A Phase 2a, Randomized, Double-blind, Placebo-controlled, Two Period, Crossover Study to Assess the Effect of CK-2127107 on Physical Function in Subjects with Chronic Obstructive Pulmonary Disease

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STATISTICAL ANALYSIS PLAN

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
1RM	1 repetition maximum
AE	adverse event
AEE	Average Energy Expenditure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATS	American Thoracic Society
Bf	Breathing Frequency
BMI	body mass index
BMR	Basal Metabolic Rate
C-PPAC	clinical visit version of PROactive physical activity in COPD
Ca2+	Calcium
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CWR	constant work rate
CYP	cytochrome P450
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EMG	electromyogram
EOT	end of treatment
ERS	European Respiratory Society
FAS	full analysis set
FEV_1	forced expiratory volume in 1 second
FUV	follow-up visit
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GMP	Good Manufacturing Practice
IC	inspiratory capacity
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IET	incremental exercise test
INR	international normalized ratio

Abbreviations	Description of Abbreviations
IRB	institutional review board
IRT	Interactive Response Technology
IRV	Inspiratory reserve volume
LA-CRF	liver abnormality case report form
LFT	liver function tests
LHRH	luteinizing hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MEP	maximal expiratory pressure
MI	Movement Intensity
MIP	maximal inspiratory pressure
mMRC	Modified Medical Research Council
NOAEL	no observed adverse effect level
OCT	organic cation transporter
PAL	Physical Activity Level
PAR	Physical Activity Ratio
$P_{ET}CO_2$	End-tidal PCO_2
$P_{ET}O_2$	End-tidal PO_2
PKAS	pharmacokinetic analysis set
PPS	per protocol set
PRO	patient reported outcome
QoL	quality of life
RER	Respiratory exchange ratio
RPE	rating perceived exertion
RV	residual volume
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	Standard deviation
SE	Standard Error
SF-36	Short Form-36
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SOP	standard operating procedure
SPPB	short physical performance battery
S_PO_2	Arterial oxygen saturation from pulse oximetry
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TEE	Total Energy Expenditure
TLC	total lung capacity
ULN	upper limit of normal
VCO_2	Carbon dioxide output

Abbreviations	Description of Abbreviations
V_E	Minute ventilation
V_E/VCO_2	ventilator equivalent for carbon dioxide
VMU	Vector Magnitude Unit
VO_2	oxygen uptake
V_T	Tidal volume
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary
WR	work rate

List of Key Terms

Terms	Definition of terms
Sequence	Enrolled subject will be randomly assigned to 1 of 2 treatment sequences. Sequence 1: subject will receive CK-2127107 in treatment period 1 and then receive Placebo in treatment period 2 Sequence 2: subject will receive Placebo in treatment period 1 and then receive CK-2127107 in treatment period 2
Treatment period	This study is two period crossover design. Period 1 and Period 2 are the first and second period respectively in the crossover design.
Period baseline	Baseline in each period

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to database hard lock. For operational efficiency an earlier time is usually targeted and wherever possible, the SAP should be developed in parallel with protocol finalization. The SAP should be developed and approved before First Subject In (FSI). If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of GD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock except Pharmacokinetic Analysis Set (PKAS). For PKAS, analysis set classification may be held after database hard lock.

2 FLOW CHART AND VISIT SCHEDULE

Figure 1

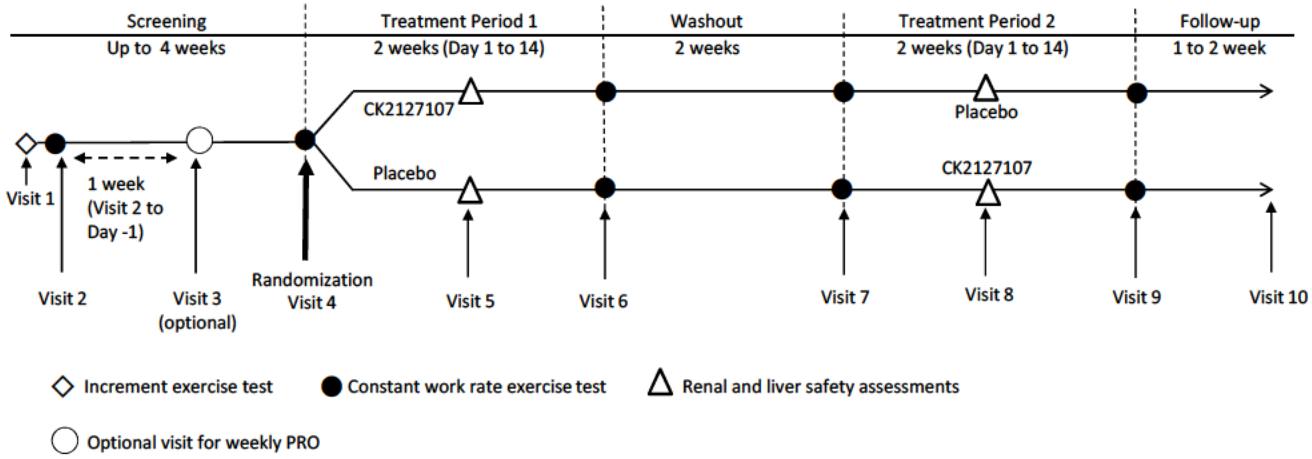

Table 1 Schedule of Assessments

Assessments	**Screening**			**Treatment Period 1**			**Washout**	**Treatment Period 2**			**Follow-up**
Day	-28 to -9	-27 to -8	-19 to -1	1	6	14	14 days	1	6	EOT[a]/ ED	7 days after EOT/ED
Window	-	-	-	-	+3	+3	+7	-	+3	+3	+7
Visit Number	1	2	3[b]	4	5	6	-	7	8	9	10
Informed consent	X										
Inclusion/Exclusion	X										
Medical history	X			X				X			
Demographics	X										
Drug and alcohol screen[c]	X			X				X			
Randomization				X							
Dispense/Collect study drug				X		X		X		X	
Administration of study drug[d]				←	—	→		←	—	→	
Physical examination[e]	X			X		X		X		X	X
Vital signs[f]	X			X		X		X		X	X
Hematology	X			X		X		X		X	X
Serum chemistries	X			X	X[g]	X		X	X[f]	X	X
Serology	X										
Urinalysis	X			X		X		X		X	X
Serum pregnancy test	X									X	X
Spirometry[h]	X			X		X		X		X	X
Respiratory muscle strength tests (MIP, MEP)				X		X		X		X	
12-lead ECG	X			X		X		X		X	X
CWR exercise test		X[i]		X		X		X		X	
QoL outcomes (SGRQ-C, SF-36)				X		X		X		X	
Physical performance test (SPPB)				X		X		X		X	
IET	X										

Table continued on the next page

Assessments	**Screening**			**Treatment Period 1**			**Washout**	**Treatment Period 2**			**Follow-up**
Day	-28 to -9	-27 to -8	-19 to -1	1	6	14	14 days	1	6	EOT[a]/ ED	7 days after EOT/ED
Window	-	-	-	-	+3	+3	+7	-	+3	+3	+7
Visit Number	1	2	3[b]	4	5	6	-	7	8	9	10
PRO (C-PPAC)				X		X					
Blood sampling for pharmacokinetics[j]						Predose 6h		Predose		Predose 6h	
Optional blood sampling for pharmacogenomics[k]				X							
Concomitant medication	X	X	X	X	X	X[l]	X	X	X[l]	X	X
Adverse events assessment	X	X	X	X	X	X[l]	X	X	X[l]	X	X

C-PPAC: clinical visit version of PROactive physical activity in COPD; CWR: constant work rate; ECG: electrocardiogram; ED: early discontinuation; EOT: end of treatment; IET: incremental exercise test; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; PRO: patient reported outcome; SF-36: Short Form-36; SGRQ-C: St. George's Respiratory Questionnaire for COPD; SPPB: short physical performance battery

a. EOT: day 14 of treatment period 2.

b. Visit 3 will be considered optional if the subject successfully completes the CWR at visit 2. Subjects who do not attend visit 3 will resume their visit schedule with visit 4.

c. A standard urine screen for drugs of abuse (e.g., cannabinoids, cocaine and amphetamines) and benzodiazepines, and blood, urine, or breathalyzer alcohol screen will be performed by a central laboratory.

d. The time of daily study drug dosing is to be recorded in the paper diary. Subjects will take study drugs as follows: once a day after dinner at day 1, twice a day within 2 hours after breakfast and dinner between day 2 and day 13 and once a day within 2 hours after breakfast at day 14. In order to collect the trough pharmacokinetic sample on day 14, the subject is to wait and take the morning dose at the site after pharmacokinetic sample collection has been performed.

e. A full physical examination will be performed at screening visit 1 and follow-up visit 10. Body systems to be evaluated include general appearance, skin, lymphatic, head and neck, ears, nose and throat, chest and lungs, cardiovascular, abdomen, extremities, musculoskeletal, and neuromuscular. At visits 4, 6, 7, and 9, a symptom-directed physical exam will be performed.

f. Vital signs include blood pressure, heart rate and body temperature.

g. Specifically for the monitoring of creatinine, blood urea nitrogen (BUN), cystatin C and liver enzymes (renal and liver safety assessments) at visits 5 and 8.

h. At screening visit, subjects perform spirometry both pre and postbronchodilator, but only postbronchodilator thereafter: Subjects will receive 2 puffs of albuterol in the laboratory 10 to 15 minutes prior to the spirometry assessment on each study day.

Footnotes are continued on the next page

i. At screening CWR will be completed at least 24 hours after IET at visit 2 and may be retested within the next 5 days at the investigator's discretion (within the visit window) if target exercise duration is not obtained. If this cannot be achieved with 2 adjustments (a total of 3 CWR tests), the subject will be classified as a screen failure and no additional assessments completed. All exercise tests (IET and CWR) will record heart rate and ECG simultaneously with breath-by-breath gas exchange and ventilatory variables during all exercise performance. Borg CR10 is performed with CWR at all of the time points shown in the schedule. The Electromyogram (EMG) is also performed with the CWR, but only at visits 4, 6, 7 and 9/EOT.

j. Blood samples for pharmacokinetics of CK-2127107 and possible metabolite(s) (if applicable) will be collected from EVERY subject. A single pharmacokinetic sample will be collected at each of the following time points: prior to evening dose at day 1 of treatment period 2, prior to morning dose (trough) and then approximately 6 hours postmorning dose at day 14 of both treatment period 1 and 2.

k. Sample to be collected 1 time prior to first dose at day 1 of treatment period 1.

l. If a subject experiences an AE or change in concomitant medications during days 7 to 13 or washout, they should call the study site to inform them of this change.

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objective

To assess the effect of CK-2127107 relative to placebo on cycle ergometer exercise tolerance, assessed as change from period baseline in CWR endurance time, utilizing a breath-by-breath metabolic measurement system with integrated electrocardiogram (ECG). The time to intolerance is assessed by a stopwatch and verified from electronic recordings of the cycle ergometer.

3.1.2 Secondary Objectives

- To assess cardiopulmonary and neuromuscular effects of CK-2127107 relative to placebo on:
  - The change from period baseline in oxygen uptake (VO_2), ventilation (V_E), ventilatory equivalent for carbon dioxide (V_E/VCO_2) and other breath-by-breath cardiometabolic variables, inspiratory capacity (IC) and perceived exertion for dyspnea and leg discomfort (Borg CR10), at iso time and peak during CWR test
  - Activation of accessory respiratory muscles (by electromyogram [EMG]) at isotime* and peak exercise during CWR test
- To assess the effect of CK-2127107 on resting spirometry relative to placebo
- To assess the safety and tolerability of CK-2127107
- To assess the pharmacokinetics of CK-2127107

3.1.3 Exploratory Objectives

- To explore the effects of CK-2127107 relative to placebo on:
  - Patient reported outcomes (PROs) and physical activity assessed by an accelerometer
  - Physical performance via a short physical performance battery (SPPB) and leg muscle strength via a leg extensor strength test (1 repetition maximum [1RM])
  - Respiratory muscle strength by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)

*Isotime is the shortest duration of all of the CWR tests performed before and after treatment, not including screening.

3.2 Study Design

This is a phase 2a, randomized, double-blind, placebo-controlled, two period, crossover study to assess the potential effects on physical function and safety of CK-2127107 in subjects with COPD. Approximately 40 subjects will be randomly assigned to 1 of 2 treatment sequences and will receive both CK-2127107 and matching placebo over 2 treatment periods as per the following schedule [Table 2]. If the discontinuation rate in the first treatment period exceeds 10%, additional subjects will be recruited to ensure a total of at least 36 subjects completing the study.

Table 2 Treatment Sequence

Sequence	Treatment Period 1	Treatment Period 2
1	CK-2127107	Placebo
2	Placebo	CK-2127107

Each treatment period consists of 14 days dosing of CK-2127107 or matching placebo. Each medication period is separated by a 14-day washout period. The total study duration including screening period and follow-up visit (FUV) for an individual subject will be approximately 12 weeks (see Flow Chart [Figure 1] and Schedule of Assessments [Table 1]).

3.3 Randomization

All subject numbers will be assigned using the interactive response technology (IRT) starting at screening. All subjects will have a unique, ten-digit subject number. The first five digits of this number will be the Investigator's research number. The second five digits assigned will represent the subject's accession number. This will be the number that identifies a subject during the course of the study.

All Baseline procedures will be performed prior to Randomization. Only subjects who meet all inclusion criteria and exhibit none of the exclusion criteria will be randomly assigned to one of 2 treatment sequences in a 1:1 ratio and will receive CK-2127107 as two 250 mg tablets (500 mg twice a daily [1000 mg daily total]) or 2 tablets twice daily of matching placebo during the 2 treatment periods.

Randomization will be performed via IRT. If a subject is assigned a subject number, but does not receive study drug, the subject number will not be used again.

The randomization schedules that determine subject treatment will be computer-generated by a designated Contract Research Organization (CRO) before the beginning of the study.

Specific procedures for randomization through the IRT are contained in the study-specific IRT manual.

4 SAMPLE SIZE

A sample size of 40 subjects will provide 84% power to detect a difference of 60 seconds in CWR duration from period baseline for CK-2127107 versus placebo with a 1-sided alpha error of 0.05, assuming the standard deviation for change from period baseline is 100 seconds. In order to maintain the statistical power of 80%, approximately 36 subjects would need to complete period 1. Should the discontinuation rate in the first treatment period exceed 10% (approximately 5 subjects), additional subjects will need to be recruited to account for the discontinued subjects.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock except Pharmacokinetic Analysis Set (PKAS). The allocation of subjects to PKAS will be determined after database hard lock.

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are randomized and receive at least 1 dose of study drug and have at least 1 baseline measurement and 1 post baseline measurement in either treatment period for CWR endurance time. Subjects will be included in the treatment arm based on actual treatment received. This will be the primary analysis set for efficacy analyses.

5.2 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least 1 dose of study medication. Subjects will be included in the treatment arm based on actual treatment received.

5.3 Pharmacokinetic Analysis Set (PKAS)

The PKAS consists of the administered population for which at least one quantifiable plasma trough concentration or concentration at 6 hours is available for CK-2127107 or CK-2127106 and for whom the time of dosing on the day of sampling is known.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

The following table provides definitions for the efficacy parameters.

Parameter	Definition
Constant Work Rate (CWR) Endurance Time	The CWR defines how long it takes until the subject reaches symptom limitations while simultaneously being monitored and is called “CWR time to intolerance” which determines the “CWR endurance time”.
Inspiratory Capacity (IC)	The volume of air that can be inspired after a normal expiration; it is the sum of the tidal volume (V_T) and the inspiratory reserve volume.
Minute ventilation (V_E)	Volume of gas exhaled from the lungs in 1 minute.
Oxygen uptake (VO_2)	Volume of O_2 extracted from inspired air in a given period of time.
Carbon dioxide output (VCO_2)	Volume of CO_2 exhaled from the body per unit of time.
Ventilatory equivalent for carbon dioxide (V_E/VCO_2)	Ratio of V_E to VCO_2. It is a dimensionless quantity. This ratio indicates how many liters of air exhaled breathed to eliminate 1 liter of CO_2.

End-tidal PO_2 ($P_{ET}O_2$)	Partial pressure of oxygen in the expired gas at the end of an exhalation. This represents the mean partial pressure of oxygen in the pulmonary alveoli.
End-tidal PCO_2 ($P_{ET}CO_2$)	Partial pressure of carbon dioxide in the expired gas at the end of an exhalation. This represents the mean partial pressure of carbon dioxide in the pulmonary alveoli.
Tidal volume (V_T)	Volume of gas exhaled in each respiratory cycle. Tidal volume is typically measured as an average value over several respiratory cycles and expressed in liters.
Ventilatory reserve (V_E/MVV)	Expresses the rate if expired ventilation to the capacity. Ventilatory capacity is estimated from the maximum voluntary ventilation (MVV), and in this suited is calculated from 40 times the forced expiratory volume in 1 second (FEV_1). The ratio of V_E/MVV is expressed as a percentage.
Arterial oxygen saturation from pulse oximetry (S_PO_2)	Noninvasive estimation of arterial hemoglobin oxygen saturation, using a device that utilizes the combined principles of spectrophotometry and pulse plethysmography.
Breathing frequency (Bf)	The number of breaths (an entire inspiratory and expiratory respiratory cycle) per minute.

For efficacy variables, the following predicted parameter results are entered in eCRF. Appendix 1 provides the predictive equations that are used to calculate the results for these parameters. These results are applicable for healthy subjects and only going to be used to derive the percent of predicted parameters for the subjects in this study. Derivation details for percent of predicted parameters that will be used for analysis are presented in Section 6.1.2 and Section 7.2.3.1

Predicted FEV_1 (L)

Predicted FVC (L)

Predicted FRC (L)

Predicted SVC (L)

Predicted IC (L)

Predicted TLC (L)

Predicted VA (L)

Predicted DLCO (L)

Predicted VO_2max (L/min)

6.1.1 Primary Efficacy Endpoints

The primary endpoint is the change from period baseline in CWR endurance time relative to placebo.

For change from baseline in CWR endurance time, a positive change indicates an improvement from baseline (i.e., a favorable outcome).

CWR endurance time will be performed during screening and on day 1 and day 14 during each of the 2 treatment periods or at early discontinuation (ED) [Table 1].

6.1.2 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- Change from period baseline in VO_2, $V_{E,}$ V_E/VCO_2, IC, as well as other cardiometabolic variables and perceived exertion for dyspnea and leg discomfort (Borg CR10) at isotime* and peak during CWR as compared to placebo
  Other cardiometabolic variables:
  - $P_{ET}O_2$
  - $P_{ET}CO_2$
  - V_T
  - Bf
  - V_E/MVV
    V_E/MVV (%) = (V_E/MVV) x 100 where MVV = FEV_1 x 40
  - HR
  - SBP
  - DBP
  - S_PO_2
  - IRV
    IRV (L) = V_T (L) – IC (L)
  - RER
    RER = VCO_2 (L/min) / VO_2 (L/min)
  - Dyspnea (Borg CR10)
  - Leg Effort (Borg CR10)
- Change from period baseline in activation of accessory respiratory muscles (by EMG) at isotime* and peak exercise during CWR
- Change in resting spirometry compared to placebo
  For change from baseline in spirometry parameters, a positive change indicates an improvement from baseline (i.e., a favorable outcome).

  Pre-Exercise Parameters:

  - FEV_1 (L)
  - FVC (L)
  - FEV_1 percent predicted (%)
    FEV_1 percent predicted (%) = (FEV_1 (L) / FEV_1 predicted (L)) x 100

In the numerator, FEV_1 (L) is the result from pre-exercise spirometry at each visit. In the denominator, FEV_1 predicted (L) result is from Screening Pulmonary Function CRF.

- FVC percent predicted (%)
  FVC percent predicted (%) = (FVC (L) / FVC predicted (L)) x 100
  In the numerator, FVC (L) result is from pre-exercise spirometry at each visit. In the denominator, FVC predicted (L) result is from Screening Pulmonary Function CRF.

Follow-up Parameters:

- Post-Bronchodilator measured FEV_1 (L)
- Post-Bronchodilator measured FVC (L)
- Post-Bronchodilator FEV_1 percent predicted (%)
  Post-Bronchodilator FEV_1 percent predicted (%) = (Post-Bronchodilator FEV_1 (L) / FEV_1 predicted (L)) x 100
  In the numerator, Post-Bronchodilator FEV_1 (L) result is from Follow-up Spirometry CRF. In the denominator, FEV_1 predicted (L) result is from Follow-up Spirometry CRF.
- Post-Bronchodilator FVC percent predicted (%)
  Post-Bronchodilator FVC percent predicted (%) = (Post-Bronchodilator FVC (L) / FVC predicted (L)) x 100
  In the numerator, Post-Bronchodilator FVC (L) result is from Follow-up Spirometry CRF. In the denominator, FVC predicted (L) result is from Follow-up Spirometry CRF.

*Isotime is the shortest duration of all of the CWR tests performed before and after treatment, not including screening.

These endpoints relate to the isotime physiologic measurements that underpin the increase in exercise tolerance and represent an integrated examination of cardiopulmonary measurements. The analysis of variables that are recorded breath-by-breath (e.g., VO_2, V_E, V_E/VCO_2) are facilitated by averaging data over 20 second intervals within the metabolic cart system (recorded by the Vmax breath-by-breath metabolic measurement system). Surface accessory muscle EMG activity is recorded throughout the exercise and analyzed over the same time intervals as the breath-by-breath data. IC is recorded every 2 minutes during exercise; its measurement requires the subject to produce a maximum inspiration (from end-inspiration) on command every 2 minutes during the exercise test. This allows the determination of whether IC is reduced during exercise as a consequence of dynamic hyperinflation, which is common during exercise in COPD. The exercise system software stores this maneuver and facilitates post-test examination of each maneuver to assess quality. Therefore IC assessment of dynamic hyperinflation is obtained with 2-minute resolution.

Resting spirometry is measured before exercise but after inhalation of albuterol. It is measured at approximately the same time of day, at the same duration after the subjects' morning dose of normal bronchodilator medications. Subjects will receive 2 puffs of albuterol in the lab 10 to 15 minutes prior to the spirometry assessment on each study day.

6.1.3 Exploratory Efficacy Endpoints

The exploratory endpoints are as follows:

- Change from period baseline in QoL outcomes (SGRQ-C, SF-36) relative to placebo
- Change from baseline in physical activity using the PROactive approach (DynaPort®© accelerometer and combined PRO). This will be assessed during only the first treatment period. Therefore, this will represent the response to placebo for half the subjects and the response to the study drug for the other half of subjects.

Physical Activity Monitoring

Physical activity will be measured by wearing the accelerometer during waking hours (movement intensity, different body positions, steps) for 7 days. From the accelerometer, the following daily parameters will be reported for various positions or combination of the positions: lying, sitting, walking, stair walking, cycling, standing, shuffling, cycling, overall worn and not worn.

- Maximum wearing time
- Average wearing time
- Median wearing time
- Total wearing time
- Number of transitions from one position to another position
- Number of periods

  This is the number of periods of each activity.

- Average movement intensity (MI)

  MI is derived from the acceleration signals. MI gives an indication of the power of movements.

- Vector magnitude unit (VMU)

  VMU is comparable with the MI and gives an indication of the power of the movements. The VMU is only based on the movements captured by the medial-lateral axis of the sensor.

- Active Energy Expenditure (AEE)

  This is total activity related energy expenditure from each position.

- Total Energy Expenditure (TEE)

  This is sum of AEE, Basal metabolic rate (BMR) and diet induced thermogenesis. Diet induced thermogenesis is the amount of energy utilized for digestion, absorption and transportation of nutrients.

- Physical Activity Ratio (PAR)

This is the ratio of energy expenditure during a specific physical activity i.e., TEE/BMR or also called as Metabolic equivalent of task (MET). The PAR of all activities of a whole day is called the Physical Activity Level (PAL). A chair- or bed-bound lifestyle corresponds to an average PAL value of 1.2, while a lifestyle of strenuous work or highly active leisure corresponds to a PAL value of 2.0 to 2.4.

Also the following daily parameters will be reported:

- Number of steps
- BMR spent during wearing time

  BMR is the minimum amount of energy that a body requires when lying in physiological and mental rest.
- MET minutes (number of MET minutes above or equal to 3 METs)

  This is summation of all periods with a MET value >=3 multiplied by the duration of the periods in minutes.

For the daily parameters: average MI, VMU, AEE, TEE and number of steps, if daily total wearing time is less than 8 hours then that daily parameter value will be not valid i.e., set to missing in the calculation of the following weekly parameters. Also for the applicable weekly parameters, weighted mean is calculated as Sum(weight x daily parameter result)/sum(weight) where weight is the total wearing time. Using the daily parameter results, the following weekly parameters will be derived for each subject as follows:

- Mean total wearing time on valid days

  Arithmetic mean of non-missing daily total wearing time collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the total wearing time is missing on all of the days during the time window, then the mean total wearing time for that time point will be set to missing.
- Mean total wearing time on all days

  Arithmetic mean of non-missing daily total wearing time collected within time window per visit windows defined in Section 7.10.4.2 Table 5. If the total wearing time is missing on all of the days during the time window, then the mean total wearing time for that time point will be set to missing.
- Mean average MI during total wearing time

  Weighted mean of non-missing daily average MI collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the average MI is missing on all of the days during the time window, then the mean average MI for that time point will be set to missing.

- Median VMU/min during total wearing time

  Median of non-missing daily VMU/min collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the VMU/min is missing on all of the days during the time window, then the median VMU/min for that time point will be set to missing.

- Median VMU group during total wearing time
  - 0: median VMU/min < 60
  - 1: median VMU/min ≥ 60 to ≤ 130
  - 2: median VMU/min > 130 to ≤ 210
  - 3: median VMU/min > 210 to ≤ 370
  - 4: median VMU/min > 370

- Mean AEE during total wearing time

  Weighted mean of non-missing daily AEE collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the AEE is missing on all of the days during the time window, then the mean AEE for that time point will be set to missing.

- Mean TEE during total wearing time

  Weighted mean of non-missing daily TEE collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the TEE is missing on all of the days during the time window, then the mean TEE for that time point will be set to missing.

- Median number of steps during total wearing time
  Median of non-missing daily number of steps collected on valid days within time window per visit windows defined in Section 7.10.4.2 Table 5. If the number of steps is missing on all of the days during the time window, then the median number of steps for that time point will be set to missing.

- Median steps score group during total wearing time
  - 0: median number of steps < 1500
  - 1: median number of steps ≥ 1500 to ≤ 2500
  - 2: median number of steps > 2500 to ≤ 4500
  - 3: median number of steps > 4500 to ≤ 6500
  - 4: median number of steps > 6500

C-PPAC questionnaire

The following items will be derived:

- Difficulty Score
  Q1 (about walking) score + Q2 (about chores outside the house) score + median weekly steps score group + median weekly VMU score group from the physical activity data.
  If the response is missing for any of the individual questions involved in this derivation then the score will be set to missing.
- Amount Score
  Sum of remaining questions Q3 to Q12 scores.
  If the response is missing for any of the individual questions involved in this derivation then the score will be set to missing.
- Total Score
  Difficulty score + amount score.
  If the score is missing for the difficulty or amount then the total score will be set to missing.

- Change from period baseline in physical performance tests battery score (SPPB) relative to placebo
- Change from period baseline in leg muscle strength relative to placebo (as assessed by the maximal weight a subject can lift with one repetition [1RM])
- Change from period baseline in MIP and MEP relative to placebo. This test is performed before exercise testing and is part of the resting assessment.
- Change from period baseline in VO_2, $V_{E,}$ V_E/VCO_2, IC, as well as other cardiometabolic variables and perceived exertion for dyspnea and leg discomfort (Borg CR10) at rest during CWR as compared to placebo
  Other cardiometabolic variables:
  - $P_{ET}O_2$
  - $P_{ET}CO_2$
  - V_T
  - Bf
  - V_E/MVV
    V_E/MVV (%) = (V_E/MVV) x 100 where MVV = FEV_1 x 40
  - HR
  - SBP
  - DBP
  - S_PO_2
  - IRV
    IRV (L) = V_T (L) – IC (L)
  - RER
    RER = VCO_2 (L/min) / VO_2 (L/min)
  - Dyspnea (Borg CR10)
  - Leg Effort (Borg CR10)
- Change from period baseline in activation of accessory respiratory muscles (by EMG) at rest during CWR

6.2 Safety Variables

6.2.1 Adverse Events

Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that started or worsened in severity **after** first dose of study drug up to 14 days after the last dose of study drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent.

TEAEs will be summarized by treatment group. TEAEs at treatment period 1 will be defined as TEAE which occurs after first dose of study drug at treatment period 1 up to first dose of study drug at treatment period 2. If a subject discontinues in treatment period 1, TEAEs at treatment period 1 will be defined as TEAE which occurs after first dose of study drug at treatment period 1 up to 14 days after the last dose of study drug. TEAEs at treatment period 2 will be defined as TEAE which occurs after first dose of study drug at treatment period 2 up to 14 days after the last dose of study drug.

Drug-related TEAE will be defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

TEAE variables are frequency, severity, seriousness, relationship to study drug, and count.

Imputed date for the AE onset date may be used to determine a TEAE (Section 7.10.1.3).

6.2.2 Clinical Laboratory Variables

Clinical laboratory variables are raw values (i.e., values at each scheduled visit) and changes from period baseline for hematology and urinalysis parameters at Day 14. Biochemistries will be summarized as the change from period baseline at Day 6 and at Day 14.

Liver function tests including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin and alkaline phosphatase (ALP) will be assessed at Screening, Baseline and Day 14. The following groups will be defined, as flags on a subject level, during the treatment period, based on the maximum value during study period, according to the Upper Limit of Normal (ULN):

- ALT > 3× ULN, > 5× ULN, > 10× ULN, and > 20× ULN
- AST > 3× ULN, > 5× ULN, > 10× ULN, and > 20× ULN
- ALT or AST > 3× ULN
- Total Bilirubin > 2× ULN
- ALP > 1.5× ULN
- ALT and/or AST > 3× ULN and Total Bilirubin > 2× ULN

For the ALT and/or AST > 3× ULN and Total Bilirubin > 2× ULN criteria, the subject's ALT and/or AST and Total Bilirubin values must be measured within the same sample to be counted.

The maximum value during the study period, defined as the maximum value of all post-Baseline assessments, will be derived for liver function tests.

6.2.3 Vital Signs

Vital signs variables are raw values for and changes from Baseline in temperature, pulse rate, systolic blood pressure and diastolic blood pressure at Day 14.

6.2.4 Electrocardiograms (ECGs)

The 12-lead ECG scheduled assessments will be made at Screening, Baseline and Day 14. The results will be recorded as normal or abnormal. ECG variables are raw values (categorical) at each scheduled visit and changes from Baseline (shift from Baseline) at Day 14.

6.3 Pharmacokinetic Variables

Pharmacokinetics of CK-2127107 and CK-2127106:

- Day 1 (only treatment period 2): predose plasma concentration
- Day 14 (of both treatment period 1 and 2): C_{trough} and C_{6h}

6.4 Other Variables

Other variables include the following variables:

- Duration of exposure

  For each subject at each period, duration of exposure (defined as length of time on 2 weeks of treatment period) will be calculated in days, using the following formula:

  Duration of exposure in each period = Date of last dose of study drug up to Week 2/EOT – Date of first dose of study drug +1,

  where the date of first dose of study drug and the date of last dose of study drug up to Week 2/EOT are defined as the first study drug dosing date and the last study drug dosing date.

  Total duration of exposure in this study will be calculated as below:

  Total duration of exposure = Duration of exposure of period 1 + Duration of exposure of period 2.

  Total duration will be calculated for only period 1 if subjects discontinue before period 2.

- Treatment compliance

  Subjects will be instructed to take tablet two times per day. Treatment compliances based on number of tablets will be calculated as follows:

  Treatment compliance in each period (%) with tablets = 100 × (total number of tablets actually taken during 2 weeks of treatment period / total number of tablets planned to receive during 2 weeks of treatment period),

  where

  - Total number of tablets planned to receive during 2 weeks in each treatment period = 4 × duration of exposure – 4 (if more than one day of dosing) - 2 (if only one day of dosing). Duration of exposure will be calculated as described above.
  - Total number of tablets actually taken during 2 weeks in each treatment period = total number of tablets dispensed during 2 weeks in each treatment period – total number of tablets returned during 2 weeks in each treatment period, where
    - Total number of tablets dispensed during 2 weeks in each treatment period will be calculated as the sum of tablets contained in the kits dispensed prior to Week 2/EOT Visit (i.e., excluding the kits dispensed at Week 2/EOT Visit),
    - Total number of tablets returned during 2 weeks in each treatment period will be calculated as the sum of tablets returned in the kits dispensed prior to Week 2/EOT Visit,
    - Total number of tables dispensed and returned during 2 weeks in each treatment period will be obtained from the IRT Accountability.

- Exposure rate

  Exposure rate based on number of tablets will be calculated as follows:

  $$\frac{\text{Total number of tablets taken during 2 weeks in each treatment period}}{[(\text{Last visit date} - \text{First visit date} + 1) \times 4] - 4} \times 100$$

  Total number of tablets calculation is provided in previous bullet for treatment compliance.

  First visit date:

  Period 1: Visit 4 CRF visit date

  Period 2: Visit 7 CRF visit date

  Last visit date:

  Period 1: Last CRF visit date on or prior to CRF Visit 6 date or CRF Visit 9/EOT date if the subject is discontinued in period 1

  Period 2: Last CRF visit date on or prior to CRF Visit 9 date

- Previous and concomitant medication

  Previous medication is defined as medication with at least one dose taken before the date of first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose of study drug and the date of last dose of study up to EOT.

Imputed dates for the medication start date and stop date may be used to determine whether a medication is a previous or a concomitant medication (Section 7.10.1.4).

7 STATISTICAL METHODOLOGY

7.1 General Considerations

Efficacy, safety, PD and other variables will be summarized by treatment group, by treatment group and visit (schedule of assessments is provided in Table 1), or in combination as appropriate. Summaries will be provided as follows:

- For continuous variables: number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.
- For continuous PK plasma concentration: n, geometric mean, SD, median, minimum, maximum, and coefficient of variation. Geometric mean will be obtained by exponentiating the mean of log of the values; additional information will be provided in the TLF Specs document for the study.
- For categorical variables: number and percentages of subjects.

Statistical hypothesis testing will be performed only if specified in this SAP. If statistical testing is performed, then treatment groups will be compared (CK-2127107 versus placebo) using two-sided tests at the 0.10 significance level. No multiplicity adjustments will be made.

All data, including observed and derived data, will be presented in subject data listings.

All data processing, summaries, and analyses will be performed using SAS® Version 9.3 or higher.

Definitions and Calculations:

Period baseline will be defined as the last non-missing measurement prior to the first dose of study drug in each period. That is, Baseline are the visit 4 and visit 7 in Figure 1 [Section 2] for period 1 and period 2, respectively if the value at each visit is not missing; if the value at each visit is missing, then the Baseline will be considered a missing value.

EOT Value

For the physical activity data collected using accelerometer, the available post-baseline measurements within the visit window as defined in Section 7.10.4.2 will be used to derive the EOT value.

For other efficacy data, the last available post-baseline measurement within the treatment period as defined by the visit window in Section 7.10.4.2 will be used as the EOT value.

Change from baseline to post-baseline will be calculated as: post-baseline value – baseline value.

Percent change from baseline to post-baseline will be calculated as: 100 × (change / baseline).

Handling of baseline value of 0 in analysis involving percent change is discussed in the TLF Specs for this study.

For follow-up visit, if a subject has at least one dose of study drug in period 2, then baseline result from period 2 will be used to calculate change from baseline and percent change from baseline. If a subject discontinues after at least one dose of study drug in period 1, period 1 baseline result will be used to calculate change from baseline and percent change from baseline.

Treatment Period or Follow-up Period

Treatment Period

Treatment period for efficacy variables is defined as any assessment after the first dose day (Day 1) of study drug through last dose day of study drug in each period + 3 days. Treatment period for safety variables is defined as any assessment after the first dose day (Day 1) of study drug through last dose day of study drug in each period + 6 days.

Follow-up Period for Safety Data

Follow-up period for safety variables is defined as any assessment ≥ last dose day of study drug in last period + 7 days.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be presented:

- Number of subjects screened (i.e., with informed consent), number of subjects rescreened (i.e., with informed consent), number and percentage of subjects screen-failed, the primary reasons for screen failure (percentage will be based on number of subjects screen-failed), and randomized (overall only). For rescreened subjects, the results from the subject's new ID will be used.
- Number and percentage of subjects randomized in each analysis set, by sequence and overall.
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation for randomized subjects and SAF, by sequence and overall.
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation for randomized subjects, by sequence and overall.
- Number and percentage of subjects for each protocol version by treatment sequence and 'Total' over all treatment sequences for randomized subjects, as well as, number and percentage of subjects for each protocol version for screen failures and total number of subjects including screen failures. For rescreened subjects, the results from the subject's new ID will be used.

7.2.2 Protocol Deviations

Protocol deviations, as defined in the study protocol (Section 8.1.6 [Protocol Deviations]), will be assessed for all randomized subjects. Number and percentage of subjects meeting any protocol deviation criteria will be summarized for each criterion and overall criteria, by sequence and overall. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by subject.

Protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 – Entered into the study even though they did not satisfy entry criteria

PD2 – Developed withdrawal criteria during the study and was not withdrawn

PD3 – Received wrong treatment or incorrect dose

PD4 – Received excluded concomitant treatment

PD5 – Plasma samples were not drawn

7.2.3 Demographic and Other Baseline Characteristics

The following demographic variables will be summarized by sequence and overall for all randomized subjects, SAF and FAS:

- Sex (Male, Female)
- Age (years) at Screening, calculated as: (date of Screening visit – date of birth + 1) / 365.25, truncated to whole numbers
- Age group (< 65 years, 65 – 75 years, > 75 years)
- EudraCT Age Category (Adults (18 – 64 years) , 65 – 84 years)
- Race (White, Black or African-American, Asian, American Indian or Alaska Native, Native Hawaiian or other pacific islander, Other).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg) at Screening
- Height (cm) at Screening
- Body mass index (BMI) (kg / m^2) at Screening, calculated as weight / [(height / 100)^2], where weight is measured in kg and height is measured in cm.
- FEV_1 at Screening
    - pre-Bronchodilator measured (L)
    - post-Bronchodilator measured (L)
    - pre-Bronchodilator percent predicted (%) = (Pre-Bronchodilator measured (L) / Predicted (L)) x 100
      In the numerator, Pre-Bronchodilator measured (L) is from Screening Pulmonary Function CRF. In the denominator, predicted (L) result is from Screening Pulmonary Function CRF.

    - post-Bronchodilator percent predicted (%) = (Post-Bronchodilator measured (L) / Predicted (L)) x 100
      In the numerator, Post-Bronchodilator measured (L) is from Screening Pulmonary Function CRF. In the denominator, predicted (L) result is from Screening Pulmonary Function CRF.
  - FVC at Screening
    - pre-Bronchodilator measured (L)
    - post-Bronchodilator measured (L)
    - pre-Bronchodilator percent predicted (%) = (Pre-Bronchodilator measured (L) / Predicted (L)) x 100
      In the numerator, Pre-Bronchodilator measured (L) is from Screening Pulmonary Function CRF. In the denominator, predicted (L) result is from Screening Pulmonary Function CRF.
    - post-Bronchodilator percent predicted (%) = (Post-Bronchodilator measured (L) / Predicted (L)) x 100
      In the numerator, Post-Bronchodilator measured (L) is from Screening Pulmonary Function CRF. In the denominator, predicted (L) result is from Screening Pulmonary Function CRF.
- Pre-Bronchodilator measured FEV_1/FVC ratio (%) at Screening
  Pre-Bronchodilator measured FEV_1/FVC ratio (%) at Screening = (Pre-Bronchodilator measured FEV_1 (L) at Screening / Pre-Bronchodilator measured FVC (L) at Screening) x 100
- Post-Bronchodilator measured FEV_1/FVC ratio (%) at Screening
  Post-Bronchodilator measured FEV_1/FVC ratio (%) at Screening = (Post-Bronchodilator measured FEV_1 (L) at Screening / Post-Bronchodilator measured FVC (L) at Screening) x 100
- FRC measured (L) at Screening
- FRC percent predicted (%) at Screening
  FRC percent predicted (%) at Screening = (FRC measured (L) at Screening / FRC predicted (L) at Screening) x 100
- SVC measured (L) at Screening
- SVC percent predicted (%) at Screening
  SVC percent predicted (%) at Screening = (SVC measured (L) at Screening / SVC predicted (L) at Screening) x 100
- TLC measured (L) at Screening
- TLC percent predicted (%) at Screening
  TLC percent predicted (%) at Screening = (TLC measured (L) at Screening / TLC predicted (L) at Screening) x 100
- IC measured (L) at Screening
- IC percent predicted (%) at Screening
  IC percent predicted (%) at Screening =(IC measured (L) at Screening / IC predicted (L) at Screening) x 100
- VA measured (L) at Screening

- VA percent predicted (%) at Screening
  VA percent predicted (%) at Screening = (VA measured (L) at Screening / VA predicted (L) at Screening) x 100
- DLCO measured (mL/min/mmHg)
- DLCO percent predicted (%) at Screening
  DLCO percent predicted (%) at Screening = (DLCO measured (mL/min/mmHg) at Screening / DLCO predicted (mL/min/mmHg) at Screening) x 100
- IET Ramp rate (watt/min) at Screening (Exercise protocol)
- IET Ramp duration (min) at Screening (Exercise protocol)
- CWR work rate (watt) at Screening (Exercise protocol)
- CWR duration (min) at Screening (Exercise protocol)
- IET Peak parameters at Screening (IET Physiology Parameters)
  - IET WR (watt)
  - IET VO_2 (mL/min/kg)
    IET VO_2 (mL/min/kg) = (IET VO_2 (L/min) at Screening x 1000) / Weight (kg) at Screening
  - IET VCO_2 (L/min)
  - IET $P_{ET}O_2$ (mmHg)
  - IET $P_{ET}CO_2$ (mmHg)
  - IET V_T (L)
  - IET Bf (breaths/min)
  - IET V_E (L/min)
  - IET IC (L)
  - IET HR (beats/min)
  - IET SYSBP (mmHg)
  - IET DIABP (mmHg)
  - IET S_PO_2 (%)
  - IET Borg (Dyspnea)
  - IET Borg (Leg Effort)

  The above results are from Screening Procedures – IET Physiology CRF. From this CRF, results from Peak will be used.
  In addition the following parameters will be derived:
  - IET V_E/MVV (%) Peak at Screening
    IET V_E/MVV (%) = (V_E (L/min) x 100) / (FEV_1 (L) at Screening (Pre-exercise spirometry) x 40)
    In the numerator, V_E (L/min) result is from Screening Procedures – IET Physiology CRF. V_E result from Peak will be used as V_E (L/min). In the denominator, FEV_1 (L) at Screening result is from pre-exercise spirometry Screening Procedures – IET CRF.
  - IET IRV measured (L) Peak at Screening
    IET IRV measured (L) at Screening = IET V_T (L) at Screening – IET IC (L) at Screening

V_T (L) and IET IC (L) results are from Screening Procedures – IET Physiology CRF. V_T result from Peak and IC result from Peak will be used.

- IET RER Peak at Screening
  IET RER = IET VCO_2 (L/min) at Screening / IET VO_2 (L/min) at Screening
  In the numerator, VCO_2 (L/min) result is from Screening Procedures – IET Physiology CRF. VCO_2 result from Peak will be used as VCO_2 (L/min). In the denominator, VO_2 (L/min) result is from Screening Procedures – IET Physiology CRF. VO_2 result from Peak will be used as VO_2 (L/min).
- IET VO_2 percent predicted (%) Peak at Screening
  IET VO_2 percent predicted (%) = (VO_2 measured (L/min) / VO_2max predicted (L/min)) x 100
  In the numerator, VO_2 measured (L/min) result is from Screening Procedures – IET Physiology CRF. VO_2 result from Peak will be used as VO_2 measured (L/min). In the denominator, VO_2max predicted (L/min) result is from Screening Procedures – IET CRF.

- IET Rest parameters at Screening (IET Physiology Parameters)
  - IET WR (watt)
  - IET VO_2 (mL/min/kg)
    IET VO_2 (mL/min/kg) = (IET VO_2 (L/min) at Screening x 1000) / Weight (kg) at Screening
  - IET VCO_2 (L/min)
  - IET $P_{ET}O_2$ (mmHg)
  - IET $P_{ET}CO_2$ (mmHg)
  - IET V_T (L)
  - IET Bf (breaths/min)
  - IET V_E (L/min)
  - IET IC (L)
  - IET HR (beats/min)
  - IET SYSBP (mmHg)
  - IET DIABP (mmHg)
  - IET S_PO_2 (%)
  - IET Borg (Dyspnea)
  - IET Borg (Leg Effort)

  These results are from Screening Procedures – IET Physiology CRF. From this CRF, results from Rest will be used.
- IET LT parameters at Screening (IET Physiology Parameters)
  - IET WR (watt)
  - IET VO_2 (mL/min/kg)
    IET VO_2 (mL/min/kg) = (IET VO_2 (L/min) at Screening x 1000) / Weight (kg) at Screening
  - IET VCO_2 (L/min)
  - IET $P_{ET}O_2$ (mmHg)
  - IET $P_{ET}CO_2$ (mmHg)

  - IET V_T (L)
  - IET Bf (breaths/min)
  - IET V_E (L/min)
  - IET IC (L)
  - IET HR (beats/min)
  - IET SYSBP (mmHg)
  - IET DIABP (mmHg)
  - IET S_PO_2 (%)
  - IET Borg (Dyspnea)
  - IET Borg (Leg Effort)

  These results are from Screening Procedures – IET Physiology CRF. From this CRF, results from LT will be used.
- IET FEV_1 (L) at Screening (Pre-exercise spirometry)
- IET FVC (L) at Screening (Pre-exercise spirometry)
- IET FEV_1/FVC ratio (%) at Screening (Pre-exercise spirometry)

Number and percentage of subjects randomized in each country will be presented by sequence and overall for all randomized subjects.

7.2.3.1 Medical History

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by sequence and overall for the SAF.

7.2.4 Previous and Concomitant Medications

Previous medications are coded with World Health Organization – Drug Dictionary (WHO-DD), and will be summarized using number and percentage of subjects by therapeutic subgroup (ATC 2^{nd} level), chemical subgroup (ATC 4^{th} level) and preferred WHO name by sequence and overall for the SAF.

Concomitant medication will be summarized similarly. Subjects taking the same medication multiple times will be counted once per medication. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

7.3 Study Drugs

Duration of exposure and treatment compliance will be summarized for each treatment by sequence and overall for the SAF and FAS.

7.3.1 Exposure

Duration of exposure will be summarized as below:

- As a continuous variable: number of subjects exposed, mean duration of exposure, SD, median, minimum and maximum.
- As a categorical variable: number and percentage of subjects in each of the following duration categories:

- 0 day
- 1 to 13 days
- 14 days
- >14 days

7.3.2 Treatment Compliance

Treatment compliance will be summarized in two ways:

- As a continuous variable: mean compliance and other descriptive statistics.
- As a categorical variable: number and percentage of subjects in each of the following compliance categories:
  - < 50%
  - 50% - < 75%
  - 75% - < 90%
  - 90% - ≤ 100%
  - > 100%

7.3.3 Exposure Rate

Exposure rate will be summarized in two ways:

- As a continuous variable: descriptive statistics will be presented.
- As a categorical variable: number and percentage of subjects in each of the following exposure rate categories:
  - < 50%,
  - ≥ 50% to < 75%,
  - ≥ 75% to < 90%,
  - ≥ 90% to ≤ 100%, and
  - >100%.

7.4 Analysis of Efficacy

7.4.1 Overview of Efficacy Analyses

Efficacy analysis will be conducted on the FAS. The interpretation of results from statistical tests will be based on the FAS. Table 3 summarizes the analyses of the primary, secondary and exploratory efficacy variables. The table footnotes provide explanatory information and details. Handling of missing data is addressed in Section 7.10.1, if applicable.

Table 3 Overview of Planned Efficacy Analyses

Analysis Variable /Analysis Type		Analysis Method
Primary Efficacy Variable: Change from period baseline in CWR endurance time at the end of each period		
1.1	**Primary Analysis:**	Mixed effect model: subject as a random effect; treatment and period as fixed effects
1.1.1	**Exploratory data (physical activity weekly parameters and C-PPAC parameters) Primary Analysis**	Analysis of Covariance (ANCOVA) model: baseline as covariate; treatment as a fixed effect
1.2	**Secondary Analyses:**	
1.2.1	Baseline, Post-baseline and change from baseline by each treatment and sequence	Descriptive statistics
1.3	**Sensitivity Analyses:**	
1.3.1	Carry-over effect is a covariate	Mixed effect model: subject as a random effect; treatment, period and carry-over as fixed effects
1.4	**Subgroup Analyses:**	
1.4.1	Gender	Descriptive statistics: Repeat 1.2.2 by each subgroup
1.4.2	Race	
1.4.3	Age Group	
Secondary Efficacy Variables: - Change from period baseline in Physiological parameters (VO_2, VCO_2, V_E/VCO_2, $P_{ET}O_2$, $P_{ET}CO_2$, V_T, Bf, V_E, IC, V_E/MVV, HR, SBP/DBP, S_PO_2, IRV, RER) at isotime - Change from period baseline in peak physiological parameters - Change from period baseline in change from rest to peak value of IC - Change from period baseline in Borg CR10 at isotime and peak for dyspnea and leg effort - Change from period baseline in activation of accessory respiratory muscles by EMG at isotime - Change from period baseline in peak activation of accessory respiratory muscles by EMG - Change from period baseline in spirometry (resting FEV_1/FVC, resting FEV_1, resting FEV_1 percent predicted, resting FVC and resting FVC percent predicted)		
X.1	Same as primary analysis in primary endpoint	Mixed effect model: subject as a random effect; treatment and period as fixed effects
X.2.2	Baseline, Post-baseline and change from baseline by each period and sequence	Descriptive statistics
X.3.1	Carry-over effect is a covariate	Mixed effect model: subject as a random effect; treatment, period and carry-over as fixed effects

Table continued on next page

Exploratory Efficacy Variables: - Change from period baseline in SGRQ-C (Total score and each domain score), SF-36 (Total score and each domain score), SPPB, 1RM, MIP and MEP - Change from period baseline in resting physiological parameters - Change from period baseline in Borg CR10 at rest for dyspnea and leg effort - Change from period baseline in resting activation of accessory respiratory muscles by EMG		
X.1	Same as primary analysis in primary endpoint	Mixed effect model: subject as a random effect; treatment and period as fixed effects
X.2.2	Baseline, Post-baseline and change from baseline by each period and sequence	Descriptive statistics
X.3.1	Carry-over effects a covariate	Mixed effect model: subject as a random effect; treatment, period and carry-over as fixed effects
Exploratory Efficacy Variables: Change from period baseline in PROactive (physical activity weekly parameters and C-PPAC parameters)		
X.1.1	Analysis of Covariance (ANCOVA) with baseline as covariate	ANCOVA model: baseline as covariate; treatment as a fixed effect for physical activity weekly continuous parameters excluding mean total wearing time parameters
X.2.2	Baseline, Post-baseline and change from baseline	Descriptive statistics

Analysis Results Presentation

The following statistics will be provided in tables summarizing results from analysis.

Mixed effect model or ANCOVA tables of results:

- n, mean and standard error (SE) for each treatment group
- Difference in LS means (CK-2127107 vs. placebo) and SE
- Two-sided 90% CI for treatment difference
- Two-sided p-value for each fixed effect
- Two-sided p-value for treatment difference

Descriptive tables of results:

n, mean, SD, median, minimum, and maximum for each period and sequence

7.4.2 Analysis of Primary Endpoint

The primary endpoint is the difference in change from period baseline in CWR endurance time at the end of each period.

7.4.2.1 Primary Analysis

An overview of the planned analyses of the primary variable is provided in Table 3. The primary analysis for the change from period baseline in CWR endurance time will be a mixed effect model with subject as a random effect and treatment and period as fixed effects. A mixed effect model is a standard model for a crossover trial. It improves efficiency by taking in to account both within-subject and between-subject variances. Compound symmetry will be used as a covariance structure. Restricted maximum likelihood will be used to estimate the

model parameters. Two-sided 90% confidence interval will be provided based on this model. In addition, statistical tests will be performed based on the model. The hypothesis for comparisons is given as follows:

H0: The change from baseline at the end of period for CK-2127107 and placebo are the same

H1: The change from baseline at the end of period for CK-2127107 and placebo are not the same

Comparisons will be performed at a two-sided 0.10 significance level. The primary analysis will use the FAS. In a mixed effect model analysis, the subject who has at least either one of the change from period baseline from period 1 and period 2 will be included in the analysis.

7.4.2.2 Secondary Analysis

Period baseline, period post-baseline and change from period baseline for the primary endpoint by period and sequence will be summarized as descriptive statistics.

7.4.2.3 Sensitivity Analysis

The same analysis of the primary endpoint as described in [Section 7.4.2.1] will be conducted with a model that adds carry-over as a fixed effect to the primary analysis model.

7.4.2.4 Subgroup Analysis

Period baseline, period post-baseline and change from period baseline for the primary endpoint by each period and sequence will be summarized separately by gender, race and age group.

7.4.3 Analysis of Secondary Endpoints

An overview of the planned analyses of the secondary endpoints is provided in Table 3. The analyses for the primary endpoint [Section 7.4.2.1, 7.4.2.2 and 7.4.2.3] will be repeated for change from period baseline in each secondary endpoint, and period baseline, period post-baseline and change from period baseline for all secondary endpoints by period and sequence will be summarized as descriptive statistics:

- Physiological parameters (VO_2, VCO_2, V_E/VCO_2, $P_{ET}O_2$, $P_{ET}CO_2$, V_T, Bf, V_E, IC, V_E/MVV, HR, SBP/DBP, S_PO_2, IRV, RER) at isotime
- Peak physiological parameters
- Change from rest to peak value of IC
- Borg CR10 at isotime
  - Dyspnea
  - Leg Effort
- Borg CR10 at peak
  - Dyspnea
  - Leg Effort
- Activation of accessory respiratory muscles by EMG at isotime
- Peak activation of accessory respiratory muscles by EMG

- Spirometry (resting FEV_1/FVC, resting FEV_1, resting FEV_1 percent predicted, resting FVC and resting FVC percent predicted)

7.4.4 Analysis of Exploratory Endpoints

An overview of the planned analyses of the exploratory endpoints is provided in Table 3. The analyses for the primary endpoint [Section 7.4.2.1, 7.4.2.3 and 7.4.2.4] will be repeated for each exploratory endpoint, and period baseline, period post-baseline and change from period baseline for all secondary endpoints by period and sequence will be summarized as descriptive statistics:

- Change from period baseline in physiological parameters (VO_2, VCO_2, V_E/VCO_2, $P_{ET}O_2$, $P_{ET}CO_2$, V_T, Bf, V_E, IC, V_E/MVV, HR, SBP/DBP, S_PO_2, IRV, RER) at rest
- Change from period baseline in Borg CR10 at rest
  - Dyspnea
  - Leg Effort
- Change from period baseline in SGRQ-C total score and each domain score
- Change from period baseline in SF-36 total score and each domain score
- Change from period baseline in activation of accessory respiratory muscles (by EMG) at rest during CWR
- Change from baseline in PROactive
  An overview of the planned analyses of the exploratory endpoints is provided in Table 3. For the weekly continuous physical activity parameters excluding mean total wearing time parameters, change from baseline result at week 2 will be analyzed using an ANCOVA with baseline as a covariate and treatment as a fixed effect. Weekly derived parameters median steps score group and median VMU group, baseline value, postbaseline value will be summarized using number and percentage of subjects by treatment. For the weekly derived parameters mean total wearing time on valid days, mean total wearing time of all days, mean average MI, median VMU, mean AEE, mean TEE and median number of steps, baseline value, postbaseline value and change from baseline to each specified postbaseline time point will be summarized using descriptive statistics.
  For the C-PPAC parameters difficulty, amount and total scores, baseline value, postbaseline value and change from baseline to each specified postbaseline time point will be summarized using descriptive statistics.
- Change from period baseline in SPPB
- Change from period baseline in 1RM
- Change from period baseline in MIP
- Change from period baseline in MEP

7.5 Analysis of Safety

All safety variables will be presented using descriptive statistics by treatment group and total for SAF, unless specified otherwise. No statistical hypothesis testing will be performed.

7.5.1 Adverse Events

Summaries and listings of serious adverse events (SAEs) and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be Medical Dictionary for Regulatory Activities (MedDRA). It will be used to summarize AEs by SOC and PT.

In the subject count, subjects reporting more than one AE for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one occurrence of the same AE within a SOC will be counted only once for the SOC total. Subjects reporting more than one AE will be counted only once in the overall AE total.

An overview table will summarize the following details:

- Number of the following TEAE variables:
    - TEAEs
    - Drug related TEAEs (defined as any TEAE with possible, probable or missing relationship to study drug as assessed by the investigator)
    - Serious TEAEs
    - Drug related serious TEAEs
    - TEAEs leading to death
    - Drug related TEAEs leading to death
    - TEAEs leading to permanent discontinuation of study drug
    - Drug related TEAEs leading to permanent discontinuation of study drug
- Number and percentage of subjects with the following TEAE variables:
    - TEAEs
    - Drug related TEAEs
    - Deaths
    - Serious TEAEs
    - Drug related serious TEAEs
    - TEAEs leading to death
    - Drug related TEAEs leading to death
    - TEAEs leading to permanent discontinuation of study drug
    - Drug related TEAEs leading to permanent discontinuation of study drug
- Number of deaths reported after the first study drug administration.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs
- Drug related TEAEs
- Serious TEAEs
- Drug related serious TEAEs
- TEAEs leading to permanent treatment discontinuation of study drug
- Drug related TEAEs leading to permanent treatment discontinuation of study drug

- TEAEs excluding serious adverse events that equal or exceed a threshold of 5.0% in any treatment group
- Common TEAEs (≥ 5.0% in any treatment group)
- TEAEs by severity

  If a subjects has multiple TEAEs with the same SOC and PT, but with differing severity, then the subject will be counted only once with the worst severity, however, if any of the severity values are missing then the subject will be counted only once with missing severity.

  TEAE with missing severity will be displayed with a missing category.

- Drug related TEAEs by severity
- TEAEs by relationship to study drug

  If a subjects has multiple TEAEs with the same SOC and PT, but with differing relationship, then the subject will be counted once with the highest degree of relationship, however, if any of the relationship values are missing, then the subject will be counted only once with missing relationship.

  TEAE with missing relationship to study drug missing will be counted as drug related.

The number of TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- Serious TEAEs
- Drug related serious TEAEs
- TEAEs excluding serious adverse events that equal or exceed a threshold of 5.0% in any treatment group

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment group.

7.5.2 Clinical Laboratory Evaluation

Raw values at each scheduled laboratory measurement visit, changes from Baseline at each post-baseline scheduled visit, and shifts from Baseline will be summarized for each laboratory parameter (as appropriate) in International System of Units (SI) using descriptive statistics. It will be summarized 1) by treatment group, and 2) by sequence and treatment group.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. The number and percentage of subjects below and above reference range will be summarized for each treatment group at each visit.

For hematology and biochemistry variables, shift relative to normal ranges from Baseline to each scheduled post-Baseline laboratory measurement.

Number and percentage of subjects with positive and negative results in qualitative urinalysis variables will be presented for each treatment group at each visit.

All laboratory measurements, including the derived outcomes (changing from Baseline and flagging of abnormal value with high and low) will be presented in listing.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's maximum value during the study period will be used, which is defined in Section 6.2.2

Parameter	Criteria
ALT	> 3×ULN > 5×ULN > 10×ULN > 20×ULN
AST	> 3×ULN > 5×ULN > 10×ULN > 20×ULN
ALT or AST	> 3×ULN
Total Bilirubin	> 2×ULN
ALP	> 1.5×ULN
ALT or AST and Total Bilirubin*	(ALT and/or AST > 3×ULN) and Total Bilirubin > 2×ULN
The denominator will be the number of subjects who had at least one non-missing post-baseline value in each period.	

*Combination of values measured within same sample (i.e., sample collected on the same day)

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the study period will be presented by treatment group.

The following data will be presented graphically:

- Scatter plot of individual subject maximum postbaseline relative to ULN values for ALT or AST and TBL during the study period with ALT or AST values on x-axis and total bilirubin values on y-axis [Senior, 2014]. Here maximum postbaseline relative to ULN values for ALT or AST for each subject = maximum of (maximum relative to ULN postbaseline value for ALT, maximum relative to ULN postbaseline value for AST), and
- Line plot of individual subject relative to ULN values for liver enzymes and total bilirubin and list of adverse events for selected subjects experiencing potentially clinically significant criteria of postbaseline ALT > 3xULN or AST > 3xULN or TBL > 2xULN during the study period.

A listing will be presented for liver enzymes and total bilirubin results for subjects experiencing potentially clinically significant criteria of postbaseline ALT > 3xULN or AST > 3xULN or TBL > 2xULN during the study period.

7.5.2.2 Serum Creatinine and Cystatin C

The following potentially clinically significant criteria in Serum Creatinine and Cystatin C tests and their combination are defined. The subject's maximum value among all postbaseline results in each period will be used.

Parameter	Criteria
Serum Creatinine	• >=1.5 to <=2 x baseline • >=1.5 to <=2 x baseline and abnormal • >2 x baseline • >2 x baseline and abnormal
Cystatin C	• >=1.5 to <=2 x baseline • >=1.5 to <=2 x baseline and abnormal • >2 x baseline • >2 x baseline and abnormal
Serum Creatinine or Cystatin C	• Serum Creatinine >=1.5 to <=2 x baseline or Cystatin C >=1.5 to <=2 x baseline • (Serum Creatinine >=1.5 to <=2 x baseline and abnormal) or (Cystatin C >=1.5 to <=2 x baseline and abnormal)
Serum Creatinine and Cystatin C(*)	• Serum Creatinine >=1.5 to <=2 x baseline and Cystatin C >=1.5 to <=2 x baseline • Serum Creatinine >=1.5 to <=2 x baseline and abnormal Serum Creatinine and Cystatin C >=1.5 to <=2 x baseline and abnormal cystatin C
The denominator will be the number of subjects who had a non-missing baseline value and at least one post-baseline value in each period.	

Abnormal: below LLN or above ULN for the post baseline result in each period.
(*) Combination of values measured from the samples collected on the same day.

The number and percentage of subjects with potentially clinically significant values in Serum Creatinine and Cystatin C tests during the study period will be presented by treatment.

A scatter plot of maximum postbaseline relative to baseline value for serum creatinine and cystatin C during the study period with serum creatinine values on x-axis and cystatin C values on y-axis.

A listing will be presented for serum creatinine, Cystatin C and BUN results for subjects experiencing the above potentially clinically significant criteria for any postbaseline result.

7.5.3 Vital Signs

Vital signs values at each scheduled visit and changes from Baseline at scheduled post-Baseline visit will be summarized by 1) treatment group and 2) by sequence and treatment group.

7.5.4 Electrocardiograms (ECGs)

Raw values (categorical) and changes from Baseline (shift from Baseline) will be summarized, and the summaries will include number and percentage of subjects with normal and abnormal 12-lead ECG findings. It will be summarized 1) by treatment group, and 2) by sequence and treatment group. If there is more than one result reported at each time point, worst case i.e., abnormal will be used.

Number and percentage of patients with 12-lead ECG abnormalities will be summarized by treatment group and time point. If a subject has more than one abnormality at a given time point that corresponded to a single interpretation then the subject will be counted once for each abnormality. Also at a given time point, if a subject has the same abnormality reported more than once, then the subject will be counted only once for that abnormality.

7.5.5 Pregnancies

A detailed listing of all pregnancies will be provided.

7.6 Analysis of PK

7.6.1 Plasma Concentrations

Descriptive statistics (i.e., N, mean, standard deviation, minimum, median, maximum, coefficient of variation, geometric mean and geometric cv) will be provided for plasma concentrations (day 14 C_{trough} and C_{6h} and day 1 (only for period 2) pre-dose plasma concentration) of CK-2127107 and CK-2127106.

7.6.2 Statistical Analysis

An exploration of covariates of day 14 C_{trough}, including sex, age, and body weight will be investigated. If applicable, population pharmacokinetic analysis will be further employed to explore covariates and such analysis will be performed by pharmacokinetic modeling and simulation group. The population analysis will be reported separately.

7.6.3 Concentration-Response Relationship Analysis

Potential relationship between day 14 C_{trough} of CK-2127107 or CK-2127106 and efficacy/safety measures (primary/secondary/exploratory efficacy endpoints) will be explored and such analysis will be performed by pharmacokinetic modeling and simulation group. If applicable, exposures derived from the population analysis will be also utilized for the exploration exposure- efficacy measures relationships. This will be reported separately.

7.7 Subgroups of Interest

Primary efficacy endpoint will be summarized by the treatment group for the following subgroups and categories of interest.

Additional information is provided in Section 7.4.2.4

Subgroup	Subgroup Category
Sex	Female Male
Race	White Black or African-American Asian American Indian or Alaska Native Native Hawaiian or other pacific islander Other
Age group	< 65 years ≥ 65 years

7.8 Other Analyses

No specific other analyses will be performed in this study.

7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

No interim analysis will be performed in this study.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.10.1 Missing Data

7.10.1.1 Handling of Missing Efficacy Data

Unless otherwise specified, no missing data will be imputed for any descriptive statistics summaries of efficacy variables. All observed data in subject who has missing value or discontinues during the study will be used for a mixed effect model analysis.

7.10.1.2 Handling of Missing Safety Data

Unless otherwise specified, no missing data will be imputed in any summaries or analyses of the safety variables defined in Section 6.2 and of other variables defined in Section 6.4.

7.10.1.3 Handling of Missing Diagnosis/Onset Date

Missing diagnosis/onset date will be imputed as follows. If only the day of the month is missing (e.g., MAR/2016), then the first day of the month will be used (01/MAR/2016), and if both day and month are missing (e.g., 2016), then the first day of January will be used (01/JAN/2016). If an onset date is missing completely, the imputed onset date will be the latest of the following non-missing dates:

- First dose date of study drug in period 1
- Randomization date + 1 day

7.10.1.4 Handling of Missing Start and Stop Dates of Previous and Concomitant Medications

For Previous and Concomitant Medications, a missing or incomplete start and stop dates will be imputed according to the following conventions:

If start date is missing or partial:

- if day is missing, use the first day of the month under consideration
- if month is missing, use January
- if year is missing, use year of the informed consent date
- if entire date is missing, use informed consent date

If stop date is missing or partial and medication is not ongoing:

- if month is missing, use December
- if day is missing, use the last day of the month under consideration
- if year or the entire date is missing, set to December 31st, 2099

If the imputed start date is after the stop date, then the imputed start date will be one day prior to the stop date.

Medication that ended or ongoing after the first dose date of study drug is counted as both previous medication as well as concomitant medication.

If the medication is ongoing, the stop date will remain missing.

7.10.2 Outliers

All values will be included in the analyses.

7.10.3 Values BLOQ

CK-2127107, CK-2127106 and metabolite (if applicable) plasma concentrations below limit of quantification (BLOQ) will be set to 0 for calculating descriptive statistics. For plasma concentrations, in cases where more than half of the individual data in a group are BLOQ, SD, coefficient of variation and geometric coefficient of variation will not be calculated. If one or more values are BLOQ, the geometric mean will not be calculated.

For laboratory safety quantitative variables, values recorded as "<X" or "<=X" or ">Y" or ">=Y" will be imputed by "X" and "Y" respectively for descriptive statistics. This will be documented in a footnote to all summary tables and all output where such a replacement was performed.

7.10.4 Visit Windows

The number of study days relative to the first dose date of study drug (Study Day), is calculated as:

- Study Day = Date of assessment – Date of first dose of study drug +1, when the date of assessment is on or after the date of first dose of study drug
- Study Day = Date of assessment – Date of first dose of study drug, when the date of assessment is before the date of first dose of study drug.

The day of the first dose of study drug is defined as Study Day 1, while the day before the date of first dose of study drug (i.e., Randomization visit) is defined as Study Day -1 (there is no Study Day 0).

7.10.4.1 Post Dosing Efficacy Observations

For efficacy variables, observations will not contribute to the efficacy analyses if the patient's last dose of study drug is as follows:

In each period, any days which are > 3 days after the last dose of study drug will not be included in the analysis related to on-treatment time points and the EOT time point. This needs to be done before implementing the visit windows in Section 7.10.4.2.

7.10.4.2 Algorithm for Computing Baseline and Post-Baseline in each period from Efficacy Variables

Baseline is defined as the last non-missing measurement prior to the first dose of study drug in each period. That is, Baseline are the visit 4 and visit 7 in Figure 1 [Section 2] for period 1 and period 2, respectively if the value at each visit is not missing; if the value at each visit is missing, then the Baseline will be considered a missing value.

EOT is defined as the last non-missing assessment in each period from the date of first dose of study drug + 1 through the date of last dose of study drug +3 days.

Table 4 Time Windows for Analyses of Efficacy Variables

Treatment Period	Time Point	Target Visit Day (Study Day)	Time Window (Study Day Range)
Screening (IET)			–28 to –9
Period 1	Baseline	1	-3 to 1
	Day 14	14	11 - 17
Period 2	Baseline	1	-3 to 1
	Day 14	14	11 - 17
Follow-up*		last dose day+7	>= last dose day+4 to <= last dose day +14

* Follow-up visit is created for spirometry data only.

Table 5 Time Windows for Physical Activity (accelerometer) Data

Treatment Period	Analysis Time Point	Visit Window (Study Day Range)
	Baseline	-26 to -1 where data from (last reported day -7) to last reported day will be used
Period 1	Week 2	7 to 14
	EOT	2 to 14 where post-baseline data from (last reported day -7) to last reported day will be used

Multiple assessments: For analysis, if a subject has more than one visit with a measurement included within a time window, the assessment closest to the target day will be used. If

multiple assessments exist in the same time window, the latest one will be picked. If more than one assessment is included on the same day, then the last assessment regarding the time on that day will be used in the analysis. If the time of assessment is not available, the worst assessment will be used (if applicable), otherwise the average will be used.

7.10.4.3 Post Dosing Safety and PD Observations

For safety and PD variables, observed days for the variables will not contribute to the analyses if the patient's last dose of study drug is as follows:

Any days which are > 6 days after the last dose of study drug will not be included in the analysis related to on-treatment time points and the EOT time point. This needs to be done before implementing the visit windows in Section 7.10.4.4

7.10.4.4 Safety and PD Analyses

For safety laboratory tests, vital signs, ECG and PD variables:

Baseline is defined as the last non-missing measurement prior to the first dose of study drug in each period. That is, Baseline are the visit 4 and visit 7 in Figure 1 [Section 2] for period 1 and period 2, respectively if the value at each visit is not missing; if the randomization visit value at period 1 is missing, then the Screening value (if applicable) will be used as the baseline value. If both the Screening and Randomization visit values are missing, the Baseline will be considered a missing value in the period 1.

Scheduled visits will use the visit window outlined in Table 6

Table 6 Visit Windows for Safety Laboratory Tests (Hematology and Urinalysis), Vital Signs, ECG and PD Variables

Treatment Period	Scheduled Visit	Target Visit Day (Study Day)	Time Window (Study Day Range)
Period 1	Baseline	1	≤ 1
	Post-baseline	14	2 - 20
Period 2	Baseline	1	–7 - 1
	Post-baseline	14	2 - 20
Follow-up		last dose day+7	>= last dose day+7

Table 7 Visit Windows for Safety Laboratory Tests (Biochemistries)

Treatment Period	Scheduled Visit	Target Visit Day (Study Day)	Time Window (Study Day Range)
Period 1	Baseline	1	≤ 1
	Post-baseline 1	6	2 – 9
	Post-baseline 2	14	10 – 20
Period 2	Baseline	1	–7 - 1
	Post-baseline 1	6	2 – 9
	Post-baseline 2	14	10 - 20
Follow-up		last dose day+7	>= last dose day+7

Unscheduled visits: If a subject has an unscheduled visit, then the unscheduled assessment will be mapped to an analysis visit according to the visit window specified in Table 6.

Multiple assessments: For analysis, if a subject has more than one visit with a measurement included within a time window, the assessment closest to the target day will be used. If multiple assessments exist in the same time window, the latest one will be picked. If more than one assessment is included on the same day, then the last assessment regarding the time on that day will be used in the analysis. If the time of assessment is not available, the worst assessment will be used (if applicable), otherwise the average will be used.

For the PK plasma concentration data, any data days which are > 6 days after the last dose of study drug in each period will not be included in the analysis related to on-treatment visits. For the plasma concentrations, nominal visits will be used as analysis visits.

For the visit 7 predose timepoint, if the actual time relative to dosing is after dosing, then the timepoint will be excluded from the descriptive statistics. For the visit 9/EOT/ED predose timepoint, if the actual time relative to dosing is after dosing or more than 4 hours prior to dosing, then the timepoint will be excluded from the descriptive statistics. For the 6 hours timepoint, if the actual time relative to dosing is more than +/- 2 hours from the planned time of 6 hours, then the timepoint will be excluded from the descriptive statistics.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	25-Jan-2016	NA	Document finalized
2.0	13-Jun-2018	**I. LIST OF ABBREVIATIONS AND KEY TERMS** Added abbreviations for physical activity parameters, efficacy parameters and removed abbreviation for SDD.	Due to the updates made to the SAP.
2.0	16-May-2018	**2 Flow Chart and Visit Schedule** are updated	Due to protocol version 3.1.
2.0	16-May-2018	**1 Introduction and 5 Analysis Sets** Updated wording about the allocation of subjects to PKAS.	Due to protocol version 3.0.
2.0	16-May-2018	**3.1.2 Secondary Objectives** The secondary objective about CWR parameters is updated.	Due to protocol version 3.1.
2.0	16-May-2018	**3.2 Study Design** Study design details are updated.	Due to protocol version 3.1 and additional details are available in the protocol.
2.0	16-May-2018	**4 Sample Size** Sample size details are updated about discontinuation rate.	Due to protocol version 3.1.

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	16-May-2018	**5.1 Full Analysis Set (FAS)** The FAS definition in the SAP is updated to provide the variable name for the FAS. Updated the word 'period' as 'treatment period'.	Due to protocol version 3.0. Protocol Section 7.2.1 definition for FAS did not list the variable needed for the analysis set. Wording update is due to typographical error.
2.0	16-May-2018	**5.2 Per Protocol Set (PPS)** PPS is removed.	Due to protocol version 3.0.
2.0	16-May-2018	**5.3 Pharmacokinetic Analysis Set (PKAS)** PKAS definition is updated as follows: The pharmacokinetic analysis set (PKAS) consists of the administered population for which at least one quantifiable plasma trough concentration or concentration at 6 hours is available for CK-2127107 or CK-2127106 and for whom the time of dosing on the day of sampling is known.	Quantifiable concentration and time of dosing is needed to determine the PKAS hence the definition for PKAS is updated.
2.0	13-Jun-2018	**6.1 Efficacy Endpoints** Definitions for efficacy variables are added. Derivation details for percent of predicted parameters that are used for the analysis are added. **7.4.3 Analysis of Secondary Endpoints** Added list of derived parameters for percent of predicted FEV_1 and FVC. **6.1.1 Primary Efficacy Endpoints** Definition of CWR duration is moved under Section 6 Efficacy Endpoints. For CWR duration, a sentence about direction of improvement is added.	To provide definitions of efficacy variables and derivation details for percent of predicted parameters using predicted results. To interpret the results for change from baseline CWR duration and to provide all definitions in one section.
2.0	13-Jun-2018	**6.1.2 Secondary Efficacy Endpoints** List of variables for other cardiometaboloic variables are added. Derivation details for MVV, IRV, RER and V_E/MVV are added. Wording for 'Accessory muscle EMG activity' is updated as 'Surface accessory muscle EMG activity'. For endpoint Change in resting spirometry compared to placebo, details about the	For clarification. Wording update is due to protocol version 3.0. To list and provide the

Version	Date	Changes	Comment/rationale for change
		parameters are added.	derivation details of spirometry parameters.
2.0	05-Jul-2018	**6.1.3 Exploratory Efficacy Endpoints** Details about physical activity parameters and C-PPAC questionnaire parameters are added**.** Added endpoints for CWR physiology at Rest (cardiometabolic variables), Borg CR10 at rest and EMG at Rest.	For clarification. To provide summaries and analyses for these endpoints.
2.0	16-May-2018	**6.2.1 Adverse Events** TEAE definition for day 1 is updated as follows: If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent.	Time is not collected on the CRF page. Instead a check box is available for adverse events that occurs on day 1 to indicate Onset of a AE after first dose of study drug.
2.0	16-May-2018	**6.2.1 Adverse Events** Added the following for TEAE treatment period 1 in second paragraph: If a subject discontinues in treatment period 1, TEAEs at treatment period 1 will be defined as TEAE which occurs after first dose of study drug at treatment period 1 up to 14 days after the last dose of study drug.	Additional details are added to associate TEAE with a period in the situation of a subject discontinue the study in period 1.
2.0	16-May-2018	**6.2.1 Adverse Events** Removed the imputation details of AEs with missing onset dates (partial or full date is missing) and added a sentence referencing to Section 7.10.1.3.	Details about imputation are provided in section 7.10.1.3 and added a sentence referencing to this section.
2.0	16-May-2018	**6.2.3 Vital Signs** Parameter respiration is removed.	Not collected in the study.
2.0	16-May-2018	**6.2.4 Electrocardiograms (ECGs)** ECG summary details are updated as follows: The 12-lead ECG scheduled assessments will be made at Screening, Baseline and Day 14. The results will be recorded as	From central reading, results are reported either normal or abnormal.

Version	**Date**	**Changes**	**Comment/rationale for change**
		normal or abnormal. ECG variables are raw values (categorical) at each scheduled visit and changes from Baseline (shift from Baseline) at Day 14.	
2.0	16-May-2018	**6.4 Other Variables** Exposure rate is added and a corresponding section (Section 7.3.3) for the summary is added.	To provide exposure rate results using first and last CRF visit dates in the denominator.
2.0	16-May-2018	**6.4 Other Variables** For treatment compliance, updated the formula for total number of tablets planned to receive as follows: Total number of tablets planned to receive during 2 weeks in each treatment period = 4 × duration of exposure - 4. Total treatment compliance (%) with tablets is removed. For Previous and concomitant medication, removed the imputation details about previous or concomitant determination with missing start or end dates (partial or full date is missing) and added a sentence referencing to Section 7.10.1.4.	Tablet strength is 250 mg hence a subject needs to take a total of 4 tablets each day. Treatment compliance for each treatment is useful in a crossover study so total treatment compliance (%) with tablets is removed. Details about imputation of the start and end dates are provided in Section 7.10.1.4 hence removed the paragraph and added a sentence referencing to this section.
2.0	16-May-2018	**7.1 General Considerations** SAS procedure names for summaries of continuous or categorical variables are removed.	No need to list the SAS procedures in the SAP.
2.0	16-May-2018	**7.1 General Considerations** EOT definition is updated. **Was:** **Week 2/EOT** will be defined as the last non-missing assessment in each period from the date of first dose of study drug through 1 day after the date of last dose of study drug up to Week 2/EOT. That is, post-baseline are the visit 6 and visit 8 in Figure 1 [Section 2] for period 1 and period 2, respectively if the value at each visit is not missing. **Updated as:** **EOT Value** For the physical activity data collected using accelerometer, the available post-baseline measurements within the visit	For clarification.

Version	Date	Changes	Comment/rationale for change
		window as defined in Section 7.10.4.2 will be used to derive the EOT value. For other efficacy data, the last available post-baseline measurement within the treatment period as defined by the visit window in Section 7.10.4.2 will be used as the EOT value.	
2.0	16-May-2018	**7.1 General Considerations** Treatment period and follow-up period definitions are added. Details about calculating change from baseline for follow-up visit are added.	For clarification.
2.0	16-May-2018	**7.2.1 Disposition of Subjects** Updated bullet points about rescreened patients. Treatment discontinuation will be presented for SAF as well. A summary is added for number and percentage of subjects for each protocol version.	To explain how to handle the results from rescreened subjects. To provide treatment discontinuation summary for SAF. To provide a summary for number and percentage of subjects for each protocol version.
2.0	13-Jun-2018	**7.2.3 Demographic and Other Baseline Characteristics** Additional screening parameters for spirometry and IET are added.	To provide summary of additional parameters for spirometry and IET.
2.0	16-May-2018	**7.3 Study Drugs** Sentence about exposure and treatment compliance is revised. **Was:** Duration of exposure and treatment compliance will be summarized by sequence and overall for the SAF and FAS. It will be also repeated by sequence and treatment. **Updated as:** Duration of exposure and treatment compliance will be summarized for each treatment by sequence and overall for the SAF and FAS.	For clarification.

Version	**Date**	**Changes**	**Comment/rationale for change**
2.0	17-Jul-2018	**7.4.1 Overview of Efficacy Analyses** Table 3: Details about exploratory efficacy data (physical activity and C-PPAC questionnaire) are added. For secondary efficacy variables missing parameters RER, IRV, V_E/VCO_2 and V_T are added. For Borg CR10 details about the parameters are added. Endpoints CWR physiology at Rest, Borg CR10 at rest and EMG at rest are moved from secondary endpoints to exploratory endpoints. Label 'Mixed effect model tables of results' is updated as 'Mixed effect model or ANCOVA tables of results'. For descriptive statistics, median, minimum, and maximum are added.	Due to the updates in Sections 6.1.2 and 6.1.3. To provide the additional statistics that will help understand the distribution of the data.
2.0	16-May-2018	**7.4.3 Analysis of Secondary Endpoints** For physiological parameters missing parameters IRV, RER, V_E/VCO_2 and V_T are added. For Borg CR10 details about the parameters are added. For EMG, removed endpoints about rest and maximum.	Due to the updates in Section 6.1.2. For EMG, the endpoints at rest is exploratory endpoint and the endpoint about maximum is redundant hence removed.
2.0	05-Jul-2018	**7.4.4 Analysis of Exploratory Endpoints** For Change from baseline in PROactive, details about analysis of the PROactive parameters and C-PPAC questionnaire are added. Added the endpoint about EMG at rest For Borg CR10 at rest and physiological parameters at rest, details about the parameters are added.	Due to the updates in Section 6.1.3.
2.0	16-May-2018	**7.5.1 Adverse Events** The following details are added for the overview of TEAEs: TEAEs leading to death Drug related TEAEs leading to death The following details are added for number and percentage of subjects with TEAEs: TEAEs leading to death	To provide summary for these variables.

Version	Date	Changes	Comment/rationale for change
		Drug related TEAEs leading to death AE summary for number of deaths reported after the first study drug administration.	
2.0	16-May-2018	**7.5.1 Adverse Events** For TEAEs and drug-related TEAEs by severity removed NCI CTCAE Grade.	NCI CTCAE grading is not used in this study.
2.0	16-May-2018	**7.5.2 Clinical Laboratory Evaluation** Removed the following sentence and moved to Section 7.5.2.1 Liver Enzymes and Total Bilirubin. A listing will be presented for liver enzymes and total bilirubin results for subjects experiencing potentially clinically significant criteria of postbaseline ALT > 3xULN or AST > 3xULN or TBL > 2xULN during the study period.	For clarification.
2.0	16-May-2018	**Section 7.5.2.1 Liver Enzymes and Total Bilirubin** Details about denominator are added. Added the following plots: Scatter plot of individual subject maximum postbaseline relative to ULN values for ALT or AST and TBL during the study period with ALT or AST values on x-axis and total bilirubin values on y-axis, and Individual display of liver enzymes and total bilirubin for selected subjects experiencing potentially clinically significant criteria of postbaseline ALT > 3xULN or AST > 3xULN or TBL > 2xULN during the study period.	For clarification and to provide plots for liver enzymes and total bilirubin.
2.0	16-May-2018	Created a new section 'Section 7.5.2.2 Serum creatinine and Cystatin C'. Removed the following sentence from Section 7.5.2.1 Liver Enzymes and Total Bilirubin: The number and percentage of subjects with potentially clinically significant values in Serum Creatinine, BUN and Cystatin C tests during the study period will be presented by treatment group.	To provide details about potentially clinically significant criteria and plots for Serum creatinine and Cystatin C.
2.0	16-May-2018	**7.5.4 Electrocardiograms (ECGs)** Updated this section as follows: Raw values (categorical) and changes from Baseline (shift from Baseline) will be	Due to protocol version 3.0.

Version	Date	Changes	Comment/rationale for change
		summarized, and the summaries will include number and percentage of subjects with normal and abnormal 12-lead ECG findings. It will be summarized 1) by treatment group, and 2) by sequence and treatment group. If there is more than one result reported at each time point, worst case i.e., abnormal will be used. Number and percentage of patients with 12-lead ECG abnormalities will be summarized by treatment group and time point. If a subject has more than one abnormality at a given time point that corresponded to a single interpretation then the subject will be counted once for each abnormality. Also at a given time point, if a subject has the same abnormality reported more than once, then the subject will be counted only once for that abnormality.	
2.0	16-May-2018	**7.6.2 Statistical Analysis and 7.6.3 Concentration-Response Relationship Analysis** Added a sentence that analysis will be performed by pharmacokinetic modeling and simulation group.	To provide the details of the function that will perform these analyses.
2.0	16-May-2018	**7.10.1.3 Handling of Missing Diagnosis/Onset Date** Imputation details for missing AE onset date are added.	To provide the imputation details of AE onset date so that TEAE determination can be made.
2.0	16-May-2018	**A new section for '7.10.1.4 Handling of Missing Start and Stop Dates of Previous and Concomitant Medications' is added.**	To provide imputation details of missing start and stop dates of previous and concomitant medications.
2.0	16-May-2018	**A new section for '7.10.3 Values BLOQ' is added and subsequent sections are renumbered.**	To provide imputation details of results BLOQ or recorded as <X, <=X, >Y or >= Y.
2.0	16-May-2018	**A new section for '7.10.4.1 Post Dosing Efficacy Observations' is added.**	To provide details about handling the efficacy data collected after last dose of study drug.
2.0	16-May-2018	**7.10.4.2 Algorithm for Computing Baseline and Post-Baseline in each period from Efficacy Variables** Baseline, Week 2, EOT definitions are	For baseline, efficacy results from study -3 to -1 are not expected to be different from day 1.

Version	**Date**	**Changes**	**Comment/rationale for change**
		updated. In Table 4, Target visit details are added. Also follow-up visit window details for spirometry are added. Table is added to provide visit windows for physical activity data. Details about handling multiple assessments are added.	For Week 2, Efficacy results from study day 11 to 13 are not expected to be different from day 14 to 17. EOT definition is updated so that it is consistent treatment period window. For clarification.
2.0	16-May-2018	**A new section for '7.10.4.3 Post Dosing Safety and PD Observations' is added.**	To provide details about handling the safety and PD data collected after last dose of study drug.
2.0	16-May-2018	**7.10.4.4 Safety and PD Analyses** In Tables 5 and 6, follow-up visit window details are updated. Tables is added to provide visit windows for physical activity data. Details about handling multiple assessments are updated. Visit window details for PK concentrations data are updated.	Follow-up visit window details are updated so that it is consistent with follow-up period window. For clarification. To clarify that nominal visits will be used as analysis visits and additional details for the timepoint windows are added.
2.0	16-May-2018	**10.2 Appendix 2: Key Contributors and Approvers** Primary Author and Contributors and Reviewers detailed are updated for SAP author, global statistical lead and clinical study manager.	Due to changes to team members.

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Jones, B. and Kenward, M. G. (2014). Design and Analysis of Cross-Over Trials, Third Edition. CRC Press.

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10 APPENDICES

10.1 Appendix 1: Predictive Equations

Spirometry (Male Adults ≥ 20 years; Female Adults ≥ 18 years)

Units: Height = cm; Age = years

FEV_1 (L) – NHANES/Hankinson		
	Equation	**Source**
Caucasian Male	0.5536-0.01303*Age-0.000172*Age^2+0.0001498*$Height^2$	Hankinson et al. *Am J Respir Crit Care Med* 159:179-187, 1999.
Caucasian Female	0.4333-0.00361*Age-0.000194*Age^2+0.00011496*$Height^2$	
African-American Male	0.3411-0.02309*Age+0.00013194*$Height^2$	
African-American Female	0.3433-0.01293*Age-0.000097*Age^2+0.00010846*$Height^2$	
Mexican-American Male	0.6306-0.02928*Age+0.00015104*$Height^2$	
Mexican-American Female	0.4529-0.01178*Age-0.000113*Age^2+0.00012154*$Height^2$	
Asian-American Male	(Caucasian Male FEV_1)*0.94	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Asian-American Female	(Caucasian Male FEV_1)*0.93	

FVC (L) – NHANES/Hankinson		
	Equation	**Source**
Caucasian Male	-0.1933+0.00064*Age-0.000269*Age^2+0.00018642*$Height^2$	Hankinson et al. *Am J Respir Crit Care Med* 159:179-187, 1999.
Caucasian Female	-0.3560+0.01870*Age-0.000382*Age^2+0.00014815*$Height^2$	
African-American Male	-0.1517-0.01821*Age+0.00016643*$Height^2$	
African-American Female	-0.3039+0.00536*Age-0.000265*Age^2+0.00013606*$Height^2$	
Mexican-American Male	0.2376-0.00891*Age-0.000182*Age^2+0.00017823*$Height^2$	
Mexican-American Female	0.1210+0.00307*Age-0.000237*Age^2+0.00014246*$Height^2$	
Asian-American Male	(Caucasian Male FEV_1)*0.89	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Asian-American Female	(Caucasian Male FEV_1)*0.94	

Lung Volumes (adults 18-70 yrs)

Units: Height = cm; Age = years

FRC (L) – ERS/ECSC/Quanjer		
	Equation	**Source**
Male	2.34*(Height/100)+(0.009*Age)-1.09	Quanjer et al., *Eur Respir J* 6 (suppl 16):5-40, 1993.
Female	2.24*(Height/100)+(0.001*Age)-1.00	
African-American race adjustment	Both male and female = (Predicted_FRC)*0.88	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.
Asian race adjustment	Male = (Predicted_FRC)*0.96 Female = (Predicted_FRC)*0.94	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Hispanic race adjustment	No adjustment	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.

SVC (L) – ERS/ECSC/Quanjer		
	Equation	**Source**
Male	5.76*(Height/100)-(0.026*Age)-4.34	Quanjer et al., *Eur Respir J* 6 (suppl 16):5-40, 1993.
Female	4.43*(Height/100)-(0.026*Age)-2.89	
African-American race adjustment	Both male and female = (Predicted_TLC)*0.88	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.
Asian race adjustment	Male = (Predicted_TLC)*0.89 Female = (Predicted_TLC)*0.94	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Hispanic race adjustment	No adjustment	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.

TLC (L) – ERS/ECSC/Quanjer		
	Equation	**Source**
Male	7.99*(Height/100)-7.08	Quanjer et al., *Eur Respir J* 6 (suppl 16):5-40, 1993.
Female	6.60*(Height/100)-5.79	
African-American race adjustment	Both male and female = (Predicted_TLC)*0.88	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.
Asian race adjustment	Male = (Predicted_TLC)*0.96 Female = (Predicted_TLC)*0.94	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Hispanic race adjustment	No adjustment	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.

IC (L) – ERS/ECSC/Quanjer		
	Equation	**Source**
Male	IC = Predicted TLC – Predicted RV RV= 1.31*(Height/100)+(0.022*Age)-1.23	Quanjer et al., *Eur Respir J* 6 (suppl 16):5-40, 1993.
Female	IC = Predicted TLC – Predicted RV 1.81*(Height/100)+(0.016*Age)-2.00	
African-American race adjustment	Both male and female = (Predicted_TLC)*0.88	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.
Asian race adjustment	Male = (Predicted_TLC)*0.96 Female = (Predicted_TLC)*0.94	Korotzer et al., *Am J Respir Crit Care Med* 161:1101–1108, 2000.
Hispanic race adjustment	No adjustment	Pellegrino et al., *Eur Respir J* 26: 948-968, 2005.

Diffusing Capacity (adult, nonsmokers, single breath DLCO method)

Units: Height = cm; Age = years

DL_{CO} (ml/mmHg/min, STPD) – Miller, Single Breath		
	Equation	**Source**
Male	12.9113+(0.4180*2.54*Height)-(0.2290*Age)	Miller et al., *Am Rev Respir Dis* 127:270-27, 1983.
Female	2.2382+(0.4068*2.54*Height)-(0.111*Age)	

DLco/TLC (L) – Miller, Single Breath		
	Equation	**Source**
Male	These equations assume VA = TLC 10.0882-(0.0570*2.54*Height)-(0.0309*Age)	Miller et al., *Am Rev Respir Dis* 127:270-27, 1983.
Female	These equations assume VA = TLC 8.3297-(0.0460*2.54*Height)-(0.0157*Age)	

Cycle Ergometry Aerobic Capacity (Adults)

Units: Weight = kg; Height = cm Age = years;

VO_{2peak} (L/min) – Hansen/Wasserman		
	Equation	**Source**
Male	Ideal weight = (0.79*Height)-60.7 Where actual weight equals or exceeds ideal weight: VO_{2peak} = (0.0337*Height)-(0.000165*Age*Height-1.963)+0.006*(actualweight-idealweight) Where actual weight is less than ideal weight: VO_{2peak} = (0.0337*Height)-(0.000165*Age*Height-1.963)+0.014*(actualweight-idealweight)	Wasserman et al. Principles of Exercise Testing and interpretation 5th Edn. Lippincott Williams and Wilkins, 2012. Pp 158.
Female	Ideal weight = (0.65*Height)-42.8 VO_{2peak} = (0.001*Height)*(14.783-0.11*Age)+0.006*(actualweight-idealweight)	

10.2 Appendix 2: Key Contributors and Approvers

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author

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Contributors and Reviewers

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