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

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Online Data Supplement

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METHODS

Randomization and dosing

The randomization code was generated by a validated computerized system under the auspices of Clinical Statistics at GSK. Separate randomizations were generated for each gender, and the randomization process assigned the container number for study treatment. Each participant received blinded study treatment with unique container numbers, which was distinct from the randomization numbers.

Procedures

Respercise was developed by GSK,[1] based on the SPACE rehabilitation program from the University of Leicester, UK.[2] The program comprised up to four strengthening exercises (bicep curls, upright rows, sit-to-stand, and stair climb) performed three-times weekly with a target of three sets of eight repetitions each, with resistance gradually increasing via increasing Theraband resistance based on individual performance. There was an additional daily physical activity goal set according to baseline and daily performance, based on input of daily step counts via a wrist-worn activity tracker (Vivofit; Garmin, Kansas City, KS, USA).

In addition to the St George's Respiratory Questionnaire-COPD-specific version and COPD Assessment Test used to measure health-related quality of life in this study, patient experience of physical activity was measured using the daily PROactive (D-PPAC) eDiary, a hybrid tool comprising a daily questionnaire and outputs from a triaxial physical activity monitor (GT9X; Actigraph, GT9X, Pensacola, FL, USA) worn for 7 days and dispensed at four time points: screening; Day -9 (baseline); Day 56; Day 80 (end of treatment). During these periods, patients also rated their physical activity daily using the D-PPAC. Patients also completed two global questions: Patient Global Impression of Change and Patient Global Rating of Severity at similar time points (**Table S2**). Patients completing the study also participated in an exit interview exploring disease impact and experience within the study. Study endpoints are described in **Table S3**.

Spirometry was performed according to American Thoracic Society/European Respiratory Society guidelines.[3] Blood samples were collected for measurement of pharmacokinetics (PK) of GSK2881078 and for safety, hematology, and blood chemistry. Routine urinalysis, vital signs, and electrocardiograms were also performed.

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Patients performed a practice incremental shuttle walking test during screening, before repeating this test at the baseline visit; the greater of the two measurements of distance walked was used to determine walking speed during the endurance shuttle walking test (ESWT) assessment. ESWT was performed at baseline and Day 90; if at baseline the ESWT lasted for 20 minutes or more, it could be repeated at the next level (greater walking speed) following a 30-minute rest.

Pharmacokinetic analysis

To evaluate the PK profile of GSK2881078, plasma samples were collected and assayed using a validated analytical method[4] based on protein precipitation, followed by high-performance liquid chromatography–tandem mass spectrometry/mass spectrometry analysis. The lower limit of quantification for GSK2881078 was 500 pg/mL. Analytical computer systems included Analyst version 1.6.2 and SMS2000 version 3. Trough GSK2881078 plasma concentration data were summarized at different time intervals over 90 days. To compare pre-dose drug levels on Day 90 between females and males, the dose of GSK2881078 was normalized from 2 mg to 1 mg.

Statistical analysis

The sample size was determined using an estimation approach based on the percentage change from baseline in strength endpoint. Sample size was planned such that for each sex, 20 evaluable patients enrolling to each treatment group would give a half width of a 90% confidence interval for the treatment difference of 5.8%. A standard deviation of 10.9% was assumed. A target of 25 randomized patients per sex for each treatment arm would be expected to result in 20 evaluable patients.

A sensitivity analysis was also conducted on the primary endpoint based on the ‘per-protocol’ population (**Table S4 and Table S5**). The per-protocol population consisted of patients in the analysis population who were compliant with protocol-specified criteria (e.g., those who did not take any prohibited medications, those who completed the end of treatment D-PPAC, lean body mass and all of the functional assessments, or those who did not permanently discontinue the treatment during the study treatment period) and who did not experience a COPD exacerbation, which needed treatment with steroids, during the treatment phase of the study. The ‘safety population’ comprised all patients who had received at least one dose of study medication. The ‘PK population’ comprised all patients who had been dosed with GSK2881078 (**Table S4**) and for whom a PK sample was obtained and analyzed.

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Table S1: Enrolment by site

Country	Site number	Address	Number randomised	Sex (Male : Female)	Mean Age (yr)	Smoking status (%current smokers)
Germany	234311	Woehrendamm 80, Pulmonary Research Institute at LungClinic Grosshansdorf, Schleswig-Holstein, Grosshansdorf, Germany	18	9 M: 9F	66	56%
Germany	234812	Schaumainkai 101-103,, Pulmonology, IKF Pneumologie Frankurt - Clinical Research Center Respiratory Diseases, Hessen, Frankfurt, Germany, 60596	15	7M : 8F	62	40%
United Kingdom	234312	Fulham Road, Royal Brompton Hospital, London, United Kingdom, SW3 6HP	2	1M : 1F	69	0%
United Kingdom	234692	Glenfield Hospital, Groby Road, University Hospitals of Leicester NHS Trust, Leicestershire, Leicester, United Kingdom, LE3 9QP	7	2M: 5F	70	57%
United Kingdom	234881	249 Westminster Bridge Road, Guy's and St Thomas' NHS Foundation Trust - St Thomas' Hospital, London, Greater London, United Kingdom, SE1 7EH	1	1M	58	0%
United Kingdom	235911	Hill End Road, Department of Respiratory Medicine, Harefield Hospital, Middlesex, Harefield, United Kingdom, UB9 6JH	2	2M	69	50%
United States	232851	CDCRC Building, 1124 W Carson Street, Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, California, Torrance, United States, 90502	5	3M: 2F	66	20%

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United States	234694	485 Simuel Road, Spartanburg Medical Research, South Carolina, Spartanburg, United States, 29303	16	7M: 9F	68	63%
United States	234769	7th Floor, Parkinson Pavilion, 3401 N. Broad Street, Temple University School of Medicine, Pennsylvania, Philadelphia, United States, 19140	1	1F	64	0%
United States	235321	141 Harold Flemingcourt, VitaLink Research, South Carolina, Spartanburg, United States, 29303	26	14M : 12F	63	70%
United States	234308	Suite 1, 4085 University Boulevard South, Jacksonville Center for Clinical Research, Florida, Jacksonville, United States, 32216	3	3M	69	67%
		Total	96*			

*Of 97 randomized participants, one was randomized in error.

Table S2: Study visits and assessments

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment period (13 weeks)**							**Follow-up**[2] V9 (42 days post last dose)	**Notes**
			V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]		
Visit window (days)	-30 to -11	-11 to -7	-2 to Day 1	12–16	24–32	52–60	76–84	85–91		126–140	There should be an attempt to conduct all assessments for a visit within a single day.[3]
Informed consent, demography/medical/medication/drug/alcohol history/HIV, hepatitis B and C screening	X										Obtained prior to performing any study-related procedures.
Physical exam, 12-lead ECG, vital signs	X		X	X	X	X		X	X	X	
Hematology (full blood count)/clinical chemistry (creatinine, urea and electrolytes, liver function tests, glucose)	X		X	X	X	X		X	X	X	Participants should fast overnight for at least 8 h prior to collection of these samples.
HbA1c	X							X			
hsCRP, fibrinogen			X					X		X	
25-OH vitamin D total, 25-OH vitamin D2, 25-OH vitamin D3	X							X		X	
Lipid panel	X		X	X	X	X		X		X	
Genetic sample			X								Obtain after participant is randomized.
Pharmacokinetic sampling				X[4]	X[4,5]	X[6]		X[4]	X		Times of dose administration for the two doses immediately preceding a PK sample should be accurately recorded.
Reproductive tissue biomarkers			X		X	X		X		X	
PSA	X		X		X	X		X		X	
Bone biomarkers			X			X		X		X	
Exploratory biomarkers			X	X	X	X		X		X	
Urinalysis	X		X					X	X	X	
DXA			X		X	X		X	X	X	
Spirometry, Sniff Nasal Inspiratory Pressure, Handgrip Strength	X		X			X		X			Follow ATS/ERS guidelines
Leg strength, Short Physical Performance Battery	X		X		X	X		X		X	
Incremental Shuttle Walk Test		X	X					X			Practice Incremental Shuttle Walk Test conducted at Day -9

Procedure	**Screening** V1 (up to 30 days before Day 1)	**V2** Day -9	**Treatment period (13 weeks)** V3 Baseline Day 1	V4 Day 14	V5 Day 28	V6 Day 56	V7 Day 80	V8 Last dose 90	Unscheduled visit [1]	**Follow-up**[2] V9 (42 days post last dose)	**Notes**
Endurance Shuttle Walk Test, St George Respiratory Questionnaire-COPD, Patient Global Rating of Severity			X					X			
COPD Assessment Test			X			X		X			
Patient Global Impression of Change				X	X	X		X		X	
Daily PROactive Physical Activity in COPD instrument and Physical Activity Monitor	X	X[7]				X	X[7]				Physical activity monitor dispensed at screening, Day -9, Day 56, and Day 80 visits. Activity monitor should be worn for 7 days at each time point and returned at the next visit.
Monitored home exercise program		X	X	←==========				X			Participants will receive training for the exercise program at Day -9, and will formally begin exercises on Day 1
Patient exit interview										X	
Randomization			X								All baseline assessments must be obtained prior to randomization.
Study treatment provided to participant			X		X	X					
Study treatment			X	←==========				X			
Study treatment accountability by study site			X	X	X	X		X			
AE, SAE, concomitant medication review			X	←==========						X	
Optional sub-study measures											
Cardiac and liver MRI (additionally prostate MRI)			X[8]					X[8]			MRI is an optional assessment undertaken at participating centers only.

Adapted schedule of activities from study protocol: procedures grouped together according to time points for collection.

1. An unscheduled clinic visit could occur at any time if the investigator believed an unscheduled visit was clinically warranted. Individual listed assessments were optional and were performed as needed to follow unresolved findings of clinical concern.
2. As stated in the protocol (Section 8.2), if a participant decided to withdraw or was withdrawn by the responsible physician, the reasons for withdrawal and the results of any relevant tests were recorded in the CRF and the planned safety follow-up procedures were performed, where possible. These included physical examination, 12-lead ECG, vital signs, blood tests, urinalysis and concomitant medication review as listed for the follow-up visit (Visit 9).
3. Attempted to conduct all visits within a single day, however, the baseline (Day 1) and last dose (Day 90) visits required participants to visit the study center on more than one day in order to complete MRI and DXA scans, and possibly other assessments. These scans, and any other assessments, were conducted within the specified visit window, and prior to randomization at the baseline visit.

4. PK sample taken prior to dosing in the clinic
5. PK sample taken 1–4 h post-dose (sites ensured that a range of times were sampled within this time window for different participants, ie, all PK samples were not taken at 1 h post-dose or 2 h post-dose).
6. PK sample taken 5–8 h post-dose (as above, sites ensured that a range of times are sampled within this time window for different participants).
7. At Visit 3 baseline Day 1 and Visit 8 last dose Day 90, the participants returned the Daily PROactive Physical Activity in COPD Instrument and the Physical Activity Monitor to the site. Participants were not dispensed the Daily PROactive Physical Activity in COPD Instrument and the Physical Activity Monitor at the end of these visits.
8. All MRI scans (cardiac MRI, liver MRI and, if applicable, prostate MRI) were scheduled on the same day. Acquisition of the cardiac MRI were prioritized above the other two scans if it becomes unfeasible to perform all the MRI scans.

AE, adverse event; ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; ERS, European Respiratory Society; HbA1c, glycated hemoglobin; hsCRP, high sensitivity C-Reactive Protein; HIV, human immunodeficiency virus. MRI, magnetic resonance imaging; PK, pharmacokinetic; PSA, prostate-specific antigen; SAE, serious adverse event.

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Table S3: Primary, secondary and exploratory endpoints

Primary endpoints
Change from baseline at Day 90 (absolute and percentage change) in leg strength
Safety and tolerability as assessed by clinical monitoring of blood pressure, heart rate, electrocardiogram, and laboratory data, and adverse event reporting
Secondary endpoints
Change from baseline at Day 90 in appendicular, and total lean mass assessed by dual-energy X-ray absorptiometry
Change from baseline at Day 90 in total SPPB score and its components (time for 5STS and 4mGS)
Change and percent change from baseline at Day 90 in peak performance from the ISWT
Change from Baseline at Day 90 in CWR duration from the ESWT
Change from baseline at Day 90 in CAT score
Change from baseline at Days 56 and 90 in the D-PPAC score (individual score, difficulty components and total score)
Change from Baseline at Day 90 in physical activity measures as assessed via an accelerometer, including mean number of steps, mean ratio of vector magnitude unit/wear time and mean moderate/vigorous activity duration
Change from baseline at Day 90 in SGRQ total score

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Change from baseline at Days 56 and 90 in sniff nasal inspiratory pressure used to assess inspiratory muscle strength
Change from baseline at Days 56 and 90 in FEV_1 %
Pharmacokinetic parameters of GSK2881078
Summary of PGIC analyzed at Days 14, 28, 56, 90, and Day 132
Summary of PGRS analyzed at Days 1 and 90
Exploratory endpoints
Change from baseline at Day 90 in handgrip strength
Patient insights on experience from exit interviews
Adherence to exercise program (daily physical activity and thrice-weekly strengthening exercises)
Changes from baseline in hepatic, cardiac and prostate (males only) structure and function as assessed by MRI

4mGS, 4-meter gait speed; 5STS, five-repetition sit-to-stand; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CWR, constant work rate; D-PPAC, Daily PROactive; ESWT, endurance shuttle walking test; FEV_1, force expiratory volume in 1 second; ISWT, incremental shuttle walking test; LBM, lean body mass; PGIC, Patient Global Impression of Change; PGRS, Patient Global Rating of Severity; SGRQ, St George's Respiratory Questionnaire; SPPB, short physical performance battery

Table S4: Study populations

Population	Female		Male	
	Placebo	GSK2881078	Placebo	GSK2881078
Screened	23	24	24	26
Enrolled	23	24	24	26
All participants	23	24	24	25
Safety	23	24	24	25
Analysis	21	21	23	23
Per protocol	14	14	11	12
Pharmacokinetic	0	21	0	24

Screened=all participants who were screened for eligibility and allocated a subject number. **Enrolled=**all participants who passed screening and entered the study. **All participants=**all randomized participants who received at least one dose of the study medication. **Safety=**all randomized participants who received at least one dose of study medication. **Analysis population=**participants in the 'All Participants' population having baseline and at least one post-baseline assessment of the lean mass or PROactive scores or any of the functional endpoints. **Per-protocol (PP)=**any Analysis population participants who were compliant with protocol-specific criteria and who did not experience an exacerbation during the treatment phase of the study. Participants with specified protocol deviations and those failing to complete the Week 13 functional assessments or PROactive scores or lean mass were excluded. **Pharmacokinetic (PK)=**participants in the 'All participants' population for whom a PK sample was obtained and analyzed for GSK2881078. All available data were used in the analyses as defined in the populations above. Missing values were not imputed.

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Table S5: Per-protocol population

	Female					Male				
	Placebo (n=14)		GSK2881078 (n=14)		Treatment difference (n=14) at Day 90 (90% CI)	Placebo (n=11)		GSK2881078 (n=12)		Treatment difference (n=12) 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)		Baseline Mean (SD)	Change at Day 90 Adjusted mean (90% CI)	Change at Day 90 Adjusted mean (90% CI)	Change at Day 90 Adjusted mean (90% CI)	
1-RM (kg)	109.2 (40.12)	8.4 (0.6, 16.3)	120.0 (45.81)	27.4 (19.5, 35.5)	19.0 (7.7, 30.2)	168.8 (55.11)	18.2 (6.0, 30.4)	202.3 (59.8)	21.2 (9.5, 32.9)	3.0 (-14.1, 20.1)
1-RM (% change from baseline)	-	7.7 (0.8, 14.6)	-	24.6 (17.7, 31.5)	16.9 (-7.1, 26.7)	-	9.1 (2.9, 15.2)	-	11.4 (5.5, 17.2)	2.3 (-6.4, 10.9)

Results for per protocol for primary endpoint. Results reported as adjusted means (90% CIs) for repeated measured mixed models. Results reported as mean (SE) for baseline visits.

1-RM, 1-repetition maximum; CI, confidence interval; SD, standard deviation; SE, standard error.

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Table S6: Summary of plasma concentration time data on Days 14 to Day 90 in females and males (PK population)

Analyte: Plasma: GSK2881078: concentration (pg/mL) **Treatment: GSK2881078 1.0 mg (N=21)**									
Analysis visit	**Planned relative time**	**n**	**No. imputed**	**Mean**	**(95% CI)**	**SD**	**Median**	**Min.**	**Max.**
Visit 4, Day 14	Predose	21	0	78923·8	(64675·9,93171·7)	31300·69	74600·0	20500	152000
Visit 5, Day 28	Predose	20	0	96630·0	(72303·3,120956·7)	51978·61	88750·0	13400	210000
	1–4 h	19	0	111252·6	(89411·4,133093·8)	45315·14	110000·0	10600	196000
Visit 6, Day 56	5–8 h	18	0	123216·7	(92995·3,153438·0)	60772·32	103400·0	31400	235000
Visit 8, Day 90	Predose	18	0	134638·9	(94761·5,174516·3)	80189·65	113000·0	36900	299000
Analyte: Plasma: GSK2881078: concentration (pg/mL) **Treatment: GSK2881078 2.0 mg (N=24)**									
Analysis visit	**Planned relative time**	**n**	**No. imputed**	**Mean**	**(95% CI)**	**SD**	**Median**	**Min.**	**Max.**
Visit 4, Day 14	Predose	24	0	120558·3	(105573·6,135543·0)	35486·62	115500·0	29200	201000
Visit 5, Day 28	Predose	23	0	148095·7	(121205·7,174985·6)	62182·97	154000·0	22900	267000
	1–4 h	23	0	160195·7	(133895·2,186496·1)	60819·74	155000·0	52100	337000
Visit 6, Day 56	5–8 h	20	0	187185	(156288·0,218082·0)	66017·13	190000·0	41800	286000
Visit 8, Day 90	Predose	20	1	184170	(150906·9,217433·1)	71072·75	196000·0	0	265000

Note: No. imputed=number of subjects who had concentration below lower limit of quantification and concentration value imputed to zero. If more than 30% of values are imputed, then SD will not be displayed.
CI, confidence interval; PK, pharmacokinetic; SD, standard deviation.

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Table S7: Change in efficacy measures at Day 90 and Day 132 follow-up period

Variable	Baseline for GSK2881078	Change from baseline for GSK2881078 at Day 90	Change from baseline for GSK2881078 at Day 132	Baseline for placebo	Change from baseline for placebo at Day 90	Change from baseline for placebo at Day 132
Females						
	n=17	n=17	n=17	n=18	n=18	n=18
1-RM % change from baseline (kg)	120.9 (47.91)	20.1 (19.41)	16.9 (17.80)	115.3 (36.95) kg	13.4 (17.09)	19.3 (20.01)
	n=16	n=16	n=16	n=19	n=19	n=19
tLBM (kg)	37.6 (5.12)	1.60 (1.76) kg	1.2 (1.65) kg	36.7 (5.23) kg	-0.5 (1.45)	-0.86 (2.59)
Males						
	n=20	n=20	n=20	n=17	n=17	n=17
1-RM (% change from baseline)	210.3 (56.44)	13.9 (12.73) %	8.8 (14.95) %	169.7 (63.21) kg	8.0 (10.68) %	5.0 (11.03) %
	n=18	n=18	n=18	n=14	n=14	n=14
tLBM (kg)	52.4 (7.08)	1.5 (2.20)	0.8 (2.60)	49.9 (8.29)	-0.4 (1.89)	-0.6 (1.49)

Data reported as unadjusted mean (SD). Results for subjects with non-missing baseline, Day 90, and follow-up data.
1-RM, 1-repetition maximum; SD, standard deviation; tLBM=total lean body mass.

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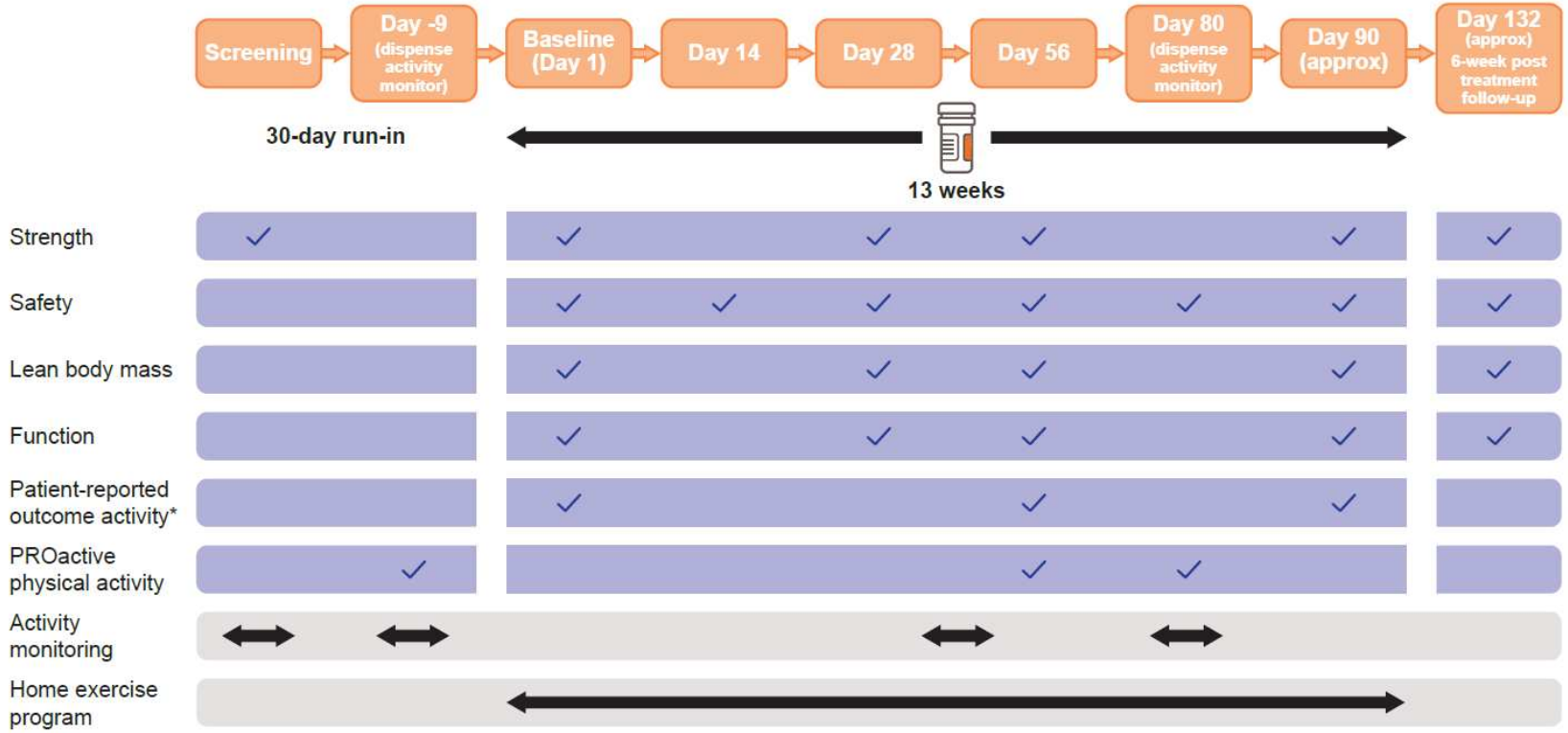
Figure S1: Study schematic



*COPD Assessment Test was scheduled on Days 1, 56, and 90; SGRQ-C was scheduled on Days 1 and 90.

COPD, chronic obstructive pulmonary disease; SGRQ, St George's Respiratory Questionnaire-COPD-specific version.

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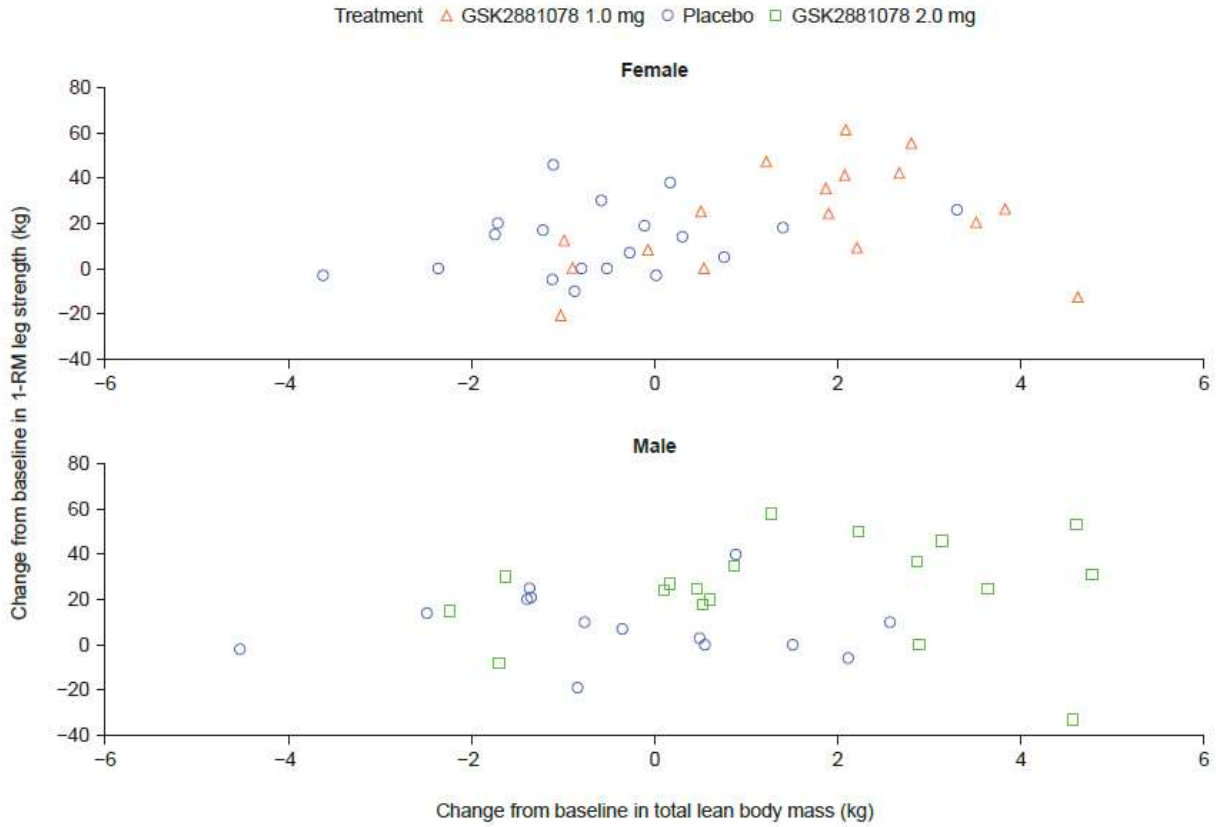
Figure S2: Relationship between change from baseline in 1-RM Leg strength (kg) and change from baseline in Total lean body mass (kg) at day 90



1-RM, 1-repetition maximum.

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