Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for a randomized double-blind (sponsor unblind), placebo-controlled, multi-centred phase IIa study to evaluate the safety and efficacy of 13 weeks of once daily oral dosing of the selective androgen receptor modulator (SARM) GSK2881078 in older men and post menopausal women with COPD and muscle weakness, participating in home exercise
Compound Number	:	GSK2881078
Effective Date	:	09-JAN-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200182 Amendment 3.
- This RAP is intended to describe the safety and efficacy analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• An interim analysis for the assessment of futility is planned (Section 5.1 in the protocol).	• Removed all references to the interim analysis	• Decided to cancel the planned interim analysis, as per the Note to File dated 5March2019
• A multivariate Bayesian approach using non-informative priors will be employed, data permitting, to further explore the relationships between changes in strength and lean mass and the functional outcomes (ISWT, ESWT,) and to inform decision making. (Section 10.3.3 in the protocol)	• Multivariate Bayesian approach will not be planned	• Decision making endpoints will be analysed using a univariate Bayesian approach and a decision-making framework prospectively defined for these endpoints. Any multivariate Bayesian analyses will be considered as post-hoc analysis if data warranted.
• NA	• Analysis of % change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA) will be planned	• To assist clinical team review of the secondary endpoints
• NA	• Analysis of % change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test and peak performance from incremental shuttle	• To assist clinical team review of the secondary endpoints

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	walking test will be planned	
• NA	• The responder definition and analysis between treatment groups (GSK2881078/ Placebo) for COPD Assessment Test (CAT) and St George Respiratory Questionnaire-COPD (SGRQ-c) will be added	• To assist clinical team review of the secondary endpoints
• NA	• A Bayesian analysis added for the endpoint 'times for chair rise'	• To assist clinical team review of the secondary endpoints
• Log-transformed leg press strength data will be conducted as supportive analysis of the primary endpoint	• Log-transformed leg press strength data will be analysed only when the model assumptions are not met, and log-transformation is applicable	• Data will only be analysed by appropriate methods, therefore transformations of the data prior to analysis will only be done if applicable.
• Log-transformed supportive analysis for all the endpoints in case of violation of assumptions	• Log-transformed data will be analysed only when the model assumptions are not met, and log-transformation is applicable	• Data will only be analysed by appropriate methods, therefore transformations of the data prior to analysis will only be done if applicable.
• Exploratory endpoint: Further exploratory analyses may include changes from baseline in size of inspiratory muscles and/ or other organs.	• Will not analysed in this RAP	• There is no data collected
• Exploratory endpoint: Gain further insights into the participants' experience with study treatment and their participation in the trial.	• Will not analysed in this RAP	• Exit interview data will be reported separately
• The 'Analysis Population' (AP) is defined as participants in the 'All Participants' population having baseline and at least one post-baseline assessment of the strength, lean mass or functional endpoint (Section	• The 'Analysis Population' (AP) is defined as participants in the 'All Participants' population having baseline and at least one post-baseline	• The endpoint PROactive scores also added to the definition.

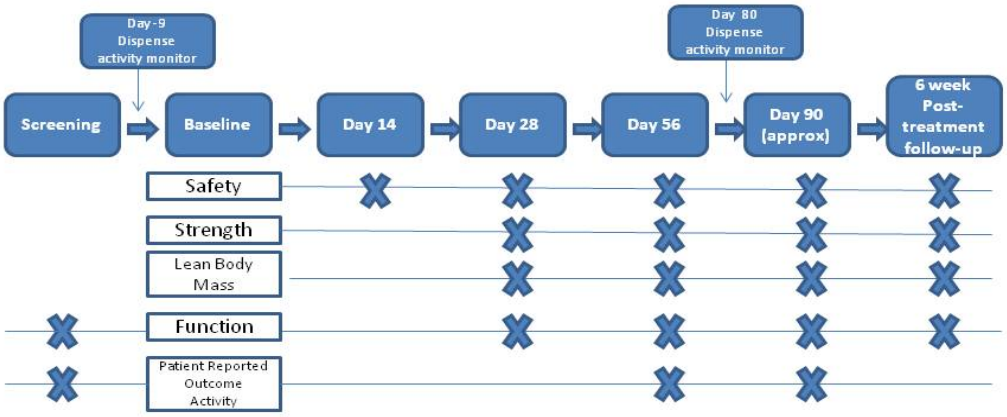
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
10.2 in the protocol).	assessment of the lean mass or PROactive scores or any of the functional endpoints.	
• The 'Per Protocol Population' will consist of any AP participants who are compliant with protocol-specific criteria and who do 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 will be excluded (Section 10.2 in the protocol).	• The 'Per Protocol Population' will consist of any AP participants who are compliant with protocol-specific criteria and who do 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 will be excluded.	• The endpoint PROactive scores also added to the definition.

2.2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Assess the safety and tolerability of approximately 13 weeks of dosing of GSK2881078.	• Safety and tolerability of GSK2881078 as assessed by clinical monitoring of blood pressure, heart rate, electrocardiogram (ECG) and laboratory safety data, as well as reporting of adverse events (AEs)
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on leg strength in older men and postmenopausal women with COPD and muscle weakness, participating in home exercise.	• % change from baseline and change from baseline in maximum leg press strength following 1 repetition maximum (1- RM)
Secondary Objectives	**Secondary Endpoints**
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on lean soft tissue mass.	• Change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA).
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on exercise capacity.	• Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed. • Change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test. • Change from baseline in peak performance from incremental shuttle walking test.
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on patient reported outcomes, levels of physical activity, activities of daily living and the patient perspective of efficacy.	• Change from baseline in COPD Assessment Test (CAT). • Change in PROactive endpoints (individual components and total score). • Change in physical activity measures as assessed via an accelerometer. • Patient Global Impression of Change. • Patient Global Rating of Severity. • Change in St George Respiratory Questionnaire-COPD (SGRQ-c) total score and domains
• Assess the effect of approximately 13 weeks of dosing of GSK2881078 on respiratory function.	• Change from baseline in forced expiratory volume in 1 second (FEV1) • Change from baseline in Sniff nasal inspiratory pressure (SnIP).

Objectives	Endpoints
• Characterise the population pharmacokinetic (PK) profile of approximately 13 weeks of dosing of GSK2881078 in older men and post-menopausal women with COPD and muscle weakness.	• Model specific PK parameters of GSK2881078 (e.g., oral clearance, oral steady-state volume of distribution).
Exploratory Objectives	**Endpoints**
• Assess the safety of 13 weeks of dosing of GSK2881078 in older men and postmenopausal women in a subset of up to 15 male and 15 female participants with COPD via magnetic resonance imaging (MRI).	• Changes from baseline in hepatic, prostate (males) and cardiac structure and function as assessed via MRI. Further exploratory analyses may include changes from baseline in size of inspiratory muscles and/ or other organs.
• Conduct semi-structured exit interviews.	• Gain further insights into the participants' experience with study treatment and their participation in the trial.
• Assess the effect of 13 weeks of dosing of GSK2881078 in older men and postmenopausal women on peripheral strength.	• Changes from baseline in handgrip strength. • Potentially explore adherence to exercise program (daily physical activity and thrice-weekly strengthening exercises).

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This study is a randomized, placebo-controlled, double-blind (sponsor unblind), parallel group, multi-centre phase IIa trial in two equal sized cohorts (male or female). Following completion of screen assessments, baseline assessments will be conducted in eligible participants and, in each cohort, the participants will be randomized 1:1 to GSK2881078 or matching placebo. • This study will assess the effect of GSK2881078 on physical strength and function after 13 weeks of treatment. The placebo group will serve as an appropriate control group to limit evaluation bias in the study endpoints. No suitable active comparator is currently available. Both treatment and control groups will be asked to participate in a standardized home exercise program.
Dosing	• Study treatment will consist of two dosing cohorts (Male: placebo or 2.0 mg of GSK2881078; Postmenopausal female: placebo or 1.0 mg of GSK2881078). • Dosing levels: 1.0 mg for women (2 x 0.5mg capsules) once daily • 2.0 mg for men (2x 1.0mg capsules) once daily • Placebo: 2 capsules once daily
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Male and post-menopausal female participants who are between 50 and 75 years of age and meet all other study entry criteria will be assigned to one of the treatments (Male: placebo or 2.0 mg of GSK2881078; Postmenopausal female: placebo or 1.0 mg of GSK2881078) in a ratio of 1:1 in accordance with the randomization schedule.

Overview of Study Design and Key Features	
Interim Analysis	• No interim analysis is planned for the study (See Note to File dated 5March2019)

2.4. Statistical Analyses

Change from baseline and percent change from baseline in maximum leg press strength following 1- RM will be analyzed separately using mixed models repeated measures (MMRM) models with effects for treatment, day, treatment x day, and baseline strength. Differences in least squares means between the GSK2881078 treated group and placebo treated group will be calculated (i.e.; GSK2881078 - placebo) along with associated 90% CIs. The analysis will be done separately for each gender.

The analyses will be performed using all available data from participants in both the analysis population and the Per Protocol Population. The effects of potential predictors of response including baseline BMI and percent predicted FEV1 will be explored.

Additionally, a Bayesian approach using a non-informative prior will be conducted to estimate the posterior distribution and to estimate the probability that the true treatment difference of % change from baseline strength at week 13 (Day90) is ≥ 9%. Additional threshold values and timepoints will also be presented for all decision-making endpoints including other key secondary endpoints.

Model and distributional assumptions underlying each analysis will be assessed and the details can be found at Appendix 9.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical comparisons will be made for the safety data.

Sample size estimations and explorations into sample size sensitivity are given in Section 10.1 of the protocol.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility and allocated a subject number.	• Screened subjects
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
All Participants	• The 'All Participants Population' is defined as all randomized participants who receive at least one dose of study medication. • This population will be based on the treatment the participant was randomized to.	• Study Population
Safety	• The 'Safety Population' is defined as all randomized participants who receive at least one dose of study medication. • This population will be based on the treatment the participant received.	• Safety
Analysis (AP)	• The 'Analysis Population' (AP) is defined as 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. • This population will be based on the treatment the participant was randomized to. The functional endpoints include leg press strength, peak performance from Incremental shuttle walking test, Constant Work Rate (CWR) duration from endurance shuttle walking test, total SPPB score and handgrip strength.	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
Per Protocol	• The 'Per Protocol Population' will consist of any AP participants who are compliant with protocol-specific criteria and who do not experience an exacerbation during the treatment phase of the study. Participants with specified protocol deviations and those failing to complete any of the Week 13 functional assessments or PROactive scores or lean mass will be excluded. This population will be based on the treatment the participant was randomized to. Further details will be given in Section 12.1.1.	• Efficacy (Strength, SGRQ, PROactive Constant Work Rate (CWR) duration from endurance shuttle walking test and time for repeated chair rise)
Pharmacokinetic (PK)	• The 'PK Population' is defined as participants in the 'All Participants' population for whom a PK sample was obtained and analysed for GSK2881078.	• PK

1. Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the 'Protocol Deviation Specification-version 6.0 dated 28 Nov 2019

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset. It will not be possible to identify whether subjects received a different treatment to the one they were randomised to until post unblinding, hence this protocol deviation will be identified after unblinding the database.
- A blinded data review meetings (BDRM) will be handled before the final database release (DBR)
- This dataset will be the basis for the summaries and listings of protocol deviations.

A listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

The analysis and summary will be separately analysed by gender. All graphical displays will present results for males and females on separate pages. Sex will be either a subtitle or subheading ("by" variable) on these displays.

For each efficacy analysis table, the results for female will displayed first and then repeated for male; for other tables, the summary will be presented in the order of female and male. Listings will be sorted by gender.

Treatment Group Descriptions			
Treatment Group		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order in TLF**
A	PTM GSK2881078 1.0mg	Placebo	1 - Female
B	GSK2881078 1.0 mg	GSK2881078 1.0 mg	2- Female
C	PTM GSK2881078 2.0mg	Placebo	1 - Male
D	GSK2881078 2.0 mg	GSK2881078 2.0 mg	2- Male

Treatment comparisons will be displayed as follows using the descriptors as specified and separated by gender:

Female: GSK2881078 1.0 mg vs Placebo

Male: GSK2881078 2.0 mg vs Placebo

5.2. Baseline Definitions

Parameter	**Study Assessments Considered as Baseline**			**Baseline Used in Data Display**
	Screening	**Day -9**	**Day 1 (Pre-Dose)**	
Efficacy				
Leg Strength	X		X	whichever is latest*
Incremental Shuttle Walk Test		X	X	whichever is higher
Endurance Shuttle Walk Test			X	Day 1
Dual-energy X-ray Absorptiometry (DXA)			X	Day 1
Short Physical Performance Battery (SPPB)	X		X	whichever is latest*
COPD Assessment Test (CAT)			X	Day 1
Patient Global Rating of Severity (PGRS)			X	Day 1
St George Respiratory			X	Day 1

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -9	Day 1 (Pre-Dose)	
Questionnaire COPD (SGRQ-c)				
PROactive Physical Activity	X	X		See detail below**
Spirometry	X		X	whichever is latest*
Sniff Nasal Inspiratory Pressure (SnIP)	X		X	whichever is latest*
Safety				
Vital Signs	X		X	whichever is latest*
12-lead ECG	X		X	whichever is latest*
Haematology	X		X	whichever is latest*
Clinical Chemistry	X		X	whichever is latest*
Urinalysis	X		X	whichever is latest*
hsCRP, Fibrinogen			X	Day 1
Lipid panel	X		X	whichever is latest*
PSA	X		X	whichever is latest*
HbA1c	X			screening
Exploratory				
Cardiac and liver MRI			X	Day 1
Handgrip strength	X		X	whichever is latest*
Reproductive Tissue Biomarkers			X	Day 1
Bone Biomarkers			X	Day 1
***Exploratory Biomarkers			X	Day 1
***Monitored home exercise program		X	X	whichever is latest*

*Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

**Baseline will be the average of the data collected from the 7-day period after Day -9 device dispense.

***Exploratory Biomarkers and home exercise program will be analysed separately and will not be reported as part of this study Statistical Analysis Complete reporting.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by investigative site. There is no analysis planned by center/investigative site.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates which will be used in descriptive summaries and statistical analyses., including the primary analysis are described in the table below. Additional covariates percent predicted FEV1 and baseline BMI will be explored as a sensitivity analysis for the primary endpoint of the leg press strength only.

Category	Details
Covariates	Treatment, Day, Treatment x Day and Baseline
Exploratory covariates	Percent Predicted FEV1 and Baseline BMI

5.4.2. Examination of Subgroups

There is no subgroup analysis planned for this RAP, however, males and females will be analysed separately since they have a different dose level.

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interests is the change from baseline and percent change from baseline in maximum leg press strength following 1 repetition maximum (1- RM). The key endpoint used for decision making purpose will be the percent change from baseline in maximum leg press strength. This analysis will be conducted separately for each gender and the two analyses will be considered co-primary (i.e. both must be considered a success for the study to be successful), therefore no multiplicity adjustment is required. There will be no multiplicity adjustments for multiple endpoints or multiple timepoints or multiple treatment comparisons. Analyses of other efficacy endpoints will not be subject to any multiplicity adjustment.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be mainly based on the All Participants population unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated	
	Table	Listing
Randomisation		
Randomisation		Y [1]
Subject Disposition		
Subjects Enrolled by Country and Site ID [6]	Y	Y
History of Rescreened Subjects [2]		Y
Reasons for Screen Failure [2]	Y	Y
Subjects for Whom the Treatment Blind was Broken		Y
Subject Disposition	Y	Y
Study Visit Dates		Y
Populations Analysed		
Study Populations [2]	Y	Y
Protocol deviations		
Important Protocol Deviations	Y	Y
Deviations leading to exclusion from PP	Y	Y
Inclusion and Exclusion Criteria Deviations		Y
Demography		
Demographic Characteristics [3]	Y	Y
Summary of Age Ranges [6]	Y	
Race & Racial Combinations [4]	Y	Y
Disease Staging		Y
Medical Conditions, Concomitant Medications		
Medical Conditions (Current and Past)	Y	Y

Exacerbation History		Y
Alcohol History		Y
History of Tobacco Use		Y
Change of Smoking Status During the Study		Y
Concomitant Medications	Y	Y
HIV, Hepatitis B and C screening (Hepatitis C viral RNA PCR if Hepatitis C screening is positive)		Y
Other		
IP Compliance [5]	Y	Y

NOTES:

- Y = Display Generated, T = Tables, L = Listings, IP = Investigational Product

1. One listing of subjects randomised but not treated.
2. Screened population.
3. Age, sex, age group, ethnicity, race, weight, height, body surface area, percent predicted FEV1 and BMI (kg/m^2) needs to be summarized.
4. The five-high level FDA race categories and designated Asian subcategories will be summarised along with all combinations of high-level categories which exist in the data. A by-subject listing of race will also be produced.
5. Dispensation information (dates, number of tablets dispensed, returned, taken and lost, compliance percentage, duration of treatment and treatment cumulative dose also will be included).
6. Enrolled population

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Summary Measure

The adjusted mean treatment difference for change and percent change from baseline in maximum leg press strength will be presented at Days 28, 56 and 90.

7.1.2. Endpoint / Variables

The primary endpoints are change from baseline and percent change from baseline in maximum leg press strength following 1 repetition maximum (1- RM). The key endpoint used for decision making purpose will be the percent change from baseline in maximum leg press strength.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the Analysis population. A supportive efficacy analyses will be based on the Per Protocol population.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.4.1. Statistical Methodology Specification

Endpoints / Variables
• % change from baseline and change from baseline in maximum leg press strength (Kg) following 1 repetition maximum (1- RM) at Days 28, 56 and 90.
Model Specification
• Change from baseline and percent change from baseline strength will be analyzed separately using mixed models repeated measures (MMRM) adjusted for treatment, day, treatment x day, and baseline strength, with day as the repeated factor. • Data falling into the analysis windows for day 28, day 56 and day 90 will be included in the model • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • In the event that this model fails to converge, the model will be re-fitted with other covariance structures such as compound symmetry and one which gives the least Akaike's Information Criteria (AIC) from the fitted model will be used as the covariance structure. • The analysis will be conducted separately by gender

- If there are any departures from the distributional assumptions for change or percentage change from baseline, the change of log-transformed data at post- baseline from log baseline will be the response variable, adjusted for treatment, log-transformed baseline strength, day and the interaction of treatment and day, with day as the repeated factor. The sensitivity analysis for the change from baseline and percentage change from baseline are the same.

Model Checking & Diagnostics

- Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- For change and percent change from baseline, adjusted means, corresponding standard error of means (SEs) and 90% confidence intervals will be presented for each treatment by day, together with estimated treatment differences (GSK2881078 – Placebo) and the corresponding 90% confidence intervals and p-value by day for both Analysis and Per Protocol population.
- A line plot of the adjusted mean of change (and percentage change) from baseline as well as the 90% confidence interval over time (day) for each treatment from the MMRM model will be provided for the analysis population.

Log-transformed data results presentation

- The estimated coefficients of the MMRM model will be transformed back (exponential transform).
- For each treatment, adjusted ratio of the post baseline value to the baseline value and corresponding 90% confidence intervals will be presented by day.
- The adjusted treatment ratio of the ratio (postbaseline value/baseline value) between the two treatments with the corresponding 90% confidence interval be presented by day.
- The plot of adjusted ratio of the post baseline value to the baseline value and its 90% confidence interval over time (day) for each treatment arm will be presented for the analysis population

Supportive Statistical Analysis - Bayesian

- % change from baseline in maximum leg press strength following 1 repetition maximum (1-RM) at Days 28, 56 and 90 will be estimated by Bayesian analysis and separately by gender.
- The posterior probability of treatment difference greater than 4% points, less than 9% points and greater than or equal to 9% points for each visit separately by gender.

Model Specification

- Create indicator variables for the categorical effect: Treatment (GSK2881078 vs. Placebo) and Day (day28, day56 and day90).

  For treatment, if treatment=placebo, then drug=0; if treatment=GSK2881078, then drug=1;
- Construct a linear model for each day(visit) in order to model within-subject observation covariance structures by multivariate normal (MVN) distribution in the MCMC procedure. For subject i on treatment j at Day k, the model can be written as:

  $PCH_{ijk}=\beta 0 + \beta 1\ drug + \beta 2\ baseline + \beta d\ Day_k + \beta dk\ drug^* Day_k + \varepsilon_{ijk}$ $\varepsilon_{ijk} \sim N(0, \sigma 2)$;

  where PCH refers to percentage change from baseline and Dayk for k=1, 2, 3 represent days 28, 56 and 90, respectively, and are indicator variables, which are intrinsically formed within

PROC MCMC from the design matrix. The last element, Day3, is excluded by setting it to 0 in the PARMS statement. • (β1+ βd1), (β1+ βd2), are the estimated treatment differences (GSK2881078 vs. Placebo) at Day 28, Day 56 respectively. β1 is the estimated treatment difference (GSK2881078 vs. placebo) at Day 90 • Reformat the input data in the way that all repeated measurements from a subject are in one row • Set seed=123456 with the simulation size of 500000, 5000 burn-in iterations. The simulation size and number of burn-in iterations could be updated during the convergence check. • The non-informative priors (normal (0, var=1e6)) will be used for the regression parameters • The 3-dimension inverse wishart scale matrix will be used as the prior of the covariance matrix. The degrees of freedom will be 3 and the positive definite scale matrix will be an identity matrix. • Multivariate normal (MVN) distribution will be specified to model all repeated measurements • Count the proportion at Day90 where β_1 greater than 4% points, less than 9% points and greater or equal to 9% points respectively from the posterior probability distribution simulation. • Similarly, Count the proportion at Day28 and Day56 where (β_1+ β_{d1}), (β_1+ β_{d2}) are separately greater than 4% points, less than 9% points and greater or equal to 9% points respectively from the posterior probability distribution. • For calculating the posterior adjusted least square mean and corresponding difference, use the coefficient of L-matrix of the covariates from the MMRM analysis mentioned in Section 7.1.4.1
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• n, posterior adjusted least square mean and 90% highest posterior density (HPD) interval, the adjusted treatment difference and its 90% HPD credible interval and standard deviation for the posterior adjusted least square mean and difference. • The treatment difference (GSK2881078 – Placebo) for the percentage change from baseline at each visit (Day 28, Day 56 and Day 90) > 4 percentage points, <9 percentage points and ≥ 9 percentage points will be reported based upon the simulation results from the posterior probability model.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

The secondary endpoints are:

- Change and % change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA).
- Change from baseline in total Short Physical Performance Battery (SPPB) score, times for chair rise and 4 m gait speed.

- Change and % change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test.
- Change and % change from baseline in peak performance from incremental shuttle walking test.
- Change in PROactive endpoints (individual components (difficulty and amount score) and total score).
- Change from baseline in COPD Assessment Test (CAT).
- Responder of COPD Assessment Test (CAT).
- Change in St George Respiratory Questionnaire (SGRQ) total score and domain scores derived from SGRQ-c raw score.
- Responder of St George Respiratory Questionnaire (SGRQ) defined by the total score.
- Change from baseline in forced expiratory volume in 1 second (FEV1).
- Patient Global Impression of Change (PGIC).
- Patient Global Rating of Severity (PGRS).
- Change from baseline in Sniff nasal inspiratory pressure (SnIP).
- Change in physical activity measures as assessed via an accelerometer.

7.2.2. Summary Measure

The adjusted mean treatment differences (GSK2881078 – Placebo) for the following endpoints will be presented:

- Change and % change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA) at Days 28, 56 and 90.
- Change from baseline in total Short Physical Performance Battery (SPPB) score, times for chair rise and 4 m gait speed at Days 28, 56 and 90.
- Change and % change from baseline in Constant Work Rate (CWR) duration from endurance shuttle walking test at Day 90.
- Change and % change from baseline in peak performance from incremental shuttle walking test at Day 90.
- Change from baseline in PROactive endpoints at Days 56 and 90. (individual components and total score).
- Change from baseline in COPD Assessment Test (CAT) score at Days 56 and 90.
- Change from baseline in St George Respiratory Questionnaire (SGRQ) total score and domain scores derived from SGRQ-c raw scores at Days 90.

The responder analysis between GSK2881078 and Placebo (GSK2881078/ Placebo) for the following endpoints will be explored

- Odds ratio between treatment groups for the COPD Assessment Test (CAT) responder at Days 56 and 90.
- Odds ratio between treatment groups for the St George Respiratory Questionnaire (SGRQ) responder defined by the total score derived from SGRQ-c raw scores at Days 90.

The descriptive summaries will be reported for the following endpoints

- Change from baseline in forced expiratory volume in 1 second (FEV1).

- Frequency and percentages of Patient Global Impression of Change (PGIC) responses.
- Frequency and percentages of Patient Global Rating of Severity (PGRS) responses.
- Change from baseline in Sniff nasal inspiratory pressure (SnIP).
- Change in physical activity measures as assessed via an accelerometer.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Analysis Population. The decision-making endpoints PROactive endpoint, SGRQ, SPPB (time for repeated chair rise endpoint) and constant work rate (CWR) duration from endurance shuttle walking test will be also analysed based on the Per Protocol population.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.4.1. Statistical Methodology Specification

Secondary Efficacy Endpoint / Variables – Multiple Post-baseline Visit
• Change and % change from baseline in appendicular, and total lean mass as assessed by Dual-energy X-ray Absorptiometry (DXA) at Days 28, 56 and 90. • Change from baseline in total Short Physical Performance Battery (SPPB) score, **time for repeated chair rise and 4 m gait speed at Days 28, 56 and 90. • Change from baseline (Day 1) in *PROactive endpoints (individual components (difficulty and amount score) and **total score) at Days 56 and 90. • Change from baseline in COPD Assessment Test (CAT) score at Days 56 and 90. *A physical activity monitor will be worn for 7 days after the Day -9 visit (Day 1), for 7 days after the Day 56 visit (Day 56), and for 7 days following the day 80 visit (Day 90). **Bayesian analysis will be performed only for the endpoints change from baseline of PROactive total scores and change from baseline in the time for repeated chair rise. The posterior probability of treatment difference greater than 3 points and less than 6 points for PROactive total scores and greater than 1.3 seconds and less than 1.7 seconds for time for repeated chair rise will be estimated for each visit separately by gender.
Model Specification
• Treatment difference (GSK2881078 – placebo) at each visit on change from baseline or percentage change from baseline (as appropriate) will be analysed using mixed models repeated measures (MMRM) models as what was described for the primary efficacy endpoint in Section 7.1.4.1. The analyses will be based on the analysis population for all endpoints additionally the endpoints PROactive and SPPB will be analysed for per-protocol population as well. • If there are any departures from the distributional assumptions for change or percentage change from baseline, the change of log-transformed data at post- baseline from log baseline will be the response variable, adjusted for treatment, log-transformed baseline value, day and

the interaction of treatment and day, with day as the repeated factor. • A Bayesian approach will also be employed for the change from baseline in PROactive weekly total score and time for repeated chair rise to estimate the treatment difference in the change from baseline for analysis population, following the similar procedures described in Section 7.1.4.1. for the primary efficacy endpoint analysis. For calculating the posterior adjusted least square mean and corresponding difference, use the coefficient of L-matrix of the covariates from the corresponding frequentist MMRM analysis.
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• For change and percent change from baseline, adjusted means and corresponding standard error of means (SEs) and 90% confidence intervals will be presented for each treatment by gender and then by time, together with estimated treatment differences (GSK2881078 – Placebo) and the corresponding 90% confidence intervals for MMRM estimation. • In case of the violation of assumptions in MMRM analysis, adjusted mean for ratio to baseline and 90% confidence intervals will be presented for each treatment by gender and then by time, together with adjusted treatment ratio of the ratio (postbaseline value/baseline value) between the two treatments with the corresponding 90% confidence interval be presented by day. • A line plot of the adjusted mean change from baseline or percentage change from baseline (as appropriate) as well as 90% confidence intervals over time (day) for each treatment by gender from the MMRM model will be provided for the analysis population. In case of violation of assumption in MMRM analysis, the adjusted mean for ratio to baseline and corresponding 90% confidence interval will be plotted. • For the Bayesian analysis, n, posterior adjusted least square mean and 90% highest posterior density (HPD) interval, the adjusted treatment difference and its 90% HPD credible interval and standard deviation for the posterior adjusted least square mean and difference will be reported along with the estimated probabilities. • For the Bayesian analysis for PROactive weekly total score, the probability of treatment difference (GSK2881078-placebo) greater than 3 points and less than 6 points will be estimated through the simulations of the posterior probability distribution. Similarly, for the Bayesian analysis for time for repeated chair rise, the probability of treatment difference (GSK2881078-placebo) greater than 1.3 seconds and less than 1.7 seconds will be estimated through the simulations of the posterior probability distribution.

Secondary Efficacy Endpoint / Variables – Categorical Variable
• Odds ratio of COPD Assessment Test (CAT) responder at Days 56 and 90. • Odds ratio of St George Respiratory Questionnaire (SGRQ) responder derived by the total score at Days 90.
Model Results Presentation
• The number of responders, odds ratio and associated 90% exact confidence intervals between treatment groups (GSK2881078 vs. placebo) will be reported for CAT and SGRQ responder analysis by gender.

Secondary Efficacy Endpoint / Variables – Single Post-baseline Visit
• Change and % change from baseline in Constant Work Rate (CWR) duration* from endurance shuttle walking test at Day 90. • Change and % change from baseline in peak performance from incremental shuttle walking test at Day 90. • Change from baseline in St George Respiratory Questionnaire (SGRQ) total score* and domain scores derived from SGRQ-c raw scores at Days 90. *Bayesian analysis will be performed only for the endpoints change from baseline of Constant Work Rate (CWR) duration and change from baseline of SGRQ total score. The posterior probability of treatment difference greater than 36 seconds and less than 48 seconds for Constant Work Rate (CWR) duration and greater than 2 points and less than 4 points SGRQ total score will be estimated.
Model Specification
• Treatment difference (GSK2881078 – placebo) in the change from baseline and percentage change from baseline at Day 90 will be analysed using ANCOVA where baseline and treatment will be included as the independent variables in the model. Each gender will be analysed separately. The analyses will be based on the analysis population for the endpoints CWR duration, peak performance from incremental shuttle walking test and SGRQ total score additionally the endpoints CWR duration and SGRQ total score will be analysed for per-protocol population as well. • If there are any departures from the distributional assumptions, the change of log-transformed data at post- baseline from log baseline will be the response variable, adjusted for treatment, and log-transformed baseline value. • A Bayesian approach will also be conducted to estimate the treatment difference in the change from baseline at Day 90 for CWR duration and change from baseline SGRQ total score for the analysis population, following the similar procedures described in Section 7.1.4.1. for the primary efficacy endpoint analysis with the model being constructed as below: • Create indicator variables for the categorical effect: Treatment (GSK2881078 vs. Placebo). For treatment, if treatment=placebo, then drug=0; if treatment=GSK2881078, then drug=1; • For subject i on treatment j, the model can be written as: $CH_{ij}=\beta_0 + \beta_1$ drug + β_2 base+ +ε_{ij} where CH refers to the change from baseline at Day 90; base means baseline assessment; drug=0 when treatment is placebo and drug=1 for GSK2881078 treatment; $\varepsilon_{ij} \sim N(0, \sigma^2)$; β_1 is the estimated treatment difference (GSK2881078 vs. placebo) at Day 90; • Set seed=123456 with the simulation size of 200000 and 5000 burn-in iterations; the sample size and the number of burn-in iterations could be updated during the convergence check. • The non-informative priors (normal (0, var=1e6)) will be used for the regression parameters β_0, β_1, and β_2. and the prior for variance σ^2 will be the inverse gamma (0.01, scale=0.01) • For calculating the posterior adjusted least square mean and corresponding difference, use the coefficient of L-matrix of the covariates from the corresponding ANCOVA analysis
Model Checking & Diagnostics
• Refer to Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation
• For change and percent change from baseline, adjusted means and corresponding standard error of means (SEs) and 90% confidence intervals will be presented for each treatment at Day 90, together with estimated treatment differences (GSK2881078 – Placebo) and the corresponding 90% confidence intervals through ANCOVA model. • In case of the violation of assumptions in ANCOVA analysis, adjusted mean for ratio to baseline and 90% confidence intervals will be presented for each treatment by gender, together with adjusted treatment ratio of the ratio (postbaseline value/baseline value) between the two treatments with the corresponding 90% confidence interval be presented. • For the Bayesian analysis, n, posterior adjusted least square mean and 90% highest posterior density (HPD) interval, the adjusted treatment difference and its 90% HPD credible interval and standard deviation for the posterior adjusted least square mean and difference will be reported along with the estimated probabilities. • For the Bayesian analysis for CWR duration, the probability of treatment difference (GSK2881078-placebo) greater than 36 seconds and less than 48 seconds will be estimated through the simulations of the posterior probability distribution. Similarly, for the Bayesian analysis for SGRQ total score, the probability of treatment difference (GSK2881078-placebo) greater than 2 points and less than 4 points will be estimated through the simulations of the posterior probability distribution.

Secondary Efficacy Endpoint / Variables – Descriptive Summary
• Forced expiratory volume in 1 second (FEV1) at Days 1, 56 and 90. • Patient Global Impression of Change (PGIC) at Days 14, 28, 56 and 90. • Patient Global Rating of Severity (PGRS) at Days 1 and 90. • Sniff nasal inspiratory pressure (SnIP) at Days 1, 56 and 90. • Physical activity measures as assessed via an accelerometer at Days 1, 56 and 80.
Summary Results Presentation
Baseline, each postbaseline visit and change from baseline, will be descriptively summarized by treatment group for endpoints: weekly average steps, vector magnitude unit/wear time and moderate/vigorous activity duration measures via an accelerometer. The number of subjects with the eligible days i.e. wear duration more than 8 hours for at least 4 days, the average eligible days for those subjects and average wear duration (minutes) during the eligible days will be summarized. Baseline, each postbaseline visit and change from baseline, will be descriptively summarized by treatment group for original FEV1 (L) and percentage predicted FEV1 and maximum SnIP. In addition, a box plot will be prepared for the change from baseline for FEV1 and SnIP at the post-baseline visits. For the categorical endpoints, PGRS and PGIC, the count and percentage will be summarized by category and treatment for each visit separately by gender.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint / Variables

The exploratory endpoints that will be analysed are:

- Changes from baseline in handgrip strength.

7.3.2. Summary Measure

Descriptive summary of baseline assessments, post-baseline assessments and change from baseline for handgrip strength.

Changes from baseline in size of inspiratory muscles and/or other organs will not be analyzed in this report because there is no data collected. In addition, exit interview data will be reported separately, thus the analysis of the endpoint 'Gain further insights into the participants' experience with study treatment and their participation in the trial' will not be performed in this RAP. The adherence to the exercise program (daily physical activity and thrice-weekly strengthening exercises) will not be explored in this RAP.

7.3.3. Population of Interest

The exploratory efficacy analyses will be based on the Analysis population, unless otherwise specified.

7.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.4.1. Statistical Methodology Specification

Endpoint / Variables
• Changes from baseline in handgrip strength.
Summary Results Presentation
• The handgrip strength of left hand and right hand will be separately summarized for baseline, Day 90 and change from baseline at Day 90 by treatment for each gender separately

7.3.4.2. Other Analyses

- An exploratory analysis will be performed on the analysis population to identify how the change from baseline of PROactive total and domain scores changes over the responses of PGIC questionnaire. This relationship between PGIC levels and change from baseline in PROactive total and domains scores will be explored by a descriptive summary table for the visits Day 56 and 90. This comparison will be by gender (males, females and overall (male + female)) and not with respect to treatment. Along with the seven levels of PGIC, the pooled categories "Much worse and Worse" and "Better and Much Better" will also be summarized.
- A sensitivity analysis has to be performed to identify the influence of center PPD on the primary analysis. The primary analysis of percentage change from baseline for leg press has to perform by removing the subjects recruited from the center PPD for the analysis population. This is the analysis supporting the SPOOS ((Significant Payments of Other Sorts) impact analysis.

Plots to be generated in R-shiny App

Shiny is an open R package from RStudio, which provides a web application framework to create interactive web applications (visualization) called "Shiny apps". Shiny combines the computational power of R with the interactivity of the modern web. Shiny web apps can be deployed locally or on the web through tools such as RStudio Connect.

The below mentioned plots will be generated in the R-shiny app at SAC. These displays will then be sent for clinical review. From the generated plots only the clinically important ones will be identified and added to the CSR and will be considered post hoc analyses. These plots will be generated for the analysis population.

- Absolute, Change and percent change from baseline in the leg press strength and change from baseline in constant work rate (CWR) duration from endurance shuttle walking test and peak performance from incremental shuttle walking test versus baseline SPPB categories will be plotted (box-plot) by treatment group for each gender separately. The box-plots for both the treatment groups will be presented in one plot for one gender; then repeat for the other gender.
- The relationship between absolute, change and percent change from baseline at Day 90 in the leg press strength , change from baseline in constant work rate (CWR) duration from endurance shuttle walking test at Day 90 and peak performance from incremental shuttle walking test at Day 90 versus baseline PROactive scores for all the domains score as well as the baseline average daily steps via an accelerometer will be explored by the scattered plots by treatment group for each gender. Baseline scores will be the x-axis and absolute or change from baseline or percent from baseline at Day 90 in the leg press strength and shuttle walk tests separately will be the y-axis
- Mean absolute, change from baseline and percentage change from baseline in leg press strength, change from baseline in appendicular and total lean mass, constant work rate (CWR) duration from endurance shuttle walking test, peak performance from incremental shuttle walking test, total SPPB score, hand grip, SGRQ (all domains) and PROactive (all domains) will be plotted by treatment group for each gender, where descriptive mean for absolute, change from baseline and percentage change from baseline for the respective endpoints will be the Y-axis in each plot and X-axis will be the visits.

8. SAFETY ANALYSES

The safety analyses will be based on the safety population and actual treatment group, unless otherwise specified. Data for male and female subjects will be analysed separately.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The AE text recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 22.0) and will be reported using the primary System Organ Class (SOC) and Preferred Term (PT). Results will be displayed irrespective of treatment phase in the order of decreasing frequency, both across SOC and within SOC. The details of the planned displays are provided in Appendix 11: List of Data Displays.

For those displays with maximum intensity, if AEs are reported more than once by a subject, the most severe intensity will be included. An adverse event will be considered as a common adverse event if it occurs in more than one patient in either gender.

8.2. Adverse Events of Special Interest Analyses

The table in Section 12.6.3 ("Safety") presents the Adverse Events of Special Interest (AESI) and the groups of terms that they comprise. AESI which are not standardized MedDRA queries (SMQs) comprise a selection of PTs defined by GSK. The final list of AESIs, and the PTs that contribute to each of the AESIs, will be provided by Safety and Medical Governance (SMG), using the MedDRA version current at the time of reporting. This list will be finalized prior to unblinding the database.

Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting. Furthermore, emerging data from on-going studies may highlight additional AESI. Therefore, the list of AESI, and the terms included for each AESI, will be based on the safety review team (SRT) agreements in place at the time of reporting. The details of the planned displays are provided in Appendix 11: List of Data Displays.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, Lipids and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 11: List of Data Displays.

A line plot of the mean change from baseline (latest pre-dose value including unscheduled visits) as well as +/- standard error over time (day) for each treatment by gender will be plotted for below mentioned sex hormones and metabolic analytes.

Sex / Reproductive Hormones

Testosterone, Free Testosterone, Sex hormone-binding globulin (SHBG), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH) and Prostate specific antigen (PSA).

Metabolic Analytes

Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglyceride, Glucose and HbA1c.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

A listing of changes from baseline in hepatic, prostate (males) and cardiac structure and function assessed via MRI scan will be presented as an exploratory analysis.

Biomarkers will be summarized descriptively. The reproductive tissue biomarkers and bone markers to summarize are given below.

Reproductive Tissue Biomarkers

Luteinizing hormone, Follicle stimulating hormone, Total testosterone, Free testosterone (calculated) in males and female, Estradiol (females), Dihydrotestosterone, Sex hormone binding globulin and Prostate specific antigen (PSA) (males).

Bone Biomarkers

Procollagen type I N propeptide (s-PINP) and C-terminal telopeptide of type I collagen (s-CTX).

9. PHARMACOKINETIC ANALYSES

PK concentration related summaries will be presented. No PK parameters will be derived in this RAP. The PK parameters for the Study will be derived as a part of Population Pharmacokinetic (POPPK) analyses. The POPPK RAP will include the detailed population PK analysis and resulting derived PK parameters including Cmax and AUC over dosing interval.

9.1. Secondary Pharmacokinetic Analyses

9.1.1. Summary Measure

Pharmacokinetic concentration data will be presented in graphical and tabular form and will be summarized descriptively by gender.

9.1.2. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

9.1.3.1. Statistical Methodology Specification

Plasma concentration time data will be descriptively summarized by the 3 sampling intervals (pre dose, 1-4h interval and 5-8 h intervals) by visit and also listed by treatment group for each gender.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

A population PK analysis will be conducted on the final data. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the analysis approach and specifications are detailed in the POP PK Data Analysis Plan by CPMS.

To support this analysis two NONMEM-specific data files will be generated by S&P using pre-defined formatted datasets provided by CPMS. The first formatted dataset will focus on the PK data and all relevant covariates. The second dataset will contain the time dependent efficacy and safety endpoints.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

12.1.1. Exclusions from Per Protocol Population

The criteria for subject exclusion from the Per Protocol population are based on 'the Protocol Deviation Specification-version 2.0-31August 2018'. Refer to the latest version of the rules document prior to finalisation of the per protocol population.

The following criteria define the protocol deviations Potential protocol deviations leading to exclusion from PP population will be reviewed by the study team to confirm that they meet these criteria. This review will occur before the clinical database has been frozen for analysis. Note: None of the protocol deviations need the data unblinding to take the decision whether the subject data to be excluded from analysis or not. So, the protocol deviation meeting post unblinding won't be conducted.

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Inclusion #1 – Subject not 50-75 years of age inclusive
02	Inclusion #3 – Did not have Confirmed Diagnosis of COPD
03	Inclusion #4 – SPPB: Score of "0" on any component of the SPPB or Timed Chair Stand Score is < 1 and > 3
04	Inclusion #5 – BMI not within 18-32 kg/m2 (inclusive)
05	Inclusion #6 – not current smokers or former smokers with a cigarette smoking history of <10 pack years
06	Exclusion #1-7 – Prohibited Medical Conditions
07	Exclusion #8-10 – Prohibited Treatments
08	Exclusion #11 – Prohibited Prior/Current Clinical Study Experience
09	Exclusion #12-13 – Key laboratory tests out of range
10	Exclusion #14 – ECG values above ranges (QTc > 480, QTcB/F > 450)
11	Exclusion #15 – Positive HIV antibody test
12	Any other deviations from inclusion/exclusion criteria which could impact the efficacy assessment.
13	Experience an exacerbation, which needed treatment with steroids during the treatment phase of the study
14	Not completing the Day 80 PROactive endpoint, Week 13 (Day 90) lean mass and all of the functional assessments (leg press strength, peak performance from Incremental shuttle walking test, Constant Work Rate (CWR) duration from endurance shuttle walking test, total SPPB score and handgrip strength).
15	Permanent discontinuation of the treatment during the study treatment period (This check must will be performed by Statistics and Programming).

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

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	X										Obtained prior to performing any study-related procedures.
Inclusion and exclusion criteria	X										
Demography/ medical/medication/ drug/ alcohol history/ PD disease staging	X										
Full physical examination	X								X	X	
Brief physical exam			X	X	X	X		X			
12-lead ECG	X		X	X	X	X		X	X	X	
Vital signs	X		X	X	X	X		X	X	X	
HIV, Hepatitis B and C screening	X										If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required

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]		
Hepatitis C viral RNA PCR									X		If evidence of Hepatitis C antibodies at screening visit, then Hepatitis C viral RNA PCR required to exclude active infection. This sample is not needed if Hepatitis C screening is negative.
Haematology (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 hours 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. **Informed consent to obtain the genetics sample** must be obtained before collecting a sample.
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	For male participants only
Bone Biomarkers			X			X		X		X	

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]		
Exploratory Biomarkers			X	X	X	X		X		X	
Urinalysis	X		X					X	X	X	
DXA			X		X	X		X	X	X	
Spirometry	X		X			X		X			Follow ATS/ ERS guidelines [Celli, 2004] and Quanjer reference equation [Quanjer, 2012].
Sniff Nasal Inspiratory Pressure	X		X			X		X			
Leg strength	X		X		X	X		X		X	
Handgrip strength	X		X					X			
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
Endurance Shuttle Walk Test			X					X			
COPD Assessment Test			X			X		X			
St George Respiratory Questionnaire COPD (SGRQ-c)			X					X			
Patient Global Rating of Severity			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 timepoint 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	

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]		
Randomization			X								All Baseline assessments must be obtained prior to randomization.
Study treatment provided to participant			X		X	X					The subject should take their first dose of study treatment in the clinic after randomization.
Study treatment			X	←==========→				X			Participants should dose study treatment in the clinic at each clinic visit during the treatment period.
Study treatment accountability by study site			X	X	X	X		X			The required counting of pills by site staff to check compliance is not considered redispensing the study medication.
AE review			X	←==========→						X	
SAE review			X	←==========→						X	
Concomitant medication review			X	←==========→						X	
Optional sub-study measures											
Cardiac and liver MRI (additionally prostate MRI in males)			X[8]					X[8]			MRI is an optional assessment undertaken at participating centres only.

ECG= Electrocardiogram; HIV= Human Immunodeficiency Virus; PK= Pharmacokinetic; PSA= Prostate Specific Antigen; DXA= Dual-energy X-ray Absorptiometry; AE= Adverse Event; SAE= Serious Adverse Event.

1. An unscheduled clinic visit may occur at any time if the investigator believes an unscheduled visit is clinically warranted. Individual listed assessments are optional and are performed as needed to follow unresolved findings of clinical concern. Note: The “Unscheduled visit” case report form (CRF) form should be completed as soon as possible following the Unscheduled visit.

2. As stated in Section 8.2 , if a participant decides to withdraw or is withdrawn by the responsible physician, the reasons for withdrawal and the results of any relevant tests will be recorded in the CRF and the planned safety follow-up procedures will be performed, where possible. These include physical examination, 12-lead ECG, vitals, blood tests, urinalysis and concomitant medication review as listed for the follow-up visit (V9).
3. Attempt to conduct all visits within a single day however the baseline (day 1) and last dose (day 90) visits may require subjects to visit the study centre on more than one day in order to complete MRI and DXA scans, and possibly other assessments. These scans, and any other assessments, should be conducted within the specified visit window, and prior to randomization at the baseline visit. Further details on the suggested order of assessments will be given in the SRM.
4. Take PK sample prior to dosing in the clinic
5. Take PK sample 1-4 hours post-dose (sites should try and ensure that a range of times are sampled within this time window for different participants, i.e. all PK samples should not be taken at 1 hour post dose or 2 hours post dose).
6. Take PK sample 5-8 hours post-dose (as above, sites should try and ensure that a range of times are sampled within this time window for different participants).
7. At V3 Baseline Day 1 and V8 Last dose 90, the patients will return the Daily PROactive Physical Activity in COPD Instrument and the Physical Activity Monitor to the site. Patients will not be 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) should preferably be scheduled on the same day. Acquisition of the Cardiac MRI should be prioritized above the other two scans if it becomes unfeasible to perform all the MRI scan.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    i. vital signs
    ii. 12-lead ECG
    iii. blood draws.

Note: The timing of the assessments should allow the blood draw to occur at the time specified in the SoA.

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Protocol Window		Target	Analysis Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint		Beginning Timepoint	Ending Timepoint	
All	All	Day -30	Day -11	Day -30 to -11	Day -60	Day -12	Screening/Visit 1
All	All	Day -11	Day -7	Day -9	Day -11	Day -5	Visit 2
All	All	Day -2	Day 1	Day 1	Day -4	Day 1	Visit 3, Day 1
All	All	Day 12	Day 16	Day 14	Day 10	Day 18	Visit 4, Day 14
All	All	Day 24	Day 32	Day 28	Day 22	Day 34	Visit 5, Day 28
All	All	Day 52	Day 60	Day 56	Day 50	Day 62	Visit 6, Day 56
All	All	Day 76	Day 84	Day 80	Day 76	Day 84	Visit 7, Day 80
All	All	Day 85	Day 91	Day 90	Day 85	Day 97	Visit 8, Day 90
All	All	Day 126	Day 140	Day 132	Day 126	Day 140	Follow-Up, Day 132

- For scheduled visits the analysis visit would equal the nominal visit irrespective of the assessment date and irrespective of whether that date falls in the visit window.

- Only unscheduled visits are slotted according to the table above and this slotting algorithm will be applicable for both efficacy and safety domains.

- After slotting of Un-scheduled visits, if there are multiple assessments at a planned time-point, then the value closest to the target day for that window will be considered. If the multiple assessments are equidistant from the target day, then mean of the assessments will be considered.

- For any time post baseline and baseline (if the definition of baseline is the latest pre-dose visit) all assessments are used irrespective of whether they fall into visit windows or not.

12.4. Appendix 4: Study Phases

12.4.1. Study Phases

Only Concomitant Medication will be reported by treatment phases and all other displays will be irrespective of the phases.

12.4.2. Study Phases for Concomitant Medication

Definition	Treatment Phase	
	Pre-Treatment	On-Treatment*
Subject did not take study treatment (e.g., screening failures) AND concomitant medication stop date >= date of Screening	Y	
Concomitant medication start date < treatment start date AND (date of Screening <= concomitant medication stop date <treatment start date)	Y	
Concomitant medication start date < (treatment start date or screening Date) and the variable that defines the status of Concomitant medication end with respect to reference time -period is ("BEFORE")	Y	
Concomitant medication start date < treatment start date AND the variable that defines the status of Concomitant medication end with respect to reference time -period is ("AFTER", "DURING", "DURING/AFTER", "ONGOING")	Y	Y
Concomitant medication start date < treatment start date AND (treatment start date < concomitant medication stop date <= treatment stop date)	Y	Y
(Concomitant medication start date < treatment start date) AND (concomitant medication stop date > treatment stop date)	Y	Y
Treatment start date <= concomitant medication start date		Y

*On-Treatment phase includes both On-Treatment and Post-Treatment concomitant medications.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software (Version 9.2 or higher).	
Reporting Area	
HARP Server	: us1salx00259
HARP Compound	: \ARPROD\GSK2881078\mid200182\
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & AdaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented as SDTM.	
Generation of RTF Files	
• RTF files will be generated for each reporting effort.	

12.5.2. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  - 4.03 to 4.23: General Principles
  - 5.01 to 5.08: Principles Related to Data Listings
  - 6.01 to 6.11: Principles Related to Summary Tables
  - 7.01 to 7.13: Principles Related to Graphics

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
- Numeric data will be reported at the precision collected on the eCRF except for the parameters specified below.

Domain	DP for Mean
Leg Press (Last Successful Lift 1-Rep Max (kg))	1 DP
Appendicular Lean Mass (kg) & Total Lean Mass (kg)	3 DP
PRO parameters & SGRQ parameters	2 DP
Total Score for SPPB	1 DP
CAT	1 DP
Time for the Fastest Walk (sec) & Time Repeated Chair Stand Test (sec)	3 DP

Incremental Shuttle Walking test - Maximum Distance Walked (m)	1 DP
CWR - Exercise Duration (sec)	1 DP

- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits

- Unscheduled visits will be assigned to a study visit using the assessment windows defined in Section 12.3. After slotting of Un-scheduled visits, if there are multiple assessments at a planned time-point, then the value closest to the target day for that window will be used. If its equidistant from the target day, then mean of the assessments will be used in summary and figures. Listing will show both the planned and un-scheduled assessments.
- Data summaries will only report visits that are planned assessment time points for each parameter (according to the T&E table) which can include the unscheduled visits if slotted.
- All unscheduled visits will be included in listings.
- Unscheduled visits can be included in the derivation of any time post baseline visits and baseline if the definition of baseline is the latest pre-dose visit (See Section 5.2).

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to IDSL Statistical Principals 7.01 to 7.13.

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements (not in case of visit slotting) will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 12.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1
Note that Treatment Start Date is considered as Study Day 1.

Post-baseline
• Post-baseline refers to the combined time periods of On-treatment and Post-treatment.
Change from Baseline
= Post-baseline -Baseline
Ratio to Baseline
= exp (log (Post-baseline) -log (Baseline))
Percent Change from Baseline
= 100*(Post-baseline – Baseline)/Baseline
Treatment compliance
= 100 * (Total Amount Taken/ (Treatment duration in days* 2)) Total Amount Taken = Total tablets dispensed – Total tablets returned – Total tablets lost.

12.6.2. Efficacy

Secondary Efficacy endpoints
Peak performance from incremental shuttle walking test
• 'Maximum distance walked' collected from incremental shuttle walk test in CRF
Constant Work Rate (CWR) duration from endurance shuttle walking test
• 'Exercise duration time (seconds)' collected from endurance shuttle walk test in CRF
St George Respiratory Questionnaire (SGRQ) total score and domains
• The total score and three component scores (Symptoms, Activity and Impacts) will be derived from St George Respiratory Questionnaire- COPD (SGRQ- c) raw scores based upon the score manual (ST

Secondary Efficacy endpoints

GEORGE'S RESPIRATORY QUESTIONNAIRE FOR COPD PATIENTS (SGRQ-C) Version No.1.3 March 2016)

- First, sum the weights for all items with a positive response:
  Symptoms component consists of all the questions (question 1 -7) in Part 1. The weights for Questions 1-7 are summed. A single response is required to each item. If multiple responses are given to an item, the weights for the multiple positive responses should be averaged then added to the sum.

  Activity component is calculated from the summed weights for the positive responses to items questions 9 and 12 in Part 2 of the questionnaire.

  Impacts component is calculated from questions 8, 10, 11, 13, 14 in Part 2 of the questionnaire. The weights for all positive responses to items in Questions 10, 11, 13 are summed together with the responses to the single item that should have been checked (ticked) in Questions 8 and 14. In the case of multiple responses to either of these items, the average weight for the item should be calculated.

  Total score is calculated by summing the weight to all the positive responses in each component.

- Then, calculate the score:
  The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the results as a percentage:
  Sum of maximum possible weights for each component and Total:
  Symptoms: 566.2 Impact: 1652.8
  Activity: 982.9 Total: 3201.9

- Last, converting SGRQ-c scores to be comparable to SGRQ:
  The adjustment is:
  Symptoms: SGRQ score = (SGRQ-C x 0.99) + 0.94 units
  Activity: SGRQ score = (SGRQ-C x 0.87) +7.01 units
  Impacts: SGRQ score = (SGRQ-C x 0.88) +2.18 units
  Total: SGRQ score = (SGRQ-C x 0.90) + 3.10 units

- <u>Handling of missing items</u>
  A Total score can be calculated in the presence of missing data, but only if the domains meet their 'missing items' rules (see below). If one domain exceeds its permitted number of missed items, then a total score cannot be calculated.
  Symptoms: The Symptoms component will tolerate a maximum of 1 missed item. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (566.2) and from the Total weight (3201.9) and then calculate the score.
  Activity: The Activity component will tolerate a maximum of 3 missed items. The weight for the missed item (s) is subtracted from the total possible weight for the Activity component (982.9) and from the Total weight (3201.9) and then calculate the score.
  Impacts: The Impacts component will tolerate a maximum of 5 missed items. The weight for the missed item (s) is subtracted from the total possible weight for the Impacts component (1652.8) and from the Total weight (3201.9) and then calculate the score.

- Responder is defined as 'Yes' when the total score at a post-baseline visit decreases by 4 or more from baseline total score, otherwise, non-responder.

Secondary Efficacy endpoints

Total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed

- Total SPPB score, 'Time for five stands done successfully' collected for chair and 'time for fastest walk for 4 m gait test' collected from CRF will be used, respectively
- SPPB at baseline will be categorized as below:
  SPPB 10-12 points fit patient, normal

  SPPB 8-9 points pre-frail patient

  SPPB ≤ 7 points frail patient

COPD Assessment Test (CAT)

- Total score of 8 questions will be used
- Responder is defined as 'Yes' when the total score at a post-baseline visit decreases by 2 or more from baseline total score, otherwise, non-responder.
- If one or more of the 8 questions are missing the total score and the responder will be missing.

PROactive endpoints (individual components (Difficulty and Amount) and total score)

- The PROactive instrument (IMI PROACTIVE IN COPD DAILY AND CLINICAL INSTRUMENTS D-PPAC and C-PPAC 2016 (Use D-PPAC for the calculation of scores)) combines a PRO questionnaire and an activity monitor to measure physical activity in COPD patients. It is 9-item daily assessments covering 2 different domains (amount and difficulty) designed for electronic administration. The 'amount' domain is covered by 2 items (questions - amount of walking outside and chores outside) and by 2 activity monitor outputs (vector magnitude units per minute (VMU/min) and steps/day). The 'difficulty' domain is covered by 5 items (questions).
- The scores for activity monitor outputs, step counts and VMU's is assigned based on the 5 level categories they are falling in (see the table below).

Scores	VMU/min	Steps/day
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.		

- Calculation of daily score for each domain (amount, difficulty) and total score:
  First, domains are scored by simple adding items, which, the values are 0-17 for 'amount' and 0-20 for 'difficulty'. The raw scores are then scaled to a score ranging from 0 to 100, based on Table 1 in the guidance (see Reference)

  The 'total score' is obtained calculating the average between two domains. This score has the same scale of two individual domains, from 0 to 100.

  PROactive scores for a day cannot be calculated if the subjects missed any of the 9 items in any day.

Secondary Efficacy endpoints
• Calculation of the weekly score for each domain (amount, difficulty) and total score: The average of the daily scores during a 7-day period will be the weekly score separately for each domain (amount, difficulty) and total score. • Score eligibility: Adequate physical activity data are considered for days where more than eight hours of wearing time is available. The activity monitor measurement days used should be concurrent with the questionnaire. At least four days with ≥ 8 hours of wearing time of activity monitor data are required for the measurements to be valid for a weekly average. These four days should be in the same week (7 days from the first day of assessments), do not need to be consecutive, and could cover weekdays or weekend days without distinction.

Physical Activity Measures
• At least four days with ≥ 8 hours of wearing time of activity monitor data are required for the measurements to be valid for a weekly average. These four days should be in the same week (7 days from the first day of assessments), do not need to be consecutive, and could cover weekdays or weekend days without distinction. Then calculate the average by dividing total with number of days. • The physical activity measures weekly average steps, weekly average vector magnitude unit/wear time and weekly average moderate/vigorous activity duration have the same derivation. • The number of subjects included: The count of subject in each visit who has wear time more than 8 hours for at least 4 days in a week. • Average number of days included per subject: This the average number of days with wear duration more than 8 hours for at least 4 days in each visit. • Average number of minutes included per subject: This the average wear duration in minutes for those subjects with more than 8 hours of wear duration for at least 4 days in a week for each visit.

12.6.3. Safety

Extent of Exposure	
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** The number of days exposure therefore does not take into account dose interruptions. • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • Actual amount taken (number of tablets) = Total tablets dispensed – Total tablets returned – Total tablets lost. • Females will take 1 mg everyday (2*0.5mg tables) and males will take 2 mg (2*1mg). So, the actual dose (mg) taken will be the same as actual amount taken for males and for females it will be actual amount taken divided by 2. • The cumulative actual dose (mg) will be the sum of the actual doses taken.	
Adverse Events	
Onset Time Since 1st Dose (Days)	If Treatment Start Datetime ≤ AE Onset Datetime , then AE Onset Datetime - Treatment Start Datetime +1 If time part is missing in any of the Datetime, then use the Treatment Start date and AE

Extent of Exposure	
	Onset date in calculation and missing otherwise.
Duration (Days)	AE Resolution Datetime – AE Onset Datetime + 1 If time part is missing in any of the Datetime, then use the AE Resolution date and AE Onset date in calculation and missing otherwise.
Drug-related	If the question 'is there a reasonable possibility that AE may have been caused by the Study Treatment' is marked 'YES' on CRF or is missing.

MRI

- Body Surface Area (BSA) (m^2) =0.007184 * Weight (kg)$^{0.425}$ * Height (cm)$^{0.725}$
- Left Ventricular End Systolic Volume Index (LVESVi)=$\frac{LVESV}{\text{Body Surface Area}}$
- Left Ventricular End Diastolic Volume Index (LVEDVi)= $\frac{LVEDV}{\text{Body Surface Area}}$

Adverse Events

Adverse Events of Special Interest (AESI))

The following table presents the AESI. AESI which are not SMQs are made up of a selection of preferred terms (PTs) defined by GSK. The complete list of AESI, including the PTs which contribute to each of the AESI will be provided by Safety and Medical Governance using the MedDRA version current at the time of reporting.

AESI	Group of terms (MedDRA SMQ, HLT or individual PTs)
Drug related hepatic disorders	Drug related hepatic disorders – comprehensive search (SMQ)
Reproductive organ effects, male	Prostatic neoplasms and hypertrophy HLT plus selected preferred terms: Prostatic specific antigen abnormal Prostatic specific antigen increased
Reproductive organ effects, female	Female gonadal function disorders HLT (includes PT of Hirsutism and Virilism)
Virilism in females	Hirsutism PT, Virilism PT, Acnes HLT, Dysphonia PT
Dyslipidaemia	Dyslipidaemia SMQ
Bone effects	Osteoporosis/osteopenia (SMQ), Plus, selected Fracture PTs (57 terms)

MedDRA PT	PT Code
Ankle fracture	10002544
Bone decalcification	10070817
Bone disorder	10005956
Bone fragmentation	10064211
Clavicle fracture	10009245
Comminuted fracture	10052614
Complicated fracture	10010149
Compression fracture	10010214

	Epiphyseal fracture	10053962
	Facial bones fracture	10016042
	Fibula fracture	10016667
	Foot fracture	10016970
	Fracture delayed union	10017081
	Fracture displacement	10053206
	Fracture reduction	10057609
	Fractured coccyx	10049164
	Fractured skull depressed	10017310
	Greenstick fracture	10018720
	Hand fracture	10019114
	Humerus fracture	10020462
	Impacted fracture	10066386
	Internal fixation of spine	10069749
	Jaw fracture	10023149
	Lower limb fracture	10061599
	Open fracture	10030527
	Osteocalcin decreased	10050940
	Osteonecrosis	10031264
	Osteonecrosis of jaw	10064658
	Patella fracture	10034122
	Scapula fracture	10039579
	Skeletal injury	10061363
	Skull fracture	10061365
	Skull fractured base	10040960
	Sternal fracture	10042015
	Stress fracture	10042212
	Tibia fracture	10043827
	Torus fracture	10066094
	Traumatic fracture	10049514
	Ulna fracture	10045375
	Upper limb fracture	10061394
	Vertebral wedging	10065317
	Atypical fracture	10072395
	Avulsion fracture	10066184
	Chance fracture	10073162
	Limb fracture	10074551
	Osteochondral fracture	10073853
	Periprosthetic fracture	10069135
	Spinal fusion fracture	10074807
	Fracture malunion	10017085
	Fracture nonunion	10017088
	Craniofacial fracture	10077603
	Spinal flattening	10077756
	Bone metabolism biochemical marker increased	10078949
	Subchondral insufficiency fracture	10079864

	Maisonneuve fracture	10081343
	Degenerative bone disease	10081730
	Internal fixation of fracture	10022576
Cardiovascular effects	See the table below.	
Hypersensitivity	Hypersensitivity (SMQ) narrow, Angioedema (SMQ) narrow, Anaphylactic reaction (SMQ) narrow	
Hostility/aggression	Hostility/aggression (SMQ)	
Sexual desire disorders	Sexual desire disorders HLT	
Embolic and thrombotic events	Embolic and thrombotic events (SMQ)	

Cardiovascular effects AESI

AESI	AESI Subgroup	Sub-SMQ	Scope
Cardiovascular effects	Cardiac arrhythmia	Arrhythmia related investigations, signs and symptoms (SMQ)	Broad
		Bradyarrhythmia terms, nonspecific (SMQ)	Broad
		Conduction defects (SMQ)	Broad
		Disorders of sinus node function (SMQ)	Broad
		Cardiac arrhythmia terms, nonspecific (SMQ)	Broad
		Supraventricular tachyarrhythmias (SMQ)	Broad
		Tachyarrhythmia terms, nonspecific (SMQ)	Broad
		Ventricular tachyarrhythmias (SMQ)	Broad
	Cardiac failure (SMQ)		Broad
	Ischaemic heart disease (SMQ)		Broad
	Hypertension (SMQ)		Broad
	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)		Broad
	Cardiomyopathy (SMQ)		Narrow

ECG Parameters
General
• The summary should be based on average value of triplicate ECG readings obtained over a brief recording period (missing readings will not be counted).
Eligibility Criteria
• The QT values at screening will be using for the eligibility checking of subjects.

ECG Parameters

Stopping Criteria

A subject who meet either of the bulleted criteria below will be withdrawn from the study:

- QT interval corrected for heart rate by Bazett's formula (QTcB) or QT interval corrected for heart rate by Fridericia's formula (QTcF) >450 msec
- QT interval corrected for heart rate (QTc) >480 msec in participants with Bundle Branch Block based on a single ECG.

Laboratory Parameters

General

- All clinical laboratory tests will be based on central laboratory assessments only. If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digits = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

Laboratory Toxicity Grade

- Toxicities will be based on FDA guidance 'Common Terminology Criteria for adverse events v4.03 (CTCAE) defined by NCI-CTEP (National Cancer Institute – Cancer Therapy Evaluation Program).
- When summarising toxicity grades for such parameters, they will be categorised as to whether they are above or below the normal range.

Parameter	Below Normal Range	Above Normal Range
Fasted glucose	Hypoglycaemia	Hyperglycaemia
Sodium	Hyponatremia	Hypernatremia
Potassium	Hypokalemia	Hyperkalemia
Calcium	Hypocalcemia	Hypercalcemia

Hepatitis Status

- Hepatitis B and C will be determined using antibody (IgM or IgG) at the screening or within 3 months prior to first dose of study treatment. If there is evidence of Hepatitis C antibodies at the screening visit, then Hepatitis C viral RNA PCR is required to exclude active infection. This sample is not needed if Hepatitis C screening is negative
- Antibody (IgM or IgG) status with 'BORDERLINE' or 'REACTIVE' will be considered Positive
- A subject will be considered positive for hepatitis B virus (HBV) if they have a positive surface antigen (HBsAg) during screening. Subjects positive for HBV are not allowed to enter the study

COPD Exacerbation Event Count

- The total number of exacerbation events is determined by summing the number of times there is a non-missing "Date of Onset" on the exacerbation CRF page" for a subject
- The number of exacerbating patients refers to the count of the unique patient in the COPD Exacerbation CRF data. In other words, it is the total number of patients who experience one or more exacerbations defied in the first bullet.

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as subjects who completed all visits of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be assigned to a planned visit or an unscheduled visit and will be slotted as per Appendix 3: Assessment Windows.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL (Female & Male)	0.075	
Haemoglobin	g/L	Male		180
		Female		180
		Δ from BL (Female & Male)	25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
Calcium	mmol/L		2	2.75
Creatinine	µmol/L	Δ from BL		44.2
Glucose	mmol/L		3	9
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2 (Bicarbonate)	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	>=3xULN
AST/SGOT	U/L	High	>=2xULN
Alkaline phosphatase	U/L	High	>=2xULN
T Bilirubin	µmol/L	High	>=1.5ULN
T. Bilirubin + ALT	µmol/L U/L	High	>=1.5ULN T. Bilirubin + >=3xULN ALT

12.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	N/A	> 500
Uncorrected QT	msec	N/A	> 600
Change from Baseline			
Increase from Baseline QTc	msec	N/A	> 60

12.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Pulse Rate	Beats/min	<40	>110
Respiratory Rate	breaths/min	N/A	>20
Temperature (skin)	°C	N/A	>38

12.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

Analysis	Mixed Model Repeated Measure (MMRM)
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.	
Analysis	Bayesian Analysis
• Non-informative prior should be plotted to make sure it is truly non-informative. • Adequate values for the number of MCMC samples / thinning / number of burn-in samples should be chosen to ensure that the ratio Monte Carlo Standard Errors (MCSE) and standard deviation of the posterior distribution for all the parameters in the model as small as possible, typically close to 0.01. • In addition, if possible, the number of tuning units and maximum number of tuning iterations may be increased to find a better proposal distribution for the model parameters, which in turn may reduce the MCSE/SD ratio. • The Geweke diagnostic test checks whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain. • The convergence diagnostics for all parameters in the Bayesian analysis will be visually checked by the trace plots. • If the trace plots show apparent trend or the autocorrelation plots show significant positive or negative autocorrelation, number of iterations will be increased or reparameterization might be explored.	
Analysis	Analysis of covariance (ANCOVA)
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.	

12.10. Appendix 10: Abbreviations & Trade Marks

12.10.1. Abbreviations

Abbreviation	Description
1-RM	1 repetition maximum
AP	Analysis Population
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
BDRM	Blinded data review meeting
BP	Blood Pressure
BS	Biostatistics
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case report form
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV	Cardiovascular
CVA	Cerebrovascular event stroke
CWR	Constant Work Rate
DAP	Data Analysis Plan
DBF	Database Freeze
DBR	Database Release
DM	Data management
DOB	Date of Birth
DP	Decimal Places
DVT	Deep vein thrombosis
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FSH	Follicle-stimulating hormone
GSK	GlaxoSmithKline
HR	Heart rate
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System

Abbreviation	Description
IP	Investigational Product
LH	Luteinizing hormone
LVEF	Left ventricular ejection fraction
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PE	Pulmonary embolism
PGIC	Patient Global Impression of Change
PGRS	Patient Global Rating of Severity
PSA	Prostate specific antigen
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcB	Bazett's QT Interval Corrected for Heart Rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAMOS	Randomization & Medication Ordering System
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
SARM	Selective Androgen Receptor Modulator
SD	Standard deviation
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SE	Standard error
SGRQ	St George Respiratory Questionnaire
SGRQ-c	St George Respiratory Questionnaire-COPD
SMG	Safety and Medical Governance
SnIP	Sniff Nasal Inspiratory Pressure
SOP	Standard Operation Procedure
SPPB	Short Physical Performance Battery
SRT	Safety Review Team
SHBG	Sex hormone-binding globulin
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TIA	Transient ischemic attack
FEV1	Forced Expiratory Volume in 1 second
SnIP	Sniff Nasal Inspiratory Pressure

12.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
None

12.11. Appendix 11: List of Data Displays

12.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.13	
Efficacy	2.1 to 2.47	2.1 to 2.9
Safety	3.1 to 3.36	3.1 to 3.4
PK	4.1	
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 89	

12.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

12.11.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

12.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Participants	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Participants	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.4.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.5.	All Participants	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.6.	Screened	SP1	Summary of Study Populations	IDSL	Headline Results & SAC
1.7.	All Participants	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	SAC
Demographic and Baseline Characteristics					
1.8.	All Participants	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Footnote: Age is imputed when full date of birth is not provided.	Headline Results & SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	Enrolled	DM11	Summary of Age Ranges	EudraCT Footnote: Age is imputed when full date of birth is not provided.	SAC
1.10.	All Participants	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
Prior and Concomitant Medications					
1.11.	All Participants	MH4	Summary of Medical Conditions	ICH E3	SAC
1.12.	All Participants	CM1	Summary of Concomitant Medications	ICH E3 Note: On-Treatment phase includes both On-Treatment and Post-Treatment concomitant medications.	SAC
Exposure					
1.13.	Safety	EX1	Summary of Extent of Exposure to Investigational Product	ICH E3	SAC

12.11.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Efficacy					
2.1.	Analysis	EFF_T1	Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model		Headline Results & SAC
2.2.	Per Protocol	EFF_T1	Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model		SAC
2.3.	Analysis	EFF_T1	Analysis of Change from Baseline in Leg Press Strength (kg) by Visit - Repeated Measure Mixed Model		SAC
2.4.	Per Protocol	EFF_T1	Analysis of Change from Baseline in Leg Press Strength (kg) by Visit- Repeated Measure Mixed Model		SAC
2.5.	Analysis	EFF_T2	Bayesian Analysis of Percentage Change from Baseline in Leg Press Strength (%) by Visit		Headline Results & SAC
2.6.	Analysis	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Leg Press Strength by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit for parameters Last Successful Lift 1-Rep Max (kg), Number of Successful Lifts and Starting Lift Weight (kg).	Headline Results & SAC

2.7.	Per Protocol	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Leg Press Strength by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit for parameters Last Successful Lift 1-Rep Max (kg), Number of Successful Lifts and Starting Lift Weight (kg).	SAC
2.8.	Analysis	EFF_T1	Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model with Exploratory Covariate	Add the exploratory covariates predicted FEV1 and BMI at baseline in the same model for Table 2.1. Update the shell footnote by adding the exploratory covariates	SAC
Secondary Efficacy					
2.9.	Analysis	EFF_T1	Analysis of Change from Baseline in Appendicular (kg), and Total Lean Mass (kg) as Assessed by Dual-energy X-ray Absorptiometry by Visit - Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	Headline Results & SAC
2.10.	Analysis	EFF_T1	Analysis of Percent Change from Baseline in Appendicular (%), and Total Lean Mass (%) as Assessed by Dual-energy X-ray Absorptiometry by Visit - Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	SAC
2.11.	Analysis	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Appendicular and Total Lean Mass as Assessed by Dual-energy X-ray Absorptiometry by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit	Headline Results & SAC
2.12.	Analysis	EFF_T1	Analysis of Change from Baseline in PROactive Total Score, Difficulty and Amount Scores by Visit- Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	Headline Results & SAC

2.13.	Per Protocol	EFF_T1	Analysis of Change from Baseline in PROactive Total Score, Difficulty and Amount Scores by Visit- Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	SAC
2.14.	Analysis	EFF_T2	Bayesian Analysis of Change from Baseline in PROactive Total Score by Visit		Headline Results & SAC
2.15.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in PROactive Total Score, Difficulty and Amount Scores by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	Headline Results & SAC
2.16.	Per Protocol	EFF_T3	Descriptive Summary of Change from Baseline in PROactive Total Score, Difficulty and Amounts Scores by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	SAC
2.17.	Analysis	EFF_T1	Analysis of Change from Baseline in COPD Assessment Test (CAT) score by Visit- Repeated Measure Mixed Model	Similar shell as EFF_T1, p-value is not required	SAC
2.18.	Analysis	EFF_T6	Responder Analysis of COPD Assessment Test (CAT)		SAC
2.19.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in COPD Assessment Test (CAT) score by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	SAC
2.20.	Analysis	EFF_T7	Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Score at Day 90 - ANCOVA Model		Headline Results & SAC
2.21.	Per Protocol	EFF_T7	Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Score at Day 90 – ANCOVA Model		SAC
2.22.	Analysis	EFF_T6	Responder Analysis of St George Respiratory Questionnaire (SGRQ)		SAC
2.23.	Analysis	EFF_T2	Bayesian Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score at Day 90	Same as EFF_T2, remove the visit column	Headline Results & SAC

2.24.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Scores by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	Headline Results & SAC
2.25.	Per Protocol	EFF_T3	Descriptive Summary of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Scores by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	SAC
2.26.	Analysis	EFF_T1	Analysis of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise (sec) and 4 m gait speed (sec) by Visit - Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	Headline Results & SAC
2.27.	Per Protocol	EFF_T1	Analysis of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise (sec) and 4 m gait speed (sec) by Visit - Repeated Measure Mixed Model	Similar shell as EFF_T1, add a by line for Parameter under the Sex p-value is not required	SAC
2.28.	Analysis	EFF_T2	Bayesian Analysis of Change from Baseline in Times for chair rise (sec) by Visit		Headline Results & SAC
2.29.	Analysis	EFF_T3	Descriptive Summary of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	Headline Results & SAC
2.30.	Per Protocol	EFF_T3	Descriptive Summary of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise and 4 m gait speed by Visit	Summarize the data for change from baseline and ratio to baseline along with the data at each visit	SAC
2.31.	Analysis	EFF_T7	Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model	Similar shell as EFF_T7, remove the column 'Parameter'	Headline Results & SAC
2.32.	Per Protocol	EFF_T7	Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model	Similar shell as EFF_T7, remove the column 'Parameter'	SAC

2.33.	Analysis	EFF_T7	Analysis of Percent Change from Baseline in Constant Work Rate (CWR) Duration (%) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model	Similar shell as EFF_T7, remove the column 'Parameter' Update footnote [1] as "[1] Lsmeans of percent change from baseline for each treatment group as well as the difference of lsmeans of percent change from baseline is estimated from ANCOVA model with baseline score as the covariate adjusting for the treatment. In case of violation of the assumptions, the same model is fitted with log of ratio to baseline and replacing the covariate baseline with log baseline. "	SAC
2.34.	Analysis	EFF_T2	Bayesian Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90	Same as EFF_T2, remove the visit column	Headline Results & SAC
2.35.	Analysis	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Constant Work Rate (CWR) Duration from Endurance Shuttle Walking Test by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit	Headline Results & SAC
2.36.	Per Protocol	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Constant Work Rate (CWR) Duration from Endurance Shuttle Walking Test by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit	SAC
2.37.	Analysis	EFF_T7	Analysis of Change from Baseline in Peak Performance from Incremental Shuttle Walking Test at Day 90 – ANCOVA Model	Similar shell as EFF_T7, remove the column 'Parameter'	SAC

2.38.	Analysis	EFF_T7	Analysis of Percent Change from Baseline in Peak Performance from Incremental Shuttle Walking Test (%) at Day 90 – ANCOVA Model	Similar shell as EFF_T7, remove the column 'Parameter' Update footnote [1] as "[1] Lsmeans of percent change from baseline for each treatment group as well as the difference of lsmeans of percent change from baseline is estimated from ANCOVA model with baseline score as the covariate adjusting for the treatment. In case of violation of the assumptions, the same model is fitted with log of ratio to baseline and replacing the covariate baseline with log baseline. "	SAC
2.39.	Analysis	EFF_T3	Descriptive Summary of Change and Percent Change from Baseline in Peak Performance from Incremental Shuttle Walking Test by Visit	Summarize the data for change from baseline, percentage change from baseline and ratio to baseline along with the data at each visit. Update footnote as "Note: When there are multiple pre-dose assessments, the highest non-missing pre-dose assessment from day -9 and day 1 is identified and captured as "Baseline (Derived)" visit"	SAC
2.40.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in Physical Activity Measures as Assessed via an Accelerometer.		SAC
2.41.	Analysis	EFF_T8	Descriptive Summary of Patient Global Impression of Change		SAC
2.42.	Analysis	EFF_T10	Descriptive Summary of Patient Global Rating of Severity.		SAC
2.43.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in FEV1 (L) by Visit	This table will include both FEV1 (L) and Percent Predicted FEV1.	SAC

2.44.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in Sniff Nasal Inspiratory Pressure (SnIP) by Visit		SAC
Exploratory					
2.45.	Analysis	EFF_T3	Descriptive Summary of Change from Baseline in Handgrip strength	First left hand, then right hand	SAC
2.46.	Analysis	EFF_T5	Descriptive Summary of Change from Baseline in PROactive total and domains scores in different levels of PGIC		SAC
2.47.	Analysis	EFF_T4	Analysis of Change from Baseline in Leg Press Strength (kg) by Visit excluding the site PPD (Impact analysis) - Repeated Measure Mixed Model	Fit the model for Table 2.3 by excluding the site PPD.	SAC

12.11.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Leg Strength					
2.1	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Change from Baseline in Leg Press Strength (kg) Over Time – Repeated Measure Mixed Model	Separately for each gender Use the same footnote about model specification as in the corresponding analysis table	SAC
2.2	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Percent Change from Baseline in Leg Press Strength (%) Over Time – Repeated Measure Mixed Model	Separately for each gender Use the same footnote about model specification as in the corresponding analysis table	SAC
Lean Mass					
2.3	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Change from Baseline in Appendicular Lean Mass (kg) and Total Lean Mass (kg) as Assessed by Dual-energy X-ray Absorptiometry Over Time – Repeated Measure Mixed Model	Separately for each gender by parameter Use the same footnote about model specification as in the corresponding analysis table	SAC
Functional Tests					
2.4	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Change from Baseline in PROactive Total Score, Difficulty and Amount Scores Over Time - Repeated Measure Mixed Model	Separately for each gender by parameter Use the same footnote about model specification as in the corresponding analysis table	SAC
2.5	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Change from Baseline in COPD Assessment Test (CAT) score Over Time - Repeated Measure Mixed Model	Separately for each gender Use the same footnote about model specification as in the corresponding analysis table	SAC

2.6	Analysis	EFF_F1	Line Plot of Adjusted Mean (90% CI) Change from Baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise (sec) and 4 m gait speed (sec) – Repeated Measure Mixed Model	Separately for each gender by parameter Use the same footnote about model specification as in the corresponding analysis table	SAC
Exploratory Variable					
2.7	Analysis	LB9	Box Plot: Change from Baseline in FEV1 (L)	Separately for each gender, X-axis is visit, Y-axis is change from baseline in FEV1 values;	SAC
2.8	Analysis	LB9	Box Plot: Change from Baseline in Sniff Nasal Inspiratory Pressure (Snip)	Separately for each gender, X-axis is visit, Y-axis is change from baseline in Snip values;	SAC
2.9	Analysis	EFF_F1	Descriptive Mean Change from Baseline in Average Daily Steps over Time		SAC

12.11.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	Headline Results & SAC
3.2.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	For AEs reported more than once by a subject, the most severe intensity will be included.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3.	Safety	AE3	Summary of Common Adverse Events by Overall Frequency	ICH E3 Note: Common adverse event is defined as events occurring more than one in either gender.	SAC
3.4.	Safety	AE3	Summary of Common Severe Adverse Events by Overall Frequency	ICH E3 Note: Common adverse event is defined as events occurring more than one in either gender.	SAC
3.5.	Safety	AE5A	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term.	ICH E3	SAC
3.6.	Safety	AE15	Summary of Common Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT Note: Common adverse event is defined as events occurring more than one in either gender.	SAC
3.7.	Safety	AE3	Summary of Common Drug-Related Severe Adverse Events by Overall Frequency	ICH E3 Note: Common adverse event is defined as events occurring more than one in either gender.	SAC
Serious and Other Significant Adverse Events					
3.8.	Safety	AE3	Summary of Fatal Serious Adverse Events		SAC
3.9.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events		SAC
3.10.	Safety	AE3	Summary of Serious Adverse Events by System Organ Class		SAC
3.11.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class	FDAAA, EudraCT	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	
3.13.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL	SAC
Special Interest AEs					
3.14.	Safety	AE3	Summary of Adverse Events of Special Interest	IDSL – To display by page for CV events and Liver events	Headline Results & SAC
Laboratory: Chemistry					
3.15.	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit	ICH E3	SAC
3.16.	Safety	LB16	Summary of Chemistry Results by Maximum Grade Increases Post-baseline Relative to Baseline	ICH E3	SAC
3.17.	Safety	LB4	Summary of Chemistry Shifts from Baseline Relative to Normal Range	IDSL	SAC
Laboratory: Haematology					
3.18.	Safety	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC
3.19.	Safety	LB16	Summary of Haematology Results by Maximum Grade Increases Post-baseline Relative to Baseline	ICH E3	SAC
3.20.	Safety	LB4	Summary of Haematology Shifts from Baseline Relative to Normal Range	IDSL	SAC
Laboratory: Urinalysis					
3.21.	Safety	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.22.	Safety	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3 Including glucose, protein, blood	SAC
3.23.	Safety	LB4	Summary of Urinalysis Shifts from Baseline Relative to Normal Range	IDSL	SAC
Laboratory: Hepatobiliary (Liver)					
3.24.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
Laboratory: Other					
3.25.	Safety	LB1	Summary of Sex/Reproductive Hormones	Summarize Testosterone, Free Testosterone, Sex hormone-binding globulin (SHBG), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH) and Prostate specific antigen (PSA).	SAC
3.26.	Safety	LB1	Summary of Lipid Panel		SAC
3.27.	Safety	LB1	Summary of hsCRP, Fibrinogen		SAC
ECG					
3.28.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.29.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
3.30.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
3.31.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
Vital Signs					

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.32.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
3.33.	Safety	VS7	Summary of Worst Case Vital Signs Results Relative to Normal Range /Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	IDSL	SAC
Biomarkers					
3.34.	Safety	LB1	Summary of Change from Baseline in Bone Biomarkers		SAC
3.35.	Safety	LB1	Summary of Change from Baseline in Reproductive Tissue Biomarkers		SAC
COPD Events					
3.36.	Safety	SAFE_T1	Summary of COPD Events		SAC

12.11.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	IDSL	SAC
3.2.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC
3.3.	Safety	EFF_F1	Line Plot of Change from Baseline in Sex/reproductive Hormones Over Time	Each hormone per page	SAC
3.4.	Safety	EFF_F1	Line Plot of Change from Baseline in Metabolic factors Over Time	Each factor per page	SAC

12.11.9. Pharmacokinetics Tables

Pharmacokinetics: Table					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1	PK	PK01	Summary of Plasma Concentration Time data		SAC

12.11.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Participants	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Participants	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	All Participants	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
5.	Enrolled	TA1 / CP_RD1x	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
6.	All Participants	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
7.	All Participants	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
8.	All Participants	POP_L4	Listing of Protocol Deviations leading to Exclusion from the Per-Protocol Population		SAC
Populations Analysed					
9.	All Participants	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10.	All Participants	DM2	Listing of Demographic Characteristics	ICH E3 Footnote: Age is imputed when full date of birth is not provided.	SAC
11.	All Participants	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
12.	All Participants	CP_CM3	Listing of Concomitant Medications	IDSL Note: On-Treatment phase includes both On-Treatment and Post-Treatment concomitant medications.	SAC
Exposure and Treatment Compliance					
13.	All Participants	EX3	Listing of Investigational Product Exposure Data	ICH E3	SAC
Adverse Events					
14.	Safety	AE8CPa	Listing of All Adverse Events	ICH E3	SAC
15.	Safety	AE8	Listing of Drug-Related Adverse Events		SAC
16.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
17.	Safety	AE8CPa	Listing of Fatal Serious Adverse Events	ICH E3	SAC
18.	Safety	AE8	Listing of Drug-Related Fatal Serious Adverse Events		SAC
19.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
20.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
21.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
Hepatobiliary (Liver)					
22.	All Participants	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
23.	All Participants	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL only subjects have such events	SAC
24.	All Participants	LIVER 5	Listing of Liver Monitoring/Stopping Event Reporting	IDSL only subjects have such events	SAC
All Laboratory					
25.	Safety	LB5A	Listing of Clinical Chemistry Laboratory Data	ICH E3	SAC
26.	Safety	LB5A	Listing of Haematology Laboratory Data	ICH E3	SAC
27.	Safety	LB14	Listing of Clinical Chemistry Laboratory Data with Character Results	IDSL	SAC
28.	Safety	LB14	Listing of Clinical Haematology Data with Character Results	IDSL	SAC
29.	Safety	LB5A	Listing of All Urine Analysis Data	ICH E3	SAC
ECG					
30.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC
31.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Findings	IDSL	SAC
32.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
33.	Safety	VS4	Listing of All Vital Signs for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC
34.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

12.11.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
35.	Enrolled	POP_L1	Listing of Subject Recruitment by Country and Site Number		SAC
36.	Screened	ES9	Listing of Subject Who were Rescreened		SAC
37.	All Participants	POP_L2	Listing of Visit Dates		SAC
38.	Screened	POP_L3	Listing of Study Population		SAC
39.	All Participants	POP_L5	Listing of Disease Stage and Exacerbation History		SAC
40.	All Participants	MH2	Listing of Current and Past Medical Conditions at Baseline		SAC
41.	All Participants	POP_L6	Listing of Alcohol History and Tobacco Use/Smoking History		SAC
42.	All Participants	POP_L7	Listing of Smoking Status Change during the Study		SAC
43.	All Participants	POP_L8	Listing of HIV and Hepatitis Test Results		SAC
44.	Safety	POP_L9	Listing of Investigational Product Accountability		SAC

Safety					
45.	Safety	SAFE_L1	Listing of COPD Exacerbation Log		SAC
46.	Safety	SAFE_L2	Listing of Hepatic, Prostate and Cardiac Structure assessed via MRI		SAC
47.	Safety	SAFE_L3	Listing of Change from baseline of Lipids and Sex hormones	List the sex hormones Testosterone, Free Testosterone, Sex hormone-binding globulin (SHBG), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH) and Prostate specific antigen (PSA).	SAC
Primary Efficacy					
48.	Analysis	EFF_L1	Listing of leg Press Strength (kg) Results		SAC
Secondary Efficacy					
49.	Analysis	EFF_L2	Listing of Appendicular (kg), and Total Lean Mass (kg) as Assessed by Dual-energy X-ray Absorptiometry (DXA)		SAC
50.	Analysis	EFF_L3	Listing of PROactive Endpoints	Total score, difficulty and amount scores will be displayed	SAC
51.	Analysis	EFF_L4	Listing of Total Short Physical Performance Battery (SPPB) Score and Times for Chair Rise (sec) and 4 m Gait Speed (sec) Results		SAC
52.	Analysis	EFF_L5	Listing of Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test		SAC
53.	Analysis	EFF_L6	Listing of Peak Performance from Incremental Shuttle Walking Test		SAC
54.	Analysis	EFF_L7	Listing of COPD Assessment Test (CAT)		SAC
55.	Analysis	EFF_L8	Listing of Patient Global Impression of Change		SAC
56.	Analysis	EFF_L9	Listing of Patient Global Rating of Severity		SAC

57.	Analysis	EFF_L10	Listing of St George Respiratory Questionnaire (SGRQ) Results	Total score, impact, symptoms and activity domain scores derived by SGRQ-c raw scores	SAC
58.	Analysis	EFF_L11	Listing of Spirometry Results		SAC
59.	Analysis	EFF_L12	Listing of Sniff Nasal Inspiratory Pressure (SnIP)		SAC
60.	Analysis	EFF_L13	Listing of Physical Activity Measures Assessed via an Accelerometer.		SAC
Exploratory					
61.	Analysis	EFF_L14	Listing of Handgrip strength		SAC
Pharmacokinetics					
62.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration time data		SAC
Supportive SAS Listing					
63.	Analysis		Supportive SAS Listing for the Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model		SAC
64.	Per Protocol		Supportive SAS Listing for Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model		SAC
65.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in Leg Press Strength (kg) by Visit - Repeated Measure Mixed Model		SAC
66.	Per Protocol		Supportive SAS Listing for Analysis of Change from Baseline in Leg Press Strength (kg) by Visit- Repeated Measure Mixed Model		SAC
67.	Analysis		Supportive SAS Listing for Bayesian Analysis of Percentage Change from Baseline in Leg Press Strength (%) by Visit		SAC

68.	Analysis		Supportive SAS Listing for Analysis of Percent Change from Baseline in Leg Press Strength (%) by Visit - Repeated Measure Mixed Model with Exploratory Covariates		SAC
69.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in Appendicular (kg), and Total Lean Mass (kg) as Assessed by Dual-energy X-ray Absorptiometry by Visit - Repeated Measure Mixed Model		SAC
70.	Analysis		Supportive SAS Listing for Analysis of Percent Change from Baseline in Appendicular (%), and Total Lean Mass (%) as Assessed by Dual-energy X-ray Absorptiometry by Visit - Repeated Measure Mixed Model		SAC
71.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in PROactive Total Score, Difficulty and Amount Scores by Visit- Repeated Measure Mixed Model		SAC
72.	Per Protocol		Supportive SAS Listing for Analysis of Change from Baseline in PROactive Total Score, Difficulty and Amount Scores by Visit- Repeated Measure Mixed Model		SAC
73.	Analysis		Supportive SAS Listing for Bayesian Analysis of Change from Baseline in PROactive Total Score, Difficulty and Amount Score by Visit		SAC
74.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in COPD Assessment Test (CAT) score by Visit- Repeated Measure Mixed Model		SAC
75.	Analysis		Supportive SAS Listing for Responder Analysis of COPD Assessment Test (CAT)		SAC
76.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Score at Day 90 - ANCOVA		SAC

77.	Per Protocol		Supportive SAS Listing for Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score and Domains Score at Day 90 – ANCOVA		SAC
78.	Analysis		Supportive SAS Listing for Responder Analysis of St George Respiratory Questionnaire (SGRQ)		SAC
79.	Analysis		Supportive SAS Listing for Bayesian Analysis of Change from Baseline in St George Respiratory Questionnaire (SGRQ) Total Score at Day 90		SAC
80.	Analysis		Supportive SAS Listing for Analysis of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise (sec) and 4 m gait speed (sec) by Visit - Repeated Measure Mixed Model		SAC
81.	Per Protocol		Supportive SAS Listing for Analysis of Change from baseline in total Short Physical Performance Battery (SPPB) score and times for chair rise (sec) and 4 m gait speed (sec) by Visit - Repeated Measure Mixed Model		SAC
82.	Analysis		Supportive SAS Listing for Bayesian Analysis of Change from Baseline in Times for chair rise (sec) by Visit		SAC
83.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model		SAC
84.	Per Protocol		Supportive SAS Listing for Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model		SAC
85.	Analysis		Supportive SAS Listing for Analysis of Percent Change from Baseline in Constant Work Rate (CWR) Duration (%) from Endurance Shuttle Walking Test at Day 90 – ANCOVA model		SAC

86.	Analysis		Supportive SAS Listing for Bayesian Analysis of Change from Baseline in Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test at Day 90		SAC
87.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in Peak Performance from Incremental Shuttle Walking Test at Day 90 – ANCOVA		SAC
88.	Analysis		Supportive SAS Listing for Analysis of Percent Change from Baseline in Peak Performance from Incremental Shuttle Walking Test (%) at Day 90 - ANCOVA		SAC
89.	Analysis		Supportive SAS Listing for Analysis of Change from Baseline in Leg Press Strength (kg) by Visit excluding the site PPD (Impact analysis) - Repeated Measure Mixed Model		SAC

12.12. Appendix 12: Example Mock Shells for Data Displays

STUDY POPULATION

Listings

Example : POP_L1
Protocol: xxxxxxx
Population: Screened

Listing xx
Listing of Subjects Recruitment by Country and Site Number

Sex: Female

Country	Site Id./ Investigator Name	Unique Subject Id	Randomization Number	Assigned Treatment	Treatment Start Date
		xxx	xx	xxx	DDMMMYXXX
		xxx	xx		DDMMMYXXX

Programming note: continue with Sex= Male

Example : POP_L2
Protocol: XXXXXXX
Population: All Participants

Listing xx
Listing of Visit Dates

Country: xxxxx
Centre ID: xxxxxx
Investigator: AAAAAA

Sex	Unique Subject Id.	Treatment	Nominal CRF Visit	Visit Start Date	Visit End Date	Analysis Visit [1]	Study Day
F	xxxxx	GSK2881078	Screening	DDMMMYYYY	DDMMMYYYY	Screening	-18
			Day 1/Visit 3	DDMMMYYYY	DDMMMYYYY	Day 1	1
			Visit 4	DDMMMYYYY	DDMMMYYYY	Visit 4	xx
			Visit 5	DDMMMYYYY	DDMMMYYYY	Visit 5	xx
			Unscheduled	DDMMMYYYY	DDMMMYYYY	Visit 6	xx
				DDMMMYYYY	DDMMMYYYY	Visit 7	xx
			...				
	xxxxx	Placebo	Screening	DDMMMYYYY	DDMMMYYYY	Screening	-29
			Day 1	DDMMMYYYY	DDMMMYYYY	Day 1	-1
			...				

[1] Analysis Visit is the slotted visits and it is derived by applying the slotting algorithm to Visit Start Date.
Programmer’s note: repeat for each site within country, then repeat for each country.

Example : POP_L3
Protocol: XXXXXXX
Population: Screened

Listing xx
Listing of Study Populations

Sex: Female
Treatment: None

Site Id./Investigator Id./Investigator Name	Randomized	All Participants	Analysis	Per-Protocol	Safety
xxxxx/xxx	No	No	No	No	No
xxxxx/xxx	No	No	No	No	No
xxxxx/xxx	No	No	No	No	No
...					

Sex: Female
Treatment: GSK2881078

Site Id./Investigator Id./Investigator Name	Randomized	All Participants	Analysis	Per-Protocol	Safety
xxxxx/xxx	Yes	Yes	Yes	Yes	Yes
xxxxx/xxx	Yes	Yes	Yes	No	No
xxxxx/xxx	Yes	No	No	No	No
...					

Treatment: Placebo
...

Programmer's note: Include all analysis populations specified in RAP and give its definition as a footnote.
Example : POP_L4
Protocol: xxxxxxx
Population: All Participants

Listing xx
Listing of Protocol Deviations Leading to Exclusion from the Per-Protocol Population

Sex: Female
Treatment: GSK2881078

Inv.	Unique Subj.	Age	Protocol Deviations	Deviation Start Date/ Day
xxxxx	xxx	xx	xxxxxxxxxxxxxxxxxxx	DDMMMYXXX/ XXX
	xxx	xx	xxxxxxxxxxxxxxxxxxx	DDMMMYXXX/ XXX
...				
...				

Example : POP_L5
Protocol: XXXXXXX

Population: All Participants

Listing xx
Listing of Disease Stage and Exacerbation History

Sex: Female
Treatment: GSK2881078

Site Id./ Unique Subject Id.	Disease Initial Diag. Date	Age (yrs)	Exacerbation History (Number of Exacerbations in the last 12 Months)			
			Without Corticosteroids and/or Antibiotics	Need Corticosteroids and/or Antibiotics	Required Hospitalised	Period Prior to Visit [1]
xxx/xxx	DDMMMYYYY	xx	xx	xx	xxxx	xx
xxx/xxx	DDMMMYYYY	xx				
xxx	DDMMMYYYY	xx				
xxx	DDMMMYYYY	xx				
xxx	DDMMMYYYY	xx				

[1] Period Prior to Visit is the Evaluation Interval considered while collecting Exacerbation history.

Example : POP_L6
Protocol: XXXXXXX
Population: All Participants

Listing xx
Listing of Alcohol and Tobacco Use/Smoking History

Sex: Female
Treatment: GSK2881078

Site Id./Unique Subject Id	Alcohol		Tobacco Use and Smoking History					
	Assessment Date	Alcohol History/# Unit Per Week	Tobacco Smoking History	Last Smoke Date	Smokeless Tobacco Use History	Number of Cigarettes per Day	Years Smoking Tobacco	Pack Year
xxx/xxx	DDMMMYYYY	xx/xx	Smoked	DDMMMYYYY	Current User	xxxx		xx
xxx/xxx	DDMMMYYYY	xx						

Example : POP_L8
Protocol: XXXXXXX
Population: All Participants

Listing xx
Listing of HIV and Hepatitis Test Results

Sex: Female
Treatment: GSK2881078

Site Id./Unique Subject Id.	Sample Date	Age (yrs)	HIV Test Results/[1]	Hepatitis B Test Result	Hepatitis C Test Result/RBA PCR [2]
xxx/	DDMMMYYYY	xx	Negative	Non-Reactive	Non-Reactive
xxx	DDMMMYYYY	xx		Non-Reactive	Reactive
xxx/	DDMMMYYYY	xx		Non-Reactive	Non-Reactive
xxx	DDMMMYYYY	xx		Non-Reactive	Non-Reactive
xxx	DDMMMYYYY	xx		Non-Reactive	Non-Reactive

[1] only when HIV test is reactive;
[2] only when Hepatitis C test is reactive

Example : POP_L9
Protocol: XXXXXXX
Population: Safety

Listing xx
Listing of Investigational Product Accountability

Sex: Female
Treatment: GSK2881078

Site Id.	Unique Subject Id.	Compliance Percentage	Date IP Dispensed/ Study Day	Date IP Returned / Study Day	Tablets Dispensed	Tablets Returned	Amount Taken	Number of Tables Lost	Container Number
xxxxx	xxxx	xx	DDMMMYYYY/ xx	DDMMMYYYY/ xx	xx	xx	xx	xx	xxxxxx
					xx	xx	xx	xx	xxxxxx
		xx	DDMMMYYYY/ xx	DDMMMYYYY/ xx	xx	xx	xx	xx	xxxxxx
					xx	xx	xx	xx	Xxxxxx

Note : Treatment compliance = 100 * (Total Amount Taken/ (Actual treatment duration in days* frequency)).

EFFICACY

Tables

Example : EFF_T1
Protocol: XXXXXXX
Population: XXXXXXX

Table xx
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Sex: Female

Visit		Placebo (N=xxx)	GSK2881078 (N=xxx)
Visit X, Day X	n	xxx	xxx
	Adjusted Mean [1] (SE)	x.xxx (x.xxx)	x.xxx (x.xxx)
	90% C.I.	(x.xxx, x.xxx)	(x.xxx, x.xxx)
	GSK2881078 vs. Placebo		
	Difference [2]		x.xxx
	90% C.I.		(x.xxx, x.xxx)
	p-value		xxx

[1] Estimates were calculated from a repeated measures model including the following covariates: Treatment, Day, Treatment* Day and baseline xxxxxx, with Day as the repeated factor. In case of violation of the assumptions, the same model is fitted with log of ratio to baseline and replacing the covariate baseline xxxxx with log baseline xxxxx. The correlation matrix for within-subject errors used is unstructured.
[2] GSK2881078-Placebo.

Programming note: Please repeat for Sex: Male.
Programming note: Update the footnotes with the appropriate endpoints and covariate as per RAP.

If data has been log-transformed, then use the following shell:

Protocol: XXXXXXX
Population: XXXXXX

Table EFF_T1
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Sex: Female

Visit		Placebo (N=xxx)	GSK2881078 (N=xxx)
Visit X, Day X	n	xxx	xxx
	Model-Adjusted Geometric Mean for Ratio to Baseline (90% CI)[1]	xx.xx (x.xxx, x.xxx)	xx.xx (x.xxx, x.xxx)
	Adjusted Treatment Ratio of Geometric Means (90% CI)[2]		xx.xx (x.xxx, x.xxx)
	p-value		xxxx

[1] Estimates were calculated from a repeated measures model including the following covariates: Treatment, Day, Treatment* Day and baseline xxxxxx, with Day as the repeated factor. In case of violation of the assumptions, the

same model is fitted with log of ratio to baseline and replacing the covariate baseline xxxxx with log baseline xxxxx. The correlation matrix for within-subject errors used is unstructured.
[2] GSK2881078 ratio to Placebo.
Programming note: Please repeat for Sex: Male.
Programming note: Update the footnotes with the appropriate endpoints and covariate as per RAP.

Example : EFF_T2
Protocol: XXXXXXX
Population: XXXXXXX

Table xx
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Sex: Female

Visit		Placebo (N=xxx)	GSK2881078 (N=xxx)
Visit X, Day X	n	xxx	xxx
	Posterior Adjusted Mean (SD)[1]	x.xxx (x.xxx)	x.xxx (x.xxx)
	90% HPD Credible Interval	(x.xxx, x.xxx)	(x.xxx, x.xxx)
	GSK2881078 vs. Placebo		
	Posterior adjusted mean for treatment difference [SD][2]		x.xxx
	90% HPD Credible Interval		(x.xxx, x.xxx)
	Posterior probability treatment difference >=x%		x.xxx
	Posterior probability treatment difference >x%		x.xxx
	Posterior probability treatment difference <x%		x.xxx

[1] Estimates were calculated from a Bayesian repeated measures model including the following covariates: Treatment, Day, Treatment* Day and baseline xxxxxx, with Day as the repeated factor.
[2] GSK2881078-Placebo.
Note: HPD - Highest Posterior Density.
Programming note: Please repeat for Sex: Male.
Programming note: Update the footnotes with the appropriate endpoints and covariate as per RAP. Add the probabilities x% based on the domain.

Example : EFF_T3
Protocol: XXXX
Population: XXXXXX

Table XX
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Parameter: xxxxxxxxxxxxxxxxxx

		Female		Male	
Visit	Statistics	Placebo (N=20)	GSK2881078 (N=22)	Placebo (N=24)	GSK2881078 (N=22)
Baseline	n	xx	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xxx
	Max.	xxx	xxx	xxx	xxx
Visit X, Day X	n	xx	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xxx
	Max.	xxx	xxx	xxx	xxx

Change from Baseline at Visit X, Day X	n	xx	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xxx.x	xxx.x	xxx.x
	Min.	xx	xx	xx	xxx
	Max.	xxx	xxx	xxx	xxx

(a)Note: When there are multiple pre-dose assessments, the latest non-missing pre-dose assessment is identified and captured as "Baseline (Derived)" visit.
(b)Note: "Visit X, Day X" is considered as Baseline.
Programming note: Repeat for other visits and summarize its change from baseline, percent change from baseline and ratio to baseline whereever applicable Programming note: If the baseline is a derived visit add the footnote (a) else if it is a single visit add footnote (b)
Example : EFF_T4
Protocol: XXXXXXX
Population: XXXXXXX

Table xx
Analysis of Change from Baseline in Leg Press Strength (kg) by Visit excluding the site PPD (Impact analysis) - Repeated Measure Mixed Model

Sex: Female

Visit		Placebo (N=xxx)	GSK2881078 (N=xxx)
Visit X, Day X	n	xxx	xxx
	n1	xxx	xxx
	Adjusted Mean [1] (SE)	x.xxx (x.xxx)	x.xxx (x.xxx)
	90% C.I.	(x.xxx, x.xxx)	(x.xxx, x.xxx)
	GSK2881078 vs. Placebo		
	Difference [2]		x.xxx
	90% C.I.		(x.xxx, x.xxx)
	p-value		xxx

[1] Estimates were calculated from a repeated measures model including the following covariates: Treatment, Day, Treatment* Day and baseline leg strength with Day as the repeated factor. In case of violation of the assumptions, the same model is fitted with log of ratio to baseline and replacing the covariate baseline leg strength with log baseline leg strength. The correlation matrix for within-subject errors used is unstructured.
[2] GSK2881078-Placebo.
Note: n1 indicates the number of analysable subjects excluding the site PPD .
Programming note: Please repeat for Sex: Male.
Programming note: Update the footnotes with the appropriate endpoints and covariate as per RAP.

Example : EFF_T5
Protocol: xxxxxxx
Population: Analysis

Table XX

Analysis of Change from Baseline in PROactive total and domains scores in different levels of PGIC

Parameter: XXXXXXXXXXX

Visit	PGIC Level	Statistics	Males (N=XXX)	Females (N=XXX)	Overall (Males + Females) (N=XXX)
Visit X, Day X	Much Better	n	xx	xx	Xx
		Mean	xx.xx	xx.xx	xx.xx
		SD	xx.xxx	xx.xxx	xx.xxx
		Median	xx.xx	xx.xx	xx.xx
		Min.	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
		Max.	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Better	n	xx	xx	Xx
		Mean	xx.xx	xx.xx	xx.xx
		SD	xx.xxx	xx.xxx	xx.xxx
		Median	xx.xx	xx.xx	xx.xx
		Min.	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
		Max.	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Programming Note: Continue with all PGIC Levels and add levels 'Much Worse and Worse' and 'Better and Much Better' to the existing levels of PGIC. Repeat for Day 90 and Parameters of PROactive Scores.
Example : EFF_T6
Protocol: XXXXXXX
Population: Analysis

Table XX
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Sex: Female

Visit	Treatment	N	Responder Rate n1/n (%)	Odds Ratio (90% C.I.)
Visit X, Day X	GSK2881078	xx	xx/xx (xx.x%)	x.xxx (x.xxx, x.xxx)
	Placebo	xx	xx/xx (xx.x%)	

Note: A subject is defined as a responder when the total score at a post-baseline visit decreases XX or more from baseline total score.
Note: n1 is the number of responders in each treatment group and the percentages are calculated using n.
Note: The confidence interval for odds ratio (GSK2881078/Placebo) is calculated using the Exact method.
Programming note: continue for the next visit and repeat for Sex: Male.

Example : EFF_T7
Protocol: XXXXXXX
Population: XXXXXXX

Table XX

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Sex: Female

Parameter		Placebo (N=xxx)	GSK2881078 (N=xxx)
xxxxxxxx	n	xxx	xxx
	Adjusted Mean [1] (SE)	x.xxx (x.xxx)	x.xxx (x.xxx)
	90% C.I.	(x.xxx, x.xxx)	(x.xxx, x.xxx)
	GSK2881078 vs. Placebo		
	Difference [2]		x.xxx
	90% C.I.		(x.xxx, x.xxx)

[1] Lsmeans of change from baseline for each treatment group as well as the difference of lsmeans of change from baseline is estimated from ANCOVA model with baseline score as the covariate adjusting

for the treatment. In case of violation of the assumptions, the same model is fitted with log of ratio to baseline and replacing the covariate baseline with log baseline.
[2] GSK2881078-Placebo.

Example : EFF_T8
Protocol: XXXXXXXX
Population: Analysis

Table **XX**
Descriptive Summary of Patient Global Impression of Change

Sex: Female

Visit	Treatment	N	n	PGIC Category						
				Much Worse	Worse	Slightly Worse	No Change	Slightly Better	Better	Much Better
Day 14	GSK2881078	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Placebo	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 28	GSK2881078	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Placebo	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…..										

Note: The percentages have been calculated based on n.

Programming note: Continue with Visit= Day 56, Day 90 and then repeat for Sex: Male

Example : EFF_T9
Protocol: XXXXXXXX
Population: Analysis

Table XX
Descriptive Summary of Patient Global Rating of Severity

Sex: Female
Treatment: Placebo

Analysis Visit	N	n	PGRS Category				
			None	Mild	Moderate	Severe	Very Severe
Baseline	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Day 90	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

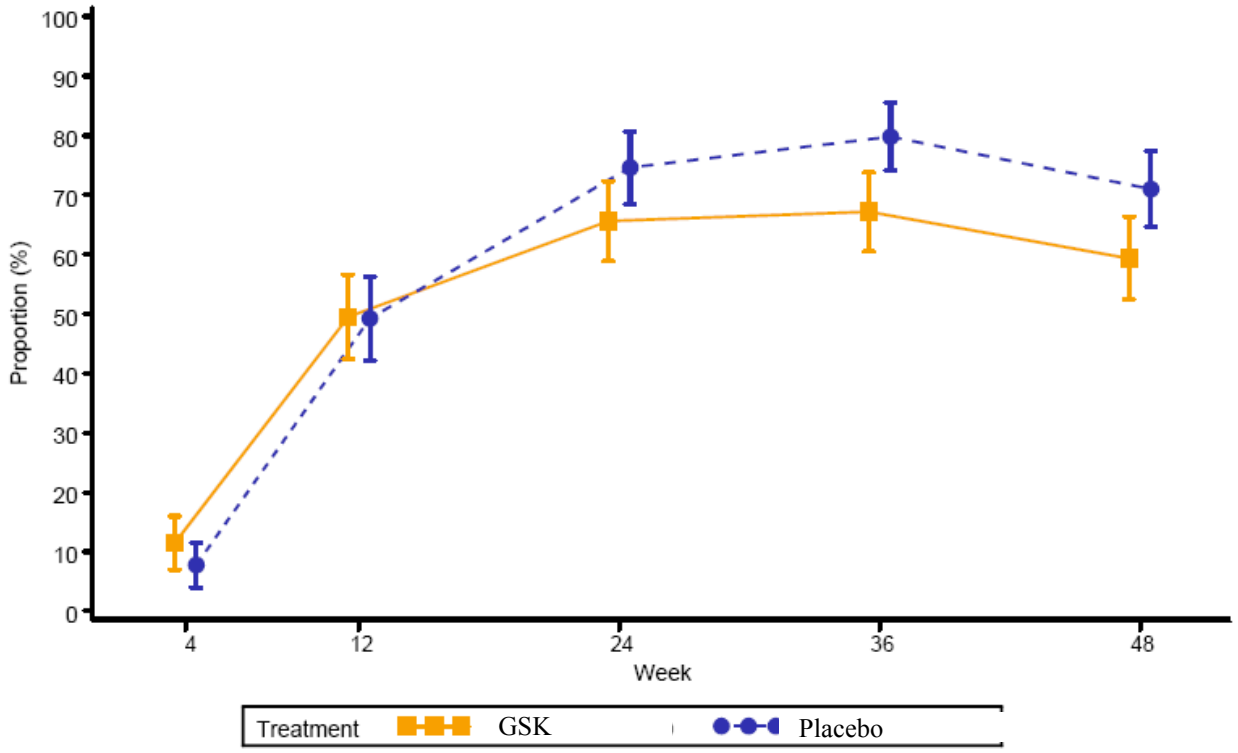
…..

Programming note: repeat for Sex: Male

Figures

Example : EFF_F1
Protocol: XXXXXXX
Population: XXXXXXXX

Figure XX
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx



Listings

Example : EFF_L1
Protocol: XXXXXX
Population: Analysis

Listing XX
Listing of Leg Press Strength (kg) Results

Sex: Female
Treatment: XXXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assessment Date/Day	Parameter	Leg Press Performed? (if no, provide reason)	Assessment Value	Change/Percent Change from Baseline
	Unscheduled / Visit X Day	DDMMMYYYY/1	Number of Successful Lifts	Yes	xx	xxxx / xxx.x
				No		
			Starting Lift Weight (Unit)	Yes	xx (xxx)	xxxx / xxx.x
			Last Successful Lift 1-RM (Unit)	No		

Note: Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

Programming note: Sorted by treatment, Center, Subject, Visit and continue for SEX: Male
Programming note: Use assessment datetime instead of date if time collected and update the label as “Assessment Datetime/Day”

Example : EFF_L2
Protocol: XXXXXX
Population: Analysis

Listing xx

Listing of Appendicular (kg), and Total Lean Mass (kg) as Assessed by Dual-energy X-ray Absorptiometry (DXA)
Sex: Female
Treatment: XXXXXXXXXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assessment Date/Day	Appendicular Lean Mass		Total Lean Mass	
			Assessment (Unit)	Change from Baseline (Unit)	Assessment (Unit)	Change from Baseline (Unit)
xxxx/xxxx	Day 1 / Baseline	DDMMMYYYY/1	xx (xxx)		xx (xxx)	
	Unscheduled / Visit X Day X		xx (xxx)		xx (xxx)	xxxx / xxx.x

Note: "Visit 3, Day 1" is considered as Baseline.

Programming note: Sorted by treatment, Center, Subject, Visit and continue for SEX: Male
Programming note: Use assessment datetime instead of date if time collected and update the label as “Assessment Datetime/Day”

Example : EFF_L3
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of PROactive Endpoints

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Analysis Visit	Individual Component Score		Total Score	
		Amount /Change from Baseline	Difficulty /Change from Baseline	Assessment	Change from Baseline
xxxx/xxxx	Baseline	xx	xx	xx	
	Visit X Day X	xx /xxx	xx /xxx	xx	xxxx

Note: "Visit 3, Day 1" is considered as baseline and is calculated as average of the data collected from the 7-day period after Day -9 device dispense.

Programming note: Use assessment datetime instead of date if time collected and update the label as “Assessment Datetime/Day”

Programming note: Sorted by treatment, Center, Subject,Visit and continue for SEX: Male

Example : EFF_L4
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Total Short Physical Performance Battery (SPPB) Score and Times for Chair Rise (sec) and 4 m Gait Speed (Sec) Results

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	SPPB Performed?	Assessment Date/Day	Balance Tests	Gait Speed Tests				Chair Stand Test		SPPB Total Score
				Total Balance Score	Gait Test Performed?	Walking Aids	Time for the Fastest Walk (Unit)	4 Meter Walk Test Score	Five Successful Stand Time (unit)	Repeated Chair Test Score	
xxxx/xxxx	Baseline	Yes	DDMMMYYYY/1	xx	Yes	xxxx	xx(xx)	xx	xx (xxx)	xx (xxx)	xxxx
		No									
	Unscheduled / Visit X Day X	Yes									xxxx

Note: Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.
Programming note: Sorted by treatment, Center, Subject, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L5
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Constant Work Rate (CWR) Duration (sec) from Endurance Shuttle Walking Test

Sex: Female

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assesment Date/Day	Endurance Time (seconds)	Distance Walked (meters)	Reason for Stopping Test	Endurance Time Change from Baseline
	Day 1/Baseline	DDMMMYYYY	xx	xx	xxxxx	
	Unscheduled / Visit X Day X	DDMMMYYYY	xx	xx	xxxxx	xxxx

Note: "Visit 3, Day 1" is considered as Baseline.

Programming note: Sorted by treatment, Center, Subject, Visit and continue for SEX: Male
Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L6
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Peak Performance from Incremental Shuttle Walking Test

Sex: Female
Treatment: XXXXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assesment Date/Day	Maximum Distance Walked (meters)	Speed (km/hr)	Endurance Walking Speed Level	Reason for Stopping Test	Max Walked Distance Change from Baseline
	Day -9 Day 1 / Baseline	DDMMMYYYY	xxx	xx	xx	xxxxx Reason for Stopping Test	
	Unscheduled / Visit X Day X	DDMMMYYYY					xxxx

Note: When there are multiple pre-dose assessments, the highest non-missing pre-dose assessment from day -9 and day 1 is identified and captured as "Baseline (Derived)" visit.
Programming note: Sorted by treatment, Center, Subject, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L7
Protocol: XXXXXXX
Population: Analysis

Listing xx
Listing of COPD Assessment Test (CAT)

Sex: Female

Treatment: XXXXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assesment Date/Day	Individual Question Score								Total Score/Chang from Baseline
			1	2	3	4	5	6	7	8	
xxxxxx/ xxxxxx	Xx	DDMMMYYYY	Xx	xx	xx	xx	xx	xx	xx	xx	
xxxxxx/ xxxxxx	Unscheduled / Day xx	DDMMMYYYY									

Note: 1="Frequency of Cough", 2="Amount of Phlegm in My Chest", 3="Tightness in Chest", 4="Breathless Walking Upstairs", 5="Limited Doing Home Activities", 6="Confident Leaving Home", 7="Sleeping Soundly", 8="Amount of Energy".
Note: "Visit 3, Day 1" is considered as Baseline.
Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male
Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L8
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Patient Global Impression of Change

Sex: Female
Treatment: XXXXXX

			PGIC Category						
Site Id/ Unique Subject Id	Assessment Date/Day	Visit / Analysis Visit	Much Worse	Worse	Slightly Worse	No Change	Slightly Better	Better	Much Better
	DDMMMYYYY /14	Visit x / Visit X Day X	No	No	No	No	Yes	No	No
	DDMMMYYYY/1	xx							

Programming note: Sorted by treatment, Center,Subjects, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L9
Protocol: XXXXXXXX
Population: Analysis

Listing xx
Listing of Patient Global Rating of Severity (PGRS)

Sex: Female
Treatmet: XXXXX

Site Id/ Unique Subject Id	Assessment Date/Day	Visit / Analysis Visit	PGRS Category				
			None	Mild	Moderate	Severe	Very Severe
Xxxx/xxxx		Baseline / Visit X Day X					Yes

…..

Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male
Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L10
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of St. George Respiratory Questionnaire (SGRQ) Results

Sex: Female
Treamtment: XXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assessment Date/Day	Individual Domain Score			Total Score	
			Symptoms /Change from Baseline	Activity /Change from Baseline	Impacts/Change from Baseline	Assessment	Change from Baseline
xxxx/xxxx	Baseline / Visit X Day X	DDMMMYYYY/1	xx	xx	xx	xx	xxxx
	Unscheduled / Visit X	DDMMMYYYY/1	xx /xxx	xx /xxx	xx /xxx	xx	xxxx

Day X

Note: "Visit 3, Day 1" is considered as Baseline.
Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L11
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Spirometry Results

Sex: Female
Treatment: XXXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assesment Date/Day	FEV1 (L)	Predicted FEV1 (L)	Percent Predicted FEV1 (%)	FVC (L)	Predicted FVC (L)	Percent Predicted FVC (%)	FEV1/FVC
xxxx/xxxx	Screening/ Baseline	DDMMMYYYY:hh:mm/-xx	xx	xx	xx	xx	xxxxx	xx	xx.x
	Day 1/Visit X Day X	DDMMMYYYY:hh:mm/1	xx	xx	xx	xx	xxxxx	xx	xxx.x

Note: Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.
Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male

Example : EFF_L12
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Sniff Nasal Inspiratory Pressure (SNIP)

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assesment Datetime/Day	Maximum SnIP	Maximum SnIP Change from Baseline
xxxx/xxxx	Screening/ Baseline	DDMMMYYYY:hh:mm/-xx	xx.x	
	Unscheduled	DDMMMYYYY:hh:mm/1	xxx.x	

/ Visit X
Day X

Note: Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L13
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Handgrip Strength

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assessment Date/Day	Left or Right	Performed? (No,reason)	Reading 1	Reading 2	Reading 3	Average of 3 Readings
xxxxxxx	Day 1/Baseline	DDMMMYYYY /-xx	xx	xx	xx	xx	xxxxx	xx

Unsheduled / Visit X Day X	DDMMMYYYY /1	xx	xx	xx	xx	xxxxx	xx

Note: Baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male

Programming note: Use assessment datetime instead of date if time collected and update the label as "Assessment Datetime/Day"

Example : EFF_L14
Protocol: XXXXXX
Population: Analysis

Listing xx
Listing of Physical Activity Measures Assessed via an Accelerometer

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Analysis Visit	Weekly average steps	Weekly Average Wear duration	Number of days with wear duration	Weekly Average Vector magnitude	Weekly Average Moderate/vigorous activity duration

				more than 8 h	unit/wear time	
xxxx/xxxx	Baseline	xx	xx	Xx	xx	
	Visit X Day X	xx /xxx	xx /xxx	xx	xx	xxxx

Note: "Visit 3, Day 1" is considered as baseline and is calculated as average of the data collected from the 7-day period after Day -9 device dispense.

Programming note: Use assessment datetime instead of date if time collected and update the label as “Assessment Datetime/Day”

Programming note: Sorted by treatment, Center, Subject,Visit and continue for SEX: Male

SAFETY

Tables

Example: SAFE_T1
Protocol: 200182
Population: Safety

Table xx
Summary of COPD Events

	Female			Male		
	Placebo (N=xx)	GSK2881078 (N=xx)	Total (N=xx)	Placebo (N=xx)	GSK2881078 (N=xx)	Total
Number of events in total	x (x%)	x (x%)	x	x (x%)	x (x%)	x
Number of exacerbating patients	x (x%)	x (x%)	x	x (x%)	x (x%)	x

Listings

Example: SAFE_L1
Protocol: XXXXXX
Population: Safety

Listing xx
Listing of COPD Exacerbation Log

Sex: Female
Treatment: XXXX

Site Id./ Unique Subject Id.	Onset Date/Day/ Resolution Date	Outcome	Primary Cause (Other, Specify)	1	2	3	4	5	6	7	8
	DDMMMYYYY /xx/DDMMYYYY	xx	Other, xxx	No	No	No	No	No	No	No	xxxx
	DDMMMYYYY/1	xx	xx							Yes, xxxx	

Note: 1= withdrawn due to the exacerbation, 2=corticosteroids taken for this exacerbation, 3=antibiotics taken for this exacerbation, 4= hospitalized due to this exacerbation, 5=visited the emergency room, 6=intubated for this exacerbation, 7=medication taken for this exacerbation, 8=adverse event reference identifier

Programming note: If medications is taken, show the reference identifier; Sorted by treatment, Center, Subjects and continue for SEX: Male

Example: SAFE_L2
Protocol: XXXXXX
Population: Safety

Listing xx
Listing of Hepatic, Prostate and Cardiac Structure assessed via MRI

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Visit / Analysis Visit	Assessment Date/Day	Liver Volume (Unit)	Spleen Volume (Unit)	Prostate Volume (Unit)	Left Ventricular Volume (Unit)	Left Ventricular Ejection Fraction	Left Ventricular End Diastolic Volume Index/ Left Ventricular End Systolic Volume Index
xxxx/xxxx	Day 1/Baseline	DDMMMYYYY /1	xx	xx	xxxxx	xx	xx.x	xx
	Unsheduled / Visit X Day X	DDMMMYYYY /xx	xx	xx	xxxxx	xx	xxx.x	xx

Note: "Visit 3, Day 1" is considered as Baseline.

Programming note: Sorted by treatment, Center, Subjects, Visit and continue for SEX: Male

Example : SAFE_L3
Protocol: XXXXXX

Population: Safety

Listing xx
Listing of Change from baseline of Lipids and Sex hormones

Sex: Female
Treatment: XXXX

Site Id/ Unique Subject Id	Test (Units)	Visit / Analysis Visit	Assesment Datetime/Day	Analysis Value	Change from Baseline
xxxx/xxxx	PSA	Screening/ Baseline	DDMMMYYYY:hh:mm/-xx	xx.x	
		Unscheduled / Visit X Day X	DDMMMYYYY:hh:mm/1	xxx.x	xxxx

Note: The baseline value will be the latest pre-dose assessment between Screening and Day 1 with a non-missing value, including those from unscheduled visits.