Protocol WI203720

A Phase 1b/2, Open-Label, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of PF-06252616 in Ambulatory Participants with LGMD2I

Statistical Analysis Plan (SAP)

Version: 1.0

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

This is a list of abbreviations that may be used in the SAP.	
Abbreviation	**Term**
2MWT	two minute walk test
4SC	four stair climb
10MR	ten meter run
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
CL	clearance
C-SSRS	Columbia Suicide Severity Rating Scale
DXA	dual energy x-ray absorptiometry
ECG	Electrocardiogram
FAS	full analysis set
FEV1	Forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GDF-8	growth differentiation factor 8
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
InQoL	Individualized Neuromuscular Disease Quality of Life
IRB	institutional review board
IV	intravenous
LH	luteinizing hormone
LGMD2I	limb girdle muscular dystrophy 2I
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
MEP	mean expiratory pressure
MIP	mean inspiratory pressure
MMT	manual muscle testing
MRC	Medical Research Council
MRI	magnetic resonance imaging
Nab	neutralizing antibodies
PK/PD	pharmacokinetic/pharmacodynamics
PT	prothrombin time
PUL	Performance of Upper Limb
RNA	ribonucleic acid
SAP	statistical analysis plan
SF-36	Short Form 36 Health Survey
SMC	Safety Monitoring Committee
SOP	standard operating procedure
TEAEs	treatment emergent AEs

TIBC	total iron binding capacity
TUG	timed up and go

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the initial version of the statistical analysis plan.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicized***.

2.1. Study Design

This is a Phase 1b/2, open-label multiple ascending dose study to evaluate the safety, tolerability, efficacy, PK and PD of PF-06252616 administered to in ambulatory participants diagnosed with LGM2I. Three IV infused dose levels administered every 28 days will be investigated in a dose escalating fashion.

PF-06252616 dose levels:

- *5 mg/kg.*
- *20 mg/kg.*
- *40 mg/kg.*

Approximately 20 eligible subjects will be consecutively assigned to 1 of 3 cohorts for approximately 96 weeks (cohort 1) or 64 weeks (cohorts 2 and 3).

Cohort 1 (n=4):

- *Lead-in period (16 weeks)*
- *Treatment A: PF-06252616 5 mg/kg (32 weeks)*
- *Treatment B: PF-06252616 40 mg/kg (32 weeks)*
- *Follow-up period (16 weeks)*

Cohort 2 (n=8):

- *Lead-in period (16 weeks)*
- *Treatment: PF-06252616 20 mg/kg (32 weeks)*
- *Follow-up period (16 weeks)*

Cohort 3 (n=8):

- *Lead-in period (16 weeks)*

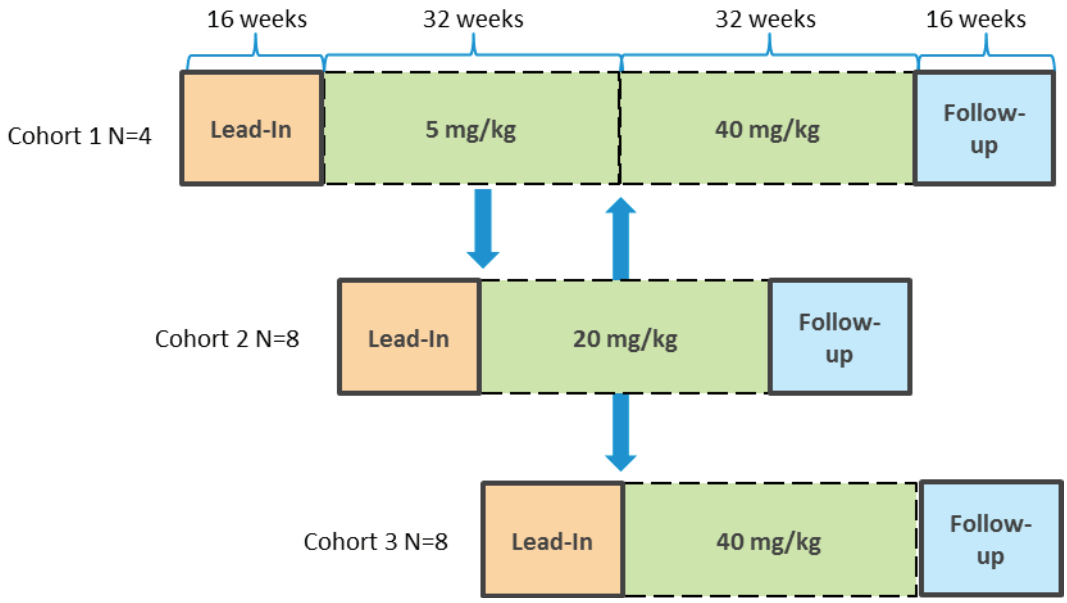
- *Treatment: PF-06252616 40 mg/kg (32 weeks)*
- *Follow-up period (16 weeks)*

At each dose level, subjects will be followed for an initial 16-week lead-in period to establish individual change in disease progression.

The study will begin with 4 subjects being enrolled into Cohort 1. Following the lead-in period, subjects in Cohort 1 will be dosed with 5 mg/kg for a total of 32 weeks (8 doses). Cohort 2 will begin dosing at the mid dose level (20 mg/kg) once safety has been confirmed with subjects in Cohort 1 who have been treated for 16 weeks. Cohort 1 and 3 will begin dosing at the highest dose level (40 mg/kg) once safety has been confirmed with subjects in Cohort 2 who have been treated for 16 weeks.

Each dose level will be evaluated for 32 weeks (8 doses each). Cohort 1 is the only cohort who will receive 2 dose levels (5 mg/kg and 40 mg/kg) and their total treatment time will be 64 weeks.

At the conclusion of the treatment period, subjects will be followed for an additional 16 weeks to monitor for safety, PK and duration of response.



2.2. Safety Monitoring and Dose Escalation

Safety monitoring will be conducted by the Investigator, Pfizer Medical Monitor and an External Medical Monitor. This group will be refered to as the Safety Monitoring Committee (SMC). Safety monitoring by these individuals will include the following reviews:

- *Dose escalation*

- *Quarterly safety and*
- *Ad hoc safety*

At each review, a consideration will be made of the number of subjects who have severe AEs or serious AEs in the same organ system which are determined to be related to investigational product. The first dose escalation decision, whether or not to increase from 5 mg/kg in Cohort 1 to 20 mg/kg in Cohort 2 will occur after review of all safety data after the 4th subject of Cohort 1has completed the planned 16 weeks (day 85) or 4 doses. The second dose escalation decision, whether or not to increase from 20 mg/kg in Cohort 2 to 40 mg/kg in Cohorts 1 and 3 will occur after the 4th subject in Cohort 2 had completed the planned 16 weeks (day 85) or 4 doses. The SMC may determine it is necessary to close or adjust a dose level within the study.

2.2.1. Dose Escalation and Stopping Rules

Table 1. Criteria to Determine Dose Escalation or Stopping

DECISION	***CRITERIA***
Dose Escalation	*SMC review of aggregate safety data from either:* • *Cohort 1 (n=4) 16 weeks (day 85) or* • *Cohort 2 (n=4) 16 weeks (day 85)* *and agree that safety is met and* *The estimate as determined by R2* value is within the normal range (R2*≤139 Hz at 3.0 T) [1,2,,3]*
No Escalation, Stop Dosing	*SMC review of aggregate safety data from either:* • *Cohort 1 (n=4) 16 weeks (day 85) or* • *Cohort 2 (n=4) 16 weeks (day 85)* *And agree that the current dose is* not safe *or* *The liver iron content estimate as determined by R2* value is above the "mild overload" range for any subject within the cohort (R2* >369 Hz at 3.0 T) [1,2,3]*

If dosing is terminated at any dose level, subjects will continue to be followed for resolution of the safety finding or until a new baseline is established. Depending on the nature of the reason for stopping dosing, the SMC will consider if the enrolled subjects can be continued at a lower dose level.

2.2.2. Safety Monitoring Committee (SMC)

The SMC will be composed of three members: The Investigator, Pfizer Medical Monitor and an External Medical Monitor. The External Medical Monitor will be a clinical trialist and an expert in the neuromuscular field. The External Medical Monitor will not be a member of the Investigator's institutions (Johns Hopkins School of Medicine [JHSOM] and Kennedy Krieger Institute [KKI]) nor an employee of Pfizer. The SMC will be responsible for ongoing safety monitoring from the initiation of the study through the final study visit. Reviews will

include aggregate safety, targeted medical events of special interest including liver toxicity, and serious AE data. The SMC may also complete ad hoc safety reviews. Ad hoc PK data may be provided to the SMC as requested.

Following the data review, the SMC will determine if the study should be continued with no changes, modified, or stopped (eg, due to safety). Decision to continue the study must be unanimous. Decision to stop the study can be made by any of the three memebers. In all other decisions, the External Medical Monitor will cast the deciding vote. The recommendations made by the SMC to modify the study will be forwarded to JHSOM IRB for final decision. At any time the SMC may indicate that the limit of safety and/or tolerability has been reached and that any of the dose levels will be removed from the study.

The SMC will consider the following safety criteria during their safety review:

- *The number of subjects who have severe AEs or serious AEs in the same organ system which are determined to be related to study medication.*
- *Other findings that indicate that dose escalation should be halted.*

3. BLINDING

This study is open label. Subjects, investigators and pharmacists will be aware of the active treatment and dose level.

4. STUDY OBJECTIVES

4.1. Objectives

4.1.1. Primary

- *To determine the safety and tolerability of multiple ascending repeat IV doses of PF-06252616 in ambulatory participants with LGMD2I.*

4.1.2. Secondary

- *To assess the PK exposures of PF-06252616 in LGMD2I.*
- *To evaluate the PD activity of PF-06252616 based on the percent change of muscle volume as measured on MRI compared to baseline.*
- *To evaluate the PD activity of PF-06252616 based on GDF-8 (myostatin) modulation in blood and in tibialis muscle.*
- *To characterize the functional effects of PF-06252616 on muscle strength and functional assessments compared to baseline.*
- *To characterize the effects of PF-06252616 on respiratory function compared to baseline.*

- *To characterize the effects of PF-06252616 on Patient reported outcome measures.*
- *To evaluate the immunogenicity of PF-06252616.*

4.1.3. Exploratory

- *To evaluate functional outcome measures in LGMD2I.*

4.2. Endpoints

4.2.1. Primary Safety

- *Incidence of dose limiting or intolerability treatment related AEs by day 337 or 561.*
- *Incidence, severity and causal relationship of treatment emergent AEs (TEAEs) and withdrawals due to TEAEs by day 337 or 561.*
- *Incidence and magnitude of abnormal laboratory findings (clinical laboratory tests [hematology, chemistry], GGT, GLDH, PT, aPTT, creatine kinase, amylase, serum ferritin, serum iron, % transferrin saturation, Total Iron Binding Capacity (TIBC), LH, FSH, estrogen, cardiac troponin I, fecal occult blood and urinalysis) by day 337 or 561.*
- *Abnormal and clinically relevant changes in liver MRI and physical examinations, weight, vital signs, ECG, echocardiogram measured LVEF, DXA (bone mineral density), menstruation cycle as monitored by diary and C-SSRS (See Appendix 1 And Appendix 2* of the protocol*) parameters by day 337 or 561.*

4.2.2. Secondary Endpoints

4.2.2.1. Pharmacokinetic

- *All subjects receiving active drug: serum PF-06252616 C_{max} and C_{trough} for all visits with PK collections and at steady-state.*

4.2.2.2. Pharmacodynamic

- *Mean percent change from baseline in muscle volume as measured on MRI.*
- *Total serum GDF-8 concentrations for all visits with GDF-8 collections*

4.2.2.3. Strength and Function

- *Mean change from baseline on function tests including PUL, Timed up-and-go (TUG), 10-meter walk/run (10MR), 2-meter walk test (2MWT), and 4 stair climb (4SC).*
- *Mean change from baseline on pulmonary function tests including forced vital capacity (FVC), FEV1(forced expiratory volume in 1 second), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).*

- *Mean change from baseline on muscle strength by manual muscle test (MMT) and Hand-Held dynamometry.*

4.2.2.4. Patient Reported Outcomes

- *Mean change from baseline on Patient reported outcomes (InQoL, SF-36)(See Appendix 3 and Appendix 4* of the protocol*).*

4.2.2.5. Immunogenicity

- *Incidence of ADA and NAb development.*

4.2.3. Exploratory Endpoint

4.2.3.1. Pharmacologic

- *Mean percent change from baseline in lean body mass by DXA.*
- *Mean percent change from baseline in muscle quality (fat infiltration) as measured by quantitative Dixon.*
- *Mean change from baseline in muscle quality as measured by T1/STIR.*

4.2.3.2. Function

- *Evaluate the utility and changes from baseline of Functional Workspace as an outcome measure for LGMD2I.*

5. ANALYSIS SETS

5.1. Full Analysis Set

All analyses will be based on the full analysis set (FAS) which includes all enrolled *subjects who have received at least one dose of study drug.*

5.2. Safety Analysis Set

Safety analyses will be based on the full analysis set.

5.3. Other Analysis Sets

5.3.1. PK Concentration Analysis Set

The PK concentration population is defined as all enrolled subjects who received at least 1 dose of PF-06252616 and in whom at least 1 concentration value is reported.

5.3.2. GDF-8 Concentration Analysis Set

The GDF-8 concentration population is defined as all enrolled subjects in whom at least 1 concentration value is reported.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

Safety data will be summarized according to current Pfizer data standards including incidence of anti-drug antibodies and neutralizing antibodies by days 1 (to capture low dose safety) and 561 (last visit) for cohort 1 and day 337 (last visit) for cohorts 2 and 3.

At the screening visit, the " Baseline/Screening" assessment from the Columbia Suicide Severity Rating Scale will be performed. At all other visits the " Since Last Visit" assessment will be performed. The score at the screening visit will be the baseline. All adverse events will be reported under the treatment last received prior to the onset of the adverse event.

6.1.1. Vitals,ECGs and Cardiac Echocardiogram

Baseline values for vital signs , ECG and Cardiac Echocardiogram will be the last acceptable pre-dose measurement taken either on the day of dosing or at the baseline or screening visit.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula: QTcF = QT / (RR)^(1/3), where RR = 60/HR (if RR is not provided).

Echocardiograms should be collected at times specified in the Schedule of Activities (please see protocol). *To ensure safety of the subjects, a qualified individual at the investigator site will evaluate the echocardiogram for ejection fraction (EF) and left ventricular end systolic volume (LVESV).*

6.1.2. Laboratory Data

Using the current Pfizer data standards, the last pre-dose value before the first day of dosing is used as the baseline for all laboratory parameters.

Clinical laboratory tests include hematology with complete blood count and differential, comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, glucose, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase), cardiac troponin I, gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase and urinalysis. If total bilirubin is abnormal, direct bilirubin will be tested reflexively. The samples for serum ferritin, serum iron, transferrin saturation and TIBC should be collected in the morning following an 8 hour fast. Hormone testing will include LH,FSH and estrogen in female subjects only. Laboratory monitoring will also be performed to detect ADA and NAb.

6.1.3. Adverse Events

Severity is the key baseline information for adverse events. To judge an increase in adverse event severity after dosing, the post-dosing adverse event severity will be compared to the adverse event severity reported prior to the first day of study drug administration will be used.

6.1.4. Physical Examination/Nose and Throat Exam

The physical examination will include head,ears,eyes,nose,mouth,skin,heart and lung examinations, lymph nodes, gastrointestinal musculoskeletal, and neurological systems. A targeted and throat muscosal exam will be performed according to the Protocol's *Schedule of Activities to monitor for any signs of mucosal telangiectasias.*

6.2. Secondary Endpoints

- *Mean change from baseline on function tests including PUL, Timed up-and-go (TUG), 10-meter walk/run (10MR), 2-meter walk test (2MWT), and 4 stair climb (4SC).*
- *Mean change from baseline on pulmonary function tests including forced vital capacity (FVC), FEV1(forced expiratory volume in 1 second), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP).*
- *Mean change from baseline on muscle strength by manual muscle test (MMT) and Hand-Held dynamometry.*

Functional Assessment :

Functional assessments will be obtained according to the Protocol *Schedule of Activities. In order to provide optimal testing conditions and consistency in endpoint measurements, the functional assessments will be performed after the MRI and before needle muscle biopsy whenever possible. All functional assessments will be conducted by a trained physiotherapist.*

Pulmonary Function

Pulmonary function testing will be completed to evaluate the maximal lung function recording FVC, FEV1, MIP and MEP.

4 Stair Climb (4 SC)

The 4 SC quantifies in seconds the time required for a subject to ascend 4 standard steps. The method the subject uses (eg, using the hand rails) to climb the stairs is recorded to understand any change in technique that occurs over time.

Two Minute Walk Test (2MWT)

The 2-minute walk test (2MWT) is a shorter measure of walking performance than the 6-minute walk test (6MWT). In this test, subjects start from a clearly marked line of tape on the

floor and walk up and down a 21 meter hallway for 2 minutes at a fast but comfortable speed wearing their regular footwear.

10-meter walk/run

The 10-meter walk/run is a frequently used timed function test in muscular dystrophy trials demonstrating good test-retest reliability in several different populations and has been used in studies of LGMD2I [19,27]. Individuals are instructed to walk at a fast but comfortable speed in a long cooridor with an even surface. Measurement of time begins at a still-standing start and stops when the individual passes the 10-meter mark while continuing to walk 2.5 meters beyond the mark.

Timed Up & Go (TUG)

The Timed Up & Go is a measure of hip strength as well as dynamic balance. This timed function test has good test-retest reliability and has been used in studies of LGMD2I [19,27]. The individual is asked to rise from a seated position in a standardized armchair (44-45 cm), walk at a comfortable and safe pace to a tape mark on the floor 3 meters away, turn around the mark, go back to the chair, turn and sit down.

Strength Assessment

Muscle strength will be quantified by means of manual muscle testing (MMT) quantified by the modified Medical Research Council (MRC) scale and by handheld dynamometer quantified in pounds (lbs). The following muscle groups will be evaluated: shoulder abduction, elbow flexion, elbow extension, hip extension, hip flexion, knee extension, knee flexion.

Performance of Upper Limb (PUL)

The PUL scale has been devised to assess motor performance of the upper limb. Motor performance will be impacted by muscle strength and contractures and the scale aims to incorporate performance of shoulder, elbow, wrist and hand function.

For all the above endpoints except forced vital capacity, more than one assessment may be performed at the site. If more than one assessment is performed, the site is to record the best (maximum) score in the case report forms. For the forced vital capacity, 3 attempts will be made and the percent predicted will be calculated based on the maximum forced vital capacity.

6.2.1. Patient Reported Outcomes

- *Mean change from baseline on Patient reported outcomes (InQoL, SF-36)(See* Protocol *Appendix 3 and Appendix 4).*

InQoL

InQoL survey consists of 45 questions within 10 sections. Four sections focus on the impact of key muscle disease symptoms (weakness, locking, pain, and fatigue), five look at the

impact (degree and importance of impact) muscle disease has on particular areas of life, and one section asks about the positive and negative effects of treatment[4].

SF36

SF-36 questionnaire is a multi-purpose, short form patient-reported health survey with only 36 questions. It is a generic measure, providing an 8-scale profile of functional health as well as measuring physical and mental health. Each scale is transformed into a 0-100 scale, with a score of 0 being equivalent to maximum disability and a score of 100 being indicative of no disability[5]*. It provides a measure of relative disease burden and allows differentiating the health benefits produced by various different treatments.*

6.2.2. PK Endpoints

Blood samples for PK analysis of PF-0625616 will be taken according to the Schedule of Activities in the protocol. Serum PF-06252616 concentration data for the following subjects and visits will be derived.

- *All subjects receiving active drug: C_{max}, and C_{trough} for all visits with PF-06252616 dosing.*

6.2.3. PD Endpoints

The baseline for all pharmacodynamics endpoints is the last pre-dose value before the first day of dosing.

Graphical analysis of total GDF-8 levels as absolute and percentage of baseline will be performed. Analyses will be employed to determine the effects of dose and concentration on the GDF-8 levels over time. The GDF-8 concentrations will be summarized descriptively by treatment and time points.

6.2.4. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be evaluated at times specified in the Schedule of Activities of the protocol*. The Baseline/Screening (Version 1/14/09) (Appendix 1* of the protocol*) of the C-SSRS should be completed at the Screening Visit (Visit 1). At all study visits following the Screening Visit, the Since Last Visit (Version 1/14/09) (Appendix 2* of the protocol*) of the C-SSRS should be utilized. The Since Last Visit version refers to the subject's experience since their last visit.*

At Screening or Baseline, if the subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidality behavior, then the subject is not eligible for study participation and an evaluation of suicide risk (risk assessment) must be completed.

At every visit after Screening, if the subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidality behavior, then the subject must be discontinued as outlined in Section 6 of the protocol*, Subject Withdrawal and evaluation of suicide risk (risk assessment) must be completed.*

6.3. Covariates

Covariates will be summarized for the FAS and by treatment. Continuous baseline covariates will be summarized by: n, mean, median, standard deviation, min and max. Binary and factor covariates will be summarized by percent and counts.

Additional covariates including the qualitative assessment for the 4SC will be summarized over time and may be explored in the modeling of the 4SC statistical analysis.

7. HANDLING OF MISSING VALUES

Missing data for the secondary endpoints *will be imputed using maximum likelihood techniques for a mixed effects model. This analysis is unbiased under the assumption of missing at random when the model assumptions hold. Subjects who lose motor functions (e.g. TUG, 2MWT) will be regarded as missing not at random. Additional imputation methods to assess the sensitivity of the analysis to missing not at random data may also be performed. A completer analysis will also be conducted as a sensitivity analysis.*

Missing data for the patient reported outcome will be handled according to the guidance of the developers.

Laboratory values below the limit of quantification will be analyzed at the limit of quantification for that parameter except for PK data. For laboratory listings, the <BLQ will be used with the actual limit of quantification used in place of BLQ.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

Continuous variables will be summarized by the number (N), mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by percent and counts. All summaries will be displayed by treatment. Efficacy data will be listed, tabulated and graphically represented, as appropriate.

All analyses will be based on the full analysis set (FAS) which includes all enrolled *subjects who have received at least one dose of study drug.*

Below is outlining the definition of baseline for secondary endpoints :

As per Figure 1 below shows each treatment period has been divided into 16 week intervals. Endpoint is the change from the baseline to the subsequent 16^{th} week.

A placebo group is constructed by combining the 3 cohort's running periods. Each cohort has an initial 16 week running period , they are combined together to form a placebo group which will be used as a comparison group, testing against active treatments. There will be a total of 20 subjects in the placebo group.

For cohort 1 the first comparison would be : placebo (3 cohort's running periods) vs. active treatment (1^{st} interval) which starts from the end of the running period to the end of the first 16 weeks of active treatment i.e. week 17 to week 32. The next comparison would be placebo

vs. active treatment (second interval) which starts from the end of the second 16 week active treatment i.e. week 33 to week 48. Then the next comparison would be placebo vs. active treatment (third interval) i.e. week 49 to week 64. Finally comparing placebo vs. active treatment (fourth interval) i.e. week 65 to week 80, as shown in the table 1 below.

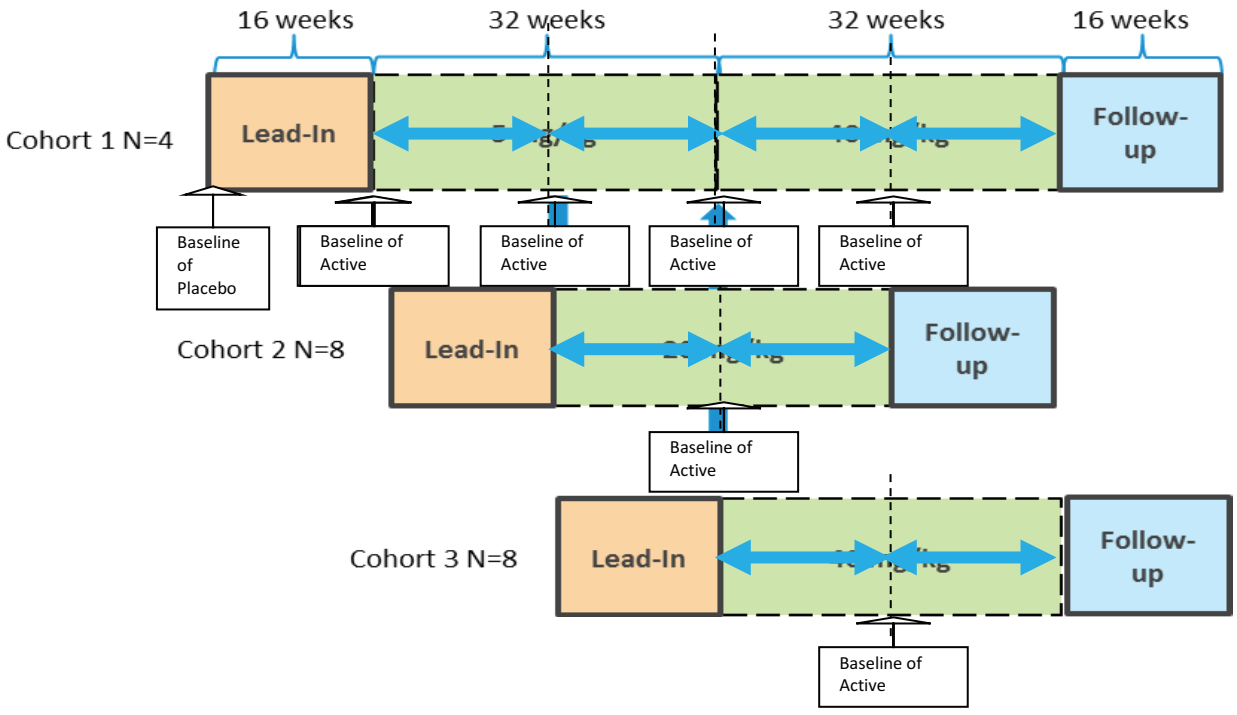
The above rational is to be used for cohorts 2 and 3.

To conclude there will be 8 statistical tests.

Table 1. Active Treatment Intervals

Active treatment Intervals		
Cohort 1	Cohort 2	Cohort 3
17-32	17-32	17-32
33-48	33-48	33-48
49-64		
65-80		

Figure 1. LGMD2i Active vs. "Placebo"



8.1. Statistical Methods

The planned statistical methods and analyses for the primary and all secondary endpoints are described in detail in Section 8.2.1and Section 8.2.2 below.

To explore the data further and to assess the goodness-of-fit of all statistical models, separate SAS datasets will be provided by the clinical programmer to the statistician. Covariates for data exploration may include baseline and/or demographic covariates such as gender, age, weight (continuous and/or Pfizer standard categorical cut-offs), site, country, etc.

8.2. Statistical Analyses

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for safety (adverse events and laboratory data), pharmacokinetics (PK) and all secondary efficacy measures (FAS). Frequency counts will be supplied for subject discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by treatment cohort in accordance with the sponsor reporting standards.

The following data will also be summarized by treatment and in accordance with the current sponsor reporting standards:

Discontinuations, adverse events, laboratory data, vital signs, ECG and concomitant medication data will be summarized by treatment and in accordance with current Pfizer data standards.

8.2.1. Safety Analysis

For all safety variables and vital signs, the baseline will be predose measurement taken either on the day of dosing or at the baseline or screening visit.

8.2.1.1. Adverse Events

All adverse event summaries will be presented for the complete study. Additionally, summary tables of the most frequent adverse events will be presented by cohorts. Based on the review of the frequency and timing of adverse events, additional summaries may be requested.

8.2.1.2. Vital Signs

Systolic blood pressure, diastolic blood pressure and pulse rate will be listed and tabulated by dose group and week with descriptive statistics. Change from baseline will also be summarized using the same descriptive statistics by dose group and visit.

8.2.1.3. Electrocardiogram

The following ECG data will be listed: QT, QTc (Fridericia's), heart rate, QRS duration, PR and RR interval.

Baseline and change from baseline for QT, QTcF, heart rate, QRS, PR and RR will be summarized using descriptive statistics by treatment and study week. Any triplicate measurements will be averaged prior to the calculation of summary statistics. For QTcF a classification of absolute values and increase from baseline will be used.

The number of subjects with average of the triplicate QTcF <450 ms, 450 ms ≤QTcF <480 ms, 480 ms ≤ QTcF <500 ms and QTcF values ≥500 ms will be tabulated by treatment and visit. The number of subjects with maximum increase from baseline QTcF <30 ms, 30 ms ≤ QTcF <60 ms and QTcF ≥60 ms will be tabulated by treatment and study week. In addition, the number of subjects with uncorrected QT values ≥500 ms will be summarized.

Triplicate measures will be averaged prior to categorizing subjects. However, the number of subjects with any single uncorrected QT value ≥500 ms (not the average) will be summarized.

8.2.1.4. Cardiac MRI/Echocardiogram

The mean absolute and percent change from baseline in LVEF and LVESV will be evaluated. LVEF shift tables will be prepared for cohorts and the total.

8.2.1.5. Liver MRI

The mean absolute and percent change from baseline in the R2 value will be tabulated for each subject.* Summaries of the categorical assessment of iron overload (normal, above normal, etc.) will be presented.

8.2.1.6. Other Safety Data

C-SSRs, DXA (spine and hip), prior medication(s), medical history and physical examination will be listed in accordance with the sponsor reporting standards but not subjected to formal statistical analysis.

Any other screening data that is captured on the study database will be listed.

8.2.1.7. Immunogenicity

Immunogenicity analysis will be based on the immunogenicity analysis population which will be the same as the safety analysis population. This will include anti-drug antibody and neutralizing antibody development by all visits with ADA samples until the end of follow-up. Both continuous endpoints (titer) and categorical endpoints (i.e. positive, negative and inconclusive) will be reported for the anti-drug antibody and neutralizing antibody assays by dose and sampling time points. Data permitting, the incidence of anti-drug antibody and neutralizing antibody will be summarized by time points within each dose cohort and may be

also summarized by dose. The impact of anti-drug antibody and neutralizing antibody on PK and PD parameters and profiles, efficacy and safety may be also evaluated but no formal statistical inference will be drawn.

8.2.2. Secondary Analyses

The secondary endpoints, change from baseline in FVC, muscle strength, timed function tests and patient reported outcome measures, will be analyzed based on the FAS using a mixed effects model with REML estimation. The change over the lead-in period, treatment, time and treatment by time interaction and will be included as fixed effects in the model. The following covariance structures and random effects will be considered: Marginal Unstructured, Marginal Variance Components, Marginal Compound Symmetry, Variance Components with Random Intercept, Unstructured with Random Intercept and Slope, Compound Symmetry with Random Intercept and Slope, Spatial Linear with Random Intercept and Slope. Choice of final model will be based on minimum AIC.
.

The dependent variable: change from Visit 3 at each ***post-baseline interval***, i.e.:

Change over post-baseline interval 1: (visit 7 –visit 3)
Change over post-baseline interval 2: (visit 11-visit 3)
Change over post-baseline interval 3: (Visit 15-Visit 3), for Cohort 1 only
Change post-baseline interval 4: (Visit 19-Visit 3), for Cohort 1 only

Covariates are :

- Fixed effects:
  - Baseline interval change (Visit 3 – Visit 2)
  - Treatment category (Dose= “5mg/kg”, “5 + 40 mg/kg”, “20mg/kg” or “40mg/kg”)
  - Time coded as Interval Indicator
  - Treatment category by time interaction
- Random effects:
  - Choice among Marginal Model, Random Intercept Model, and Random Intercept and Slope are selected based on the minimum AIC

Model-estimated change over each post-baseline interval with, 95% two-sided confidence intervals, will be displayed in tabular format.

For each dose level graphical displays will show model-based estimates of change in the mean functional measure from visit 3 at each visit and corresponding confidence intervals derived from the model.

Additionally a completer analysis will also be conducted as a sensitivity analysis for the missing data handling under the mixed effects modeling. The completer analysis will only

include subjects that completed all assessments at the last scheduled visit using the same longitudinal mixed effects model as the primary analysis.

Transformation of the data will be considered if model assumptions are not met.

8.2.3. PK Analyses

8.2.3.1. Concentrations below the limit of quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

8.2.3.2. Deviations, missing concentrations and anomalous values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

8.2.3.3. Pharmacokinetic parameters

Nominal PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (i.e. not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (i.e. analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as incomplete administration of the IV infusion dose), this will be footnoted in summary tables and will not be included in the calculation of summary statistics.

The PK parameters will be listed and summarized for subjects in the PK parameter analysis set. Parameters will be summarized by cohort and dose. Each PK parameter will include the set of summary statistics as specified in the table below:

Table 3. PK Parameters

Parameter	*Summary Statistics*
Cmax, Ctrough,	*N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric CV%*

8.2.3.4. PK Concentrations

To assess the PK profile of PF-06252616, PK concentrations will be listed, summarized and plotted for subjects in the PK analysis set, where missing and BLQ values will be handled as detailed in Section 8.2.4.2.

Presentations for PF-06252616 will include:

- A listing of all concentrations sorted by dose, subject ID, cohort and nominal time postdose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by cohort, dose and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median trough (predose) concentrations against nominal dosing week by cohort and dose. Individual subject trough concentrations will also be plotted. Linear scale.

- Median concentrations at the end of infusion (nominally at 2 hour post start of infusion) against nominal dosing week by cohort and dose, as described above for trough concentrations. Individual subject end of infusion concentrations will also be plotted. Linear scale.

The range for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06252616 concentration is quantifiable in the matrix.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

8.2.4. GDF-8 Analysis

8.2.4.1. Deviations, missing concentrations and anomalous values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

8.2.4.2. GDF-8 Concentration

To assess the PD profile of PF-06252616, GDF-8 concentrations will be listed, summarized and plotted for subjects in the PD analysis set, where missing the data will be handles as outlined in Section 8.2.5.1.

- A listing of all concentrations sorted by dose, subject ID, cohort and nominal time postdose. The listing of concentrations will include the actual sample collection times, and the time of dosing. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by dose, cohort and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median total GDF-8 concentrations and Change from Baseline against nominal time postdose by cohort and Dose. Linear scale.

- Mean total GDF-8 concentrations and Change from Baseline against nominal time postdose by cohort and Dose. Linear scale.

- Individual total GDF-8 concentrations and Change from Baseline against actual time postdose by cohort and Dose (including all subjects). Linear scale.

The range for the x-axes of these plots will be decided on review of the data, and will depend on how long GDF-8 concentration is quantifiable in the matrix.

For summary statistics and median plots by sampling time, the nominal GDF-8 sampling time will be used. For individual subject plots by time, the actual GDF-8 sampling time will be used.

8.2.5. Other Analyses

8.2.5.1. Exploratory Analyses

All exploratory endpoints, including the pharmacologic and health outcome endpoints will be summarized by treatment group. Additional analyses may be performed to understand the relationship between these endpoints and treatment.

Any population PK/PD analysis conducted will be reported separately.

Additionally, data permitting, relationships between PF-06252616 PK, GDF-8, imaging data (DXA, MRI), functional assessment, immunogenicity and any safety signals may be explored.

9. REFERENCES

1 Hankins, J. S. *et al. R2* magnetic resonance imaging of the liver in patients with iron overload*. Vol. 113 (2009).

2 Wood, J. C. *et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients*. Vol. 106 (2005).

3 Storey, P. *et al.* R2* imaging of transfusional iron burden at 3T and comparison with 1.5T. *Journal of Magnetic Resonance Imaging* **25**, 540-547, doi:10.1002/jmri.20816 (2007).

4 Marshall, W. A. & Tanner, J. M. Variations in the Pattern of Pubertal Changes in Boys. *Arch Dis Child* **45**, 13-23 (1970).

5 Ware, J. E. SF-36 Health Survey Update. *Spine* **25**, 3130-3139 (2000).

APPENDIX 1.

Planned Data Display

Item	Number	Title	Population
		ENROLLMENT AND DISPOSITION	
Table	Table 14.1.1.1	Subject Evaluation Groups by Cohort	All Enrolled Subjects
Listing	Table 14.1.1.2	Subject Evaluation Groups	All Enrolled Subjects
Listing	Table 14.1.1.3	Subject Discontinuation	All Enrolled Subjects
		DEMOGRAPHICS	
Table	Table 14.1.1.4	Subject Demographics and Baseline Characteristics	FAS
Listing	Table 14.1.1.5	Subject Demographics and Baseline Characteristics	FAS
Listing	Table 14.1.1.6	Clinical Significance of Physical Examination	FAS
		Study Drug	
Table	Table 14.1.1.7	Summary of Number of Subjects by Cohort and Dose Level	FAS
Listing	Table 14.1.1.8	Administration Schedule	FAS
Listing	Table 14.1.1.9	Infusion Site Assessment	FAS
Listing	Table 14.1.1.10	Dose Administration by Dose Level and Visit	FAS
Listing	Table 14.1.1.11	Dose Administration by Dose Level, Cohort and Visit	FAS
Listing	Table 14.1.1.12	Dose Administration by Cohort, Total and Visit	FAS
		Safety	
Table	Table 14.1.1.13	Treatment-Emergent Adverse Events (All Causalities) by Dose Level and Cohort	FAS
Table	Table 14.1.1.14	Treatment-Emergent Adverse Events (All Causalities) by Cohort and Total	FAS
Table	Table 14.1.1.15	Incidence and Severity of Treatment-Emergent Adverse Events by Dose Level and Cohort (All Causalities)	FAS
Table	Table 14.1.1.16	Incidence and Severity of Treatment-Emergent Adverse Events by Cohort and Total (All Causalities)	FAS
Table	Table 14.1.1.17	Treatment-Emergent Adverse Events (Treatment Related) by Dose Level and Cohort	FAS
Table	Table 14.1.1.18	Treatment-Emergent Adverse Events (Treatment Related) by Cohort and Total	FAS
Table	Table 14.1.1.19	Incidence and Severity of Treatment-Emergent Adverse Events by Dose Level and Cohort (Treatment Related)	FAS
Table	Table 14.1.1.20	Incidence and Severity of Treatment-Emergent Adverse Events by Cohort and Total (Treatment Related)	FAS
Table	Table 14.1.1.21	Serious Adverse Events by System Organ Class by Dose Level and Cohort (All Causalities)	FAS
Table	Table 14.1.1.22	Serious Adverse Events by System Organ Class by Cohort and Total (All Causalities)	FAS
Table	Table 14.1.1.23	Serious Adverse Events by System Organ Class by Dose Level and Cohort (Treatment Related)	FAS
Listing	Table 14.1.1.24	Discontinuations Due to Adverse Events	FAS
Listing	Table 14.1.1.25	Adverse Events	FAS
Listing	Table 14.1.1.26	Individual Listing of Deaths	FAS
Listing	Table 14.1.1.27	Serious Adverse Events	FAS
Listing	Table 14.1.1.28	Treatment Related Serious Adverse Events	FAS
		Clinical Laboratory	
Table	Table 14.1.1.29	Incidence of Laboratory Test Abnormalities (without Regard to Baseline Abnormality) by Dose Level and Cohort	FAS
Table	Table 14.1.1.30	Serum Iron Indices (Total Iron Binding Capacity, Serum Iron,	FAS

		Serum Ferritin, % Transferrin Saturation) - Observed values, Change and Percent Change from Baseline	
Table	Table 14.1.1.31	Categorical Summary of Serum Ferritin, Serum Iron and % Transferrin Saturation	FAS
Table	Table 14.1.1.32	Serum Iron Indices (Total Iron Binding Capacity, Serum Iron, Serum Ferritin, % Transferrin Saturation)	FAS
Table	Table 14.1.1.33	Serum Ferritin, Serum Total Iron, and % Transferrin Saturation Values Meeting Categorical Summarization Criteria	FAS
Table	Table 14.1.1.34	Serum PF-06252616 Concentration (ng/mL) versus Time Summary	FAS
Listing	Table 14.1.1.35	Laboratory Abnormalities, by Cohort and Subject	FAS
Listing	Table 14.1.1.36	Laboratory Abnormalities, by Dose Level and Subject	FAS
Listing	Table 14.1.1.37	Laboratory Abnormalities, by Cohort, Dose Level and Test	FAS
		Vital Signs	
Figure	Figure 14.1.1.1	Vital Signs Absolute Values by Dose level	FAS
Figure	Figure 14.1.1.2	Vital Signs Change from baseline by Dose Level	FAS
		Electrocardiogram	
Table	Table 14.1.1.38	Mean Baseline and Mean Changes from Baseline	FAS
Table	Table 14.1.1.39	Categorical Summary of Post-Baseline ECG Data - Absolute Values	FAS
Table	Table 14.1.1.40	Categorical Summary of Post-Baseline ECG Data - Increases from Baseline	FAS
Table	Table 14.1.1.41	Number (%) of Subjects with Single Uncorrected QT Values Greater than or Equal to 500 msec	FAS
Table	Table 14.1.1.42	ECG Change from Baseline	FAS
Table	Table 14.1.1.43	ECG Qualitative Results	FAS
Table	Table 14.1.1.44	ECG Post-Baseline Values Meeting Categorical Summarization Criteria	FAS
Figure	Figure 14.1.1.3	QTcF Interval (Fridericia's Correction) values over Time by Dose Level - Box Plots	FAS
Figure	Figure 14.1.1.4	QTcF Interval (Fridericia's Correction) values change from baseline over Time by Dose Level - Box Plots	FAS
Figure	Figure 14.1.1.5	QT versus Heart Rate by Dose Level	FAS
		Cardiac MRI/Echocardiogram	
Table	Table 14.1.1.45	Shift Table of Left Ventricular Ejection Fraction over time by and Echocardiogram	FAS
Table	Table 14.1.1.46	Mean absolute and percent change from baseline in Left Ventricular Ejection Fraction(LVEF)	FAS
Table	Table 14.1.1.47	Mean absolute and percent change from baseline in Left Ventricular End Systolic Volume (LVESV)	FAS
Listing	Table 14.1.1.48	Echoardiagram	FAS
		Liver MRI	
Table	Table 14.1.1.49	Summary of Average R2* Values and Percent Change from Baseline by Visit and Magnet Field Strength	FAS
Table	Table 14.1.1.50	Summary of Iron Accumulation	FAS
Table	Table 14.1.1.51	Number (%) of Liver Enzyme Abnormalities by dose level	FAS
Listing	Table 14.1.1.52	Liver Enzyme Abnormalities	FAS
Listing	Table 14.1.1.53	Liver MRI	FAS
Listing	Table 14.1.1.54	Liver MRI Abnormalities: R2* Elevations	FAS

		DXA	FAS
Table	Table 14.1.1.55	Bone Mineral Density over Time by Treatment (Whole Body)	FAS
Table	Table 14.1.1.56	Bone Mineral Density over Time by Treatment (Hip)	FAS
Table	Table 14.1.1.57	Bone Mineral Density over Time by Treatment (Lumbar Spine)	FAS
Listing	Table 14.1.1.58	DXA	FAS
		Concomitant Medication	
Listing	Table 14.1.1.59	Concomitant Medications	FAS
		CSSR	
Listing	Table 14.1.1.60	C-SSRS by Time (Baseline/screen Version and Since last Visit)	FAS
Listing	Table 14.1.1.61	C-SSRS by Time (Baseline/screen Version and Since last Visit) – Cont.	FAS
		ADA	
Table	Table 14.1.1.62	Anti-drug Antibodies (ADA) Status by Dose Level	FAS
		Secondary Endpoints:	
Table	Table 14.1.1.63	Summary of absolute value for Forced Vital Capcity (FVC)	FAS
Table	Table 14.1.1.64	Mean Change from Baseline for Forced Vital Capcity (FVC)	FAS
Table	Table 14.1.1.65	Mean Forced Vital Capcity (FVC) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.66	Mean Forced Vital Capcity (FVC) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.6	Plot of Mean Absolute Value on Frorced Vital Capcity	FAS
Figure	Figure 14.1.1.7	Plot of Mean Change from Baseline on Frorced Vital Capcity	FAS
Table	Table 14.1.1.67	Summary of absolute value for Performance of Upper Limb(PUL)	FAS
Table	Table 14.1.1.68	Mean Change from Baseline for Performance of Upper Limb(PUL)	FAS
Table	Table 14.1.1.69	Mean Performance of Upper Limb(PUL) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.70	Mean Performance of Upper Limb(PUL) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Table	Table 14.1.1.71	Listing of Performance of Upper Limb	FAS
Listing	Table 14.1.1.72	Listing of items, Description and Scores Performance of Upper Limb	
Figure	Figure 14.1.1.8	Plot of Mean Absolute Value on Performance of Upper Limb(PUL)	FAS
Figure	Figure 14.1.1.9	Plot of Mean Change from Baseline on Performance of Upper Limb(PUL)	FAS
Table	Table 14.1.1.73	Summary of absolute value for Timed Up & Go (TUG)	FAS
Table	Table 14.1.1.74	Mean Change from Baseline for Timed Up & Go (TUG)	FAS
Table	Table 14.1.1.75	Mean Timed Up & Go (TUG) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.76	Mean Timed Up & Go (TUG) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population

Figure	Figure 14.1.1.10	Plot of Mean Absolute Value on Timed Up & Go (TUG)	FAS
Figure	Figure 14.1.1.11	Plot of Mean Change from Baseline on Timed Up & Go (TUG)	FAS
Table	Table 14.1.1.77	Summary of absolute value for for10-meter walk/run (10MR)	FAS
Table	Table 14.1.1.78	Mean Change from Baseline for10-meter walk/run (10MR)	FAS
Table	Table 14.1.1.79	Mean 10-meter walk/run (10MR) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.80	Mean 10-meter walk/run (10MR) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.12	Plot of Mean Absolute Value on 10-meter walk/run (10MR)	FAS
Figure	Figure 14.1.1.13	Plot of Mean Change from Baseline on 10-meter walk/run (10MR)	FAS
Table	Table 14.1.1.81	Summary of absolute value for Two Minute Walk Test (2MWT)	FAS
Table	Table 14.1.1.82	Mean Change from Baseline for Two Minute Walk Test (2MWT)	FAS
Table	Table 14.1.1.83	Mean Two Minute Walk Test (2MWT) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.84	Mean Two Minute Walk Test (2MWT) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.14	Plot of Mean Absolute Value on Two Minute Walk Test (2MWT))	FAS
Figure	Figure 14.1.1.15	Plot of Mean Change from Baseline on Two Minute Walk Test (2MWT)	FAS
Table	Table 14.1.1.85	Summary of absolute value for 4 Stair Climb (4SC)	FAS
Table	Table 14.1.1.86	Mean Change from Baseline for 4 Stair Climb (4SC)	FAS
Table	Table 14.1.1.87	Mean 4 Stair Climb (4SC) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.88	Mean 4 Stair Climb (4SC) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.16	Plot of Mean Absolute Value on 4 Stair Climb (4SC)	FAS
Figure	Figure 14.1.1.17	Plot of Mean Change from Baseline on 4 Stair Climb (4SC)	FAS
Table	Table 14.1.1.89	Summary of absolute value for Forced Expiratory Volume in 1 second (FEV1)	FAS
Table	Table 14.1.1.90	Mean Change from Baseline for Forced Expiratory Volume in 1 second (FEV1)	FAS
Table	Table 14.1.1.91	Mean Forced Expiratory Volume in 1 second (FEV1) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.92	Mean Forced Expiratory Volume in 1 second (FEV1) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.18	Plot of Mean Absolute Value on Forced Expiratory Volume in 1 second (FEV1)	FAS
Figure	Figure 14.1.1.19	Plot of Mean Change from Baseline on Forced Expiratory Volume in 1 second (FEV1)	FAS
Table	Table 14.1.1.93	Summary of absolute value for Maximal Inspiratory Pressure (MIP)	FAS
Table	Table 14.1.1.94	Mean Change from Baseline for Maximal Inspiratory	FAS

		Pressure (MIP)	
Table	Table 14.1.1.95	Mean Maximal Inspiratory Pressure (MIP) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.96	Mean Maximal Inspiratory Pressure (MIP) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Figure	Figure 14.1.1.20	Plot of Mean Absolute Value on Maximal Inspiratory Pressure (MIP)	FAS
Figure	Figure 14.1.1.21	Plot of Mean Change from Baseline on Maximal Inspiratory Pressure (MIP)	FAS
Table	Table 14.1.1.97	Summary of absolute value for Maximal Expiratory Pressure (MEP)	FAS
Table	Table 14.1.1.98	Mean Change from Baseline for Maximal Expiratory Pressure (MEP)	FAS
Table	Table 14.1.1.99	Mean Maximal Expiratory Pressure (MEP) Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.100	Mean Maximal Expiratory Pressure (MEP) Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Figure	Figure 14.1.1.22	Plot of Mean Absolute Value on Expiratory Pressure (MEP)	FAS
Figure	Figure 14.1.1.23	Plot of Mean Change from Baseline on Maximal Expiratory Pressure (MEP)	FAS
Table	Table 14.1.1.101	Summary of absolute value for Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry	FAS
Table	Table 14.1.1.102	Mean Change from Baseline for Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry	FAS
Table	Table 14.1.1.103	Mean Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry Mixed Model Repeated Measures (MMRM) of Change from Baseline	FAS
Table	Table 14.1.1.104	Mean Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry Mixed Model Repeated Measures (MMRM) of Change from Baseline	Completer Population
Listing	Table 14.1.1.105	Listing of Manual Muscle Test (MMT) and Hand-Helded dynamometry (Manual Muscle Test)	FAS
Listing	Table 14.1.1.106	Listing of Manual Muscle Test (MMT) and Hand-Helded dynamometry (Hand Held Myometry)	FAS
Figure	Figure 14.1.1.24	Plot of Mean Absolute Value on Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry	FAS
Figure	Figure 14.1.1.25	Plot of Mean Change from Baseline on Muscle Strength BY Manual Muscle Test (MMT) and Hand-Hels dynamometry	FAS
Table	Table 14.1.1.107	Total Score for InQol	FAS
Table	Table 14.1.1.108	InQol: Summary Statistics for Weakness Symptom	FAS
Table	Table 14.1.1.109	InQol: Summary Statistics for Locking Symptom	FAS
Table	Table 14.1.1.110	InQol: Summary Statistics for Pain Symptom	FAS
Table	Table 14.1.1.111	InQol: Summary Statistics for Fatigue Symptom	FAS
Table	Table 14.1.1.112	SF-36 Questionnaire : Listing of Physical and Mental Components	FAS
		GDF-8 Concentration	
Table	Table 14.1.1.113	Serum Total GDF-8 Concentration (NG/ML) versus Time Listing	

Figure	Figure 14.1.1.25	Individual Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.26	Individual Change from Baseline of Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Table	Table 14.1.1.114	Serum Total GDF-8 (NG/ML) versus Time Summary	
Table	Table 14.1.1.115	Changes from Baseline for Serum Total GDF-8 (NG/ML)	
Figure	Figure 14.1.1.27	Median Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.28	Median Change from Baseline of Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.29	Mean Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.30	Mean Change from Baseline of Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.31	Median Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.32	Median Change from Baseline of Serum Total GDF-8 Concentration (NG/ML) - Time Plot by Cohort (Linear Scale)	
Figure	Table 14.1.1.116	Descriptive Summary of Serum Total GDF-8 Parameters	
		PK Summary	
Table	Table 14.1.1.117	Serum PF-06252616 Concentration [NG/MG] versus Time Summary for All Subjects	
Table	Table 14.1.1.118	Serum PF-06252616 Concentration [NG/MG] versus Time Summary for Subjects with Additional Sampling	
Figure	Figure 14.1.1.33	Median Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale) for All Subjects	
Figure	Figure 14.1.1.34	Median Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale) for Subjects with Additional Sampling	
Figure	Figure 14.1.1.35	Mean Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale) for All Subjects	
Figure	Figure 14.1.1.36	Mean Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale) for Subjects with Additional Sampling	
Figure	Figure 14.1.1.37	Median Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale) for All Subjects	
Figure	Figure 14.1.1.38	Median Trough Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale)	
Figure	Figure 14.1.1.39	Median End of Infusion Serum PF-06252616 Concentration - Time Plot by Cohort (Linear Scale)	
Table	Table 14.1.1.119	Descriptive Summary of Serum PF-06252616 PK Parameters for All Subjects	
Table	Table 14.1.1.120	Descriptive Summary of Serum PF-06252616 PK Parameters for Subjects with Additional PK Sampling	
Table	Table 14.1.1.121	Descriptive Summary of Serum PF-06252616 PK Parameters for All Subjects – Process 1 vs Process 2	

CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM			
Identifier	**Version**	**Title**	**Effective Date**
DMB02-GSOP-RF01	6.0	STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE FORM	01-Nov-2018

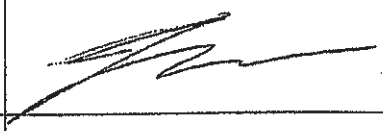
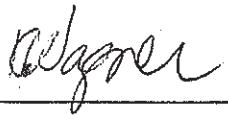
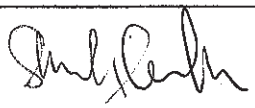
NOTE: This form is used to document the approval of a Statistical Analysis Plan (SAP) and any subsequent amendment of the SAP.

SAP Title: Include protocol number and format per following example: A### Statistical Analysis Plan	AWI203720 Statistical Analysis Plan
☒ **Approval of SAP** ☐ **Approval of Amendment to SAP**	**SAP Version: 1.0**

Name and Title of Person Submitting form: (SAP Author)	Nazila Shahri
Date Submitted: (dd-Mmm-yyyy)	12 Feb 2019

Approval indicates that the SAP provides analysis specifications consistent with the analysis outlined in the protocol and meets the standards and requirements used for programming of tables, listings and figures.

SAP Approver's Name:	Nazila Shahri
SAP Approver's Title:	Statistician
Signature:	N. Shahri
Date: (dd-Mmm-yyyy)	12 Feb 2019
SAP Approver's Name:	Jeffrey Palmer
SAP Approver's Title:	Senior Director, Biostatistics (Pfizer)

Signature:	
Date: (dd-Mmm-yyyy)	12-FEB-2019
SAP Approver's Name:	Kathryn Wagner
SAP Approver's Title:	Principal Investigator
Signature:	
Date: (dd-Mmm-yyyy)	12 FEB 2019
SAP Approver's Name:	Shirley Galbiati
SAP Approver's Title:	Biostatistician (Emmes)
Signature:	
Date: (dd-Mmm-yyyy)	12 Feb 2019