0.4 to 0.3)	4.5 (1.19)	–0.1 (–0.5 to 0.3)	–0.0 (–0.6, 0.5)	4.5 (1.06)	–0.1 (0.4, 0.1)	4.6 (1.11)	–0.4 (–0.6 to –0.2)	–0.2 (–0.5, 0.1)
ESWT (s)	224.6 (78.93)	–6.5 (–51.9 to 38.8)	316.1 (251.91)	4.6 (–45.0 to 54.1)	11.1 (–57.1 to 79.2)	253.4 (121.42)	105.1 (12.3 to 197.9)	297.0 (116.39)	–44.2 (–132.1 to 43.6)	–149.3 (–280.6 to 18.1)
ISWT (m)	318 (106.38)	–10.5 (–35.5 to 14.4)	363.8 (144.41)	–17.2 (–42.9 to 8.4)	–6.7 (–42.7 to 29.2)	341.3 (105.41)	–7.5 (–34.2 to 19.3)	399.1 (143.75)	–42.3 (-67.6 to –16.9)	–34.8 (–72.0 to 2.4)
CAT score	20.2 (6.08)	–1.3 (–2.6 to 0.1)	18.1 (6.86)	–2.2 (–3.6 to –0.7)	–0.9 (–2.9 to 1.1)	17.6 (6.18)	–1.4 (–3.0 to 0.1)	16.7 (6.98)	0.8 (–0.7 to 2.3)	2.2 (0.0 to 4.5)
SGRQ-C score	48.4 (15.88)	–3.9 (–6.8 to –1.0)	41.8 (13.69)	–0.9 (–4.1 to 2.3)	3.0 (–1.4 to 7.4)	43.5 (14.89)	–1.7 (–4.9 to 1.5)	39.5 (16.69)	0.4 (–0.2.6 to 3.4)	2.1 (–2.3 to 6.5)

*Results for analysis population (N=21 each for female placebo and GSK2881078 groups and N=23 each for male placebo and GSK2881078 groups; for individual analyses, n ranged from 16 to 23).
†Results reported as mean (SE) for baseline visits, adjusted means (90% CIs) for repeated measures mixed models for endpoints measured at more than one study time point, and as mean (90% CIs).
CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; ESWT, endurance shuttle walk test; ISWT, incremental shuttle walk test; 4mGS, 4 m gait speed; 1-RM, one-repetition maximum; SGRQ-C, St George's Respiratory Questionnaire-COPD; SPPB, short physical performance battery; 5STS, five-repetition sit-to-stand; tLBM, total lean body mass.

administered in patients with COPD, stratified by functional limitation based on the sit-to-stand test. Treatment resulted in meaningful increases in LBM in males and females, accompanied by an increase leg strength in males, when expressed as per cent change. The magnitude of changes in LBM were similar to those observed for GSK2881078 in age-matched healthy volunteers,[15] arguing against the concept of anabolic resistance in COPD.

Critique of the method

It may be argued that our choice of endpoints is not pertinent to quality of life in patients with COPD (eg, compared with exercise capacity). The primary aim of this study was to assess the safety and feasibility of SARMs as a medicine in COPD. For this reason, many of the endpoints related to safety, and the efficacy outcome was 1-RM. This is a practical test of muscle strength and is directly relevant to muscle cross-sectional area and thus the anabolic power of a medicine. In concept, it is similar to the maximal voluntary contraction force, but the latter is a continuous variable, whereas the 1-RM is an integer variable being the largest weight the patient can lift and has been widely used in prior anabolic studies.[13] It is the locomotor muscles, which are primarily affected in COPD and thus 1-RM is more relevant to physical function and quality of life than measures of body composition such as BMI or fat-free mass index.

Many anabolic compounds fail to demonstrate improved functional outcomes, whether it is the stair-climb test,[19] 6-minute walk test,[20] leg strength,[20 21] constant work rate exercise[13 21] or HRQoL.[13 20 21] We were similarly unable to demonstrate improvements in functional endpoints such as the ISWT and ESWT, and it may require a larger study to observe an impact on functional outcomes, including those for which we saw trends to improvement especially daily physical activity (step counts), which, numerically, approached a clinically meaningful magnitude.[22 23] We would highlight that this study was known to be not powered to generate statistically significant benefits in the secondary endpoints.

It might also be argued that the gain in strength that we observed was too small to effect outcomes. However, the combined effect of training and GSK2881078 in 1-RM (17.9% for women and 14.2% for men) using a straightforward pre–post intervention comparison is of a similar order of magnitude to other interventions that were associated with increased exercise capacity, including PR (14%)[8] and quadriceps neuromuscular electrical stimulation (10.5%).[24]

Since we used a concurrent exercise programme, it remains unknown what the value of GSK2881078 used in isolation might be, although prior experience with testosterone suggests a synergistic effect of androgens and training. Since PR is known to be beneficial, we suggest that regulators and payers will be most interested in quantifying those effects of anabolic therapies which are additional to PR, although this might not preclude use of this class of compounds in patients unable to access PR if

Table 4 Secondary and exploratory outcomes

	Female*				Male*			
	Placebo (N=21)		GSK2881078 (N=21)		Placebo (N=23)		GSK2881078 (N=23)	
Efficacy measure	Baseline†	Day 90†	Baseline†	Day 90†	Baseline†	Day 90†	Baseline†	Day 90†
FEV_1 (% predicted)	46.4 (11.19)	46.8 (11.89)	48.7 (9.53)	47.8 (9.87)	51.9 (10.19)	53.9 (10.64)	47.3 (11.73)	48.3 (13.13)
SnIP (cm H_2O)	66.5 (18.47)	66.5 (19.76)	58.1 (18.79)	57.8 (19.32)	78.7 (27.33)	80.8 (31.99)	72.2 (26.11)	75.9 (30.02)
Average steps/day	3097.6 (1571.42)	3091.6 (1747.82)	3937.1 (2790.79)	4712.9 (3398.26)	3361.4 (2140.77)	2657.2 (1526.58)	3603.5 (2138.55)	4591.2 (3054.74)
D-PPAC total score	57.7 (9.50)	61.0 (11.62)	60.8 (8.20)	61.2 (12.25)	57.6 (7.53)	58.4 (7.89)	60.6 (11.00)	60.7 (12.40)
D-PPAC amount average	49.4 (11.25)	53.0 (12.75)	49.3 (12.29)	54.2 (15.04)	45.6 (13.12)	45.7 (10.42)	52.5 (11.82)	52.3 (16.51)
D-PPAC difficulty average	66.0 (14.42)	68.9 (15.05)	72.3 (12.22)	68.1 (16.02)	69.5 (11.84)	71.1 (12.63)	68.7 (14.68)	69.1 (16.30)
Handgrip strength (kg)‡	20.9 (6.99)	21.1 (5.95)	21.3 (4.72)	21.8 (6.08)	33.4 (8.88)	35.4 (8.34)	34.4 (8.17)	35.0 (7.85)

No clinically meaningful differences between GSK2881078 and placebo groups were observed for HRQoL and other patient-reported measures.
*Results for analysis population (N=21 each for female placebo and GSK2881078 groups and N=23 each for male placebo and GSK2881078 groups; for individual analyses, n ranged from 16 to 23).
†Values reported as unadjusted mean (SD).
‡Handgrip strength was measured using the right hand.
D-PPAC, Daily PROactive; FEV_1, forced expiratory volume in 1 s; HRQoL, health-related quality of life; SnIP, sniff nasal inspiratory pressure.

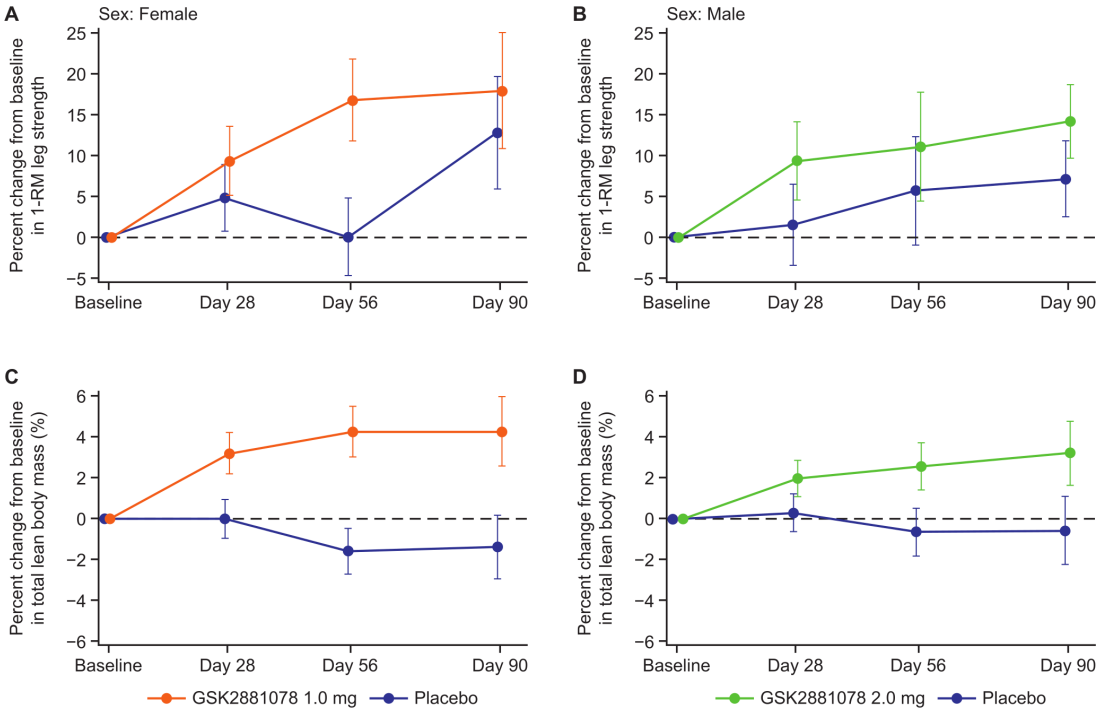

Figure 2 Changes in muscle strength (A) and (B) and LBM (C) and (D). (A) and (B) Changes in muscle strength (adjusted means and 90% CI), measured by 1-RM percentage change from baseline at day 28, day 56 and day 90 in females (3A) and males (3B). The number of participants at baseline, day 28, day 56 and day 90 were: GSK2881078 1 mg: 21, 20, 18 and 18; female placebo: 21, 21, 20 and 19; GSK2881078 2 mg: 23, 23, 21 and 20; and male placebo: 23, 22, 21 and 18. Estimates were calculated from a repeated measures mixed model, including the following covariates: treatment, day, treatment×day and baseline leg press strength, with day as the repeated factor. (C) and (D)Changes in tLBM, measured by dual-energy X-ray absorptiometry percentage change from baseline at day 28, day 56 and day 90 in females (3C) and males (3D). The number of participants at baseline, day 28, day 56 and day 90 were: GSK2881078 1 mg: 20, 19, 17 and 17; female placebo: 21, 21, 21 and 21; GSK2881078 2 mg: 22, 22, 18 and 18; and male placebo: 20, 20, 17 and 15. Estimates were calculated from a repeated measures mixed model, including the following covariates: treatment, day, treatment×day and baseline tLBM, with day as the repeated factor. 1-RM, one-repetition maximum; LBM, lean body mass; tLBM, total lean body mass.

efficacy could be demonstrated. A home-based programme was used for practicality, and although we accept that it might not be as effective as a supervised programme,[25] such a programme offers the opportunity to standardise global clinical trials, and could potentially be offered for maintenance of benefits in combination with an anabolic therapy if approved. Our home-based programme was a combined programme consisting of resistance and endurance training, and as such was recapitulating elements of PR in trying to improve both strength and exercise capacity, both of which are important for improving activities of daily living in patients with COPD; we did not study the effects of resistance or endurance training in isolation.

Our study is not without limitations. The relatively small sample size, which was further limited by separating analyses by gender, may have resulted in insufficient power to demonstrate treatment superiority, making it difficult to draw definitive conclusions regarding functional outcomes. The multicentre nature of this study may also contribute to increased variability in functional measures, which already are known to have considerably high intrasubject SD. Specifically, the study sample size was calculated on the basis of results from a single centre randomised control study in COPD, whereas in our multicentre study, we observed SD in the 1-RM measure of almost twice that of observed by Casaburi *et al*,[13] although the variability in 1-RM was more comparable to that observed by Polkey *et al* in their multicentre randomised control trial.[20] The lack of an effect on disease-specific HRQoL measures suggests that more focused measurement of the patient experience of anabolic effects is required for future studies. The anabolic benefits from GSK2881078 may be more potent in a weaker or cachectic population[26] experiencing active weight loss, than in the population evaluated here. Acute exacerbations of COPD were an exclusion criterion for our study, and we conducted analyses including patients who exacerbated during the study as well as excluding those patients, but the latter severely limited the numbers of study patients for analysis. While patients with COPD with frequent exacerbations are among a group most likely to benefit clinically from anabolic therapies,[27] studying this group in shorter duration clinical trials, especially where study numbers are small, is difficult without the confounding effect of acute muscle loss within a short period.[28 29] Although the per-protocol population who did not have any exacerbations requiring treatment with steroids was very small, it was encouraging that findings from this group did not materially change our conclusions (online supplemental table S5).

Lack of an improvement in patient-reported outcomes such as the St George's Respiratory Questionnaire-COPD-specific version, COPD Assessment Test and Daily PROactive eDiary (D-PPAC) indicate that measuring HRQoL endpoints for anabolic therapies is complex. Increased leg strength was not fully reflected in these measures, which assess both a more holistic and more distal aspect of disease experience. Additionally, in the case of D-PPAC, differential change in each of the domain scores may be expected[23]: increased activity may also result in an accompanying increase (worsening) in difficulty performing physical activity due to increased demands from more tasks.

Significance of the findings

Earlier SARMs did experience some problems such as liver enzyme disturbances; here, we confirmed that the main treatment-related AEs were only the known class effects of HDL lowering, which were fully reversible, and elevation in liver enzymes, which was transient in most subjects. Against this background, it is encouraging that GSK2881078 could be safely used in patients with COPD.

Several prior studies have evaluated anabolic steroids in COPD, for example,[30 31] but these were not stratified by functional limitation. Similarly a prior study, investigating activin 2b receptor blockade[20] used entry criteria based on body composition rather than functional performance. Thus, this was the first study for an anabolic compound that selected patients based on physical function impairment or leg muscle weakness. 5STS was chosen as a stratification tool because it was strongly associated with quadriceps strength[32] and hospitalisation[3] in the ERICA cohort of 729 people with a wide range of COPD severity, suggesting that 5STS was clinically useful for discriminating magnitude of leg muscle weakness in patients with COPD. Our aim was to evaluate a strategy, which allowed room for functional improvement, and yet excluded patients who were too frail to demonstrate improvement in a functional endpoint in a clinical trial setting (10% of the patients in the ERICA cohort were unable to perform the 5STS, while 29% of patients had the maximum score of 4). The 5STS has the added advantage of being performed in less than 5 min in the outpatient setting, with a standard chair and stopwatch or smartphone being the

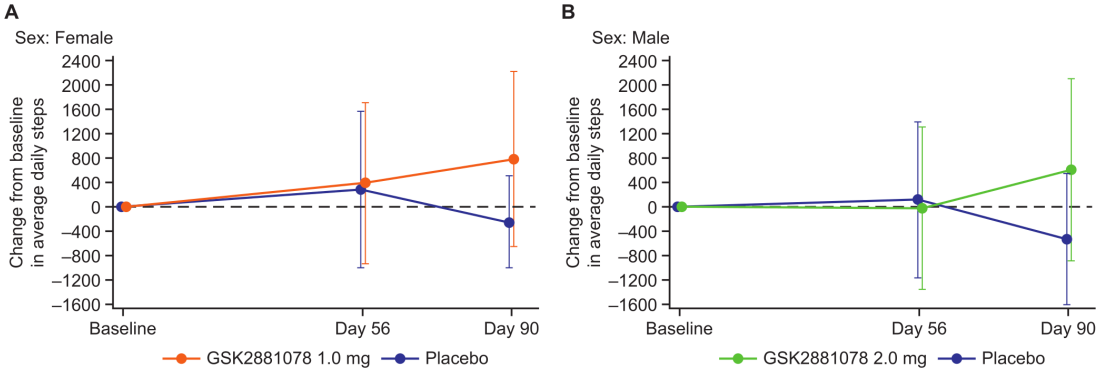

Figure 3 Change in daily step counts*. *Change from baseline in average daily step count measured by actigraphy at baseline, day 56 and day 90 for placebo and GSK2881078 treatment groups for (A) females and (B) males. Participants wore an accelerometer for 7 days continuously; data were analysed for participants with a minimum of 8-hour daily wear time for at least 4 days. Note: the number of participants at baseline, day 56 and day 90 were: GSK2881078 1 mg: 20, 14 and 17; female placebo: 20, 17 and 17; GSK2881078 2 mg: 21, 17 and 14; and male placebo: 20, 14 and 14. Error bars indicate ±SD from the mean.

only equipment required. We, therefore, propose the 5STS as a screening tool for future studies of anabolic therapies enrolling patients with COPD, or other chronic conditions, especially given the lack of consensus for a clinical tool to diagnose muscle weakness. Consistent with this view, the SPPB and the 5STS have been proposed as stratification or identification tools in both the sarcopenia guidance[33] and by the European Medicines Agency.[34]

As discussed in the protocol, the sample size was calculated on 1-RM from a single-centre study of testosterone supplementation in male patients with COPD, where much less variability was observed. It is, therefore, encouraging that an increase in LBM were observed in both men and women, and that improvements were observed in men, although only when expressed as percent change from baseline rather than in kilogramme. Nevertheless, the trends observed for strength were favourable suggesting that for this outcome, and for many of the secondary outcomes, a statistically significant result could potentially be obtained if a large enough study were undertaken; data from this multicentre study, and that from Polkey *et al*, can help inform future studies in this regard.

The increase in leg strength and LBM demonstrated in males was close to that demonstrated with testosterone supplementation in males with low endogenous testosterone,[13] and treatment effects on LBM confirm that GSK2881078 is a potent anabolic agent, with PK data supporting that a maximal effect for LBM gain was seen at the doses used. We did not see a strong relationship between increases in leg strength and increased LBM, however. Taken together with the prior results of a study of activin IIb receptor inhibition, which showed improvements in thigh muscle volume,[20] these data suggest there that skeletal muscle synthesis in COPD is not a primary limitation to explain loss of muscle mass.

It is of value to speculate how one might use this class of medicine, if efficacy could be demonstrated. In this context, the link between poor physical performance and both admission and readmission should be noted. One context of use could be in patients discharged after AECOPD with the aim of reducing readmission; however, since the majority of readmissions occur within the first month, it is arguable that insufficient muscle function could be gained in time to impact this endpoint. More promising could be seasonal use of an anabolic medicine in the summer months with the aim of building muscle to reduce the chances of admission during the winter when infective triggers for AECOPD are more prevalent. This use would also be within the safety data described in the current study, particularly since due to the long half-life of GSK2881078 gains in LBM remained evident after 90 days dosing (ie, at day 132) in comparison to baseline in the treatment arm (online supplemental table S6). This is in contrast to continued decline of LBM below baseline levels in the placebo arms (online supplemental table S7).

There is unequivocal support among physicians and patients that muscle weakness is a problem facing a large proportion of patients with chronic disease, including COPD. However, there remains several barriers to development of suitable therapeutic compounds for muscle weakness. Even though SARMs, such as GSK2881078, have an acceptable safety profile, demonstrating benefit in terms of functional outcomes is difficult in smaller, earlier phase trials, while the absence of recognition by the regulators of a validated biomarker continues to act as an obstacle to development of this class of compounds in COPD and other conditions.[35]

In conclusion, the SARM, GSK2881078, has an acceptable safety profile, and combined with a home-based exercise training programme, leads to increased LBM in people with muscle weakness and COPD. Our findings support a call for additional studies to assess the impact of combined SARM and exercise training therapy in a larger population with COPD, including patient-centred outcomes.

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Competing interests CA, MB, HM, SK, ST, DM, MT, AJR, MCH and DN are current employees and shareholders of GlaxoSmithKline (GSK). CF has received grant/research support from GSK. DM is an employee and stockholder of Genentech/Roche. RT-S is a former employee and current shareholder of GSK, and reports personal fees from Immunomet, Vocalis Health, Ena Respiratory and Teva. MIP has received personal payment for lectures for GSK, Genzyme Sanofi and Novartis, and his institution received funding from GSK for conducting this study. He reports consulting fees from Omniox, and is involved in contracted clinical research with Boehringer Ingelheim, GSK, Novartis, AstraZeneca, Astellas, United Therapeutics, Genentech and Regeneron. He is a visiting professor at the University of Leeds, UK. HW reports compensation of his employer for the conduct of the study and personal fees from AstraZeneca, BerlinChemie, Boehringer Ingelheim, Chiesi, GSK, Novartis and Roche, outside the submitted work. WM reports grants from National Institute for Health Research, Pfizer and the British Lung Foundation, personal fees from Jazz Pharmaceuticals, Mundipharma and Novartis and non-financial support from GSK, outside the submitted work. RAE reports grants from National Institute for Health Research, and personal fees from GSK, Teva, AstraZeneca and Chiesi, outside the submitted work.

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