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

Study Sponsor:	Hugo W. Moser Research Institute at Kennedy Krieger, Inc.
Compound:	PF-06252616
Compound Name:	Anti-Myostatin
Protocol Number:	WI203720
Phase:	1b/2

1.1. Document History

Document	Version Date	Summary of Changes and Rationale
Final protocol	7 December, 2015	N/A
Revisions requested by JHSOM IRB II	18 March, 2016	
Version 3	01 Nov 2016	For test-retest reliability of timed function tests in LGMD2l, a second day of testing will be performed on Visit 3 (Day 1) prior to the first dose. Premedication prior to MRI of whole body and thigh for study participants who may be anxious because of the procedure and the length of time in the scanner.
Version 4	20 January 2017	The nontreatment, Lead in period of Cohort 2 may be extended depending on the timing of enrollment and evaluation of safety in the 5 mg/kg dose (Cohort 1), Dose escalation of Cohort 1 from 5 mg/kg to 40mg/kg may be delayed depending on the time of enrollment and evaluation of safety in the Cohort 2 (20 mg/kg). As a clarification in Schedule of Events for Cohort 1, MRI of liver is only obtained on Visit 11 and not Visit 3. As an exploratory endpoint, PD activity of PF-06252616 will be evaluated based on the percent change of muscle volume as measured on MRI compared to baseline as indicated by the whole body MRI evaluation and/or lean body mass DXA results. Uric acid and serum phosphorus are removed from the table of Laboratory Tests, page 67.

Version 5	04 May 2017	Collection of pharmacodynamic (PD) blood samples at the same time point as pharmacokinetic(PK) sampling to provide more information regarding GDF-8 activity . During dosing visits, vital signs will be obtained before the dose and after completion of the infusion. The Table of Contents was organized to move Pharmacodynamics under Exploratory Endpoints (page 35).
Version 6	14 February 2018	Added Extension Period and Telephone Follow-up to the study. Update on ongoing clinical studies (B5161002, B5161004) with PF-06252616 in Section 1.8

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List of Abbreviations

This is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
2MWT	two minute walk test
6MWT	six minute walk test
4SC	four stair climb
4SD	four stair descend
10MR	ten meter run
ACE	angiotensin-converting-enzyme
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
AST	aspartate transaminase
BMD	bone mineral density
BMP/TGFβ	bone morphogenetic protein/ transforming growth factor-β
CDC	Center for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DAI	dosing and administration instructions
DILI	drug-induced liver injury
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DXA	dual energy x-ray absorptiometry
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDTA	ethylene diamine triacetic acid
EF	ejection fraction
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FEV1	Forced expiratory voume in 1 second
FKRP	Fukutin-related protein
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDF-8	growth differentiation factor 8
GDF-11	growth differentiation factor 11
GGT	gamma-glutamyl transferase

GLDH	glutamate dehydrogenase
HPLC-MS/MS	high performance liquid chromatography-mass spectrometry
IB	investigator brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	Identification
IgG1	immunoglobulin G1
IND	investigational new drug application
InQoL	Individualized Neuromuscular Disease Quality of Life
INR	international normalized ratio
IP	intraperitoneal
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
LBM	lean body mass
LFT	liver function test
LH	luteinizing hormone
LGMD2I	limb girdle muscular dystrophy 2I
LLN	lower limit of normal
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
MEP	mean expiratory pressure
MHP	mental health provider
MIP	mean inspiratory pressure
MMT	manual muscle testing
MRC	Medical Research Council
MRI	magnetic resonance imaging
N	number
N/A	not applicable
Nab	neutralizing antibodies
NHP	non-human primate
NOAEL	no observed adverse effect levels
PFT	pulmonary function test
PK/PD	pharmacokinetic/pharmacodynamics
POM	proof of mechanism
PPV-23	pneumococcal polysaccharide vaccine
PT	prothrombin time
PUL	Performance of Upper Limb
PWRD	Pfizer Worldwide Research and Development
QMT	quantitative muscle test
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	Short Form 36 Health Survey
SMC	Safety Monitoring Committee
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject's identification
SWFI	sterile water for injection
TEAEs	treatment emergent AEs
TFT	timed function test
TIBC	total iron binding capacity
TK	toxicokinetic
TMDD	Target mediated drug disposition
TUG	timed up and go
ULN	upper limit of normal
US	United States
ULN	upper limit of normal
V_{ss}	steady state volume distribution
WB-MRI	Whole-Body MRI
WOCBP	women of child bearing potential

SCHEDULE OF ACTIVITIES

Table 1 Cohort 1

	Screen	Lead-In	Treatment								Follow-up		Early With-drawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**A (5 mg/kg)**								**19 (449 ±3)**	**20 (561 ±3)**	
			3 (1)	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**			
			B (40 mg/kg)										
			11 (225 ±3)	**12 (253 ±3)**	**13 (281 ± 3)**	**14 (309 ±3)**	**15 (337 ±3)**	**16 (365 ±3)**	**17 (393 ±3)**	**18 (421 ±3)**			
Entry/Safety Assessments													
Informed Consent	X												
Demography	X												
Medical History[b]	X												
Medication History	X												
Inclusion/Exclusion	X												
Enrollment[c]	X												
Physical Examination	X	X	X			X					X	X	X
Pregnancy Test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary Cards[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X											
Weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Lead-In	Treatment								Follow-up		Early With-drawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**A (5 mg/kg)**								**19 (449 ±3)**	**20 (561 ±3)**	
			3 (1)	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**			
			B (40 mg/kg)										
			11 (225 ±3)	**12 (253 ±3)**	**13 (281 ± 3)**	**14 (309 ±3)**	**15 (337 ±3)**	**16 (365 ±3)**	**17 (393 ±3)**	**18 (421 ±3)**			
12- lead ECG	X		X			X					X	X	X
Echocardiogram	X										X	X	X
Clinical Laboratory Tests[g]	X		X	X	X	X	X	X	X	X	X	X	X
Serum Ferritin, Serum Iron, Transferrin Saturation, TIBC	X		X	X	X	X	X	X	X	X	X	X	X
Hormone Testing (LH, FSH, estrogen)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
GLDH	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal Occult Blood[i]	X		X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments													
MRI-Liver	X		X[o]			X					X	X	X
MRI-Muscle[j]		X	X								X	X	X
DXA Whole Body		X	X								X	X	X
DXA Spine and Hip			X								X	X	X
Functional Assessments													
Muscle Strength		X	X				X				X	X	X

	Screen	Lead-In	Treatment								Follow-up		Early With-drawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**A (5 mg/kg)**								**19 (449 ±3)**	**20 (561 ±3)**	
			3 (1)	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**			
			B (40 mg/kg)										
			11 (225 ±3)	**12 (253 ±3)**	**13 (281 ± 3)**	**14 (309 ±3)**	**15 (337 ±3)**	**16 (365 ±3)**	**17 (393 ±3)**	**18 (421 ±3)**			
(MMT, dynamometry)													
4SC		X	X[n]				X				X	X	X
10-meter walk/run		X	X[n]				X				X	X	X
2MWT		X	X[n]				X				X	X	X
Timed up-and-go		X	X[n]				X				X	X	X
PUL		X	X[n]				X				X	X	X
InQol, SF-36			X								X	X	X
Respiratory Function (FVC, FEV1, MIP/MEP)		X	X				X				X	X	X
Study Treatment Administration													
Study Treatment Administration[k]			X	X	X	X	X	X	X	X			
PK/PD/Immunogenicity													
Needle muscle biopsy		X	X								X	X	X
Immunogenicity			X								X	X	X
PD sample[l]			X		X		X		X		X	X	X
PK samples[l]			X		X		X		X		X	X	X
Biomarkers		X					X			X			

	Screen	Lead-In	Treatment								Follow-up		Early With-drawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**A (5 mg/kg)**								**19 (449 ±3)**	**20 (561 ±3)**	
			3 (1)	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**			
			B (40 mg/kg)										
			11 (225 ±3)	**12 (253 ±3)**	**13 (281 ± 3)**	**14 (309 ±3)**	**15 (337 ±3)**	**16 (365 ±3)**	**17 (393 ±3)**	**18 (421 ±3)**			
collection[m]													
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Infusion site reaction			X	X	X	X	X	X	X	X	X		X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 2MWT=Two minute walk test; 4 SC= Four stair climb, C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; FEV1 = Forced expiratory voume in 1 second; GLDH=glutamate dehydrogenase, LH-Lutenizing hormone, MIP= Mean inspiratory pressure; MEP= Mean expiratory pressure; MMT= manual muscle testing, MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PUL=Performance of Upper Limb, TIBC=Total iron binding capacity, INQoL = Individualized Neuromuscular Disease Quality of Life, SF-36 = Short Form 36 Health Survey

SCHEDULE OF ACTIVITIES

Table 2 Cohort 2 and 3

	Screen	Lead-in	Treatment								Follow-up		Early Withdrawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**3 (1)**	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**	**11 (225 ±3)**	**12 (337 ±3)**	
Entry/Safety Assessments													
Informed Consent	X												
Demography	X												
Medical History[b]	X												
Medication History	X												
Inclusion/Exclusion	X												
Enrollment[c]	X												
Physical Examination	X	X	X			X					X	X	X
Pregnancy Test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary Cards[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X											
Weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
12- lead ECG	X		X			X					X	X	X
Echocardiogram	X										X	X	
Clinical Laboratory Tests[g]	X		X	X	X	X	X	X	X	X	X	X	X
Serum Ferritin, Serum Iron, Transferrin Saturation,TIBC	X		X	X	X	X	X	X	X	X	X	X	X
Hormone Testing (LH, FSH, estrogen)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Lead-in	Treatment								Follow-up		Early Withdrawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**3 (1)**	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**	**11 (225 ±3)**	**12 (337 ±3)**	
GLDH	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal Occult Blood[i]	X		X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments													
MRI-Liver	X					X					X	X	X
MRI-Muscle[j]		X	X								X	X	X
DXA Whole Body		X	X								X	X	X
DXA Spine and Hip			X								X	X	X
Functional Assessments													
Muscle Strength (MMT, dynamometry)		X	X				X				X	X	X
4SC		X	X^n				X				X	X	X
10-meter walk/run		X	X^n				X				X	X	X
2MWT		X	X^n				X				X	X	X
Timed up-and-go		X	X^n				X				X	X	X
PUL		X	X^n				X				X	X	X
InQol, SF-36			X								X	X	X
Respiratory Function (FVC, FEV1, MIP/MEP)		X	X				X				X	X	X
Study Treatment Administration													
Study Treatment Administration[k]			X	X	X	X	X	X	X	X			
PK/PD/Immunogenicity													
Needle muscle biopsy		X	X								X	X	X
Immunogenicity			X								X	X	X
PD sample		X	X		X		X		X		X	X	X
PK samples[l]			X		X		X		X		X	X	X

	Screen	Lead-in	Treatment								Follow-up		Early Withdrawal
Visit Number (Study Day Visit Window)[a]	**1 (-125 to -112)**	**2 (-111 to -110)**	**3 (1)**	**4 (29 ± 3)**	**5 (57 ±3)**	**6 (85 ±3)**	**7 (113 ±3)**	**8 (141 ±3)**	**9 (169 ±3)**	**10 (197 ±3)**	**11 (225 ±3)**	**12 (337 ±3)**	
Biomarkers collection[m]		X					X			X			
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X
Infusion site reaction			X	X	X	X	X	X	X	X	X		X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 2MWT=Two minute walk test; 4 SC= Four stair climb, C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; FEV1 = Forced expiratory voume in 1 second; GLDH=glutamate dehydrogenase, LH-Lutenizing hormone, MIP= Mean inspiratory pressure; MEP= Mean expiratory pressure; MMT= manual muscle testing, MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PUL=Performance of Upper Limb, TIBC=Total iron binding capacity, INQoL = Individualized Neuromuscular Disease Quality of Life, SF-36 = Short Form 36 Health Survey

a. Assessments should be conducted on the Study Day within the visit window. Visits with MRI, DXA and functional assessments may be conducted over 2 days. The following order of testing is preferred. On the first day of assessments: an am fasting blood collection followed by fasting DXA and MRI. On the second day of assessments: the functional assessments and muscle biopsy. Whenever possible, functional testing and MRI should occur prior to biopsy. Depending on the timing of enrollment and evaluation of safety in the 20 mg/kg dose (Cohort 2), the dose escalation of Cohort 1 to 40 mg/kg may be delayed. Subjects in Cohort 1 will only receive 8 doses of the 5 mg/kg dose and not proceed to the 40 mg/kg dose until review by the SMC. In addition, depending on the timing of enrollment and evaluation of safety in the 5 mg/kg dose (Cohort 1), the Lead-In period for Cohort 2 may be extended prior to initiation of treatment phase.

b. Medical history will include confirmation by genetic testing of the diagnosis of Limb Girdle Muscular Dystrophy (LDMG2I) as obtained from an approved laboratory. Results must confirm the presence of a biallelic alteration in the FKRP gene known or likely to be pathogenic.

c. Enrollment can be performed once all screening results are available and eligibility is confirmed.

d. Pregnancy tests (highly sensitive urine or serum) and hormone testing will only be conducted for women of child bearing potential (WOCBP). In addition, diary cards will be used to collect the first day of menstrual cycle for WOCBP.

e. Weight collected within a month of the visit can be used to calculate the appropriate dose by body weight.

f. Vital sign evaluations will include supine blood pressure, pulse rate, respiratory rate and oral temperature.

g. 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.

h. Hormone testing will include LH, FSH and estrogen in female subjects only.

i. Fecal Occult Blood testing will be performed at home within 1 week of the scheduled visit.

j. MRI of skeletal muscle will include a Whole Body MRI and a dedicated thigh MRI.

k. Investigational product should be delivered in a 2 hour window ±15 minutes not including the flush time. Subjects are required to be observed for 1 hour after the infusion of the investigational product is completed. If a dosing visit cannot be conducted within the visit window, attempts should be made to bring the subject back for dosing as soon as possible; however the dosing **must not occur** within 2 weeks prior to the next scheduled dose. If the subject cannot return in this timeframe, the dose should be missed and the next visit

l. PK/PD assessments will occur predose and 2 hours post dose. The window for the PK /PDassessments post dosing at 2 hours is + 30 minutes If the infusion rate is slowed (following an infusion site reaction) the PK/PD assessments should be collected at the time of infusion completion (+30 minutes).

m. Prep B1.5 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis) will be collected at: Cohort 1 at Visits 2 (baseline), 7 (Day 113), 10 (Day 197), 15 (Day 337) and 18 (Day 421) and Cohort 2 and 3 at Visit 2 (baseline), 7 (Day 113) and 10 (Day 197)
Prep B2.5 (serum collection optimized for biomarker/ proteomics/metabonomic analysis) will be collected at: Cohort 1 at Visits 2 (baseline), 7 (Day 113), 10 (Day 197), 15 (Day 337) and 18 (Day 421) and Cohort 2 and 3 at Visit 2 (baseline), 7 (Day 113) and 10 (Day 197)
Prep R1 (PAXGene whole blood collection optimized for RNA analysis) will be collected at: Cohort 1 at Visits 2 (baseline), 10 (Day 197) and 18 (Day 421) and Cohort 2 and 3 at Visit 2 (baseline)) and 10 (Day 197)
Prep 4 (Cell-free RNA) will be collected at: Cohort 1 at Visits 2 (baseline), 10 (Day 197) and 18 (Day 421) and Cohort 2 and 3 at Visit 2 (baseline)) and 10 (Day 197)
Prep D1.5 (K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis) will be collected at the Screening visit.

n Timed Function tests and PUL will be repeated on Day 2 of Visit 3 prior to the first dose.

o MRI of the liver is performed on Visit 11 only (and not on Visit 3) for Cohort 1.

SCHEDULE OF ACTIVITIES

Table 3 Extension Study

Table 3.1 Cohort 1 Extension

Cohort 1 Extension Period (40mg/kg)	**Treatment**							**Follow-up**	**Early Withdrawal**
Visit Number (Study Day Visit Window)	**21 (±3)**	**22 (±3)**	**23 (±3)**	**24 (±3)**	**25 (±3)**	**26 (±3)**	**27 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
Physical Examination				X			X		X
Pregnancy Test	X	X	X	X	X	X	X		X
Diary Cards	X	X	X	X	X	X	X		X
Contraception Review	X	X	X	X	X	X	X		X
Height							X		
Weight	X	X	X	X	X	X	X		
Vital Signs				X			X		X
12- lead ECG							X		X
Echocardiogram							X		X
Clinical Laboratory Tests				X			X		X
Serum Ferritin, Serum Iron, Transferrin Saturation,TIBC				X			X		X
Hormone Testing (LH, FSH, estrogen)							X		X
GLDH				X			X		X
PK, PD, Immunogenicity, Biomarkers							X		X
Fecal Occult Blood				X			X		X
C-SSRS				X			X		X
Questionnaires (InQol, SF-36)							X		X
MRI-Liver							X		X

Cohort 1 Extension Period (40mg/kg)	**Treatment**							**Follow-up**	**Early Withdrawal**
Visit Number (Study Day Visit Window)	**21 (±3)**	**22 (±3)**	**23 (±3)**	**24 (±3)**	**25 (±3)**	**26 (±3)**	**27 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
DXA Spine and Hip							X		X
Muscle Strength (MMT, dynamometry)				X			X		X
4SC; 10-meter walk/run; 2MWT ; Timed up-and-go				X			X		X
PUL				X			X		X
Respiratory Function (FVC, FEV1, MIP/MEP)				X			X		X
Study Treatment Administration	X	X	X	X	X	X	X		
Adverse event monitoring	X	X	X	X	X	X	X	X	X
Infusion site reaction monitoring	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X

Abbreviations: 2MWT=Two minute walk test; 4 SC= Four stair climb, C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; FEV1 = Forced expiratory voume in 1 second; GLDH=glutamate dehydrogenase, LH-Lutenizing hormone, MIP= Mean inspiratory pressure; MEP= Mean expiratory pressure; MMT= manual muscle testing, MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PUL=Performance of Upper Limb, TIBC=Total iron binding capacity, INQoL = Individualized Neuromuscular Disease Quality of Life, SF-36 = Short Form 36 Health Survey

Table 3.2 Cohort 2 Extension

Cohort 2 Extension (40mg/kg)	Treatment										Follow-up	Early Termination
Visit Number (Study Day Visit Window)	**13 (±3)**	**14 (±3)**	**15 (±3)**	**16 (±3)**	**17 (±3)**	**18 (±3)**	**19 (±3)**	**20 (±3)**	**21 (±3)**	**22 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
Physical Examination				X			X			X		X
Pregnancy Test	X	X	X	X	X	X	X	X	X	X		X
Diary Cards	X	X	X	X	X	X	X	X	X	X		X
Contraception Review	X	X	X	X	X	X	X	X	X	X		X
Height										X		X
Weight	X	X	X	X	X	X	X	X	X	X		X
Vital Signs				X			X			X		X
12- lead ECG							X			X		X
Echocardiogram										X		X
Clinical Laboratory Tests				X			X			X		X
Serum Ferritin, Iron, Transferrin Saturation,TIBC				X			X			X		X
Hormone Testing (LH, FSH, estrogen)										X		X
GLDH				X			X			X		X
PK/ PD/Immunogenicity/Biomarkers										X		X
Fecal Occult Blood				X			X			X		X
C-SSRS				X			X			X		X
Questionnaires: InQol, SF-36										X		X
MRI-Liver										X		X
DXA Spine and Hip										X		X
Muscle Strength (MMT, dynamometry)				X			X			X		X
4SC; 10-meter walk/run; 2MWT; Timed up-and-go				X			X			X		X
PUL				X			X			X		X

Cohort 2 Extension (40mg/kg)	**Treatment**										**Follow-up**	**Early Termination**
Visit Number (Study Day Visit Window)	**13 (±3)**	**14 (±3)**	**15 (±3)**	**16 (±3)**	**17 (±3)**	**18 (±3)**	**19 (±3)**	**20 (±3)**	**21 (±3)**	**22 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
Respiratory Function (FVC, FEV1, MIP/MEP)				X			X			X		X
Study Treatment Administration	X	X	X	X	X	X	X	X	X	X		
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Infusion site reaction	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 2MWT=Two minute walk test; 4 SC= Four stair climb, C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; FEV1 = Forced expiratory voume in 1 second; GLDH=glutamate dehydrogenase, LH-Lutenizing hormone, MIP= Mean inspiratory pressure; MEP= Mean expiratory pressure; MMT= manual muscle testing, MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PUL=Performance of Upper Limb, TIBC=Total iron binding capacity, INQoL = Individualized Neuromuscular Disease Quality of Life, SF-36 = Short Form 36 Health Survey

Table 3.3 Cohort 3 Extension

Cohort 3 Extension (40mg/kg)	**Treatment**						**Follow-up**	**Early Withdrawal**
Visit Number (Study Day Visit Window)	**13 (±3)**	**14 (±3)**	**15 (±3)**	**16 (±3)**	**17 (±3)**	**18 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
Physical Examination			X			X		X
Pregnancy Test	X	X	X	X	X	X		X
Diary Cards	X	X	X	X	X	X		X
Contraception Review	X	X	X	X	X	X		X
Height						X		X
Weight	X	X	X	X	X	X		X
Vital Signs			X			X		X
12- lead ECG						X		X
Echocardiogram			X			X		X
Clinical Laboratory Tests			X			X		X
Serum Ferritin, Serum Iron, Transferrin Saturation,TIBC			X			X		X
Hormone Testing (LH, FSH, estrogen)						X		X
GLDH			X			X		X
PK/PD/Immunogenicity/Biomarkers						X		X
Fecal Occult Blood			X			X		X
C-SSRS			X			X		X
Questionnaires: InQol, SF-36						X		X
MRI-Liver						X		X
DXA Spine and Hip						X		X
Muscle Strength (MMT, dynamometry)			X			X		X
4SC; 10-meter walk/run; 2MWT; Timed up-and-go			X		X	X		X
PUL			X		X	X		X
Respiratory Function (FVC, FEV1, MIP/MEP)			X			X		X

Cohort 3 Extension (40mg/kg)	**Treatment**						**Follow-up**	**Early Withdrawal**
Visit Number (Study Day Visit Window)	**13 (±3)**	**14 (±3)**	**15 (±3)**	**16 (±3)**	**17 (±3)**	**18 (±3)**	**Telephone Follow-up 30± 3 days after final dosing visit**	
Study Treatment Administration	X	X	X	X	X	X		
Adverse event monitoring	X	X	X	X	X	X	X	X
Infusion site reaction	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: 2MWT=Two minute walk test; 4 SC= Four stair climb, C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; FEV1 = Forced expiratory voume in 1 second; GLDH=glutamate dehydrogenase, LH-Lutenizing hormone, MIP= Mean inspiratory pressure; MEP= Mean expiratory pressure; MMT= manual muscle testing, MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PUL=Performance of Upper Limb, TIBC=Total iron binding capacity, INQoL = Individualized Neuromuscular Disease Quality of Life, SF-36 = Short Form 36 Health Survey

a. Assessments should be conducted on the Study Day within the visit window. Visits with MRI, DXA and functional assessments may be conducted over 2 days. The following order of testing is preferred. On the first day of assessments: an am fasting blood collection followed by fasting DXA and MRI. On the second day of assessments: the functional assessments and muscle biopsy. Whenever possible, functional testing and MRI should occur prior to biopsy.

b. Pregnancy tests (highly sensitive urine or serum) and hormone testing will only be conducted for women of child bearing potential (WOCBP). In addition, diary cards will be used to collect the first day of menstrual cycle for WOCBP.

c. Weight collected within a month of the visit can be used to calculate the appropriate dose by body weight.

d. Vital sign evaluations will include supine blood pressure, pulse rate, respiratory rate and oral temperature.

e. 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.

f. Hormone testing will include LH, FSH and estrogen in female subjects only.

g. Fecal Occult Blood testing will be performed at home within 1 week of the scheduled visit.

h. Investigational product should be delivered in a 2 hour window ±15 minutes not including the flush time. Subjects are required to be observed for 1 hour after the infusion of the investigational product is completed. If a dosing visit cannot be conducted within the visit window, attempts should be made to bring the subject back for dosing as soon as possible; however the dosing **must not occur** within 2 weeks prior to the next scheduled dose. If the subject cannot return in this timeframe, the dose should be missed.

i. PK/PD assessments will occur predose.

j. Prep B1.5 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis), Prep B2.5 (serum collection optimized for biomarker/ proteomics/metabonomic analysis), Prep R1 (PAXGene whole blood collection optimized for RNA analysis), and Prep 4 (Cell-free RNA) will be collected at: Cohort 1 at Visit 27, Cohort 2 at Visit 22, and Cohort 3 at Visit 18, or at Early Termination.

k. MRI of the liver is performed on Visit 27 for Cohort 1, Visit 22 for Cohort 2, and Visit 18 for Cohort 3, or at Early Termination.

1. INTRODUCTION

1.2. Mechanism of Action/Indication

The investigational product PF-06252616, a humanized anti-myostatin monoclonal antibody that neutralizes myostatin (GDF8) is in development for the treatment of Limb Girdle Muscular Dystrophy 2I (LGMD2I) and Duchenne Muscular Dystrophy (DMD) to preserve and/or improve muscle function. Other potential indications for PF-06252616 include other muscular dystrophies, muscle frailty conditions such as cancer cachexia and sarcopenia and rehabilitation of muscle strength.

The safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of PF-06252616 have been demonstrated in healthy adults following administration of either single ascending intravenous (IV) or a subcutaneous (SC) dose(s) and, subsequently, repeat IV doses in adult healthy subjects.

This study will provide the clinical assessment of the safety, tolerability, PK and PD of PF-06252616 following repeat IV doses in ambulatory adults with LGMD2I.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure.

1.3. Background and Rationale

1.3.1. Myostatin Role in Muscle Regulation

Myostatin or growth and differentiation factor 8 (GDF-8) is a member of the bone morphogenetic protein, transforming growth factor-β (BMP/TGFβ) superfamily of secreted differentiation factors [1]. The muscle-specific, negative regulatory role of GDF-8 is well conserved between zebrafish, dogs, cattle, mice and humans. GDF-8 has been best studied in skeletal muscle where GDF-8 null mice possess muscles that are 100% to 200% larger than wild-type controls due to a combination of muscle fiber hyperplasia and hypertrophy [2]. Despite having increased skeletal muscle and decreased fat, the GDF-8 null mice appear to be normal and healthy. Consistent with its role in mice, genetic loss of myostatin is associated with increased muscle mass in many different species [1]. One case of a human has been reported with a homozygous mutation of the GDF-8 gene, associated with an absence of GDF-8 protein, increased muscle strength and, by age 4, no apparent untoward health effects [3]. Pharmacologic inhibition of GDF-8 activity in rodents results in increased muscle mass and improved muscle function in both normal and dystrophic animals [4]. Given its effect on skeletal muscle and the absence of abnormality in knockout mice, GDF-8 represents an attractive target for diseases associated with muscle loss.

1.4. Limb Girdle Muscular Dystrophy 2I

LGMD2I is a genetic, autosomal recessive, disorder. It is one of the most common forms of LGMD accounting for at lease 10% of all known LGMDs [5]. LGMD2I is caused by mutations in the gene for Fukutin-related protein (FKRP), which codes for an enzyme that glycosylates α-dystroglycan on the muscle membrane [6,7]. In the absence of FKRP, α-dystroglycan is

improperly glycosylated and does not make crucial linkages of the muscle membrane to laminin in the basal lamina. This loss of linkage results in muscle cell death. Reduction in dystroglycan glocyoslyation by FKRP as well as other enzymes causes several different LGMDs and congenital muscular dystrophies which are referred to collectively as dystroglycanopathies [5].

There is a wide variability in the clinical severity of LGMD2I with childhood onset and fast progression to mid-adult onset and slow progression [8]. The majority of people with LGMD2I have initial symptoms of weakness and wasting in the hip, with difficulty walking and climbing stairs during teenage or early adult years. As the condition progresses, shoulder girdle muscles may also become weak although scapular winging is absent. Mobility becomes increasingly difficult and may result in loss of ambulation. Cardiomyopathy develops in approximately half of LGMD2I patients [8,9]. Repiratory involvement requiring noninvasive nighttime ventilation has been described [8].

Treatment of LGMD2I is supportive only. This includes, for example, bracing, mobility equipment and ventilatory support, generic to most muscular dystrophies. Cardiomyopathy is frequently treated with angiotensin converting enzyme (ACE) inhibitors [10]. There are no pharmacological therapies known to improve the progressive skeletal muscle weakness associated with the disorder. Anecdotal reports describe positive responses to corticosteroids but there have been no randomized controlled trials of corticosteroids in LGMD2I and such treatment is not currently widely practiced or considered standard of care [11].

This study will provide the initial clinical assessment of the safety, tolerability, efficacy, PK and PD of PF-06252616 following repeat IV doses in adult ambulatory participants with LGMD2I.

1.4.1. PF-06252616

PF-06252616, also referred to as Anti-Myostatin, is a humanized recombinant antibody immunoglobulin G1 (IgG1) that neutralizes GDF-8 (myostatin). PF-06252616 was developed by humanization of a mouse monoclonal antibody, designated mRK35, generated by immunizing GDF-8 knockout mice with recombinant GDF-8 and isolating monoclonal antibodies by splenic fusion using standard hybridoma methodology. The substitution of specific amino acid residues in the Fc region of PF-06252616 has reduced the effector functions of the molecule. The humanized recombinant antibody has a human kappa constant domain and a human IgG1 constant domain with 3 mutations to reduce potential effector function. PF-06252616 investigational drug product is supplied as a lyophilized sterile powder for solution for injection in a single use vial. The vials will be reconstituted with sterile water for injection (SWFI). The reconstituted PF-06252616 drug product is clear and colorless to slightly yellow.

1.5. Nonclinical Pharmacodynamics

Initial studies in mouse demonstrated that mRK35 was superior to a previous anti-myostatin monoclonal antibody, MYO-029, which prompted humanization of the antibody (PF-06252616). Administration of PF-06252616 to naïve and dystrophic mdx mice resulted in increased muscle mass and function. Subsequent studies demonstrated that PF-06252616

could significantly increase lean mass and muscle volume in nonhuman primates (NHP) in a dose-dependent manner. In one NHP study, the animals were monitored during a washout period following the last dose, which showed the muscle that accrued during the study was maintained for several weeks after the last dose. Collectively the pharmacology data show that muscle anabolic activity of PF-06252616 has been observed in all studies, in both mice and NHP.

The epitope to which PF-06252616 binds in myostatin is also highly conserved with growth differentiation factor 11 (GDF-11), another member of the TGF-β superfamily, and PF-06252616 binds both proteins with comparable affinity. PF-06252616 binds with 360x lower affinity to BMP-6 than myostatin. PF-06252616 demonstrates no significant binding against other BMPs, activins, inhibins, and TGF-β.

1.6. Nonclinical Pharmacokinetics

PK of PF-06252616 after a single IV dose of 10 mg/kg in mice, rats and monkeys, was characterized by low clearance, low apparent volume of distribution (at steady state) and long terminal elimination half-lives. The calculated bioavailability following a single subcutaneous (SC [10 mg/kg]) or intraperitoneal (IP [1, 3, and 10 mg/kg]) dose in mice ranged from 47 to 118%, while bioavailability following a single SC (10 mg/kg) dose in monkeys was 80%.

Following weekly IV or SC administration up to 1 month in rats (15, 50, 150, 282.5 and 565 mg/kg) and monkeys (10, 30, 100 and 282.5 mg/kg), systemic PF-06252616 exposure, as assessed by C_{max} and AUC_{168}, increased with increasing dose and was generally similar for males and females. All rats (up to 150 mg/kg) and monkeys (up to 100 mg/kg) were negative for the induction of anti-drug antibodies (ADA). ADA was not assessed at the other doses in these studies.

Serum and cerebrospinal fluid (CSF) concentrations of PF-06252616 were determined after weekly IV administration for 26 weeks to male and female juvenile rats (50, 150 and 471.5 mg/kg) and monkeys (10, 50 and 284 mg/kg). In general, serum toxicokinetic (TK) parameters were similar for males and females for all dose groups. Systemic exposure increased with dose in a less than dose proportional manner in rats and a dose proportional manner for monkeys. Mean CSF/serum ratios were low, indicating limited central nervous system (CNS) penetration of PF-06252616 in these species. No induction of ADA was detected in juvenile rats during treatment phase. However, 2 rats from the recovery phase tested positive for ADA. All juvenile monkeys were negative for the induction of ADA in both the dosing and recovery phases.

The PK and tissue distribution of [^{125}I]PF-06252616 in female C57BL/6 mice (n=4/time point) were determined after a single IV dose of 8 mg/kg. Following administration, [^{125}I]PF-06252616 was eliminated from circulation with a serum clearance (CL) of 12.7 mL/day/kg, and a terminal elimination half-life ($t_{½}$) of 123 hours (5.1 days). The relatively low steady state volume distribution (V_{ss}) of 89.0 mL/kg suggested that the test article was mainly confined to the vascular space.

The concentrations of [^{125}I]PF-06252616 in all tissues of interest were significantly lower for all the time points tested compared to corresponding serum concentrations. The tissue to serum ratio (T/S) AUC_{inf} ratios were less than 0.1 for all tissues of interest except lung and skin, with values of 0.154 and 0.159, respectively. The T_{max} for skeletal muscle was 24 hours with a C_{max} of 2.5 ±0.5 (µg eq./gram) and a T/S AUC_{inf} ratio of 0.036. Radioactive equivalent concentrations in tissues of interest, such as skeletal muscle, declined with time in parallel to that for serum.

1.7. Toxicology

PF-06252616 was administered to rats (n=10/sex) and cynomolgus monkeys (n=3/sex) once weekly via IV and SC routes in initial pivotal 1-month toxicity studies that also included assessments of neurofunctional activity in rats and respiratory rate and cardiovascular function in cynomolgus monkey. Subsequent 1-month studies in rats and monkeys with IV dosing once weekly were conducted at the maximum feasible dose. The no observed adverse effect levels (NOAELs) in these studies were the highest doses tested, which were 565 and 282.5 mg/kg/week in the rat and cynomolgus monkey, respectively.

Test-article related increases in body weight and skeletal muscle in rats and/or monkeys and increases in lean muscle mass and quadriceps, gastrocnemius, and/or sternocephalicus muscles in monkeys were observed in the 1-month toxicology studies in rats and/or 8-week pharmacokinetic/pharmacodynamics (PK/PD) study in monkeys.

PF-06252616 produced no effects on the CNS function in rats or on respiration rate in cynomolgus monkeys. Although there were no changes in cardiac function as assessed by electrocardiogram (ECG) and ultrasound analysis, reductions in heart rate were noted in the initial 1-month IV/SC study in male cynomolgus monkeys and appeared to show a dose dependency although rates remained within the normal range observed for cynomolgus monkeys. This effect was not observed in the subsequent studies conducted up to 26 weeks at the higher doses up to 284 mg/kg/week, and when present was not considered adverse. Additional nonadverse test article-related effects related to administration of PF-06252616 were considered attributable to its pharmacological effect on muscle; specifically, effects on red blood cell (RBC) mass parameters, creatinine, and phosphorus.

Subsequently, PF-06252616 was administered by IV (bolus) injection to juvenile Wistar Han rats and cynomolgus monkeys (age 5.5 weeks and 18 months, respectively) at doses up to 471.5 mg/kg/week in rats and 284 mg/kg/week in cynomolgus monkeys for 26 weeks followed by a 13-week recovery phase to assess reversibility.

In the 26-week study in juvenile rats (n=15/sex), hepatic iron accumulation was present at all doses (≥50 mg/kg/week) in males and females, and associated with liver lesions in females only. Microscopic findings in the liver of females given ≥50 mg/kg/week consisted of minimal hepatocellular foci of alteration (basophilic), minimal to moderate predominantly periportal hepatocellular hypertrophy, and minimal to mild hepatocellular cytomegaly; these findings persisted through the recovery period. Hepatocellular hypertrophy was frequently associated with disruption of the hepatic cords in the portal regions, and additionally some females had distinct cytomegalic hepatocytes, often bi- or multinucleated or contained an

increased number of mitotic figures, that were notably larger than the adjacent hypertrophied hepatocytes. Based on the abnormality of the cytomegalic hepatocytes, this finding and the more pronounced hypertrophy with hepatic cord disruption finding were considered adverse at all doses in females. Following recovery (n=5/sex), microscopic findings in liver were similar to those observed at the end of the dosing period. In males, there was an increased incidence and severity of hemorrhage and erosion in the glandular stomach with associated inflammation at 471.5 mg/kg/week, which was considered adverse, based on the severity of the findings. The findings in the glandular stomach were reversible during the recovery period.

Weekly IV administration of PF-06252616, to juvenile cynomolgus monkeys (n=4/sex) for up to 26 weeks at doses of 0, 10, 50, or 284 mg/kg/week also resulted in hepatic iron accumulation at all doses, and adverse findings at 284 mg/kg/week affecting liver in both sexes and reproductive organs in females. The findings in the liver consisted of moderate to severe iron deposits in hepatocytes associated with portal macrophage accumulation and/or fibrosis, single cell necrosis and hepatocellular cytoplasmic rarefaction with correlating increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. Pigment deposit was also observed in the kidney, pancreas and duodenum of 1 female. Adverse findings in the female reproductive tract consisted of arrested development of ovarian follicles and atrophy of the endometrium, cervical mucosa, and vaginal epithelium. Following a 13-week recovery period (n=2/sex), adverse PF-06252616-related microscopic findings were still noted in the liver of male and female monkeys. In the liver, single cell necrosis and macrophage accumulation were present, and there was no reversal of the pigment deposit (iron/hemosiderin) and its associated changes. Pigment deposition was also present in the pancreas (including pancreatic lymph nodes) and kidney. Hepatic cytoplasmic rarefaction was not observed at the end of the recovery period suggesting a complete reversal of this change. In the female reproductive tract, some of the changes were still evident for 1 female while a complete recovery was noted for the other female.

Although differences are apparent in the nature of the hepatic findings noted in toxicity studies in rats and cynomolgus monkeys, excessive iron accumulation resulting in hepatic overload is considered to be the basis of the findings in both species. Experimental models of oral and parenteral iron overload in rats have shown that iron has a mitogenic effect on the liver characterized by a proliferative hepatocellular response that develops in the absence of accompanying hepatocellular necrosis/degeneration, fibrosis, or inflammation [12]. Morphologically periportal hepatocellular hypertrophy [13], and/or oval cell proliferation [14] were observed. The increased sensitivity of female rats administered PF-06252616 is consistent with reports that the severity of pigmentation of parenchymal and nonhepatocytic cells in the livers of iron overloaded rats was greater in females compared with males [15]. However, test article-related increases in hepatic iron and associated hepatic findings in female cynomolgus monkeys were comparable in severity with male cynomolgus monkeys. This is consistent with the absence of female sensitivity, and sometimes relative insensitivity compared with males, to hepatic injury in human genetic iron disorders, as female primates are afforded some protection through menses that does not occur in female rodents [16,17].

Additional investigative efforts have provided in vivo and in vitro evidence that direct anti-BMP-6 activity of PF-06252616, resulting in suppression of BMP-6 induced hepcidin

expression, is the mechanism leading to hepatic iron overload in the 26-week studies in rats and cynomolgus monkeys.

In the 26-week IV studies, the NOAELs were 150 (males only) and 50 mg/kg/week for rats and cynomolgus monkeys, respectively. The margins at these NOAELs were 7x and 3x the predicted exposure (C_{av}) at the highest projected dose in humans for rats and cynomolgus monkeys, respectively.

1.8. Clinical Experience with PF-06252616

As of June 2015, there are one completed clinical study (B5161001) and one ongoing clinical study (B5161002) with PF-06252616.

The initial clinical program for PF-06252616 was a Phase 1 first in human, randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled study (B5161001) evaluating the safety, tolerability, PK, PD, and pharmacologic (anabolic) effects of escalating single doses of PF 06252616 in healthy adult subjects. This study fully enrolled 73 subjects at a single site and completed in July 2014. Doses of 1, 3, 10, 20, and 40 mg/kg administered by the intravenous (IV) route and 3 mg/kg administered by the subcutaneous route, or placebo have been studied. In addition, a repeat IV administration of PF 06252616 10 mg/kg at 2 week intervals over a 28-day treatment period has been investigated. Safety was demonstrated at all dose levels and there were no dose-related trends in frequency of reported treatment emergent adverse events (TEAEs).

PF-06252616 serum concentrations in Study B5161001 were measured using a validated enzyme-linked immunosorbent assay (ELISA) method. Target mediated drug disposition (TMDD) was evident at the lower concentration levels mainly below 1 μg/mL. The individual and mean PK serum profiles following the single dose administrations and the PF-06252616 serum concentrations following the repeat dose were analyzed. PF-06252616 demonstrated a bi-phasic PK profile with a mean terminal half-life in days (~12 to 19 days), slow CL (2.38 to 3.54 mL/day/kg) and small volume of distribution (56 to 78 mL /kg), all attributes of a typical IgG1molecule. Following SC administration, PF-06252616 was absorbed slowly with a median time to maximum concentration of 7 days, a half-life of approximately 13 days, and apparent bioavailability of ~61%.

The PD activity of PF-06252616 was evaluated in Study B5161001, by measuring total serum GDF-8 (myostatin) levels using a validated liquid chromatography/mass spectrometry (HPLC-MS/MS) method. Following PF-06252616 administration, total serum GDF-8 levels were modulated at all dose levels. The mean time to maximum GDF-8 levels was generally between 11 and 30 days. The extent of modulation increased between 1 and 10 mg/kg IV doses and seemed to plateau at higher doses. In the repeat-dose cohort, the median GDF-8 baseline level was 3.1 ng/mL on Day 1 and following 10 mg/kg IV dosing, the median GDF-8 concentration increased to 18.6 ng/mL after the third dose.

One of the secondary objectives of Study B5161001 was to demonstrate proof of mechanism (POM) for evidence of a pharmacologic effect based on a percentage change in lean body mass (LBM) as measured in dual-energy x-ray absorptiometry (DXA) in the repeat dose cohort (10 mg/kg IV every 2 weeks for 1 month). Per the analysis criteria, the percent change

in LBM in the repeat dose cohort did not reach significance at any time point evaluated. The criteria were then applied in an exploratory analysis to the magnetic resonance imaging (MRI) T1 measurements of muscle volume and the T2 measurements of muscle fat content at each time point. On the T1 measurement of quadriceps muscle volume an increase in muscle volume at Day 113, where a mean 4.48% difference from baseline, relative to placebo, was observed. On the T2-mapping, an increase of 6.11% (change from baseline as compared to placebo at Day 113) in the proportion of tissue exhibiting T2 signals associated with muscle rather than fat.

Study B5161002 is a first-in-patient Phase 2, randomized, 2-period, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, PK, and PD of PF-06252616 administered to ambulatory boys with DMD. Three (3) IV-infused dose levels (5, 20, and 40 mg/kg) will be investigated in a "within subject" dose-escalating fashion. Approximately 120 subjects will be enrolled. The first subject first visit was November 2014. As of 26 January 2018, 120 subjects were enrolled in the study and 38 of whom had completed the study. Subjects who completed Study B5161002 have the option to enroll in the Open-label extension study (Study B5161004). Thirty one subjects are currently enrolled in this extension study.

1.9. Immunogenicity Risk Assessments

1.9.1. Nonclinical Immunogenicity

Antigenicity studies with PF-06252616 have not been conducted. However, in general, anti-PF-06252616 antibodies were not detected post dose up to 26 weeks in rats and cynomolgus monkey. It should be noted that circulating levels of PF-06252616 may have interfered with the detection of any anti-PF-06252616 antibodies. In addition, toxicokinetics up to 26 weeks in rats and cynomolgus monkeys indicate drug levels increase with time following repeated dosing suggesting no production of ADA.

The potential for immunotoxicity was evaluated in rats and cynomolgus monkeys up to 26 weeks. No adverse effects were observed in hematology parameters or on microscopic examination of lymphoid organs. Since no adverse findings or indications of immunotoxicity were observed no further evaluations have been performed.

1.9.2. Immunogenicity Results B5161001

Following PF-06252616 administration in Study B5161001, 5 adult healthy subjects in the single dose groups (1 in the 1 mg/kg IV group, 2 in the 20 mg/kg IV group, and 2 in the 3 mg/kg SC group) and 1 subject in the 10 mg/kg IV repeat dose group were found to have treatment-induced ADA responses. Among the 6 subjects with ADAs, 4 subjects (1 in each of the 1 mg/kg IV, 3 mg/kg SC, 20 mg/kg IV, and 10 mg/kg repeat dose IV cohorts) have shown neutralizing antibodies (NAb). However, none of these subjects with NAb showed any discernibly lower GDF-8 levels than others in the same cohort. In summary, for Study B5161001, there was a confirmed ADA incidence rate of 11.3% but without any obvious impact on the PF-06252616 PK or GDF-8 modulation. None of these subjects experienced clinical signs or symptoms consistent with an immune response.

1.10. Rationale for Dosage Selection and Method of Administration

PF-06252616 has been administered to healthy adult subjects in Study B5161001 and found to be safe and well tolerated as a 2-hour intravenous infusion at single doses of 1, 3, 10, 20, and 40 mg/kg, as a subcutaneous injection in a single dose of 3 mg/kg, and in repeat intravenous doses of 10 mg/kg at 2 week intervals over a 28-day treatment period.

A target mediated drug disposition PK/PD model was developed based on healthy volunteer data from study B5161001 and used to predict PF-06252616 exposures and corresponding GDF-8 coverage of the proposed dosing regimens for the current study. Based on available data from the investigator's database, the range of body weights, BMI and lean body weights for LGDM2I subjects is expected to be similar to healthy adult volunteers. As such, it is assumed that the weight normalized population PK parameters and the GDF-8 binding parameters will be similar between healthy adult volunteers and LGMD2I subjects, especially since PF-06252616 is to be administered as a body weight based (mg/kg) dosing. These parameters are then used to simulate both the expected PK profile (to compare to toxicology exposure margins) (see Table 1) and the expected PD profile (considering target coverage in serum).

For this study, 5 mg/kg administered every 4 weeks is being proposed as the starting dose in Cohort 1, as it is expected to show median GDF-8 serum coverage over 80% and therefore may demonstrate pharmacologic activity while providing sufficient safety multiple of 17.2 and 28.7 for C_{max} and $C_{av,}$ respectively, at steady state. A mid dose of 20 mg/kg administered every 4 weeks is expected to provide target coverage similar to the 10 mg/kg every 2 weeks dose in Study B5161001, which produced positive MRI signal changes in healthy volunteers. The highest dose of 40 mg/kg administered every 4 weeks is expected to maximize the potential for efficacy while still maintaining a 2-fold safety margin to the toxicology limits.

Table 1. Predicted Exposures and Margins Relative to Toxicokinetics Limits at Planned PF-06252616 Doses

IV Dose (mg/kg)	Predicted C_{max} (µg/mL)	Fold Difference with C_{max} Cynomologus Monkey NOAEL	Predicted C_{av} (µg/mL)	Fold Difference with C_{av} Cynomolgus Monkey NOAEL
5	156	17.2	65	28.7
20	598	4.5	265	7.1
40	1200	2.2	550	3.4

Toxicology limit set by the NOAEL of 50 mg/kg in 26 week non-human primate juvenile study (C_{max} = 2690 µg/mL, C_{av} = 1870 µg/mL).
The predicted human AUC_{672} was converted to C_{av} as follows: $AUC_{672}/672 = C_{av}$.
C_{max} = maximum concentration at steady-state; C_{av}= average concentration at steady state.

1.11. Study Design Rationale

This study is a Phase 1b/2, open-label multiple ascending dose escalation study to evaluate the safety, tolerability, efficacy, PK and PD of PF-06252616 in ambulatory adults with LGMD2I. The study design is intended to determine the optimal safe and pharmacologically active dose of PF-06252616 in LGMD2I while providing an opportunity for all subjects to receive active

drug for a rare and disabling disorder. The study will be conducted in four periods: Lead-In, Treatment, Follow-up, and Extension periods. The Lead-In and Follow-up periods will each be approximately 16 weeks to allow an assessment of the change of various outcome measures of this period of time and comparison of change in function before, during and after treatment. The Treatment period will be 32 weeks. This time of active treatment was chosen to maximize the possibility of observing trends in efficacy. After the Follow-up period, the subject will be given the option to continue treatment in the Extension period.

This study is primarily a safety and tolerability study of PF-06252616 in LGMD2I adults. The rationale for dose selection and escalation has been described above. A limited number of patients (4) will be enrolled in cohort 1 and will receive an initial dose of 5mg/kg PF-06252616 IV every 4 weeks. Following 16 weeks of treatment and a safety review, if no stopping rules have been met, 8 subjects will be enrolled in cohort 2 and receive 20mg/kg of PF-06252616. Subjects in cohort 2 will received 16 weeks of treatment and then a safety review will be performed. If no stopping rules have been met, cohort 1 will escalate to receive 40 mg/kg. This will occur after they have already received 5 mg/kg of PF-06252616 for 32 weeks. At the same time, cohort 3 will be enrolled and begin dosing at 40 mg/kg. For cohort 1, subject will receive 32 weeks of treatment with 5 mg/kg followed by an additionl 32 weeks of treatment with 40 mg/kg PF-06252616. The rationale for this design is that it provides a dose escalation to determine safety of each dose and allows each cohort to potentially receive a meaningful dose. Thirty-two weeks of treatment maximizes the opportunity to determine if there is a treatment effect at any given dose level. Finally, the design will provide long-term, 64 week dosing data on a limited number of subjects (4). All subjects, who completed the Follow-up period, will have the option to continue treatment in the extension period at 40mg/kg for up to 28 weeks in Cohort 1, up to 40 weeks in Cohort 2, and up to 24 weeks in Cohort 3

Exploratory outcome measures of efficacy will also be obtained. There has been only one published drug intervention trial to date which has included LGMD2I subjects [18]. This was a trial of myostatin neutralizing antibody MYO-029 which was trialed in subjects with various different adult muscular dystrophies. Various assessments of efficacy were obtained in this trial including manual muscle testing (MMT), quantitative muscle testing (QMT), timed function tests (TFTs), pulmonary function tests (PFTs), MRI, DXA and subject-reported outcomes. These assessments of efficacy were found to be feasible in the LGMD2I population. However, no efficacy was found in the combined LGMD group to provide information on optimal outcome measures for LGMD. There is one published natural history study on adult LGMD2I [19]. In this study various functional outcome measures were studied in 32 individuals over 12 months. QMT, timed up and go (TUG), 4 stair-climb (4SC), 4 stair-descend (4SD), 10 meter run (10MR), 6 minute walk test (6MWT) and forced vital capacity (FVC) were assessed. Of these functional measures, only FVC had a statistically significant decline in 12 months. The study also evaluated fat fraction by quantitative Dixon MRI and found increased fatty infiltration in 9 of 14 muscles within 12 months. Qualitative assessment of T1 weighted MRI was insensitive to change within this time frame. FVC and quantitative Dixon MRI therefore are high priorty outcome measures of this trial. However, considering the possibility that PF-06252616 will improve function rather than stabilize function, other outcome measures will be included as described above.

1.12. Anticipated Risks and Safety Monitoring

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure.

Anticipated risks are based on clinical and toxicology data.

A total of 53 healthy adult subjects have received PF-06252616 in a phase 1 study. Forty-two received single IV or SC doses and 11 received a repeat dose (3 doses of 10 mg/kg PF-06252616 IV over a 4 week period). There are no safety findings of concern from this study. In 1 month toxicology studies performed with PF-06252616 in rat and monkey, no adverse findings were reported. Consistent with the pharmacological response anticipated from this anti-myostatin monoclonal antibody, effects on skeletal muscle were noted. In the 26-week repeat dose toxicity studies in juvenile rats and monkeys, adverse and/or clinically relevant findings were noted and provide the basis of the warnings and precautions below.

1.12.1. Hepatic Injury

Accumulation of iron in the liver resulting in fibrosis and single cell necrosis of the liver is considered a potential side-effect of treatment with PF-06252616. In the intended indication of LGMD2I, transaminase elevation related to muscle pathology is common. Alternative biomarkers of liver injury that are not affected by muscle pathology include GGT and GLDH which will be monitored in this trial. The prevention of hepatic iron accumulation is the best strategy for avoidance of liver injury in this disease. Approaches developed in the treatment and prevention of hepatic damage in haemochromatosis and iron overload syndromes provide a basis for monitoring using % Transferrin saturation (serum iron/total iron binding capacity x 100) [20] and MRI measurement of hepatic iron [21].

Abnormal values for serum ALT or AST concurrent with abnormal elevations in total bilirubin that meet the criteria for Hy's law and in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events. Subjects meeting these criteria will follow the steps for confirmation required in Section 8.6.2. The utility and necessity of continued monitoring of liver iron by MRI will be formally reviewed prior to dose escalation.

1.12.2. Gastric Erosion and Haemorrhage

An increase in gastric erosion and haemorrhage was seen at necropsy observed in male rats administered 471.5 mg/kg/week for 26 weeks. Study subjects will be asked specifically to report symptoms that may be associated with such pathology. Monitoring of haemoglobin, haematocrit and fecal occult bloods will be performed.

1.12.3. Bone Metabolism

In the 26 week rat study, bone biomarker changes were identified suggestive of a decrease in bone turnover. Bone mineral density (BMD) as measured by peripheral quantitative computed tomography however was generally increased at the end of the study. The biomarker changes were reversible. In the monkey studies BMD and bone strength was increased. A positive effect on BMD would clearly be considered a positive PD effect. Spine and hip DXA will be used to monitor for changes in bone mineral density.

1.12.4. Cardiac

Based on recent literature on the biology of GDF-8 and GDF-11 in modulation of cardiomyocyte and cardiac function and the potential for cardiac dysfunction in the target population of LGMD2I subjects, it is appropriate to focus on the potential for an interaction. In monkey toxicity studies up to 26 weeks, no abnormality of cardiac function or histology was observed. In rats dosed with ≥150 mg/kg/week for 26 weeks, a reduction in heart weight was noted, but there were no microscopic findings. In light of the hypothetical risk of an effect of PF-06252616 on cardiac muscle development or function, monitoring with 12-lead ECG for rhythm or morphological change by echocardiography to evaluate left ventricular ejection fraction (LVEF) and left ventricular end systolic volume (LVESV) and cardiac Troponin I for cardiac muscle tissue injury will be performed. Additional cardiac parameters (eg, cardiac strain) may be collected by echocardiogram for exploratory analyses. Abnormal values for each of these measures have been reported in LGMD2I [22,23]. In light of the variability of findings in disease, no pre-specified stopping rules have been defined.

1.12.5. Special considerations in females

In the 26-week female juvenile rat toxicity study, adverse hepatic changes were seen at all doses, and a NOAEL was not identified. Female cynomolgus monkeys were not different from males in their sensitivity to iron accumulation or hepatocellular injury. It is possible therefore that in human studies, females may have a higher sensitivity to liver injury and appropriate care is taken to monitor using GLDH and iron parameters.

Reproductive and developmental toxicity studies with PF-06252616 have not been conducted. In the absence of evidence to the contrary, it must be assumed that administration of PF-06252616 would pose a risk to the fetus in early pregnancy. Adult female patients who are of child bearing potential may be enrolled into clinical studies with PF-06252616 if they are using at least one highly effective means of contraception as outlined in the Section on Contraception. These methods must be in place at the start of screening continued until the final study visit.

In a 26-week juvenile cynomolgus monkey study, there was no evidence of menses and marked arrested development of sexual organs was noted in female cynomolgus monkeys dosed at 284 mg/kg/week. These changes were partially to fully reversible. Despite >3x margin from the NOAEL exposure at the dose of 40 mg/kg/4 weeks, it is appropriate to monitor adult female patients reproductive health.

1.12.6. Radiation

Possible risks related to subject's undergoing evaluation with DXA include the risk of radiation exposure. The average effective dose of radiation received for a single DXA scan may vary due to the instrument and the subject's body. Subject may require a skull X-ray prior to MRI if there is a question of intraocular metal. This skull X-ray also carries the risks associated with radiation exposure. The maximum amount of radiation that a subject could receive is from 5 whole body DXA scans (in cohort 1), 3 DXA scans of the hips, 3 DXA scans of the spine and 1 skull X-ray. The expected total radiation dose for this maximum exposure is not expected to exceed 30 mrem. This is less than 1 year of natural background radiation which is approximately 300 mrem per year [24].

1.12.7. Needle Muscle Biopsy

Needle muscle biopsy is used to obtain small amounts of tissue (milligrams) for molecular studies in a clinic setting without the requirement of recovery time. Needle muscle biopsies have been used previously in clinical trials of muscular dystrophy for this purpose where histology is not needed [25]. There is a risk of reaction to local anesthesia (1% lidocaine with 1:100,000 epinephrine). There is also a risk of bleeding, bruising, hematoma formation, infection and peripheral nerve damage. The combined risk of any of these adverse events occurring from needle muscle biopsy is estimated to be less than 1%.

1.12.8. Other possible risks

Possible risks related to the administration of the study drug and/or as a consequence to phlebotomy may include hematoma or bruising.

1.12.9. Other Safety Monitoring

Additional safety monitoring will include the parameters of adverse events (AEs), physical examination, vital signs, and clinical laboratory parameters (comprehensive metabolic panel [sodium, postassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, glucose, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase], gamma-glutamyl transferase [GGT], glutamate dehydrogenase [GLD], prothrombin time [PT], activated partial thromboplastin time [aPTT], creatine kinase, amylase, cardiac troponin I and urinalysis) and Columbia Suicide Severity Rating Scale (C-SSRS). Laboratory monitoring will also be performed to detect ADA and NAb.

1.13. Summary of Risk Benefit

This is a therapeutic study being conducted in adult subjects with LGMD2I. There is no accepted pharmacological treatment for this disorder. There has been only one other therapeutic trial to date in this rare disease which did not demonstrate efficacy. PF-06252616 may demonstrate pharmadynamic activity in subjects.

In view of the initial clinical evidence of safety and the monitorable nature of key nonclinical toxicological findings, data support an acceptable risk profile for PF-06252616 in the current study and support a favorable benefit risk profile in the indication of LGMD2I. Authorities will be kept informed of any additional data (eg, results from clinical studies) which may affect the assessment of the risk/benefit ratio for PF-06252616.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary

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

2.1.2. Secondary

- To assess the PK exposures of PF-06252616 in LGMD2I.

- 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.

2.1.3. Exploratory

- To evaluate functional outcome measures 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 as indicated by the whole body MRI evaluation and/or lean body mass DXA results**.**

2.2. Endpoints

2.2.1. 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) parameters by day 337 or 561.

2.2.2. Seconday Endpoints

2.2.2.1. Pharmacokinetic

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

- Total serum GDF-8 concentrations for all visits with GDF-8 collections

2.2.2.2. 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 incuding 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

2.2.2.3. Patient Reported Outcomes

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

2.2.2.4. Immunogenicity

Incidence of ADA and NAb development.

2.2.3. Exploratory Endpoint

2.2.3.1. 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

2.2.3.2. Function

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

2.2.3.3. Pharmacodynamic

- Mean percent change from baseline in muscle volume as measured on MRI as indicated by the whole body MRI evaluation and/or lean body mass DXA results.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b/2, open-label multiple ascending dose study to evaluate the safety, tolerability PK and PD of PF-06252616 administered to 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)
- Extension period: PF-06252616 40 mg/kg (28 weeks)

Cohort 2 (n=8):

- Lead-in period (16 weeks)
- Treatment: PF-06252616 20 mg/kg (32 weeks)
- Follow-up period (16 weeks)
- Extension period: PF-06252616 40 mg/kg (40 weeks)

Cohort 3 (n=8):

- Lead-in period (16 weeks)
- Treatment: PF-06252616 40 mg/kg (32 weeks)
- Follow-up period (16 weeks)
- Extension period: PF-06252616 40 mg/kg (24 weeks)

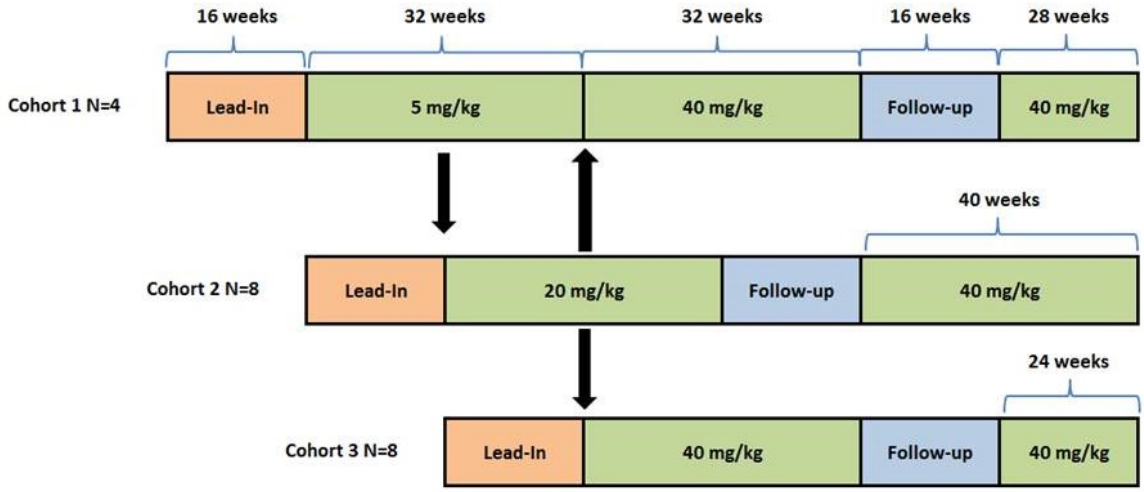
At each dose level, subjects will be followed for an initial approximate 16-week lead-in period to establish individual change in disease progression.

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 a minimum of 64 weeks. Subjects in Cohort 1 will only receive 8 doses of the 5 mg/kg dose and not proceed to the 40 mg/kg dose until safety review and approval by the SMC.

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.

All subjects completing the follow-up period will have the option to continue treatment with 40mg/kg dose in the Extension Period.



3.2. Duration of Subject Participation

Subject's participation will begin during screening (up to 2 weeks) followed by a lead-in period (16 weeks), treatment period (64 weeks for Cohort 1, 32 weeks for Cohorts 2 and 3) , follow-up period (ending 16 weeks after the last study dose in the treatment period), and the extension period (up to 28 weeks for Cohort 1, up to 40 weeks for Cohort 2, and up to 24

weeks in Cohort 3). Periods of participation are estimates and are dependent on enrollment and safety review of concurrent dosing cohorts. Subjects will return to the site monthly for study drug administration as well as completion of safety and efficacy assessments.

In order to ensure consistency in assessment collection, visits that include functional assessments and imaging assessments (DXA and WB-MRI) will be collected over 2 consecutive days, within the study visit window. In the case where subjects are traveling from a distance, the site will offer nearby overnight accommodations.

3.3. Approximate Duration of Study

The study is estimated to complete in approximately 151 weeks allowing for 27 weeks of enrollment and up to124 weeks on the study.

The end of the study will be the last visit of the last subject for purposes informing the institutional review board/ethics committee (IRB/EC), and ceasing to send Council for International Organizations of Medical Sciences (CIOMS) reports.

3.4. Planned Number of Subjects

A minimum of 20 subjects will participate. In order to ensure adequate enrollment, a sufficient number of subjects may be screened.

3.5. 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 SMC may determine it is necessary to close or adjust a dose level within the study. 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. A break in dosing of subjects in Cohort 1 between 5 mg/kg and 40 mg/kg may occur to ensure all safety data from Cohort 2 at 20 mg/kg has been evaluated by the SMC. Should a break be required in Cohort 1 between Day 197 and 225 (±3 days) which is longer than the planned 28 days between dosing visits and outside the visit schedule, the window will not be applied. When the dosing resumes in Cohort 1 at the highest dose, the first day of dosing will be Visit 11 and the remaining dosing schedule will follow the Schedule of Activities, whereby dosing will occur every 28 days (± 3 days).

3.5.1. Dose Escalation and Stopping Rules

Table 2. 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) [17,21,26]
No Esclation, 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) [17,21,26]

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.

3.5.2. 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 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 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.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male and female patients age ≥ 18
2. Diagnosis of LGMD2I as defined by clinical presentation consistent with LGMD2I and FKRP gene testing showing biallelic alterations known or likely to be pathogenic. Diagnosis must be confirmed in subject's medical history and by genetic testing obtained during routine clinical care for diagnostic purposes as reported from an appropriate regulated laboratory using a clinically validated genetic test (genetic testing is not provided by the sponsor).
3. Ability to walk/run 10m
4. Abilit to rise from chair
5. Adequate hepatic and renal function on screening laboratory assessments

    - GGT ≤ upper limit of normal (ULN).

    - Alkaline phosphatase ≤ ULN.

    - Total Bilirubin ≤ ULN.

    - Serum Albumin ≥ LLN.

    - Serum creatinine ≤ ULN.

6. Iron content estimate on the screening liver MRI within the normal range as determined by R2* value (R2* ≤ 139 Hz at 3.0T).
7. Participant must provide written informed consent for participating in study.
8. Participant must possess the ability, per the Principal Investigator (PI), to understand and comply with protocol instruction for the entire duration of the study.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Known cognitive impairment or behavioral issues that would impede the ability to provide informed consent or to follow study instructions.
2. History of major surgical procedure within 6 weeks of signing the informed consent or planned surgery during the study.
3. Any injury which may impact functional testing. Previous injuries must be fully healed prior to consent. Prior lower limb fractures must be fully healed and at least 3 months from injury dates.
4. Previous treatment with another investigational product within 30 days or 5 half-lives, (whichever is longer) prior to consenting.
5. Corticosteroid treatment within 3 months prior to consenting.
6. Compromised cardiac function (left ventricular ejection fraction <50%).
7. Unwilling or unable (e.g. metal implants, requires sedation) to undergo examination with closed MRI without sedation.
8. History of allergic or anaphylactic reaction to a therapeutic or diagnostic protein.
9. Female subjects who are pregnant or nursing.
10. Subjects who, are biologically capable of having children who are unwilling or unable to use highly effective methods of contraception (as outlined in this protocol) during sexual activity for the duration of the study and through completion of final study visit.
11. Predisposition to iron accumulation. (Serum iron >1.2 X ULN, serum ferritin >1.2 ULNN).
12. Underlying disposition for bleeding disorder on screening laboratory assessment (PT/INR>1.25 X ULN, aPTT > 1.25 ULN, fecal occult blood is positive)
13. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic, or allergic disease.
14. Unwillingness or inability to comply with the requirements of this protocol (in the opinion of the PI) including, but not limited to, the presence of any condition (physical, mental, or social) that is likely to affect the participant's ability to return for study visits or adhere to the visit schedule.

Note: Screening laboratory tests with results considered by the investigator to be transient and inconsistent with the subject's clinical condition may be repeated once during the screening period for confirmation of eligibility.

4.3. Enrollment Criteria

Subjects will be enrolled into the study and begin the Lead-in period, provided they have satisfied all selection criteria. Women of child bearing potential (WOCBP), must have a negative highly sensitive pregnancy test recorded within one month of intiating dosing.

4.4. Lifestyle Guidelines

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

Subjects should maintain their normal dietary intake throughout the study with the following exceptions:

- Subjects should abstain from large amounts of caffeine within 24 hours of study visits. Negligible amounts are not of concern.
- Subjects will be asked to fast for at least 8 hours prior to collection of blood to evaluate serum ferritin, serum iron, trasferrin saturation, and TIBC.
- For at least 4 hours prior to the DXA scan, subjects should fast, or at a minimum avoid large meals. No calcium supplements should be taken within 24 hours of a DXA scan.
- Two days prior to collection of stool sample for fecal occult blood testing, *whenever possible*, subjects should refrain form eating red meat, turnips, horseradish or medications containing aspirin or vitamin C. It is recommened that subjects consume small amounts of chicken, canned tuna fish, peanuts, popcorn, bran cereal, vegetables and fruit.

4.4.2. Activity

Subjects should be instructed to continue with routine physical therapy including stretching or use of orthoses to prevent or minimize contractures or muscle deformities.

Subjects will be instructed to maintain normal activity levels and avoid activities that are not part of their normal daily routine within 24 hours of study visits where imaging or functional assessments will be performed.

4.4.3. Contraception

All male and female subjects who, in the opinion of the investigator are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly from screening until the final study visit. The investigator, in consultation with the subject will confirm the subject has selected the most appropriate method of contraception for the individual subject and his/her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. The investigator or his/her designee will discuss the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. At each study visit, the investigator will confirm and document consistent and correct use. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected birth control method is discontinued or if partner pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

In addition, all sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing through the final study visit.

4.5. Rater Qualifications

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

Clinical staff must be trained to complete the C-SSRS. Training is web-based and available on Columbia's Training Campus. Upon completion a certification will be provided to the trained individual.

Should a risk of suicide ideation or behavior be identified during completion of the C-SSRs, the risk assessment for the C-SSRS must be then performed by a clinically qualified mental health provider (MHP). In the United States, clinically qualified MHPs include the following: (1) general psychiatrists, (2) Psy.D or Ph.D. level Clinical Psychologists, (3) licensed Master's level Clinical Social Workers, or (4) licensed psychiatric Nurse Practitioners who have training and experience in the diagnosis and treatment of individuals with psychiatric disorders.

4.5.2. Physiotherapists

Functional assessments including the respiratory function (FVC, FEV1, MIP and MEP) 4SC, strength (MMT, QMT), PUL, 10-meter walk/run (10 MR), 2MWT and TUG will be conducted by a trained physiotherapist.

5. STUDY TREATMENTS

Subjects will be treated with IV infused PF-06252616 in this open-label, multiple ascending dose study. Please refer to the Dosing and Administration Instruction (DAI) for complete information on storage, stability, preparation and administration of drug product (PF-06252616).

Table 3. Dosing Schedule for Cohort 1

Study Visit Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**
Cohort 1	5mg/kg once every 4 weeks							
Study Visit Day	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**
Cohort 1	40 mg/kg once every 4 weeks							
Study Visit Day	**589**	**617**	**645**	**673**	**701**	**729**	**757**	
Cohort 1	**EXTENSION PERIOD: 40 mg/kg once every 4 weeks**							

Table 4. Dosing Schedule for Cohort 2 and 3

Study Visit Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	
Cohort 2	**20 mg/kg once every 4 weeks**								
Study Visit Day	365	393	421	449	477	505	533	561	589	617
Cohort 2	**EXTENSION PERIOD: 40 mg/kg once every 4 weeks**								
Study Visit Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	
Cohort 3	**40 mg/kg once every 4 weeks**								
Study Visit Day	365	393	421	449	477	505			
Cohort 3	**EXTENSION PERIOD: 40 mg/kg once every 4 weeks**								

This study is a 3 cohort clinical trial. In a dose escalating fashion, subjects will be enrolled in one of 3 cohorts and will receive treatment on a 28 day schedule, per the Schedule of Activities. The dose will be dependent on the cohort and calculated based on the subject weight at each visit prior to each infusion.

Subjects in Cohort 1 will receive treatment with 5 mg/kg of PF-06252616 for 32 weeks and after safety and tolerability review of Cohort 1 subjects receiving 5 mg/kg and Cohort 2 subjects receiving 20 mg/kg will be escalated to 40 mg/kg of PF-06252616 for an additional 32 weeks. Subjects in Cohort 2 will receive treatment with 20 mg/kg of PF-06252616 for 32

weeks. Subjects in Cohort 3 will receive treatment with 40 mg/kg of PF-06252616 for 32 weeks. Subjects who completed the Follow-up period and opt to continue in the Extension period will receive treatment with 40mg/kg of PF-06252616 for up to 28 weeks in Cohort 1 and up to 40 weeks in Cohort 2, and 24 weeks in Cohort 3.

Subjects should be administered the investigational product within the visit window according to the Schedule of Activities. If a dosing visit cannot be conducted within the visit window, attemps should be made to bring the subject back for dosing as soon as possible; however the dosing must not occur within 2 weeks prior to the next scheduld dose. If the subject cannot return for dosing in this timeframe, the dose should be missed and the next visit should be conducted per the Schedule of Activities.

5.1. Allocation to Treatment

Subjects will be consecutively enrolled into cohorts. The first 4 subjects to successfully complete screening will be enrolled in Cohort 1. Following demonstration of safety in subjects enrolled in cohort 1 as described in the Section Safety Monitoring and Dose Escalation, the subsequent 8 subjects will be enrolled in Cohort 2. The final 8 subjects will be enrolled in Cohort 3.

5.2. Blinding

This study is open label. Subjects, investigators and pharmacists will be aware of the active treatment and dose level. As this study is planned to be conducted at the same time as a double-blind, placebo-controlled Duchenne muscular dystrophy (DMD) study is being conducted, by the same investigator, the following steps will occur to assure the blind is maintained in the DMD study:

- Subjects in the LGMD2I will be dosed in separate rooms from the pediatric subjects who are dosed in the DMD study.
- Separate research nurses will be used to infuse subjects from the LGMD2I study and the DMD study. They will not work on both studies.
- IV infusion bag, will covered with an amber sleeve
- IV drip chamber, will be covered transparent colored tape

5.3. Subject Compliance

Study treatment will be administered under the supervision of investigator site personnel.

5.4. Drug Supplies

5.4.1. Dosage Form(s) and Packaging

PF-06252616 will be provided by Pfizer Worldwide Research and Development (PWRD) as a lyophilized powder for injection as single use, sterile vials. The drug product is supplied in a glass vial sealed with a coated lyophylized stopper and an aluminum overseal and labeled according to local regulatory requirements. The drug product is designed to be reconstituted

with SWFI for IV infusion. The reconstituted solution of PF-06252616 is clear and colorless to slightly yellow in appearance.

Details of the drug product and preparation are provided in the DAI.

PF-06252616 will be packaged as open-label supplies. The external packaging (carton) will describe its contents indicating it as active drug product. Each carton will contain ten vials of study medication. Each carton will be packaged with a tamper-resistant seal. Pfizer must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used.

5.4.2. Preparation and Dispensing

See the DAI for instructions in how to prepare the investigational product for administration.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced unblinded member of the study staff (eg, pharmacist, pharmacist technician) designated to participate in the study as allowed by local, state, and institutional guidance. Site pharmacists will receive study specific training on the obligations of the role and will sign an agreement that will be maintained in the Master File.

Subject's body weight will be measured at each visit. Weights obtained within one month may be used to calculate the dose of study drug to be administered.

Under aseptic conditions, PF-06252616 should then be prepared according to the DAI document provided by the sponsor.

5.5. Investigational Product Administration

Following preparation of the study treatment investigational product (PF-06252616) by the site pharmacist, the prepared product will be provided to the nurse administrator. Topical anesthetics (eg, topical lidocaine at the site of infusion) may be administered to subjects, consistent with institutional guidelines.

The IV infusion should be administered by qualified healthcare professionals trained to detect any infusion related issues. Infusion times, rates, any infusion interruptions or infusion rate reduction, will be recorded. The study drug should be infused over a 2-hour period where time 0 is the beginning of the infusion. The infusion time will be recorded, but the flush time will not be reported.

Should subjects experience any infusion site reaction during the IV infusion period, the treatment administration should be interrupted and supportive care should be provided according to the investigator's standard practice (eg, treatment with an antihistamine). Treatment administration may resume if the reaction resolves. Following the interruption at the discretion of the investigator, the infusion rate may be decreased to half the required rate (eg, decreased from 50mL /hr to 25mL/hr or duration may be increased from 2 to 4 hours). If the infusion rate should be decreased, the window for delivery (± 15 minutes) will not be applied. Should the infusion be decreased, the PK will be collected per the Schedule of Activities. The duration of the treatment interruption should not exceed the limits of stability

of the drug product solution per the DAI. Consult the DAI for detailed instructions regarding study drug preparation, stability and administration. No more than 1 treatment interruption should occur during any single infusion.

Subjects should be obsereved for 1 hour following completion of the investigational product administration.

5.6. Investigational Product Storage

The pharmacy personnel, (eg, pharmacist, pharmacy technician) will ensure that all investigational products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Upon receipt at the study site, the investigational products (PF-06252616) must be stored in a 2 to 8°C temperature-monitored refrigerator and in the original carton, according to labeled storage conditions. The investigational product cannot be used after the expiration date. Please refer to the DAI for complete information on storage, handling and stability of the investigational products both prior to and following reconstitution.

Storage conditions stated in the single reference safety document (SRSD) (ie, Investigator's Brochure [IB]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions.

5.7. Investigational Product Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product.

5.8. Destruction of Investigational Product Supplies

Pfizer or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.9. Concomitant Treatment(s)

- Subjects will abstain from all prohibited concomitant medications, except if required for treatment of AEs.

- All concomitant medications taken during the study will be recorded with the indication and start and stop dates of administration. All subjects will be questioned about concomitant medications at each visit.

- Medications taken within 28 days prior to Day 1 will be documented as prior medication. Medications taken from the time of Day 1 will be documented as concomitant medications.

5.9.1. Permitted Therapies

- Subjects will be permitted to receive ACE inhibitors, ARB (angiotensin II receptor blocker), aldosterone blocker and/or β blockers; however, subjects must have initiated treatment more than 3 months prior to screening and plan to remain on a stable dose during the study.

- Supplements such as vitamin D, coenzyme Q10, carnitine, aminoacids (glutamine, arginine), anti-inflammatory/anti-oxidants (eg, fish oil, vitamin E, green-tea extract) are permitted but must be be initated more than 3 months prior to screening and remain stable during the study. Calcium is permitted but should not be taken with 24 hours of a DXA scan. Multi-vitamin without iron is permitted.

5.9.2. Prohibited Therapies

The following are prohibited from the time of signing the informed consent through the final study visit.

- Immunosuppressant therapy (including glucocorticosteroids).

- Other investigational therapies.

- Androgens or human growth hormones current and in the past 3 months. Testosterone replacement in hypogonadal males will be permitted as long as the subject has been on a stable dose for the past 3 months prior to enrollment and is anticipated to remain on a stable dose for the length of the study.

- Multi-vitamin with iron or iron supplements.

5.9.3. Rescue Medication

Should subjects experience an infusion site reaction during the IV infusion period, the treatment administration should be paused for the subject and supportive care should be provided according to the investigator's standard practice (eg, treatment with an antihistamine).

6. STUDY PROCEDURES

Every attempt should be made to schedule the visits on the day specified in the Schedule of Activities. In order to provide optimal testing conditions and consistency in endpoint measurements, at visits when the functional assessments, imaging and clinical laboratory assessments are scheduled to be completed at the same visit, the visit should be completed on two days within the visit window and at approximately the same time of day in the order described below.

There is no window for Day 1(first dosing day). The visit window for the additional treatment visits is ±3 Day. For the final follow up visit, the window is ±3 days. The window for the PK assessments post dosing at 2 hours is +30 minutes. If the infusion rate is decreased (following an infusion site reaction) the PK/PD assessment should be collected at the time of infusion completion and flush (within a +30 minute window). Subjects are required to be observed for 1 hour after administration of PF-06252616.

6.1. Screening: Visit 1 (Screening Day -125 to -112)

During screening, subjects will be assessed for study eligibility. All screening must be completed and reviewed for subject eligibility before the subject is enrolled into the study. Screening laboratory tests with results considered by the investigator to be transient and inconsistent with the subject's clinical condition may be repeated once during the screening period for confirmation of eligibility. Imaging based examinations for screening must be reviewed before the subject is enrolled to assure an adequate baseline image has been acquired. If the image is determined to be of poor quality, it will be repeated. The visit window (Day -125 to -112) for screening is to allow for the analysis of laboratory testing, assurance of imaging quality and to provide multiple days to perform the assessments in the order described below. As soon as this is completed and subject's eligibility has been confirmed, they may be randomized into the study.

- **Informed Consent:** The subject must sign the informed consent document (ICD) prior to initiation of any screening assessments.

- **Demographics:** Information such as date of birth, race, and gender will be collected.

- **Medical History:** Medical history will include confirmation by genetic testing of the diagnosis of LGMD2I as obtained as reported from an appropriate regulated laboratory using a clinically validated genetic test (genetic testing is not provided by the sponsor). Results must confirm the biallelic alteration in the FKRP gene known to be or likely to be pathogenic and associated with LGMD2I. The mutation type will be reported. Medical history will also be reviewed for any significant medical/surgical histories and concurrent illnesses that required or are requiring specialist consultation or treatment.

- **Medication History:** Complete history will include all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.

- **Physical Examination, including Nose and Throat Mucosal Exam**

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all women of childbearing potential (WOCBP).

- **Diary Cards:** Will be provided with instructions to all WOCBP to record the first day of each menstruation cycle.

- **Contraception Review:** Confirmation of use of acceptable forms of contraception.

- **Weight**

- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

- **12-lead ECG:** ECGs will be performed in triplicate.

- **Echocardiogram**

- **Clinical laboratory testing:**

    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.

- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection

- **Horomone Testing:** LH, FSH, estrogen in WOCBP

- **GLDH**

- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week of scheduled visit and mailed to site for testing.

- **C-SSRS**

- **MRI-liver**: Liver MRI will be obtained for iron accumulation

- **Inclusion/Exclusion Criteria**: Subjects will be assessed against inclusion and exclusion criteria.

- **Enrollment:** Enrollment can be performed once all screening results are available and eligibility is confirmed

6.2. Lead-in Period: Visit 2 (Baseline Day -111 to -110 prior to dosing on Day 1)

The following procedures and studies should be performed in the morning (before noon) of Visit 2 whenever possible

- **Physical Examination, including Nose and Throat Mucosal Exam**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects and must be confirmed as negative within 1 month of receiving first dose.
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Height:** Height should be measured in the morning.
- **Weight**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **C-SSRS**
- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality

The following procedures should be performed in the afternoon of Visit 2 whenever possible:

- **DXA:** Whole body DXA will be performed for lean body mass.
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Needle muscle biopsy:** Following WB-MRI and functional assessments a needle muscle biopsy of the tibialis muscle will be performed.
- **PD sample collection**

- **Biomarker collection:** Blood will be collected for proteomic, metabolomic, and genomic biomarker analysis
- **Adverse event monitoring**
- **Concommitant medications**

6.3. Active Treament Period: Visit 3 (Day 1) and for Cohort 1, Visit 11 (Day 225±3)

Visit 3 will be divided into a 2 day visit

Prior to dosing, the following procedures will be completed:

- **Physical Examination, including Nose and Throat Mucosal Exam**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12-lead ECG:** ECGs will be performed in triplicate
- **Clinical laboratory tests**:
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal occult blood**: Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**

- **Immunogenicity:** Baseline
- **PD sample collection: Predose**
- **PK sample collection: Predose**
- **MRI-liver**: Liver MRI will be obtained for iron accumulation (visit 11 only)
- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality
- **DXA Whole Body:** Whole body DXA will be performed for lean body mass.
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Quality of Life assessments**
  - InQol
  - SF-36

On Day 2 of Visit 3 (Day 1)- prior to dosing,

- **Functional assessments:** Must be conducted in the following order: 4SC, 2MWT, 10-meter walk/run, TUG, and PUL.
- **Needle muscle biopsy:** Following the Functional assessments, a needle muscle biopsy of the tibialis muscle will be performed.

Dosing

- **Study treatment administration.**

After dosing, the following procedures will be completed:

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature after completion of infusion.**PK sample collection**: Collected at end of infusion (hour 2)
- **PD sample collection**: Collected at end of infusion (hour 2)
- **Infusion site reaction monitoring.**
- **Adverse event (AE) monitoring.**

- **Concomitant medication monitoring.**

6.4. Active Treatment: Visit 4 (Day 29±3), 8 (Day 141±3), 10 (Day 197±3) and for Cohort 1, Visit 12 (Day 253±3), 16 (Day 365±3), 18 (Day 421±3)

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**

Dosing

- **Study treatment administration.**

<u>After dosing, the following procedures will be completed:</u>

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature after completion of infusion.**Infusion site reaction monitoring.**
- **AE monitoring.**

- **Concomitant medication monitoring.**

6.5. Active Treatment: Visit 5 (Day 57±3), 9 (Day 169±3) and for Cohort 1, Visit 13 (Day 281±3), 17 (Day 393±3)

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **PK/PD sample: predose**

Dosing

- **Study treatment administration.**

<u>After dosing, the following procedures will be completed:</u>

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature at - after completion of infusion.

- **PK/PD sample collection**: Collected at end of infusion (hour 2)
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**

6.6. Active Treatment: Visit 6 (Day 85±3) and for Cohort 1, Visit 14 (Day 309±3)

- **Physical Examination, including Nose and Throat Mucosal Exam.**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12 lead ECG:** ECGs will be performed in triplicate
- **Clinical laboratory sample collection:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **MRI of liver:** Liver MRI will be obtained for iron accumulation

Dosing

- **Study treatment administration.**

After dosing, the following procedures will be completed:

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature after completion of infusion.**Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**

6.7. Active Treatment: Visit 7 (Day 113±3) and for Cohort 1, Visit 15 (Day 337±3)

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **PK/PD sample: predose**

- **Biomarker collection:** Blood will be collected for proteomic, metabolomic, and genomic biomarker analysis

- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.

Dosing

- **Study treatment administration.**

After dosing, the following procedures will be completed:

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature after completion of infusion.**PK/PD sample collection**: Collected at end of infusion (hour 2)

- **Infusion site reaction monitoring.**

- **AE monitoring.**

- **Concomitant medication monitoring.**

6.8. Follow up: For Cohort 1, Visit 19 (Day 449±3) and for Cohort 2 and 3, Visit 11 (Day 225±3)

This visit will occur over 2 days.

- **Physical Examination, including Nose and Throat Mucosal Exam.**

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects

- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.

- **Contraception Review:** Confirmation of use of acceptable forms of contraception

- **Weight**

- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

- **12-lead ECG:** ECGs will be performed in triplicate

- **Echocardiogram**

- **Clinical laboratory testing:**

  - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.

- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **MRI-liver**: Liver MRI will be obtained for iron accumulation
- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality
- **DXA Whole Body:** Whole body DXA will be performed for lean body mass assessment.
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Needle muscle biopsy:** Following WB-MRI and functional assessments, a needle muscle biopsy of the tibialis muscle will be performed.
- **Quality of Life assessments**
  - InQol
  - SF-36
- **Immunogenicity** sample collection.
- **PD sample collection**
- **PK sample collection**

- **Adverse Event monitoring**
- **Infusion site reaction monitoring**
- **Concomitant medication**

6.9. Follow-up: For Cohort 1, Visit 20 (Day 561±3) and for Cohort 2 and 3 Visit 12 (Day 337±3)

- **Physical Examination, including Nose and Throat Mucosal Exam.**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12-lead ECG:** ECGs will be performed in triplicate
- **Echocardiogram**
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **MRI-liver**: Liver MRI will be obtained for iron accumulation

- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality
- **DXA Whole Body:** Whole body DXA will be performed for lean body mass assessment.
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Needle muscle biopsy:** Following WB-MRI and functional assessments, a needle muscle biopsy of the tibialis muscle will be performed.
- **Quality of Life assessments**
  - InQol
  - SF-36
- **Immunogenicity** sample collection.
- **PK sample collection**
- **PD sample collection**
- **Adverse Event monitoring**
- **Concomitant medication**

6.10. Extension Period: For Cohort 1 (Visits 21,22,23,25, and 26), for Cohort 2 (Visits 13,14,15,17,18,20,21), for Cohort 3 (Visits 13,14, 16, 17)

- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Dosing**: study treatment administration
- **Infusion site reaction monitoring.**
- **AE monitoring.**

- **Concomitant medication monitoring.**

6.11. Extension Period: For Cohort 1 (Visit 24), for Cohort 2 (Visits 16 and 19), and for Cohort 3 (Visit 15)

- **Physical Examination, including Nose and Throat Mucosal Exam**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12-lead ECG:** ECGs will be performed in triplicate (only in Cohort 2- Visit 19)
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Dosing**: study treatment administration
- **Infusion site reaction monitoring.**
- **AE monitoring.**

- **Concomitant medication monitoring.**

6.12. Extension Period: For Cohort 1 (Visit 27), for Cohort 2 (Visit 22), and for Cohort 3 (Visit 18)

- **Physical Examination, including Nose and Throat Mucosal Exam**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Cards:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Weight**
- **Height**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12-lead ECG:** ECGs will be performed in triplicate
- **Echocardiogram**
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **MRI-liver**: Liver MRI will be obtained for iron accumulation
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.

- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry) and PUL.
- **Quality of Life assessments**
  - InQol
  - SF-36
- **Dosing**: study treatment administration
- **Immunogenicity** sample collection.
- **PK sample collection**
- **PD sample collection**
- **Biomarker collection:** Blood will be collected for proteomic, metabolomic, and genomic biomarker analysis
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**

6.13. Telephone Follow-up: 30 +/-3days after final dosing visit

- **AE monitoring.**
- **Concomitant medication**

6.14. Unscheduled Visits

Subjects may return for unscheduled visits as determined by the investigator or the sponsor to complete unscheduled safety assessments. These assessments may include:

- **Fecal occult blood.**
- **C-SSRS**
- **Weight.**
- **Physical Examination, including Nose and Throat Mucosal Exam.**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12 lead ECG.**

- **Echocardiogram**
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **Preganancy test:** A highly sensitive urine pregnancy test will be performed on all female subjects
- **PK sample collection.**
- **PD sample collection**.
- **MRI-liver**: Liver MRI will be obtained for iron accumulation
- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality
- **DXA Whole Body:** Whole body DXA will be performed for lean body mass assessment.
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.
- **Infusion site reaction monitoring.**
- **Adverse event (AE) monitoring.**
- **Concomitant medication monitoring.**

6.15. Subject Withdrawal

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her. The subject should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments and to be questioned regarding their reason for withdrawal. The following assessments may be performed according to the Schedule of Activities:

Assessments in the Early Withdrawal visit may include:

- **Physical Examination, including Nose and Throat Mucosal Exam.**
- **Pregnancy Test**: A highly sensitive urine pregnancy test will be performed on all female subjects
- **Diary Card:** For collection of first day of each menstrual cycle for WOCBP.
- **Contraception Review:** Confirmation of use of acceptable forms of contraception
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **12-lead ECG:** ECGs will be performed in triplicate
- **Echocardiogram**
- **Clinical laboratory testing:**
    - 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) gamma-glutamyl transferase (GGT), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I. Urinalysis.

- **Serum ferritin, serum iron, % transferrin saturation, TIBC:** fasting blood collection
- **Horomone Testing:** LH, FSH, estrogen in WOCBP
- **GLDH**
- **Fecal Occult Blood:** Fecal sample is to be collected at home within 1 week prior to scheduled visit.
- **C-SSRS**
- **MRI-liver**: Liver MRI will be obtained for iron accumulation
- **MRI-muscle:** WB-MRI and dedicated thigh MRI will be performed for muscle quantity and quality
- **DXA Whole Body:** Whole body DXA will be performed for lean body mass assessment.
- **DXA Spine and Hip:** Spine and hip DXA will be performed for BMD.
- **Functional assessments:** Must be conducted in the following order: Respiratory function (FVC, FEV1, MIP, MEP), 4SC, 2MWT, 10-meter walk/run, TUG, strength assessment (MMT, hand-held dynamometry), and PUL.
- **Needle muscle biopsy:** Following WB-MRI and functional assessments, a needle muscle biopsy of the tibialis muscle will be performed.
- **Quality of Life assessments**
  - InQol
  - SF-36
- **Immunogenicity** sample collection.
- **PD sample collection**
- **PK sample collection**
- **Adverse Event monitoring**
- **Infusion site reaction**
- **Concomitant medication**

In the extension period, all the tests and procedures listed in the early withdrawal visit will be completed except for MRI- muscle, DXA of the whole body, and needle muscle biopsy.

In the event of clinically important treatment-emergent suicidal ideation or suicidal behavior, the subject will be withdrawn from the study and will receive the appropriate medical care. The Investigator will follow up until the subject's condition has stabilized. Additionally, a risk assessment or evaluation of suicide risk will be completed by a mental health provider as part of the psychiatric evaluation and assessment of subject safety. Refer to Section7, Assessments. Clinically important suicidality includes but is not limited to:

- Suicidal behavior (with or without intent of suicide or serious self-harm).
- Determination of "yes" on question 4 (Active Suicidal Ideation with Some Intent or Act, Without Specific Plan) for the Suicidal Ideation section of the C-SSRS.
- Determination of "yes" on question 5 (Active Suicidal Ideation with Specific Plan and Intent) for the Suicidal Ideation section of the C-SSRS.
- Determination of "yes" on the question of Actual Attempt, Interrupted Attempt, Aborted Attempt, or Preparatory Acts or Behavior for Suicidal Behavior section of C-SSRS.
- Acute suicidality to such a degree that precaution against suicide must be exercised.

6.16. Subject Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1. Safety

7.1.1. Clinical Laboratory

The following safety laboratory tests will be performed at times defined in the Schedule of Activities section of this protocol. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Laboratory Tests

HEMATOLOGY	CHEMISTRY	URINALYSIS	OTHER	
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and Creatinine Glucose Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[a] HCG[b]	GLDH GGT PT/INR aPTT Creatine kinase Amylase Cardiac Troponin I Serum Ferritin[c] Serum Iron[c] Total Iron Binding[c] Capacity (TIBC)[c] % Transferrin Saturation[c] **Horomone Testing:** LH, FSH, estrogen	Fecal Occult Urine Pregnancy Test
	Additional Tests[d]			

	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT GLDH PT/aPTT			

[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[b]. A urine HCG pregnancy test will be performed in female subjects as per the Schedule of Activities. A positive urine HCG pregnancy test will trigger a blood HCG test.

[c]. Following an 8 hour overnight fast.

[d]Additional testing for potential Hy's Law cases only.

7.1.2. Physical Examinations/Nose and Throat Exam

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. The physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. A targeted nose and throat mucosal exam will be performed according to the Schedule of Activities to monitor for any signs of mucosal telangiectasias.

7.1.3. Vitals

Supine blood pressure, pulse rate, respiratory rate and oral temperature will be measured at times specified in Schedule of Activities section of this protocol. Unscheduled collection times will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after at least 5 minutes of rest. Whenever possible, the same arm (preferably the dominant arm) should be used throughout the study.

The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

7.1.4. Electrocardiogram (ECG)

ECGs should be collected at times specified in the Schedule of Activities section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected at Day 1(Visit 3), will serve as each subject's time-controlled baseline QTc value.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the average of QTc values from the triplicate measurements remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.1.5. Echocardiogram

Echocardiograms should be collected at times specified in the Schedule of Activities section of this 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).

7.1.6. Assessment of Suicidal Ideation and Behavior –Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS: The C-SSRS will be evaluated at times specified in the Schedule of Activities. The Baseline/Screening (Version 1/14/09) (Appendix 1) 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 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, Subject Withdrawal and evaluation of suicide risk (risk assessment) must be completed.

Risk Assessment: In the event that a subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidality behavior, an evaluation of suicide risk (risk assessment) will be completed as part of the psychiatric evaluation and assessment of subject safety to participate will be performed by the following mental health provider: Psychiatrists (board certified or board eligible), Psy. D. or Ph.D. level Clinical Psychologists, licensed Master's level Clinical Social Workers (MSW) or licensed psychiatric Nurse Practitioners (PNP) who have training and experience in the diagnosis and treatment of psychiatric disorders.

Written documentation of the risk assessment should be included in the subject's source documentation and the risk assessment CRF will be completed. The risk assessment CRF serves as further verification that the psychiatric evaluation and assessment of subject safety have been completed for all subjects endorsing items 4 or 5 on the C-SSRS ideation section or reporting suicidal behavior.

7.2. Banked Biospecimens

7.2.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in a bioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the SSID number. Samples will be kept in a locked freezer. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 2-mL blood biospecimen **Prep D1.5 (K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis)** will be collected at the Screening visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Additional biospecimens will be collected in the morning following an 8 hour fast to be retained for exploratory analyses in this study include the following:

- **Prep B1.5 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis):** A 2-mL blood biospecimen will be collected at Visits 2 (Screening), and Visits 7, 10, 15 and 18 for Cohort 1 and Visits 7 and 10 for Cohorts 2 and 3.

- **Prep B2.5 (serum collection optimized for biomarker/ proteomics/metabonomic analysis):** A 2-mL blood biospecimen will be collected at Visits 2 (Screening), and Visits 7, 10, 15 and 18 for Cohort 1 and Visits 7 and 10 for Cohorts 2 and 3.

- **Prep R1 (PAXGene whole blood collection optimized for RNA analysis):** A 2.5-mL blood biospecimen will be collected at Visits 2 (Screening), and Visits 10 and 18 for Cohort 1 and Visits 10 for Cohorts 2 and 3 .

- **Prep P4 Cell-free RNA:** A 10-mL blood biospecimen will be collected at Visits 2 (Screening), and Visits 10 and 18 for Cohort 1 and Visits 10 for Cohorts 2 and 3.The

banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.2.2. Additional Research

Subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer or the investigator is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.3. Pharmacokinetics (Serum for Analysis of PF-06252616)

During all study periods, blood samples (2 mL) to provide serum for pharmacokinetic analysis will be collected into the appropriate tubes (containing no anticoagulant or gel separator) at times specified in the Schedule of Activities section of the protocol.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing as described in the Schedule of Activities.

Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacokinetics and immunogenicity of the study drugs, samples may be used for evaluation of the bioanalytical method. This additional characterization will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.4. Anti-Drug Antibody (ADA) anti-PF-06252616 and Neutralizing Antibody (NAb)

During all study periods, blood samples (2 mL) to provide serum for analysis of anti-PF-06252616 will be collected into the appropriate tubes (containing no anticoagulant or gel separator) at times specified in the Schedule of Activities section of the protocol.

All efforts will be made to obtain the samples at the exact nominal time relative as described in the Schedule of Activities.

Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. All samples that are positive in a screening assay will be confirmed for antibody specificity and further characterized for titer. Samples that are determined to be positive for ADA may be further tested for the presence of neutralizing antibodies.

The PK and immunogenicity samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of understanding the pharmacokinetics or immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.5. Pharmacodynamics/Serum for Total GDF-8

All efforts will be made to obtain the samples at the exact nominal time relative as described in the Schedule of Activities.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

The PD samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of understanding the pharmacodynamics of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

Blood samples (2 mL) to provide serum will be collected into appropriately labeled tubes (containing no anticoagulant or gel separator) to provide a minimum of 1 mL serum for GDF-8 analysis at times specified in the Schedule of Activities section of the protocol. Allow to clot in upright position at room temperature for at least 30 minutes. Place clotted samples into an ice bath for approximately 10 minutes prior to centrifugation. Centrifuge samples at approximately 1200 x g for about 15 minutes at 4°C. Withdraw serum (approximately 1 mL) and equally divide into 2 aliquots (approximately 0.5 mL each) and transfer into appropriately labeled screw-capped polypropylene tubes. Place into a -70°C (or lower) non-frost-free freezer within approximately 70 minutes of collection and ship frozen samples on dry ice. Blood samples will be collected for the analysis of total GDF-8 at times specified in the Schedule of Activities.

7.6. Imaging Assessments

7.6.1. Liver MRI

Liver MRI will be obtained according to the Schedule of Activities to monitor for safety by quantifying iron accumulation. All images will be acquired using a standardized imaging protocol with consistent analysis.

7.6.2. MRI of Skeletal Muscle

Magnetic resonance imaging will be used for qualitiative, semi-quantitative and quantitative assessment of muscle quantity and quality. The imaging procedures will include a whole-body MRI exam as well as thigh imaging protocols. Both whole-body and thigh imaging will use quantitative and qualitative methods to evaluate muscle quantity and quality.

Quantitative measures will focus on thigh muscle volume and fat fraction. Qualitatitive and semi-quantitative assessments will be used to evaluate signal changes corresponding to inflammation, edema, and/or fat content.

The MRI of the skeletal muscle takes approximately 2 hours for scanning and positioning. Because of the length of time inside the scanner, some participants may become anxious about the procedure. They may be premedicated, as needed, with Ativan (Lorazepam) 1 mg orally 30 minutes before the procedure. If needed, another dose of Ativan 1 mg may be given after 30 minutes.

7.6.3. Duel-energy X-ray Absorptiometry (DXA) and X-ray

7.6.3.1. DXA

DXA scans will be obtained according to the Schedule of Activities to measure the percent change in lean body mass (LBM) over time and to evaluate bone mineral density (BMD) on the spine and hip. Ideally, whole body scans will be taken at approximately the same time of day (morning) and subjects will have fasted for at least 4 hours prior to the scan, but should be in a state of euhydration.

7.6.3.2. Radiation Exposure

Possible risks related to subject's undergoing evaluation with DXA include the risk of radiation exposure. The average effective dose of radiation received for a single DXA scan may vary due to the instrument and the subject's body. Subject may require a skull X-ray prior to MRI if there is a question of intraocular metal. This skull X-ray also carries the risks associated with radiation exposure. The maximum amount of radiation that a subject could receive is from 5 whole body DXA scans (in cohort 1), 3 DXA scans of the hip, 3 DXA scans of the spine and 1 skull X-ray. The expected total radiation dose for this maximum exposure is not expected to exceed 30 mrem. This is less than 1 year of natural background radiation which is approximately 300 mrem per year (Blake, Naeem et al., 2006).

7.7. Functional Assessments

Functional assessments will be obtained according to the 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.

7.7.1. Pulmonary Function

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

7.7.2. 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.

7.7.3. 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.

7.7.4. 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.

7.7.5. 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.

7.7.6. 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 contactures and the scale aims to incorporate performance of shoulder, elbow, wrist and hand function.

7.7.7. 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 footware. The 6MWT has been used extensively in pediatric DMD trials [28]. The 2MWT may be more feasible in populations such as LGMD2I where the 6MWT is too fatiguing. Studies of the 2MWT in adult patient populations have reported good test-retest and interrater reliability [29].

7.8. Quality of Life Assessments

7.8.1. InQoL

This 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 [30].

7.8.2. SF-36

This 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 [31]. It provides a measure of relative disease burden and allows differentiating the health benefits produced by various different treatments.

7.9. Needle Muscle Biopsy

Needle muscle biopsy is used to obtain small amounts of tissue (milligrams) for molecular studies in a clinic setting without the requiment of recovery time. Needle muscle biopsies have been used previously in clinical trials of muscular dystrophy for this purpose where histology is not needed [25]. In this procedure, the skin overlying the tibialis muscle is sterilely prepped and local anesthesia (1% lidocaine with 1:100,000 epinephrine) is infused subcutaneously and into the soft tissue to be biopsied. A nick is made in the skin with the tip of a scalpel. Through the skin incision, measuring less than 0.5 cm, a 14 gauge biopsy needle is inserted. Several small samples of skeletal muscle can be withdrawn through the same skin incision with the biopsy needle, each measuring less than 0.5cm by 0.02 cm. A sterile bandage is applied following the procedure.

7.10. Triggered Requirements

Condition/ Criteria	Action
Moderate Iron overload/ If the liver iron content estimate as determined by R2* value is above the "mild overload" range (R2* >369 Hz at 3.0 T	The subject should be referred to a hepatologist for further assessment
Cardiomyopathy/ If the LVEF falls 10% of baseline on the cardiac echocardiogram at any follow-up visit	The subject should be referred to a cardiologist for further assessment.

7.11. Infusion Site Monitoring

From the initiation of the IV infusion subjects will be monitored for signs of any infusion site reactions including but not limited to erythema, swelling, bruising, pain or prutitis.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 112 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to Pfizer if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to Pfizer.

- AEs (serious and nonserious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error

case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, Pfizer should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between study drug and an event specified below, these events should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section on this protocol. These events are anticipated to occur commonly in a population with LGMD2I. However, these events should still be captured as AEs in the CRF.

Protocol-specified events that will not normally be reported in an expedited manner:

- Loss of mobility or ambulation.
- Muscle weakness.
- Cardiomyopathy.
- Fracture.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epi data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a quarterly basis by the SMC.

8.6.2. Potential Cases of Drug-Induced Liver Injury

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥3 X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase and GLDH. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the

subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within

24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject's parent/legally acceptable representative. In addition, each study subject's parent/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

As noted in the Protocol-Specified Serious Adverse Event section, should an investigator judge one of the identified protocol-specified SAE to have a causal relationship with the investigational product the investigator must report the event to Pfizer within 24 hours of investigator awareness.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including reporting suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

No formal sample size calculation was performed. The sample size is based on feasibility and appropriateness for a safety trial.

9.2. Efficacy Analysis

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 randomized subjects who have received at least one dose of study drug.

9.2.1. Analysis of Primary Endpoint

Change from baseline in FVC will be analyzed using a longitudinal mixed effects model. The baseline result, treatment, time and treatment by time interaction will be included as fixed effects in the model. Subject will be included as a random effect and the model will be fit with an unstructured covariance for the repeated measures. Additionally, non-Gaussian models may be explored in the case of non-normal data for the FVC.

Missing data 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.

9.2.2. Analysis of Secondary Endpoints

Secondary endpoints of change from baseline in functaional assessments, quality of life questionnaires and imaging endpoints will be analyzed using the same longitudinal mixed model as described for the primary analysis. Transformation of the data will be considered if model assumptions are not met.

9.2.3. Analysis of Exploratory Endpoints

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.

9.2.4. Analysis of Pharmacokinetics

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. The following PK concentrations for PF-06252616 following administration of PF-06252616 will be characterized.

Parameter	Definition	Method of Determination
C_{max}	Maximum serum concentration	Observed directly from data as the end of infusion concentration
C_{trough}	Trough (predose) serum concentration	Observed directly from data

No formal inferential statistics will be applied to PK data.

The serum PF-06252616 concentrations will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentations which will be detailed in the statistical analysis plan. Briefly, serum concentrations for PF-06252616 will be listed and summarized descriptively by nominal PK sampling time and dose.

Any population PK analysis if conducted will be reported separately.

9.2.5. Analysis of Pharmacodynamics

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

Graphical analysis of total GDF-8 levels as absolute and percentage of baseline will be performed. Analyses may be employed to determine the effects of dose and concentration on the GDF-8 levels over time. From the GDF-8 data the following parameters will be reported.

The GDF-8 concentrations will be summarized descriptively by treatment and time points.

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.

9.3. Safety Analysis

Safety analyses will be based on the full analysis set.

9.3.1. 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 month.

9.3.2. Electrocardiogram

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

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. The baseline for ECG parameters will be the average of the triplicate pre-dose measurements at Week 0. 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 maximum absolute QTcF <450 ms, 450 ms ≤QTcF <480 ms, 480 ms ≤ QTcF <500 ms and QTcF values ≥500 ms will be tabulated by treatment and study week. 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.

9.3.3. Cardiac Echocardiogram

The mean absolute and percent change from baseline in LVEF and LVESV will be evaluated.

9.3.4. Liver MRI

The mean absolute and percent change from baseline in the R2* value will be tabulated. Other exploratory analyses may be performed.

9.3.5. Other Safety

Adverse event data, laboratory data and concomitant medications will be tabulated and listed but not subjected to formal statistical analysis.

Other safety data will be listed.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During the study, periodic monitoring will be conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. Review of source documents will be completed to confirm that the data recorded on CRFs are accurate.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The use of initials should be avoided. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject’s actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures. In addition, the ongoing study may be publicized through DMD advocacy groups.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of trial is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06252616 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results

During the study, periodic monitoring will be conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. Review of source documents will be completed to confirm that the data recorded on CRFs are accurate.

The study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the possible audits or inspections and that sufficient time is devoted to the process.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

16. REFERENCES

1 McNally, E. M. Powerful Genes — Myostatin Regulation of Human Muscle Mass. *New England Journal of Medicine* **350**, 2642-2644, doi:doi:10.1056/NEJMp048124 (2004).

2 McPherron, A. C., Lawler, A. M. & Lee, S.-J. Regulation of skeletal muscle mass in mice by a new TGF- beta superfamily member. *Nature* **387**, 83-90 (1997).

3 Schuelke, M. *et al.* Myostatin mutation associated with gross muscle hypertrophy in a child. *New England Journal of Medicine* **350**, 2682-2688 (2004).

4 Bradley, L., Yaworsky, P. J. & Walsh, F. S. Myostatin as a therapeutic target for musculoskeletal disease. *Cellular and Molecular Life Sciences* **65**, 2119-2124, doi:10.1007/s00018-008-8077-3 (2008).

5 Nigro, V. & Savarese, M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. *Acta Myologica* **33**, 1-12 (2014).

6 Esapa, C. T., Benson, M. A., Schroder, J. E. & al., e. Functional requirements for fukutin-related protein in the Golgi apparatus. *Hum Mol Genet* **11**, 3319-3331 (2002).

7 Brockington, M., Yuva, Y. & Prandini, P. Mutations in the fukutin-related protein gene (FKRP) identify Limb Girdle Muscular Dystrophy wI as a milder allelic variant of congenital muscular dystrophy MDC1C. *Hum Mol Genet* **10**, 2851-2859 (2001).

8 Pope, M. *et al.* The phenotype of limb-girdle muscular dystrophy type 2I. *Neurology* **60**, 1246-1251 (2003).

9 Willis, T. A. *et al.* Quantitative Magnetic Resonance Imaging in Limb-Girdle Muscular Dystrophy 2I: A Multinational Cross-Sectional Study. *PLOS One* **9**, e90377 (2014).

10 Petri, H. *et al.* Progression of cardiac involvement in patients with limb-girdle type 2 and Becker muscular dystrophies: a 9-year follow-up study. *International J Cardiology* **182**, 403-411 (2015).

11 Darin, N. *et al.* Inflammation and response to steroid treatment in limb-girdle muscular dystrophy 2I. *Eur J Paediatr Neurol* **11**, 353-357 (2007).

12 An, S., Soe, K., Akamatsu, M., Hishikawa, Y. & Koji, T. Accelerated proliferation of hepatocytes in rats with iron overload after partial hepatectomy. *Histochem Cell Biol* 773-786 (2012).

13 Whittaker, P., Hines, F. A., Robl, M. G. & Dunkel, V. C. Histopathological evaluation of liver, pancreas, spleen, and heart from iron-overloaded Sprague-Dawley rats. *Toxicol Pathol* (1996).

14 Smith, P. G. J. & Yeoh, G. C. T. Chronic iron overload in rats induces oval cells in the liver. *Am J Pathol* **149** (1996).

15 Masson, R. & Roome, N. O. Spontaneous iron overload in Sprague-Dawley rats. *Toxicol Pathol* **25**, 308-316 (1997).

16 Alexander, J. & Kowdley, K. V. HFE-associated hereditary hemochromatosis *Genet Med* **11**, 307-313 (2009).

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

18 Wagner, K. R. *et al.* A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. *Annals of Neurology* **63**, 561-571, doi:10.1002/ana.21338 (2008).
19 Willis, T. A. *et al.* Quantitative Muscle MRI as an Assessment Tool for Monitoring Disease Progression in LGMD2I: A Multicenter Longitudinal Study. *PLOS One* **8**, e70993 (2013).
20 Danjou, F. *et al. A decisional algorithm to start iron chelation in patients with beta thalassemia*. Vol. 99 (2014).
21 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).
22 Gaul, C. *et al.* Cardiac involvement in limb-girdle muscular dystrophy 2I. *J Neurol* **253**, 1317-1322 (2006).
23 Hollingsworth, K. G. *et al.* Subepicardial dysfunction leads to global left ventricular systolic impairment in patients with limb girdle muscular dystrophy 2I. *Eur J Heart Failure* **15**, 986-994 (2013).
24 Blake, G. M., Naeem, M. & Boutros, M. Comparison of effective dose to children and adults from dual X-ray absorptiometry examinations. *Bone* **38**, 935-942, doi:http://dx.doi.org/10.1016/j.bone.2005.11.007 (2006).
25 Wagner, K. R. *et al.* Gentamicin treatment of Duchenne and Becker muscular dystrophy due to nonsense mutations. *Ann Neurol* **49**, 706-711 (2001).
26 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).
27 Hammeraren, E., Ohlsson, J. A., Lindberg, C. & al., e. Reliability of static and dynamic balance tests in subjects with myotonic dystrophy type 1. *Adv Physiother* **14**, 48-54 (2012).
28 McDonald, C. M. *et al.* The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. *Muscle & Nerve* **41**, 500-510, doi:10.1002/mus.21544 (2010).
29 Connelly, D. M., Thomas, B. K. & Smith, R. E. Clinical utility of the 2-minute walk test for older adults living in long-term care. *Physiotherapy Canada* **61**, 78-87 (2009).
30 Marshall, W. A. & Tanner, J. M. Variations in the Pattern of Pubertal Changes in Boys. *Arch Dis Child* **45**, 13-23 (1970).
31 Ware, J. E. SF-36 Health Survey Update. *Spine* **25**, 3130-3139 (2000).

Appendix 1. Columbia-Suicide Severity Rating Scale: Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	___

Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 2. Columbia-Suicide Severity Rating Scale (C-SSRS): Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____

Deterrents

Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
What did you do?
Did you_____ as a way to end your life?
Did you want to die (even a little) when you_____?
Were you trying to end your life when you _____?
Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? *(*Self-Injurious Behavior without suicidal intent)

If yes, describe:

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Preparatory Acts or Behavior:
Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
If yes, describe:

Suicidal Behavior:
Suicidal behavior was present during the assessment period?

Suicide:

Answer for Actual Attempts Only

Actual Lethality/Medical Damage:
0. No physical damage or very minor physical damage (e.g., surface scratches).
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Potential Lethality: Only Answer if Actual Lethality=0
Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

 C-SSRS—Since Last Visit (Version 1/14/09)

Appendix 3. InQoL

HOW YOUR MUSCLE CONDITION AFFECTS YOU

This questionnaire is designed to see how your muscle condition affects you.

The first section will ask about your symptoms and how much they affect your life. NOT all the symptoms mentioned may apply to you in which case please indicate this where asked and move on to the next question.

The second section will be questions asking how you feel about your physical ability, independence, relationships, how you feel emotionally and the way you look.

The third and last section will ask about any treatment you might receive. You will be asked about the effects this treatment has had and the effects you expect it to have.

The information you provide will help doctors to understand your problems. This will mean they can work towards better care and treatment for you.

Please read the questions carefully and answer <u>all</u> the questions that apply to you.

Thank you.

SECTION 1

QUESTION 1:- YOUR MUSCLE WEAKNESS

1 Do you have any muscle weakness due to your muscle condition?
By weakness we mean any weakness in your face, arms, hands, legs and feet.

PLEASE CHECK ONE BOX

NO	
YES	

→ PLEASE GO TO **QUESTION 2** (NEXT PAGE)

a) How much weakness would you say you have in the muscles affected by your condition?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does your muscle weakness cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by your muscle weakness?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 2:- YOUR PAIN

2 Do you have any pain as a result of your muscle condition?

PLEASE CHECK ONE BOX

NO	→ PLEASE GO TO **QUESTION** 3 (NEXT PAGE)
YES	↓

a) How much pain would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does your pain cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by your pain ?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 3:- HOW TIRED YOU FEEL

3 Do you feel tired/ fatigued as a result of your muscle condition?

PLEASE CHECK ONE BOX

NO	☐ → PLEASE GO TO **QUESTION 4** (NEXT PAGE)
YES	☐ ↓

a) How much tiredness/ fatigue would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does your tiredness/ fatigue cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by your tiredness/ fatigue?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 4:- THE 'LOCKING' OF YOUR MUSCLES

4 Do you have any 'locking' (seizing up) of your muscles as a result of your muscle condition? By locking we mean a specific muscle symptom of myotonia which refers to difficulty relaxing the muscles after voluntary muscle contraction. Your particular muscle disease may not be associated with myotonia in which case check NO and go on to the next question.

PLEASE CHECK ONE BOX

NO	☐ → PLEASE GO TO **QUESTION 5** (NEXT PAGE)
YES	☐ ↓

a) How much muscle 'locking' would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does the 'locking' of your muscles cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by the 'locking' of your muscles?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 5:- DROOPY EYELIDS

5 Do you have any drooping of the eyelids as a result of your muscle condition?

PLEASE CHECK ONE BOX

NO	→ PLEASE GO TO **QUESTION 6** (NEXT PAGE)
YES	↓

a) How much drooping of the eyelids would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does the drooping of the eyelids cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by the drooping of the eyelids?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 6:- DOUBLE VISION

6 Do you have any double vision as a result of your muscle condition?

PLEASE CHECK ONE BOX

NO	→ PLEASE GO TO **QUESTION 6** (NEXT PAGE)
YES	↓

a) How much double vision would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does the double vision cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by the double vision?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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QUESTION 7:- SWALLOWING DIFFICULTY

7 Do you have any swallowing difficulty as a result of your muscle condition?

PLEASE CHECK ONE BOX

NO	→ PLEASE GO TO **QUESTION 7** (NEXT PAGE)
YES	↓

a) How much swallowing difficulty would you say you have at the moment?

PLEASE CIRCLE ONE NUMBER

Very little	Some	A fair amount	A moderate amount	A considerable amount	A lot	An extreme amount
1	2	3	4	5	6	7

b) Does the swallowing difficulty cause difficulties in your life at the moment?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moderate amount	A considerable amount	Very many	An extreme amount
0	1	2	3	4	5	6

c) How important to you are any difficulties caused by the swallowing difficulty?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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SECTION 2

QUESTION 1: THE THINGS YOU DO

A At the moment, does your muscle condition affect your ability to do the following activities?

PLEASE CIRCLE ONE NUMBER FOR EACH ITEM

	Not at all	Slightly	A fair amount	Moder-ately	Consid-erably	Very much	Extrem-ely
I. Daily activities (for example, bathing, dressing & housework)	0	1	2	3	4	5	6
II. Leisure activities	0	1	2	3	4	5	6
III. Work activities	0	1	2	3	4	5	6

If you have **no paid employment** (for example, you are unemployed or retired or do house-work), please check here ☐

If you are **not working due to your condition**, please check here ☐

B I. In the face of my condition, my ability to do all the things I want to do is:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like it to be	Good, but not quite how I would like it to be	OK, but not how I would like it to be	Neither good nor bad	Quite bad, but it could be much worse	Bad, but it could be worse	The worst it could possibly be
0	1	2	3	4	5	6

II. How important to you is the effect of your muscle condition on your ability to do all the things you want to do?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If your ability is '**exactly as you would like**', please check here ☐

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QUESTION 2: YOUR INDEPENDENCE

A **At the moment, how much help do you need from other people in carrying out your activities?** (for example, daily activities & going out)

None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very much	An extreme amount
0	1	2	3	4	5	6

B I. **In the face of my condition, my level of independence is:**

PLEASE CIRCLE ONE NUMBER

Exactly as I would like it to be	Good, but not quite how I would like it to be	OK, but not how I would like it to be	Neither good nor bad	Quite bad, but it could be much worse	Bad, but it could be worse	The worst it could possibly be
0	1	2	3	4	5	6

II. **How important to you is the effect of your muscle condition on your level of independence?**

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If your independence is '**exactly as you would like**', please check here ☐

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QUESTION 3: YOUR RELATIONSHIPS

A At the moment, does your muscle condition cause any difficulties in your relationships with the following people?

PLEASE CIRCLE ONE NUMBER FOR EACH ITEM

	None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very many	An extreme amount
I. Partner/ spouse	0	1	2	3	4	5	6
↓ If you are **not married or in a relationship** at the moment **or** if you are **widowed** please check here ☐							
II. Other family members	0	1	2	3	4	5	6
III. Friends	0	1	2	3	4	5	6
IV. Other people For example, strangers, acquaintances & co-wokers.	0	1	2	3	4	5	6

B I. In the face of my condition, my close family relationships are:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like them to be	Good, but not quite how I would like them to be	OK, but not how I would like them to be	Neither good nor bad	Quite bad, but they could be much worse	Bad, but they could be worse	The worst they could possibly be
0	1	2	3	4	5	6

II. How important to you is the effect of your muscle condition on your close family relationships?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If your close family relationship are '**exactly as you would like**', please checkhere ☐

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III. In the face of my condition, my close friendships are:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like them to be	Good, but not quite how I would like them to be	OK, but not how I would like them to be	Neither good nor bad	Quite bad, but they could be much worse	Bad, but they could be worse	The worst they could possibly be
0	1	2	3	4	5	6

IV. How important to you is the effect of your muscle condition on your close friendships?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If your close friendships are '**exactly as you would like**', please check here ☐

V. In the face of my condition, my relationships with other people (for example, acquaintances, strangers and co-workers) are:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like them to be	Good, but not quite how I would like them to be	OK, but not how I would like them to be	Neither good nor bad	Quite bad, but they could be much worse	Bad, but they could be worse	The worst they could possibly be
0	1	2	3	4	5	6

VI. How important to you is the effect of your muscle condition on your relationships with these other people?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If your relationships with others are '**exactly as you would like** ', please check here ☐

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QUESTION 4: HOW YOU FEEL

A At the moment, does your muscle condition make you feel:

PLEASE CIRCLE ONE NUMBER FOR EACH ITEM

	Not at all	Slightly	A fair bit	Moder-ately	Consid-erably	Very much	Extrem-ely
I. Anxious/worried	0	1	2	3	4	5	6
II. Depressed	0	1	2	3	4	5	6
III. Frustrated	0	1	2	3	4	5	6
IV. Low in confidence/ self-esteem	0	1	2	3	4	5	6

B I. In the face of my condition, the way I feel emotionally is:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like to be	Good, but not quite how I would like to be	OK, but not how I would like to be	Neither good nor bad	Quite bad, but I could be much worse	Bad, but I could be worse	The worst I could possibly be
0	1	2	3	4	5	6

II. How important to you is the effect of your muscle condition upon the way you feel emotionally?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If the way you feel emotionally is '**exactly as you would like**', please check here ☐

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QUESTION 5:- THE WAY YOU LOOK

A At the moment, does your muscle condition affect the way you look?
Your muscle condition might affect the way your body, face or skin looks or perhaps the way you move or whether you need to use a cane or wheelchair.

PLEASE CIRCLE ONE NUMBER

Not at all	Slightly	A fair amount	A moder-ate amount	A consid-erable amount	Very much	An extreme amount
0	1	2	3	4	5	6

B I. In the face of my condition, the way I look is:

PLEASE CIRCLE ONE NUMBER

Exactly as I would like to be	Good, but not quite how I would like to be	OK, but not how I would like to be	Neither good nor bad	Quite bad, but it could be much worse	Bad, but it could be worse	The worst it could possibly be
0	1	2	3	4	5	6

II. How important to you is the effect of your muscle condition upon the way you look?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

OR If the way you look is '**exactly as you would like**', please check here ☐

SECTION 3

QUESTION 1: TREATMENT

A Do you receive, or are you about to start receiving treatment for your muscle condition? (For example, surgery, tablets, injections or physiotherapy)

PLEASE CHECK ONE BOX

NO	→ PLEASE GO TO LAST PAGE
YES	↓

I. Do you feel the treatment you receive for your muscle condition has had beneficial effects?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very many	An extreme amount
0	1	2	3	4	5	6

If you are **not yet receiving treatment,** please check here ☐
If you are **unsure**, please check here ☐

II. Do you feel the treatment you receive for your muscle condition will have beneficial effects in the future?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very many	An extreme amount
0	1	2	3	4	5	6

If you are **unsure**, or if you have **not thought about it** please check here ☐

III. How important to you are the beneficial effects of treatment?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

B I. Do you feel the treatment you receive for your muscle condition has had harmful side effects?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very many	An extreme amount
0	1	2	3	4	5	6

If you are **not yet receiving treatment,** please check here ☐
If you are **unsure**, please check here ☐

II. Do you think the treatment you receive for your muscle condition will have side effects in the future?

PLEASE CIRCLE ONE NUMBER

None at all	Some	A fair amount	A moder-ate amount	A consid-erable amount	Very many	An extreme amount
0	1	2	3	4	5	6

If you are **unsure**, or if you have **not thought about it** please check here ☐

III. How important to you are the side effects of treatment?

PLEASE CIRCLE ONE NUMBER

Not at all important	Slightly important	Reason-ably important	Moderate-ly important	Consider-ably important	Very important	Extremely important
0	1	2	3	4	5	6

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COMMENTS

If you have any comments you would like to make about your condition and the way it affects you, please use the space below.

Your name (please print): _____

Today's date: ___/___/____

THANK YOU VERY MUCH FOR YOUR HELP

Appendix 4. SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3
g Walking more than a mile	☐1	☐2	☐3
h Walking several hundred yards	☐1	☐2	☐3
i Walking one hundred yards	☐1	☐2	☐3
j Bathing or dressing yourself	☐1	☐2	☐3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
›ody I know	☐1	☐2	☐3	☐4	☐5
¡et worse	☐1	☐2	☐3	☐4	☐5
	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!