CLINICAL PROTOCOL

A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG TERM SAFETY OF PF-06252616 IN BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

Compound:	PF-06252616
Compound Name:	Anti-myostatin
United States (US) Investigational New Drug (IND) Number:	113,863
European Clinical Trials Database (EudraCT) Number:	2016-001615-21
Protocol Number:	B5161004
Phase:	2

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes
Original Protocol	08 April 2016	Not applicable (N/A)

TABLE OF CONTENTS

APPENDICES

PROTOCOL SUMMARY

Background

This study is an open-label extension (OLE) to Protocol B5161002 and will provide an assessment of the long term safety, efficacy, pharmacodynamics (PD) and pharmacokinetics (PK) of intravenous (IV) dosing of PF-06252616 in boys with Duchenne muscular dystrophy (DMD).

Objectives and Endpoints

Objectives

- To evaluate the long-term safety of IV dosing of PF-06252616 in boys with DMD.
- To evaluate the long-term efficacy of PF-06252616 using functional assessments and strength.
- To assess the PK and immunogenicity of PF-06252616.
- To evaluate PD markers that may be informative in demonstrating the pharmacologic effect of PF-06252616.
- To evaluate the long-term functional health effects of PF-06252616 on Pediatric Outcomes Data Collection Instrument (PODCI) Parent-report and Adolescent self-report scores.
- To assess the long-term effects of PF-06252616 on health-related quality of life (HRQL) and healthcare resource utilization (HRU) in boys with DMD.
- To evaluate the long-term effects of PF-06252616 on caregiver burden, HRQL and work productivity and activity impairment.
- To collect exploratory biomarker samples for biobanking.

Endpoints

- Safety:
  - Incidence and/or rate of intolerability or dose limiting treatment related adverse events (AEs).
  - Incidence and/or rate, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAEs.
  - Incidence and magnitude of abnormal laboratory findings.
  - Abnormal and clinically relevant changes in liver magnetic resonance imaging (MRI) and physical examinations.

- Efficacy:
  - Baseline values and change from baseline in the following functional assessment tests; Pulmonary function test (PFTs) (to include forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1] and peak expiratory flow rate [PEFR]), 4 Stair Climb (4SC), Northstar Ambulatory Assessment (NSAA), Performance of Upper Limb (PUL), Range of motion (ROM) and 6 minute walk distance (6MWD).
  - Mean change from baseline in muscle strength measured by myometry.
- PK and Immunogenicity:
  - Trough serum PF-06252616 concentrations for all subjects receiving active drug.
  - Incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb).
- PD:
  - Change from baseline of Lean Body Mass (LBM) determined via whole body dual image x-ray absorptiometry (DXA).

Clinical Outcome Assessments (COA)

- Change from baseline in the Pediatric Outcomes Data Collection Instrument (PODCI) Parent-report and Adolescent self-report scores.
- Change from baseline in the EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) Health Questionnaire.
- Change from baseline in the EuroQol 5 Dimensions - Youth (EQ-5D-Y) Health Questionnaire.
- Change from baseline in the Healthcare Resource Utilization (HRU) questionnaire.
- Change from baseline in Zarit Burden Interview (ZBI).
- Change from baseline in the Work Productivity and Activity Impairment Questionnaire adapted for caregiving (WPAI:CG) in the percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to a child's Duchenne muscular dystrophy.

Study Design

Approximately 105 eligible subjects will be assigned to receive an individualized maximum tolerated dose based on their tolerability profile/data from B5161002. No placebo comparator will be assessed. Consenting subjects who complete the B5161002 study will be

invited to transition directly to the OLE study. Subjects' results from the B5161002 study may be used as screening data for the current study.

Study Treatments

The individual dose level selected for each subject will be based on the maximum tolerated dose from the parent Study B5161002. Subjects will be dosed with one of three PF-06252616 dose levels: 5 mg/kg, 20 mg/kg or 40 mg/kg.

Statistical Methods

Safety Analysis

Summary statistics will be performed on the following safety endpoints:

- Incidence and/or rate of intolerability or dose limiting treatment related AEs.
- Incidence and/or rate, severity and causal relationship of TEAEs and withdrawals due to TEAEs.
- Incidence and magnitude of abnormal laboratory findings.
- Abnormal and clinically relevant changes in liver MRI and physical examinations.

Analysis of efficacy and PD endpoints

Baseline values, change from baseline to last visit in PFTs, 4SC, NSAA, PUL, 6MWD, muscle strength by myometry and lean body mass by DXA will be described based on summary statistics including minimum, median, mean, maximum, and standard deviation. Change from baseline may also be assessed for any or all intermediate visits.

Analysis of PK and Immunogenicity

- Summary statistics will be provided for trough serum concentrations by dose.
- Incidence of ADA and NAb.

Analysis of Clinical Outcomes Assessments (Caregiver and patient-reported)

Summary statistics will be presented for the PODCI, EQ-5D-Y, EQ-5D-3L, Zarit Burden Interview, WPAI-CG, and HRU by baseline, treatment and time point as applicable. Methodology for any treatment group comparisons will be specified in the statistical analysis plan (SAP).

SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures for Year 1, Years 2-4 and Early Withdrawal. In order to accommodate the scheduling, assessments may be conducted on separate days within the visit window. Refer to the Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Study Flowchart: Year 1

		Year 1												
Visit Number[a]	**Screen[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week[a]		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Study Day[a]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window[a]	**Up to 42 days**		**± 3 days**											
Entry/Safety Assessments/Questionnaire														
Informed consent/Assent[b]	X													
Demography	X[a]													
Medical History	X[a]													
Medication History	X													
Inclusion/Exclusion Review	X	X												
Physical Examination[c]	X[a]				X			X			X			X
Tanner Stage and Testicular Volume[d]	X[a]													X
Height[e]	X[a]							X						X
Weight[f]	X[a]	→	→	→	→	→	→	→	→	→	→	→	→	→
Vital Signs[g]	X[a]	X			X			X			X			X
Single ECG	X[a]							X						X
Cardiac MRI (or Echocardiogram)[h]	X[a]													X

Year 1														
Visit Number[a]	**Screen**[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week[a]		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Study Day[a]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window[a]	**Up to 42 days**		**± 3 days**											
Clinical Laboratory Tests[i]	X[a]				X			X			X			X
Serum Ferritin, Serum Iron, TIBC, % Transferrin Saturation[i]	X[a]				X			X			X			X
Hormones (LH, FSH, T4, TSH, androstenedione, testosterone)[e]	X[a]													X
Fecal Occult Blood[j]	X[a]				X			X			X			X
Clinical Outcomes Assessments (Completed by Caregiver)														
PODCI Questionnaire[k]	X[a]				X			X						X
C-SSRS[L]	X[a]				X			X			X			X
EQ-5D-3L	X[m]				X			X						X
HRU	X[m]				X			X						X
ZBI	X[m]				X			X						X
WPAI-CG	X[m]				X			X						X
Clinical Outcomes Assessments (Completed by Subject)														
PODCI Questionnaire	X[m,n]				X			X						X
EQ-5D-Y	X[m]				X			X						X
Imaging Assessments														
MRI-Liver	X[a]							X						X
DXA-Spine	X[a]													X
DXA-Whole Body	X[a]													X
X-ray (hand and wrist)[d]	X[a]													X
Functional Assessments														
Ambulatory Status[o]	X	→	→	→	→	→	→	→	→	→	→	→	→	X
PFTs	X				X			X						X
4 Stair Climb[p]	X[a]				X			X						X

Year 1														
Visit Number[a]	**Screen**[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week[a]		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Study Day[a]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window[a]	**Up to 42 days**		**± 3 days**											
Northstar Ambulatory Assessment[p]	X[a]				X			X						X
Range of Motion	X[a]				X			X						X
Strength Assessment	X[a]				X			X						X
PUL	X[a]				X			X						X
6MWT[p]	X[a]				X			X						X
Investigational Product Administration														
Investigational Product administration[q]		X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD, Immunogenicity and Biobanking														
PK sample[r]	X[a]							X						X
Immunogenicity	X[a]							X						X
Group 1 and Group 2 Biomarkers	X													X
Infusion Site Reaction monitoring		X	→	→	→	→	→	→	→	→	→	→	→	X
Adverse event monitoring		X	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant medication		X	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: → = ongoing/continuous monitoring; 6MWT=Six minute walk test; C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG =electrocardiogram; EQ-5D-3L=EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y=EuroQoL 5 Dimensions - Youth; FSH=Follicle stimulating hormone; HRU=Healthcare Resource Utilization; LH=Luteinizing hormone; MRI=magnetic resonance image; PD=Pharmcodynamics; PFTs =pulmonary function tests; PK=Pharmocokinetics, PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance of Upper Limb, T4=thyroxine; TIBC=Total iron binding capacity, TSH=thyroid stimulating hormone; WPAI-CG=Work Productivity and Activity Impairment questionnaire adapted for Caregiving; ZBI=Zarit Burden Interview.

a. Subjects will enroll in the study within 42 days of completion of the Week 97 of the parent study B5161002. If this window is exceeded, the sponsor and investigator will assess if the subject may still participate in this OLE study, and which, if any assessments must be completed to confirm eligibility. If needed assessments may be performed on consecutive days within the study visit window. For example where functional assessments and imaging assessments are collected at the same visit, subjects can be assessed over a 2 day period. Demography and medical history will be collected from Study B5161002. The following assessments may be collected as screening data from subject's Week 97 visit within Study B5161002. These include: Physical

Year 1														
Visit Number[a]	**Screen**[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week[a]		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Study Day[a]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window[a]	**Up to 42 days**		**± 3 days**											

Examination, Tanner Stage and Testicular Volume, Height, Weight, Vital Signs, Single ECG, Cardiac MRI (or Echocardiogram), Clinical Laboratory Tests, GLDH, Serum Ferritin, Serum Iron, TIBC%, Transferrin Saturation, Hormones (LH, FSH, T4, TSH, andostenedione, testosterone), Fecal Occult Blood, PODCI, C-SSRS, MRI-Liver (data from Week 93), DXA-Spine, DXA-Whole Body, X-ray (hand and wrist), Functional Assessments (not including ambulatory status which is not collected in B5161002), PK, Immunogenicity.

b. Informed consent must be provided by the subject's caregiver (parent or legal guardian). Subject will be required to provide assent in compliance with local regulations and IRB/EC requirements.

c. The physical examination will also include a nose and throat mucosal exam.

d. Once sexual maturity is reached defined as Tanner Stage V, Tanner stage and Testicular Volume, x-ray (hand and wrist) and hormone testing are no longer mandatory.

e. Height and hormone testing should be performed in the morning. If a subject is unable to stand safely, an estimated height can be calculated using the subject's ulnar length and the instructions provided in the functional assessment manual.

f. Weight will be collected at each visit. The weight from the current visit or the previous month's visit can be used to calculate the appropriate dose by body weight.

g. Vital sign evaluations will include pre-dose supine blood pressure, pulse rate, respiratory rate and temperature.

h. Cardiac MRI is the preferred method of imaging, If it is not possible to perform cardiac MRI (eg, not available at the site) echocardiogram will be acceptable. The same method of cardiac imaging utilized in B5161002 should be used consistently within a single subject through Study B5161004. Cardiac MRI with gadolinium should only be performed after all other imaging assessments are completed.

i. Clinical laboratory tests include hematology, chemistry, gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, and urinalysis. In Year 1, cardiac troponin I will be collected at Screening, Week 49 and Early Withdrawal only.

j. If a Week 97 B5161002 stool sample result is not available at the screening visit, a collection kit and mailing supplies will be sent home and the caregiver will be responsible for collection and mailing the sample back to the site. For all other visits after screening, a stool sample will be collected at home within approximately 1 week prior to the scheduled visit.

k. PODCI Completed by Parent/Caregiver.

l. For the C-SSRS the "Children's Since Last Visit" assessment will be performed. This will be completed by the caregiver.

m. The PODCI Adolescent self-report, EQ-5D-Y, EQ-5D-3L, ZBI, and HRU questionnaires are new assessments not included in the parent study B5161002 and should be collected at screening and all subsequent visits outlined in the Schedule of Activities. If a subject is unwilling to provide self-reported data

Year 1														
Visit Number[a]	**Screen[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week[a]		**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Study Day[a]		**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window[a]	**Up to 42 days**		**± 3 days**											

they can still participate in the study.

n. Children will become eligible to complete the Adolescent self-report version of the PODCI when they turn 11 years of age at which time they should be asked to complete the PODCI Adolescent self-report version at indicated time points throughout the study. In addition, caregivers will continue to complete the PODCI Parent-report (2-10 years) version throughout the study. If a subject is unwilling to provide self-reported data they can still participate in the study.

o. Ambulatory status will be recorded at the screening visit. Ambulation is defined as the ability to walk unassisted and without braces for at least 10 m. At subsequent visits if subject becomes non-ambulatory this should be recorded.

p. If a loss of ambulation has occurred 4 Stair Climb, Northstar Ambulatory Assessment and 6MWT do not need to be completed. Please record date that ambulation was lost.

q. Investigational product should be delivered in a 2 hour window ±30 minutes including the flush time. 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 should be conducted per the Schedule of Activities.

r. PK samples to be taken prior to dosing.

Study Flowchart: Year 2, 3 and 4 and Early Withdrawal

	Year 2,3,4 and Early Withdrawal													
Visit Number[a]	**14 26, 38**	**15, 27, 39**	**16 28, 40**	**17, 29, 41**	**18, 30, 42**	**19, 31, 43**	**20, 32, 44**	**21, 33, 45**	**22, 34, 46**	**23, 35, 47**	**24, 36, 48**	**25, 37, 49**		**Early Withdrawal**
Study Week[a]	**53, 101, 149**	**57, 105, 153**	**61, 109, 157**	**65, 113, 161**	**69 117, 165**	**73, 121, 169**	**77, 125, 173**	**81, 129, 177**	**85, 133, 181**	**89, 137, 185**	**93, 141, 189**	**97, 145, 193**		
Study Day[a]	**365, 701, 1037**	**393, 729, 1065**	**421, 757, 1093**	**449, 785, 1121**	**477, 813, 1149**	**505, 841, 1177**	**533, 869, 1205**	**561, 897, 1233**	**589, 925, 1261**	**617, 953, 1289**	**645, 981, 1317**	**673, 1009, 1345**		
Visit Window	**± 3 days**													
Safety Assessments/Questionnaire														
Physical Examination[b]			X			X			X			X		X
Tanner Stage and Testicular Volume[c]						X						X		X
Height[d]						X						X		X
Weight[e]	X	→	→	→	→	→	→	→	→	→	→	X		X
Vital Signs[f]			X			X			X			X		X
Single ECG			X			X			X			X		X
Cardiac MRI (or Echocardiogram)[g]												X		X
Clinical Laboratory Tests[h]			X			X			X			X		X
Serum Ferritin, Serum Iron, TIBC, % Transferrin Saturation[h]			X			X			X			X		X
Hormones (LH, FSH, T4, TSH, androstenedione, testosterone)[c,d]						X						X		X
Fecal Occult Blood[i]			X			X			X			X		X
Clinical Outcomes Assessments (Completed by Caregiver)														
PODCI Questionnaire[j]						X						X		X
C-SSRS[k]						X			X			X		X
EQ-5D-3L						X						X		X
HRU						X						X		
ZBI						X						X		X
WPAI-CG						X						X		X
Clinical Outcomes Assessments (Completed by Subject)														
PODCI Questionnaire[L]	X					X						X		X
EQ-5D-Y	X					X						X		X
Imaging Assessments														

	Year 2,3,4 and Early Withdrawal													
Visit Number[a]	**14 26, 38**	**15, 27, 39**	**16 28, 40**	**17, 29, 41**	**18, 30, 42**	**19, 31, 43**	**20, 32, 44**	**21, 33, 45**	**22, 34, 46**	**23, 35, 47**	**24, 36, 48**	**25, 37, 49**		**Early Withdrawal**
Study Week[a]	**53, 101, 149**	**57, 105, 153**	**61, 109, 157**	**65, 113, 161**	**69 117, 165**	**73, 121, 169**	**77, 125, 173**	**81, 129, 177**	**85, 133, 181**	**89, 137, 185**	**93, 141, 189**	**97, 145, 193**		
Study Day[a]	**365, 701, 1037**	**393, 729, 1065**	**421, 757, 1093**	**449, 785, 1121**	**477, 813, 1149**	**505, 841, 1177**	**533, 869, 1205**	**561, 897, 1233**	**589, 925, 1261**	**617, 953, 1289**	**645, 981, 1317**	**673, 1009, 1345**		
Visit Window	**± 3 days**													
MRI-Liver						X						X		X
DXA-Spine												X		X
DXA-Whole Body												X		X
X-ray (hand and wrist) [c]												X		X
Functional Assessments														
Ambulatory status[m]	X	→	→	→	→	→	→	→	→	→	→	X		X
PFTs						X						X		X
4 Stair Climb[n]						X						X		X
Northstar Ambulatory Assessment[n]						X						X		X
Range of Motion						X						X		X
Strength Assessment						X						X		X
PUL						X						X		X
6MWT[n]						X						X		X
Investigational Product Administration														
Investigational Product administration[o]	X	X	X	X	X	X	X	X	X	X	X	X		
PK/Immunogenicity														
PK sample[p]						X						X		X
Immunogenicity						X						X		X
Biobanking Sample (Group 1 and Group 2 Biomarkers)												X		
Infusion Site Reaction monitoring	X	→	→	→	→	→	→	→	→	→	→	→		X
Adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→		X
Concomitant medication	X	→	→	→	→	→	→	→	→	→	→	→		X

Abbreviations: → = ongoing/continuous monitoring; 6MWT=Six minute walk test; C-SSRS=Columbia Suicide Severity Rating Scale, DXA=Dual-energy x-ray absorptiometry; ECG = electrocardiogram; EQ-5D-3L=EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y=EuroQoL 5 Dimensions - Youth; FSH= Follicle stimulating hormone; HRU=Healthcare Resource Utilization; LH= Luteinizing hormone; MRI=magnetic resonance image; PD=Pharmcodynamics; PFTs = pulmonary function tests; PK=Pharmocokinetics, PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance of Upper Limb, T4 =thyroxine; TIBC=Total

	Year 2,3,4 and Early Withdrawal												
Visit Number[a]	**14 26, 38**	**15, 27, 39**	**16 28, 40**	**17, 29, 41**	**18, 30, 42**	**19, 31, 43**	**20, 32, 44**	**21, 33, 45**	**22, 34, 46**	**23, 35, 47**	**24, 36, 48**	**25, 37, 49**	**Early Withdrawal**
Study Week[a]	**53, 101, 149**	**57, 105, 153**	**61, 109, 157**	**65, 113, 161**	**69 117, 165**	**73, 121, 169**	**77, 125, 173**	**81, 129, 177**	**85, 133, 181**	**89, 137, 185**	**93, 141, 189**	**97, 145, 193**	
Study Day[a]	**365, 701, 1037**	**393, 729, 1065**	**421, 757, 1093**	**449, 785, 1121**	**477, 813, 1149**	**505, 841, 1177**	**533, 869, 1205**	**561, 897, 1233**	**589, 925, 1261**	**617, 953, 1289**	**645, 981, 1317**	**673, 1009, 1345**	
Visit Window	**± 3 days**												

iron binding capacity, TSH=thyroid stimulating hormone; WPAI-CG=Work Productivity and Activity Impairment questionnaire adapted for Caregiving; ZBI=Zarit Burden Interview.

a. If needed assessments may be performed on consecutive days within the study visit window. For example where functional assessments and imaging assessments are collected at the same visit, subjects can be assessed over a 2 day period.

b. The physical examination will also include a nose and throat mucosal exam.

c. Once sexual maturity is reached defined as Tanner Stage V, Tanner stage and Testicular Volume, x-ray (hand and wrist) are no longer mandatory.

d. Height and hormone testing should be performed in the morning.

e. Weight will be collected at each visit. The weight from the current visit or the previous month's visit can be used to calculate the appropriate dose by body weight.

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

g. Cardiac MRI is the preferred method of imaging. If it is not possible to perform cardiac MRI (eg, not available at the site) echocardiogram will be acceptable. The same method of cardiac imaging utilized in B5161002 should be used consistently within a single subject through Study B5161004. Cardiac MRI with gadolinium should only be performed after all other imaging assessments are completed

h. Clinical laboratory tests include hematology, chemistry, gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, and urinalysis. Cardiac troponin I will be collected at Week 97, 145, 193 and Early Withdrawal.

i. A stool sample will be collected at home within approximately 1 week prior to the scheduled visit.

j. PODCI Completed by Parent/Caregiver.

k. For the C-SSRS the "Children's Since Last Visit" assessment will be performed. This will be completed by the caregiver.

l. The PODCI Adolescent self-report if applicable. Children will become eligible to complete the Adolescent self-report version of the PODCI when they turn 11 years of age at which time they should be asked to complete the PODCI Adolescent self-report version at indicated time points throughout the study. In addition, caregivers will continue to complete the PODCI Parent-report (2-10 years) version throughout the study. If a subject is unwilling to provide self-

	Year 2,3,4 and Early Withdrawal												
Visit Number[a]	**14 26, 38**	**15, 27, 39**	**16 28, 40**	**17, 29, 41**	**18, 30, 42**	**19, 31, 43**	**20, 32, 44**	**21, 33, 45**	**22, 34, 46**	**23, 35, 47**	**24, 36, 48**	**25, 37, 49**	**Early Withdrawal**
Study Week[a]	**53, 101, 149**	**57, 105, 153**	**61, 109, 157**	**65, 113, 161**	**69 117, 165**	**73, 121, 169**	**77, 125, 173**	**81, 129, 177**	**85, 133, 181**	**89, 137, 185**	**93, 141, 189**	**97, 145, 193**	
Study Day[a]	**365, 701, 1037**	**393, 729, 1065**	**421, 757, 1093**	**449, 785, 1121**	**477, 813, 1149**	**505, 841, 1177**	**533, 869, 1205**	**561, 897, 1233**	**589, 925, 1261**	**617, 953, 1289**	**645, 981, 1317**	**673, 1009, 1345**	
Visit Window	**± 3 days**												

reported data they can still participate in the study.

m. Ambulatory status should be reviewed at each visit. Ambulation is defined as the ability to walk unassisted and without braces for at least 10 m. If a subject becomes non-ambulatory this should be recorded in the CRF.

n. If a loss of ambulation has occurred 4 Stair Climb, Northstar Ambulatory Assessment and 6MWT do not need to be completed. Please record date that ambulation was lost.

o. Investigational product should be delivered in a 2 hour window ±15 minutes including the flush time. 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 should be conducted per the Schedule of Activities.

p. PK samples to be taken prior to dosing.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06252616 is a humanized monoclonal antibody which binds and neutralizes myostatin, also known as growth differentiation factor 8 (GDF-8), a negative regulator of muscle mass.

The proposed indication is the treatment of Duchenne muscular dystrophy (DMD).

Protocol B5161004 is an open-label extension (OLE) to Protocol B5161002 and will provide an assessment of the long term safety, efficacy, PD and PK of IV dosing of PF-06252616 in boys with DMD.

1.2. Background and Rationale

1.2.1. Myostatin Role in Muscle Regulation

Myostatin or GDF-8 is a member of the transforming growth factor-β (TGFβ) superfamily of secreted differentiation factors (McNally, 2004). The role of GDF-8 as a negative regulator of muscle fiber growth and mass is well conserved between zebrafish, dogs, cattle, mice and humans. The effect of inhibiting GDF-8 has been best studied in skeletal muscle; knockout GDF-8 -/- mice possess muscles that are 100% to 200% larger than wild type controls due to a combination of muscle fiber hyperplasia and hypertrophy (McPherron et al, 1997). Despite having increased skeletal muscle and decreased fat, the GDF-8 knockout 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 (McNally, 2004). 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, in which the boy was found to have increased muscle strength and, by age 4, no apparent untoward health effects (Schuelke et al, 2004). Pharmacologic inhibition of GDF-8 activity in rodents resulted in increased muscle mass and improved muscle function in both normal and dystrophic animals (Bradley et al, 2008). 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.

1.2.2. Duchenne Muscular Dystrophy

DMD is the most frequently inherited neuromuscular disease, and predominantly affects boys. It is an X-linked muscular dystrophy caused by a mutation at Xp21 in the gene coding for the protein dystrophin (Bushby et al, 2010; Manzur et al, 2008) which is absent from the muscle of boys with DMD. DMD is the most severe of all muscular dystrophies and is characterized by skeletal and cardiac muscle degeneration. Boys with DMD are phenotypically unremarkable at birth; onset of symptoms usually occurs around two to three years of age. Most boys lose the ability to walk between the ages of 10 and 14 (Lamperti & Moggio, 2010). Progressive cardiac problems manifest in the second decade.

There is no approved treatment that can stop or reverse the progression of DMD. Glucocorticoid therapy, although not specifically approved for use in DMD, is the only pharmacotherapy that has been demonstrated to ameliorate symptoms in patients with DMD,

irrespective of underlying mutation, and is currently the standard of care. Although glucocorticoids may improve muscle strength for a period of time and delay the loss of ambulation, (Mendell et al, 1989; Bonifati et al, 2000), chronic use is associated with well-known adverse events such as weight gain and broad hypothalamic-pituitary-adrenal axis effects which eventually lead to the discontinuation of treatment, often in the teenage years.

Additional disease management consists primarily of supportive care which ranges from physical therapy to maximize function and minimize muscle contractures, to orthotics, tendon release surgery (which provides temporary benefit as contractures will redevelop), use of wheel chair (usually by age 12), surgical correction of scoliosis and use of respiratory care including various forms of assisted ventilation (including tracheotomy). Respiratory infections may be treated with antibiotics. Death from pneumonia or cardiac involvement in late teens or early twenties is commonly observed in these patients (Manzur et al, 2008).

1.2.3. 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 in a single use glass vial. The vials will be reconstituted with sterile water for injection (SWFI). The reconstituted PF-06252616 drug product is clear to slightly opalescent and colorless to slightly colored in appearance.

1.3. Clinical Experience with PF-06252616

The clinical program for PF-06252616 was initiated in June 2012 with a Phase 1 first-in-human (FIH), randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled study (B5161001) evaluating the safety, tolerability, pharmacokinetic, pharmacodynamic, and pharmacologic (anabolic) effects of escalating single doses of PF-06252616 in healthy adult subjects. The study is complete with 73 subjects enrolled at a single site. Single 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 were studied. In addition, a repeat IV administration of PF-06252616 10 mg/kg at 2 week intervals over a 28-day treatment period was investigated. Safety was demonstrated at all dose levels and there were no dose-related trends in frequency of reported treatment-emergent adverse events (TEAEs).

The Protocol B5161002 is the first-in-patient (FIP) study with PF-06252616. This Phase 2 randomized, 2-period, double blind, placebo-controlled, multiple-ascending dose study aims to provide initial clinical assessment of the safety, efficacy, PK, and PD of PF-06252616

following repeat IV doses in ambulatory boys with DMD. Additionally, it aims to demonstrate the efficacy of treatment over 3 escalated IV dose levels of PF-06252616 based on an observed mean change from baseline on function 4SC as compared to placebo following 49 weeks of treatment. The study is ongoing and plans to enroll approximately 105 eligible subjects who will be randomly assigned to 1 of 3 sequence groups and receive placebo or investigational product PF-06252616 at 3 escalating dose levels of 5 mg/kg IV, 20 mg/kg IV, and 40 mg/kg IV administered every 4 weeks for approximately 96 weeks (2 treatment periods of approximately 48 weeks each).

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

1.4. Rationale for Dosage Selection and Method of Administration

The dose for each subject will be based on their individual maximum tolerated dose (MTD) up to 40 mg/kg from Study B5161002. This study will use the same route and frequency of administration as Study B5161002. IV was chosen as the route of administration for B5161002 to support the large dose that will be required to obtain the targeted GDF-8 coverage. The frequency of administration was chosen as 4 weeks to achieve targeted GDF-8 coverage but also to reduce the burden on subject travel to study sites.

1.5. Study Design Rationale

This is an OLE of the B5161002 study designed primarily to evaluate the long-term safety of PF-06252616 as well as to collect data regarding maintenance of effect up to 4 years.

1.6. Anticipated Risks and Safety Monitoring

Anticipated risks are based on clinical and toxicology data which can be found in the IB.

1.6.1. Hepatic Injury

CCI [redacted] In DMD, serum alanine transaminase (ALT) and aspartate transaminase (AST) elevation related to muscle pathology is common and well described (McMillan et al, 2011). Therefore the utility of these enzymes as markers of hepatocellular injury is limited. Glutamate dehydrogenase (GLDH) has been identified as a biomarker of liver injury that is independent of muscle damage. Using a validated assay, GLDH will be evaluated to provide additional information regarding liver function.

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. Subject data meeting these criteria will be referred to the external data monitoring committee (E-DMC) for review. In addition, Liver MRI will be obtained according to the Schedule of Activities to monitor for safety by

quantifying iron accumulation. The E-DMC will include a Hepatic Expert to review any cases of potential liver toxicity.

1.6.2. Gastric Erosion and Haemorrhage

CCI [redacted] Given the use of systemic glucocorticoids in the DMD population, there is a risk of increased incidence of gastric erosion and haemorrhage. Study subjects will therefore be asked specifically to report symptoms that may be associated with such pathology. Monitoring of haemoglobin, haematocrit and fecal occult blood will be performed.

1.6.3. CCI [redacted] Sexual Development

CCI [redacted] Given the target population of DMD pre-pubertal boys, this effect needs to be monitored. Tanner staging and testicular volume will be used to monitor pubertal development, in addition to the measurement of sex hormone levels and bone age with a wrist and hand X-ray assessment. Should boys reach sexually maturity during the trial as indicated by a Tanner Stage V rating, monitoring will no longer be mandatory.

1.6.4. Bone Metabolism

CCI [redacted] is therefore appropriate to examine BMD in the DMD population. CCI [redacted] effect on BMD – especially in those treated with glucocorticoids – would clearly be CCI [redacted] DXA will be used to monitor for changes in BMD.

1.6.5. Cardiac

CCI [redacted] However, based on literature regarding the biology of GDF-8 and GDF-11 and their potential modulation of cardiomyocyte and cardiac function, combined with the known cardiac dysfunction in the target population of DMD boys, it is appropriate to focus on the potential for an interaction between the drug and the underlying disease state. The ongoing Phase 2 Study (B5161002) includes monitoring with 12-lead electrocardiogram (ECG) for rhythm or morphological change, cardiac Troponin I for cardiac muscle tissue injury, and cardiac MRI with gadolinium (or echocardiography if cardiac MRI is not available at the site) to evaluate left ventricular

ejection fraction (LVEF). Subjects will remain on the same imaging modality to assure consistency in safety measure from Study B5161002 through Study B5161004. Additional cardiac parameters (eg, left ventricular wall thickness, cardiac strain, and fibrosis) may be collected during cardiac MR imaging for exploratory analyses. Abnormal values for each of these measures have been reported in DMD, even in patients under the age of 10. In light of the variability of findings during the natural history of the disease, no pre-specified stopping rules have been defined. Cardiac monitoring will continue in this study as outlined in the Schedule of Activities.

1.6.6. Radiation

The possible risks related to subjects undergoing evaluation with DXA and x-ray for bone age includes the risk of radiation exposure. The average effective dose of radiation received for a single DXA scan or hand x-ray for bone age may vary due to the instrument and the subject's body. Annual assessments include a whole body DXA scan, a DXA spine scan and a single x-ray image of the hand and wrist. The expected annual radiation dose resulting from these scans for a subject participating in this study should not exceed 0.15 mSv per year. This is less than 1 month of natural background radiation which is approximately 0.25 mSv per month (Environment, Health & Safety (EHS) Radiation Risk; Blake et al, 2006).

1.6.7. Other Risks

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

1.6.8. Other Safety Monitoring

Additional safety monitoring will include the parameters of adverse events (AEs), physical examination, vital signs, and clinical laboratory parameters (including urinalysis, hematology, gamma-glutamyl transferese [GGT], GLDH, prothrombin time/activated partial thromboplastin time [PT/aPTT], creatine kinase, amylase, and chemistry) and Columbia Suicide Severity Rating Scale (C-SSRS) (see Clinical Outcomes Assessment manual). Laboratory monitoring will also be performed to detect ADA and NAb.

1.7. Summary of Risk Benefit

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 DMD. 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 Objective

To evaluate the long-term safety of IV dosing of PF-06252616 in boys with DMD.

2.1.2. Secondary Objectives

- To evaluate the long-term efficacy of PF-06252616 using functional assessments and strength.
- To assess the PK and immunogenicity of PF-06252616.

2.1.3. Exploratory Objectives

- To evaluate PD markers that may be informative in demonstrating the pharmacologic effect of PF-06252616.
- To evaluate the long-term functional health effects of PF-06252616 on Parent-report and Adolescent self-report scores on the PODCI.
- To assess the long-term effects of PF-06252616 on HRQL and healthcare resource utilization (HRU) in boys with DMD.
- To evaluate the long-term effects of PF-06252616 on caregiver burden, HRQL and work productivity and activity impairment.
- To collect exploratory biomarker samples for bio-banking.

2.2. Endpoints

2.2.1. Primary endpoints

2.2.1.1. Safety

- Incidence and/or rate of intolerability or dose limiting treatment related AEs following up to 4 years of treatment.
- Incidence and/or rate, severity and causal relationship of TEAEs and withdrawals due to TEAEs following up to 4 years of treatment.
- Incidence and magnitude of abnormal laboratory findings (clinical laboratory tests: hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase, serum ferritin, serum iron, total iron binding capacity (TIBC), % transferrin saturation. Hormones: luteinizing hormone [LH], follicle stimulating hormone [FSH], thyroxine [T4], thyroid stimulating hormone [TSH]. Fecal occult blood, cardiac Troponin I and urinalysis) following up to 4 years of treatment.
- Abnormal and clinically relevant changes in liver MRI and physical examinations (including nose and throat mucosal exam and Tanner stage and Testicular Volume), weight, vitals, electrocardiogram (ECG), LVEF measured by cardiac MRI (or echocardiogram), bone mineral density by DXA, x-ray (hand and wrist for bone age evaluation) and C-SSRS.

2.2.2. Secondary endpoints

2.2.2.1. Efficacy

- Mean change from baseline following up to 4 years of treatment in the following functional assessment tests PFTs (to include FVC, FEV_1 and PEFR), 4SC, NSAA, PUL, ROM and 6MWD.

- Mean change from baseline in muscle strength measured by myometry following up to 4 years of treatment.

2.2.2.2. PK and Immunogenicity

Trough serum PF-06252616 concentrations for all subjects receiving active drug.

- Incidence of ADA and NAb.

2.2.3. Exploratory Endpoints

2.2.3.1. PD

To evaluate change from baseline of Lean Body Mass (LBM) determined via whole body DXA after up to 4 years of treatment.

2.2.3.2. Clinical Outcome Assessments

- To evaluate the long-term functional health effects of PF-06252616:

    - Changes from baseline in the Pediatric Outcomes Data Collection Instrument (PODCI) Parent-report and Adolescent self-report scores.

- Change from baseline in the EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) Health Questionnaire.

- Change from baseline in the EuroQol 5 Dimensions - Youth (EQ-5D-Y) Health Questionnaire.

- Change from baseline in Healthcare Resource Utilization (HRU) questionnaire.

- Change from baseline in Zarit Burden Interview (ZBI).

- Change from baseline in the Work Productivity and Activity Impairment. Questionnaire adapted for caregiving (WPAI:CG) in the percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to a child's Duchenne muscular dystrophy.

- Pooled or exploratory analyses, if conducted, utilizing the biobanked exploratory genomic and biomarker samples will be documented in the statistical analysis plan.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2 OLE to protocol B5161002 and will provide an assessment of the long term safety, efficacy, PD and PK of IV dosing of PF-06252616 in boys with DMD.

The individual dose level selected for each subject will be based on the maximum tolerated dose (MTD) from the parent study B5161002. However, dose levels may be adjusted based on emerging safety or efficacy data from B5161002.

Subjects will be dosed with one of three PF-06252616 dose levels:

- 5 mg/kg
- 20 mg/kg
- 40 mg/kg

Approximately 105 eligible subjects will be assigned to receive an individualized MTD based on their tolerability profile/data from B5161002. No placebo comparator will be assessed. Consenting subjects who complete the B5161002 study will be invited to transition directly to the OLE study. Subjects' results from the B5161002 study may be used as screening data for the current study if the subject is enrolled within 42 days of Week 97 visit of B5161002, see Schedule of Activities and Assessments for details. If this window is exceeded, the sponsor and investigator will assess if the subject may still participate in this OLE study, and which, if any, assessments must be completed to confirm eligibility.

3.2. Duration of Study and Subject Participation

The OLE study is planned to be conducted over a period of 4 years. The end of the study will be the last visit of the last subject for purposes of closing out sites, informing the institutional review board/ethics committee (IRB/EC), and ceasing to send Council for International Organizations of Medical Sciences (CIOMS) reports.

Depending on when subjects begin the OLE study, their participation may be as long as 4 years. Subjects may be withdrawn from the OLE study should the parent study, B5161002 fail to meet its planned study objectives, is terminated early for other reasons (eg, sponsor decision) or the drug is commercialized.

Subjects will be administered monthly infusions of study drug as well as completion of safety and efficacy assessments as per the Schedule of Activities.

In the case where subjects are traveling from a distance, local overnight accommodation will be offered.

3.3. Planned Number of Subjects

Approximately 105 subjects will participate in multiple centers and countries worldwide.

3.4. Safety Monitoring and the E-DMC

From the time of study initiation through completion of the study, the sponsor will conduct routine safety monitoring of the data per the safety review plans. In addition, the E-DMC will periodically review safety data as outlined in Section 3.4.1.

3.4.1. External Data Monitoring Committee (E-DMC)

The E-DMC will include experts in the field of neuromuscular diseases and/or statistics. Members of the E-DMC will not be Pfizer employees. The E-DMC will be responsible for ongoing efficacy and safety monitoring and its reviews will include aggregate safety, targeted medical events of special interest including liver toxicity, and serious adverse event (SAE) data. Additional ad hoc safety reviews may be performed as described in the E-DMC charter.

Following each data review, the E-DMC will provide a recommendation to the sponsor management to continue the study, modify the study and then continue (eg, but not limited to terminate a dose level, remove the liver MRI or other monitoring assessments), or stop the study (eg, due to safety). The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to the sponsor management for final decision. The sponsor management will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. At any time the E-DMC 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.

Additional details of the type, timing and responsibilities of the E-DMC will be included in the E-DMC charter.

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 participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject and caregiver 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. Subjects with Duchenne muscular dystrophy who enrolled and completed through Week 97 of Study B5161002.

2. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject's parent or legal guardian/caregiver has been informed of all pertinent aspects of the study. Subjects may be required to provide assent in compliance with local regulations and IRB requirements.

3. Subjects and their legal guardians/caregivers who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4. The following inclusion criteria will be assessed using data from the B5161002 study, and if data are unavailable, these assessments must be completed prior to enrollment:

    a. Adequate hepatic function on screening laboratory assessments from the Week 97 visit.

    b. GLDH ≤ 20 units/liter (2 x upper limit of normal [ULN]) from the Week 97 visit.

    c. Iron content estimate on the liver MRI within the normal range as determined by R2* value (R2*≤75 Hz at 1.5 T or R2*≤139 Hz at 3.0 T) from the Week 93 visit.

4.2. Exclusion Criteria

The following exclusion criteria will be assessed using Week 97 data from the B5161002 study, but if unavailable, these assessments must be completed prior to enrollment:

1. Unwilling or unable (eg, metal implants) to undergo examination with closed MRI. If subjects required sedation in the B5161002 study they will be permitted to enroll in the OLE. In the event that a subject becomes intolerant to MRI scanning, during the OLE, the subject may be separately consented to be administered sedation in order to complete the MRI.

2. All male subjects who are able to father children and are sexually active and at risk for impregnating a female partner, who are unwilling or unable to use with their female partner(s) a highly effective method of contraception consistently and correctly for the duration of the active treatment period and through the final study visit. In addition, all sexually active male subjects who are unwilling or unable 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.

3. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are related to Pfizer employees directly involved in the conduct of the study.

4. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

5. Participation in other studies involving investigational drug(s), with the exception of B5161002, for a minimum of 30 days or within 5 half-lives (whichever is longer) prior to signing the informed consent and/or during study participation.

6. History of allergic or anaphylactic reaction to a therapeutic or diagnostic protein or additives of this investigational product (histidine, sucrose, edetic acid [ethylenediaminetetraacetic acid], and polysorbate 80).

Note: 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. The reason for repeating the assessment should be documented.

4.3. Enrolment

Subjects will be enrolled into the study provided they have satisfied all eligibility criteria. In order to provide the screening data from Study B5161002 to Study B5161004, and for programming to recognize the continuation of the subject, the site will complete an electronic case report form (eCRF) where subject numbers are recorded for both the parent Study B5161002 and OLE Study B5161004.

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 will be asked to fast for at least 8 hours prior to collection of blood to evaluate serum ferritin, serum iron, TIBC and % transferrin saturation.

- Subjects should avoid large meals for at least 2 hours prior to the DXA scan. Juice, water and small snacks may be permitted. Subjects should be in a state of euhydration. 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 from eating red meat, turnips, horseradish, or medications containing aspirin or vitamin C and should consume only 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 subjects who are able to father children and are sexually active and at risk for impregnating a female partner, must agree to use with their female partner(s) a highly effective method of contraception consistently and correctly for the duration of the active treatment period and through the final study visit. The investigator or his or her designee, in consultation with the subject and/or the subject's legal guardian, will confirm the subject has selected the most appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss the need to use highly effective contraception consistently and correctly throughout the study and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject and/or subject's legal guardian to call immediately if the selected birth control method is discontinued or if partner pregnancy is known or suspected in the subject's partner.

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 the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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. Caregiver(s)

The parent or legal guardian of the subject will actively participate as caregiver in this study. As caregiver, the parent or legal guardian will not only provide informed consent, but will also actively participate in the study procedures, including completing the PODCI Parent-report (2-10 years) questionnaire and being interviewed for the C-SSRS on behalf of the subject. Caregivers will complete the ZBI, EQ-5D-3L, WPAI:CG questionnaires and a measure of their child's HRU electronically on a tablet or similar device. The caregiver will communicate observed safety information to the investigator or designee as appropriate. The investigational site will train the caregiver on instructions to collect and/or ship a fecal sample, as needed, and provide other instructions on preparing the subject for each study visit.

A subject's caregiver(s) must meet all of the following criteria for the subject to be eligible for enrollment in the study:

- Is ≥18 years of age and has demonstrated responsibility as a caregiver through monitoring the subject and reporting any observed AEs during the parent B5161002 study.
- Is available to accompany the subject to the clinic visits.
- Can follow instructions, including the use of electronic devices for recording subject information.
- Is willing and able to give written informed consent.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in Sponsor's Study Web Portal and the investigator's site file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational

site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.7. Rater Qualifications

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

Clinical staff must be trained to complete the C-SSRS. This training is provided by the sponsor and upon completion a certification will be provided to the trained individual. If training has already been completed and certified in the B5161002 study this does not need to be repeated.

The C-SSRS will be completed with the subject's caregiver/legal guardian throughout the study see Section 7.2.7 for further details.

4.7.2. Tanner Stage and Testicular Volume

Tanner staging and testicular volume assessments to evaluate sexual maturation will be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable according to local regulation. Training to conduct the Tanner assessment will be provided by the sponsor and upon completion, a certification will be provided to the trained individual. If training has already been completed and certified in the B5161002 study, this does not need to be repeated.

4.7.3. Clinical Evaluators (CEs)

Functional assessments including the PFTs, 4SC, NSAA, ROM, strength, PUL and 6MWT will be conducted by a physiotherapist (or exercise physiologist). Training on the functional assessments and reliability of performance of each assessment specific to this protocol will be provided by a master physiotherapist and upon completion, a certification will be provided to the individual clinical evaluator. All CEs who have previously been certified for the B5161002 study may not require repeat certification. Details of the assessments, training, certification requirements and ongoing quality control are provided in the Functional Assessment manual.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

PF-06252616 is incompatible with sodium chloride containing solutions. Therefore, do not use Normal Saline (0.9% sodium chloride) or other sodium chloride containing solutions, as

a diluent or for flushing the infusion line. Dextrose 5% solution is recommended for use during flushing to ensure complete delivery of the prepared dosing solution.

Subjects will be administered PF-06252616 by IV infusion. The investigator site will maintain the high level oversight of all subject IV infusions if an alternative infusion location is used by the site. Once the investigational product is determined to be tolerated by the subject, the investigator and sponsor may explore the possibility of alternative infusion locations, as appropriate. Additional administration instructions will be provided to facilitate the infusion of this investigational product at alternative infusion locations.

This is an open-label study. Subjects will receive monthly doses of either, 5 mg/kg, 20 mg/kg or 40 mg/kg following confirmation of their MTD from the parent study B5161002. Dose levels may be adjusted based on emerging safety or efficacy data from B5161002.

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, 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 for dosing in this timeframe, the dose should be missed and the next visit should be conducted per the Schedule of Activities.

Please refer to the dosage and administration instructions in the Investigational Product Manual and the Administration Card for complete information on storage, stability, preparation and administration of PF-06252616.

5.1. Allocation to Treatment

Allocation of the subject to a dose level will be based on their MTD from the parent study B5161002. This dose level will be confirmed by the sponsor at the completion of Study B5161002 and entered into the Interactive Response Technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR) system] by the sponsor to assure proper allocation of subject to corresponding dose level.

Note: The IRT is the source of the subject number. The IRT system will provide the unique subject's study identification (SSID) number at the end of the first IRT subject transaction. This number will be retained throughout the study.

Furthermore, the study site will obtain the container number assignment from the IRT system. Once subject screening numbers and container numbers have been assigned, they cannot be reassigned.

The dispensing personnel will be required to enter or select information including but not limited to their user identification (ID) and password, protocol number, the SSID number and the date of birth of the subject. The dispenser will be provided with the container number when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the subject number and container number assigned. The confirmation report must be retained by the dispenser in the site files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT.

5.2. Blinding

This study is open label. Subjects, investigators and pharmacists will be aware of the assigned dose level. As this study is planned to be conducted at the same time as parent study B5161002, by the same investigators, please refer to the Investigational Product Manual which outlines procedures to ensure that the blind is maintained in the parent study.

5.3. Subject Compliance

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

5.4. Investigational Product 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 in single use, sterile glass vials. Each vial will be sealed with a coated stopper and an aluminum over-seal and labeled according to local regulatory requirements. The drug product must be reconstituted with SWFI for IV infusion. The reconstituted PF-06252616 drug product is a clear to slightly opalescent solution and colorless to slightly colored in appearance.

Details of the drug product and its preparation are provided in the dosage and administration instructions in the Investigational Product Manual.

PF-06252616 will be packaged as open-label supplies. The external packaging (carton) will describe its contents indicating them as active drug product. Each carton will contain a single vial of study medication, and each carton is identified with a unique container number. Each carton will be packaged with a tamper-resistant seal. The sponsor must be notified of any investigational product in which the tamper-resistant seal has been broken and this medication should not be used. Further details will be detailed in the Investigational Product Manual.

All ancillary supplies used to prepare and administer doses will be provided by the clinical site conducting the study unless otherwise agreed by the sponsor.

5.4.2. Preparation and Dispensing

Investigational product should be prepared and dispensed by appropriately qualified and trained personnel (eg, pharmacist, pharmacist technician) as allowed by local, state, and institutional guidance. All dosage and administration calculations as well as dose preparation must be performed and checked by a minimum of two (2) clinical site personnel, one of whom must be a licensed health care professional.

Study personnel will receive study specific training on the obligations of the role and will sign an agreement that will be maintained in the Site Master File.

Subject's body weight will be measured at each time point when study drug is administered and used to calculate the dose for that visit. After the first dosing visit (Visit 1), the subsequent doses may be calculated based on the current visit's weight or on the prior month's weight.

Under aseptic conditions, PF-06252616 should then be prepared according to the dosage and administration instructions in the Investigational Product Manual provided by the sponsor.

5.5. Investigational Product Administration

Following preparation of the study treatment investigational product (PF-06252616) by the site personnel (eg, pharmacist or pharmacist technician), the prepared product together with the administration card will be provided to the 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 (±30 minutes) which includes the flush time. The time to infuse the investigational product with the flush will be recorded. 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 should be conducted per the Schedule of Activities.

5.5.1. Infusion Reaction

Should subjects experience any infusion site reaction during the IV infusion period, the administration should be interrupted and supportive care should be provided according to the investigator's standard of care 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 50 mL/hr to 25 mL/hr or the duration may be increased from 2 to 4 hours). If the infusion rate is decreased, the 2-hour window for delivery will not be applied. The duration of the treatment interruption should not exceed the limits of stability of the drug product solution per the dosage and administration instruction in the Investigational Product Manual. Consult the Investigational Product Manual for detailed instructions regarding study drug preparation, stability and administration. No more than 1 treatment interruption should occur during any single infusion. If subjects are scheduled to receive their glucocorticoids on the same day as study drug administration, the site may instruct subjects to take them in the morning prior to infusion.

Once the product is determined to be tolerated by the subject, the investigator and sponsor may explore the possibility of alternative infusion locations, as appropriate. Additional administration instructions will be provided to facilitate the infusion of this investigational product at alternative infusion locations.

5.6. Investigational Product Storage

The qualified 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.

Investigational product should be stored in its original container and in accordance with the label.

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 on the label. Please refer to the Investigational Product Manual for complete information on storage, handling and stability of the investigational products both prior to and following reconstitution. Storage conditions stated in the SRSD which for this study is the 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 that 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 the storage conditions, as soon as possible as described in the labeling. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor 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. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

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.

The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

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.

5.7.1. Destruction of Investigational Product Supplies

The sponsor 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.

5.8. 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 Day 1 of the current study will be documented as concomitant medications.

5.8.1. Permitted Therapies

- Subjects will be permitted to receive glucocorticoids (ie, deflazacort, prednisolone, and prednisone). During the study the dose regimen should, where possible, remain stable. Discontinuation or dose adjustment is permitted if deemed clinically necessary. If subjects are schedule to receive their glucocorticoids on the same day as study drug administration, the site may instruct subjects to take them in the morning prior to infusion.

- Subjects will be permitted to receive ACE inhibitors, β blockers, ARB (angiotensin II receptor antagonist) or aldosterone blocker/thiazide diuretic; however, subjects must plan to remain on a stable dose during the study. Discontinuation or dose adjustment is permitted if deemed clinically necessary.

- 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. Calcium is permitted but should not be taken with 24 hours prior to a DXA scan. A multi-vitamin without iron is permitted.

- Bisphosphonates are permitted. If they are to be administered at a study visit where imaging is also being performed, they should be administered after the imaging is complete. This will help to mitigate any potential interference they may have on the imaging.

5.8.2. Prohibited Therapies

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

- Immunosuppressant therapy (other than glucocorticoids).
- Other investigational therapies.
- Exon skipping and nonsense mutation targeted therapies and utrophin.
- Aminoglycosides (eg, gentamicin), if required for management of an infection, a short course of treatment no longer than 14 days is permitted.
- Androgens or human growth hormones current and in the past 3 months.
- Multi-vitamin with iron or iron supplements.

At the discretion of the sponsor, subjects who receive prohibited therapies may be terminated from the study.

6. STUDY PROCEDURES

Every attempt should be made to schedule the visits on the day specified in the Schedule of Activities.

During screening, subjects and caregiver(s) 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 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 for quality by the central imaging vendor 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 should be repeated. The visit window for screening is to allow for the analysis of laboratory testing, assurance of imaging quality and to provide multiple days to perform the assessments. If needed, assessments should be conducted on consecutive days within the study window if more than 1 day is required to complete all assessments. For example where functional assessments and imaging assessments are collected at the same visit, subjects can be assessed over a 2-day period. Demography and medical history will be collected from Study B5161002.

The majority of screening assessments will come from the Week 97 assessment provided in Study B5161002, including Physical Examination, Tanner Stage and Testicular Volume, Height, Weight, Vital Signs, Single ECG, Cardiac MRI (or Echocardiogram), Clinical Laboratory Tests, GLDH, Serum Ferritin, Serum Iron, TIBC%, Transferrin Saturation, Hormones (LH, FSH, T4, TSH, andostendedione, testosterone), Fecal Occult Blood, PODCI, C-SSRS, MRI-Liver (data from Week 93), DXA-Spine, DXA-Whole Body, X-ray (hand and wrist), Functional Assessments (not including ambulatory status which is not collected in B5161002), PK, Immunogenicity.

If a Week 97 B5161002 stool sample result is not available at the screening visit, a collection kit and mailing supplies will be sent home and the caregiver will be responsible for collection and mailing the sample back to the site. For all other visits after screening, a stool sample will be collected at home up to 1 week prior to the scheduled visit window.

It is important to note that some additional assessments may be required (eg, ambulatory status, PFTs to establish study baseline, medication history). As soon as these assessments are completed and a subject's eligibility has been confirmed, they may be enrolled into the study.

The PODCI child self-report (if eligible), EQ-5D-Y, EQ-5D-3L, ZBI, and HRU are new assessments not included in the parent study B5161002 and should be collected at screening and all subsequent visits outlined in the Schedule of Activities. If a subject is unwilling to provide self-reported data they can still participate in the study.

If a subject becomes a screen failure for the current study, they will not be permitted to re-screen.

6.1. Informed Consent/Assent

The subject's parent or legal guardian must sign the informed consent document (ICD) prior to initiation of any screening assessments. The subject will be required to provide assent in compliance with local regulations and IRB/EC requirements. Consent should be provided prior to conducting the assessments for the Week 97 visit in Study B5161002 to assure that there is consent to use these assessments for screening in the current study.

6.2. Procedures

All procedures for the Screening and Study Period should be conducted per the Schedule of Activities and 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 DMD 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 presence of a mutation in the dystrophin gene(s) which is clinically consistent with the diagnosis of DMD. The mutation type will be reported.

- Medical history data from B5161002 will be reviewed for any significant medical histories and concurrent illnesses that required or are requiring specialist consultation or treatment.

- **Medication History:** Complete history will include all prescription or non-prescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose. Detailed information (dose, regimen) on glucocorticoid steroids will be collected.

- **Physical Examination**: including nose and throat mucosal exam.

- **Tanner Stage** and **Testicular volume**. If sexual maturity is reached during the study as confirmed by an assessment of Tanner Stage V, these assessments are no longer mandatory.

- **Height**: Height should be measured in the morning. If a subject is unable to stand safely, an estimated height can calculated using the subject's ulnar length and the instructions provided in the functional assessment manual.

- **Weight:** The body weight is required to calculate the subject's dose. After the first dosing visit the subsequent doses may be calculated based on the current visit's weight or on the prior month's weight.

- **Vital signs**: Pre-dose supine blood pressure, pulse rate, respiratory rate, and temperature.

- **ECG:** Single 12-lead ECGs will be obtained.

- **Cardiac MRI** (with or without gadolinium) or **Echocardiogram**

- The modality used to monitor LVEF should be consistent throughout the study for each subject and should be the same modality used in Study B5161002,

- If cardiac MRI with gadolinium is used, the imaging may only performed following all other imaging at the study visit.

- **Clinical laboratory testing:**

- **Fasting blood collection:** serum ferritin, serum iron, TIBC and % transferrin saturation.

- **Blood samples** for Biomarkers: Group 1 (fasting collection) & Group 2.

- **Blood samples** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase and cardiac troponin I.

- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Blood collection for hormones should be done in the morning. If Tanner stage V is reached these samples are no longer mandatory.

- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.
- **Blood Sample for PK:** Will be collected prior to dosing.
- **Fecal occult blood:** Fecal sample is to be collected at home up to 1 week prior to scheduled visit window.
- **Clinical Outcomes Assessments (COA)**
- **PODCI**: This questionnaire will be completed by the caregiver and if possible a self-report will be completed by the subject at the same visit (subject must be 11 years or older to complete). If a subject is unwilling to provide self-reported data, they can still participate in the study.
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10) will be completed with the caregiver.
- **EQ-5D**: The **EQ-5D-3L** will be completed by the caregiver and if possible the **EQ-5D-Youth** will be completed by the subject at the same visit. These are new assessments introduced in this study and should be completed at screening and subsequent visits outlined in the Schedule of Activities. If a subject is unwilling to provide self-reported data can still participate in the study.
- **HRU questionnaire**: This assessment will be completed by the caregiver. This is a new assessment introduced in this study and should be completed at screening and subsequent visits outlined in the Schedule of Activities.
- **ZBI**: This assessment will be completed by the caregiver. This is a new assessment introduced in this study and should be completed at screening and subsequent visits outlined in the Schedule of Activities.
- **WPAI:CG**: This assessment will be completed by the caregiver. This is a new assessment introduced in this study and should be completed at screening and subsequent visits outlined in the Schedule of Activities.
- **Magnetic resonance imaging (MRI)**: liver. Baseline/screening data will be obtained from Week 93 in the B5161002 study.
- **Fasting Dual-energy x-ray absorptiometry (DXA):** whole body and spine.
- **X-ray**: non-dominant hand and wrist. The same hand imaged in the B5161002 study should be imaged in the B5161004 study. If Tanner stage V is reached during the study these assessments are no longer mandatory.

- **Ambulatory Status:** Ambulatory status will be collected at screening and as an unscheduled procedure if there should be a change from the screening assessment during the study. Ambulation is defined as the ability to walk unassisted and without braces for at least 10 m.

- **Functional assessments**: In order to provide optimal testing conditions and consistency in endpoint measurements, the functional assessments, should be completed at *approximately* the same time of day. All functional assessments should be completed in the following order, PFTs, 4SC, NSAA, ROM, Strength, PUL, 6MWT. If loss of ambulation occurs, the 4SC, NSAA and 6MWT will not be completed.

6.3. Subject Withdrawal

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/caregiver to comply with the protocol-required schedule of study visits or procedures at a given study site. Subjects may be withdrawn from the OLE study should the parent study, B5161002 fail to meet its planned study objectives, is terminated early for other reasons (eg, sponsor decision) or the drug is commercialized. 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 records. 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 to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

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.

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 child and adolescent mental health provider as part of the psychiatric evaluation and assessment of subject safety. Refer to Section 7.2.7.

Clinically important suicidality includes but is not limited to:

a. Suicidal behavior (with or without intent of suicide or serious self-harm).

b. 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.

c. Determination of "yes" on question 5 (Active Suicidal Ideation with Specific Plan and Intent) for the Suicidal Ideation section of the C-SSRS.

d. 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.

e. Acute suicidality to such a degree that precaution against suicide must be exercised.

At the time of withdrawal, procedures outlined in the early withdrawal visit should be performed as detailed in the Schedule of Activities and Assessments.

6.4. 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 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 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. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. 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. The study team will be informed of these incidents in a timely fashion.

Consistent with the institutional guidelines, a topical anesthetic (eg, topical lidocaine) may be administered to subjects prior to the blood draw.

7.1. Blood Volume

The total blood volume per month will not exceed approximately 40 mL.

The following chart provides estimates of the approximate blood volume collected by visit.

Period	Visit	Total Volume (mL) At Each Visit
Year 1	Screening	40
	Week 13	10
	Week 25	14
	Week 37	10
	Week 49	40
	All other visits (9 additional visits)	10*
	Total Volume Year 1	**204**
Year 2-4	Week 61, 109, 157	10
	Week 73, 121, 169	22
	Week 85, 133, 181	10
	Week 97, 145, 193	40
	All other visits (9 additional visits per year)	10*
	Total Volume Year 2, 3, 4	**172**
	Early Withdrawal	30

*Standard hematology/chemistry and routine safety bloods as required.

7.2. Safety

7.2.1. 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 (and morphology as applicable) Total neutrophils (Abs) Absolute neutrophils (ANC) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine Glucose Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein Serum Phosphorus	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[a]	GGT GLDH PT INR aPTT Creatine kinase Amylase Cardiac Troponin I Serum Ferritin[c] Serum Iron[c] Total Iron Binding Capacity (TIBC)[c] Unsaturated Binding capacity[c], % Transferrin Saturation[c] Hormones (LH, FSH, T4 (total and free), TSH, androstenedione, testosterone) [d]	Fecal Occult Blood
	Additional Tests[b]			
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT GLDH PT INR			

a. Only if urine is positive for blood, protein, nitrites or leukocyte esterase.
b. Additional testing for potential Hy's Law cases only.
c. Following an 8 hour overnight fast.
d. Collect blood in the morning for hormone testing.

7.2.2. 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. If the examination status is abnormal, the investigator will be asked to determine whether the abnormality is "clinically significant", and if so, document as an AE.

7.2.3. Tanner Stage and Testicular Volume

Tanner Staging will be performed according to the Schedule of Activities to monitor for signs of accelerated sexual development. The physical changes in pubertal development (genital and pubic hair growth) will be assessed using the system described by Marshall and Tanner (1970). In addition to the Tanner staging, a measurement of testicular size (volume) using orchidometer beads will be documented. If a subject reaches a Tanner Stage V during the conduct of the study, further Tanner Staging, Testicular Volume, hormone testing and x-rays will no longer be mandatory.

7.2.4. Vitals

Supine blood pressure, pulse rate, respiratory rate and 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.

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.

7.2.5. 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.

Single 12-lead ECGs will be obtained; the average of the triplicate ECG measurements collected at Week 97 from Study B5161002, will serve as each subject's time-controlled baseline QTc value.

The QTc interval should be recorded using the QTcF (QTc Fridericia) value in milliseconds. In the event that the equipment is not able to provide the QTcF, the formula below will be used to calculate.

Formula = QT/((60/HR)^(1/3))

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTcF interval is increased by ≥45 msec from

the baseline, or an absolute QTcF 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 the average of QTcF 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 QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF 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 QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

7.2.6. Cardiac MRI/Echocardiogram

Cardiac MRI or echocardiograms should be collected at times specified in the Schedule of Activities section of this protocol. The same method of cardiac imaging should be used consistently within a single subject and it should be the same method used in Study B5161002.

Cardiac MRI with gadolinium is the preferred method for cardiac imaging. When cardiac MRI with gadolinium is used, it should only be collected after all imaging required at the same visit is performed. If the subject has a contraindication to gadolinium, cardiac MRI without gadolinium will be acceptable. Cardiac MRIs will be read by a central imaging vendor and only the results of LVEF will be provided to sites. Sites will be provided with a scanning and image transmittal guide for collection of the cardiac MRI.

If it is not possible to perform cardiac MRI (eg, it is not available at the site), echocardiogram will be acceptable. Echocardiogram will be read locally at each site. To ensure safety of the subjects, a qualified individual at the investigator site will evaluate the echocardiogram for parameters such as left arterial diameter, left ventricular mass index, left ventricular end diastolic diameter, left ventricular end systolic diameter, LVEF, shortening fraction, left ventricular posterior wall thickness, tricuspid valvular regurgitation presence and pericardial effusion. Echocardiogram should be performed using a 2-D imaging collection method.

7.2.7. 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 Children's Since Last Visit (Version 6/23/10) of the C-SSRS should be utilized for all visits in B5161004. The Since Last Visit version refers to the subject's experience since their last visit (see Clinical Outcomes Assessment manual).

Given the sensitive nature of the subject matter of this assessment, the C-SSRS will be conducted with the subject's caregiver/legal guardian on the subject's behalf throughout the study, rather than administering this evaluation directly with the study subjects.

If at any visit the subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidality behavior, then an evaluation of suicide risk (risk assessment) must be completed and the subject must be discontinued. 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 child and adolescent mental health provide: In the United States: 1) Child and Adolescent Psychiatrists (board certified or board eligible), 2) psychiatrist who have training and experience in the diagnosis and treatment of psychiatric disorders in the pediatric population, or 2) 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 in the pediatric population.

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.

7.3. Banked Biospecimens

7.3.1. 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 pharmacogenomics/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 pharmacogenomics/biomarker analyses and retaining them in the Pfizer 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 facility accessible only by swiping a badge. 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 be used only for the purposes described here and in the ICD/subject 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 ICD/subject 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.

Biomarkers in Group 1 will be collected in the morning following an 8 hour fast to be retained for exploratory analyses in this study include the following:

Biomarker Group 1- Collect annually beginning at screening in current study:

- **Prep B1.5 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis):** A 2 mL blood biospecimen will be collected.

- **Prep B2.5 (serum collection optimized for biomarker/ proteomics/metabonomic analysis):** A 2.5 mL blood biospecimen will be collected.

Biomarker Group 2- Collect annually beginning at screening in current study:

- **Prep R1 (PAXGene whole blood collection optimized for RNA analysis):** A 2.5 mL blood biospecimen will be collected.

- **Prep P4 (Cell-free RNA):** A 10 mL blood biospecimen will be collected.

The banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

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

7.3.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, 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 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.

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

Blood samples (2 mL) to provide serum for pharmacokinetic analysis will be collected into the appropriately labeled 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 during the pre-dose period as described in the Schedule of Activities.

Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

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

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

Blood samples (2 mL) to provide serum for analysis of anti-PF-06252616 will be collected into the appropriately labeled 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 during the pre-dose period as described in the Schedule of Activities.

Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

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 NAb.

7.6. PK and Immunogenicity Sample Shipment

The PK and immunogenicity samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK sample 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.

7.7. Imaging Assessments

7.7.1. Liver MRI

Liver MRI will be obtained according to the Schedule of Activities to monitor for safety by quantifying iron accumulation. The standard procedure to obtain serial liver MRIs will be described in an Image Acquisition manual which will be provided to the site. The site will be trained on all aspects of obtaining quality liver MRIs. MRIs will be sent to an independent central radiology imaging facility for calculation of the average R2* value which will be used to monitor for iron accumulation in the liver. MRIs must meet the accepted standards of quality as described in the Image Acquisition manual and/or Imaging Charter or the site may be asked to repeat the liver MRI.

7.7.2. Dual-energy X-ray Absorptiometry (DXA) and X-ray

7.7.2.1. 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 whole body without head. The standard procedure to obtain serial DXA whole body and spine scans will be described in an Image Acquisition manual which will be provided to the site. The site will be trained on all aspects of obtaining a quality whole body and spine scans. Scans will be sent to an independent central radiology imaging facility for

analysis of the study endpoints. The independent central reviewer will be blinded to the study treatment assignment.

Screening DXA should meet the accepted standards of quality as described in the Image Acquisition manual and/or Imaging Charter or the site may be asked to repeat it. Ideally, whole body scans will be taken at approximately the same time of day (morning) and subjects should avoid large meals for at least 2 hours prior to the scan. Juice, water and a small snack may be permitted. Subjects should be in a state of euhydration. Food may affect the LBM measure. Calcium should be avoided for 24 hours as it may not absorb and will affect the measure of BMD and LBM.

7.7.2.2. X-ray

X-rays of the hand and wrist for bone age assessment will be obtained according to the Schedule of Activities. The standard procedure to obtain serial hand/wrist X-rays will be described in an Image Acquisition manual which will be provided to the site. X-ray images will only be acquired of the non-dominant hand/wrist and this should be the same hand/wrist selected for the B5161002 study. The site will be trained on all aspects of obtaining a hand/wrist X-ray. X-rays will be sent to an independent central radiology imaging facility for bone age analysis. The independent central radiologist will be blinded to the study treatment assignment and the subject's chronological age. The ratio of the bone age to the chronologic will be provided to the sites by the sponsor. The hand/wrist X-ray will no longer be mandatory if, during the study, the subject is assessed as having reached sexual maturity defined as Tanner stage V.

7.7.2.3. Radiation Exposure

The average effective dose of radiation received for a single DXA scan or hand x-ray for bone age may vary due to the instrument and the subject's body. Annual assessments include a whole body DXA scan, a DXA spine scan and a single x-ray image of the hand and wrist. The expected annual radiation dose resulting from these scans for a subject participating in this study should not exceed 0.15 mSv per year. This is less than 1 month of natural background radiation which is approximately 0.25 mSv per month (EHS Radiation Risk; Blake et al, 2006).

7.8. Functional Assessments

Functional assessments will be obtained according to the Schedule of Activities. If functional assessments are to be performed on the same day as the investigational product administration, they should be performed prior to the IP administration. If the subject is defined as non-ambulatory then certain functional assessments can be omitted, as outlined in the Schedule of Activities. If possible the date that the subject was defined as non-ambulatory should be recorded. In order to provide optimal testing conditions and consistency in endpoint measurements, the functional assessments should be completed at approximately the same time of day and in the morning. The order for completing all testing will be detailed in a functional assessment manual.

All functional assessments will be conducted by a trained physiotherapist (or exercise physiologist). Throughout the study they will be referred to as "Clinical Evaluators (CEs)". Training and reliability confirmation to conduct functional assessments specific to this protocol will be provided by a vendor (master physiotherapist [MP]). Following the completion of training and reliability testing a certificate will be provided which must be in place prior to conducting any functional assessments.

In order to assure ongoing quality of the CE abilities to perform functional assessments, videotaping may be used at pre-specified visits. Videos will be reviewed by the MPs to provide feedback to the CEs on the conduct of the method used to perform the functional assessment. Videos will not be used to provide scoring on subject's functional assessment. The videos will be stored at the site and retained per the record retention requirements.

The training requirements and ongoing quality control will be provided in the Functional Assessment manual.

7.8.1. Pulmonary Function Tests (PFTs)

Spirometry will be performed as outlined in the Functional Assessment manual based on American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force: standardization of lung function testing guidelines 2005 (Miller et al, 2005).

The FVC, FEV_1 will be recorded as absolute volumes in liters and in terms of predicted values (Hankinson, 1999 or equivalent) according to age, height, race and gender. The best (largest) FVC, and FEV_1 measurement from the set of 3 will be captured on the database. Note that the best measurement for FVC, FEV_1 may occur on different efforts.

PEFR will be performed to produce 3 technically adequate results. The highest PEFR should be recorded in L/min.

7.8.2. 4 Stair Climb (4SC)

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; however at no time is the subject instructed on the preferred method (with or without the use of hand rails) used to perform this test.

Subjects will also be assessed on the time to descend 4 stairs. The methods used to descend 4 stairs will also be recorded. This test can be omitted if a subject is considered non-ambulatory.

7.8.3. Northstar Ambulatory Assessment (NSAA)

The NSAA is a 17-item test that grades performance of various functional skills from 0 (unable to perform), 1 (completes independently but with modifications), and 2 (complete without compensation) (Mazzone et al. 2009). The NSAA also includes 2 timed functional tests: rise from floor and run 10 meters. The NSAA has been found to correlate with the

6MWT and other functional outcomes in boys with DMD (Mazzone et al, 2010). This test can be omitted if a subject is considered non-ambulatory.

7.8.4. Range of Motion (ROM)

Range of motion of the ankle will be evaluated by using goniometry to record any occurrences of ankle contractures. This test can be omitted if a subject is considered non-ambulatory.

7.8.5. Strength Assessment

Muscle strength will be quantified by means of a handheld dynamometer. The following muscle groups will be evaluated: knee extension, elbow flexion, elbow extension and shoulder abduction.

7.8.6. Performance of Upper Limb (PUL)

The PUL scale has been devised to assess motor performance of the upper limb for individuals with dystrophinopathies (Becker and Duchenne muscular dystrophy). The purpose of an upper limb scale for use in dystrophinopathy is to assess change that occurs in motor performance of the upper limb over a prolonged period beginning when a boy is ambulant and continuing to the time he loses all arm function when non-ambulant. Motor performance will be impacted by muscle strength, contactures and maturational development (puberty), and the scale aims to incorporate performance of shoulder, elbow, wrist and hand function.

7.8.7. Six Minute Walk Test (6MWT)

The 6MWT, originally developed for cardiac and respiratory insufficiency, has been revised for use in DMD subjects to account for the age and unique characteristics of this population (McDonald et al, 2010). The purpose of the test is to evaluate ambulation capacity (distance) by endurance of walking for six minutes. This test has been widely used in natural history and therapeutic studies with DMD. A sizeable variability in the range of 6 minute walk distance (6MWD) change at one-year (from -23 to -59 m) as well as a large standard deviation (SD) around the mean change (SD 81 to 90 m) were observed in all studies (Mazzone et al, 2013; Goemans et al, 2013; McDonald et al, 2013a; McDonald et al, 2013b). This test can be omitted if a subject is considered non-ambulatory.

7.9. Triggered Requirements

Condition/ Criteria	Action
Moderate Iron overload/ If the liver iron content estimate as determined by R2* value is above the "mild overload" threshold (R2* >190 Hz at 1.5 T or R2* >369 Hz at 3.0 T	The subject should be referred to a haematologist for further assessment
Cardiomyopathy/ If the LVEF falls below 50% on the cardiac MRI or echocardiogram at any follow-up visit	The subject should be referred to a cardiologist for further assessment.
Spine compression or fracture/ If either the bone mineral density increases >4% from the start of Period, or if there is a suspicion of a vertebral fracture upon central review of the DXA exam	The subject should have a local spine x-ray performed to confirm the presence or absences of compression or fracture

7.10. 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.

7.11. Clinical Outcome Assessments (Caregiver completed)

It is the intent to have all caregiver questionnaires complete electronically on a tablet or similar hand-held device for convenience of the patient and accurate data capture. However, if the license should in anyway prohibit use, an alternate delivery will be explored such as use of a paper version. If a suitable alternative is not found a questionnaire may be withdrawn from the protocol.

7.11.1. Pediatric Outcomes Data Collection Instrument (PODCI)

In order to evaluate subject's functional health status, the PODCI questionnaire will be collected. The PODCI is a patient-reported assessment of musculoskeletal health intended for use in children and adolescents (Daltroy et al, 1998; http://www.aaos.org/). The pediatric version intended for completion by parents or caregivers of children aged 10 years or younger will be utilized in this study. The instrument contains 86 items and is organized into multiple domains: upper extremity function, transfers and mobility, physical function and sports, comfort (pain free), happiness and satisfaction, and expectations for treatment. Each domain produces an independent score, and a summary total score is also computed. These scores range from 0-100 with lower scores representing higher levels of disability. Scores may be reported as standardized, or they may be converted to normative scores based on the scores reported in a large, healthy population (see Clinical Outcomes Assessment manual).

7.11.2. Zarit Burden Inventory (ZBI)

The Zarit Burden Interview will be used to assess caregiver burden. The ZBI originated as a 29-item questionnaire (Zarit et al, 1985; Zarit et al, 1980) but the revised version which contains 22 items will be used in this study. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale. Response options range from 0

(Never) to 4 (Nearly Always). A total score is obtained and higher scores indicate a greater level of caregiver burden associated with caring for a child with Duchenne muscular dystrophy (see Clinical Outcomes Assessment manual). The term "your relative" has been substituted with the term "your child".

7.11.3. EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L)

The EQ-5D Health Questionnaire is a self-completion standardized instrument for use as a measure of health outcome (http://www.euroqol.org/about-eq-5d.html). It consists of a descriptive system (EQ-5D) of health-related quality of life states, consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular ED-5D dimension. Additionally, the EQ-5D consists of a standard vertical 20cm visual analogue scale (EQ VAS) for recording an individual's rating for their current health state (see Clinical Outcomes Assessment manual).

7.11.4. Work Productivity and Activity Impairment Questionnaire adapted for Caregiving (WPAI:CG)

The WPAI:CG is a self-reported measure of work productivity and impairment that yields four scores: Absenteeism (work time missed); Presenteeism (impairment at work/reduced on the job effectiveness); work productivity loss (overall work impairment/absenteeism plus presenteeism); and activity impairment. Each score is expressed as a percentage (0-100%) with higher numbers indicating greater impairment and less productivity (Reily et al, 1993; http://www.reillyassociates.net/Index.html; Clinical Outcomes Assessment manual).

Percent work time missed – a measure of absenteeism, calculated as work time missed due to health problem as a proportion of hours actually worked (Question 4).

Percent impairment while working – a measure of presenteeism, the degree to which health problem impacted work.

Percent overall work impairment – a measure of overall work productivity loss due to health problem, combining absenteeism plus presenteeism.

Percent activity impairment - a measure of the degree to which health problem has affected ability to do regular activities other than work at a job.

Each score is expressed as a percentage (0-100%) with higher scores indicating greater impairment and less productivity.

In this study, the WPAI:CG will measure the effect of a child/adolescent's Duchenne muscular dystrophy on a caregiver's work productivity and regular activities.

7.11.5. Healthcare Resource Utilization (HRU) questionnaire

The Healthcare Resource Use questionnaire is completed by the caregiver and asks questions about healthcare resources utilization related to their child's use of healthcare professionals, emergency room visits, and hospitalizations during the course of the study. Caregivers are also asked to estimate out-of-pocket costs related to healthcare resource utilization (see Clinical Outcomes Assessment manual).

7.12. Clinical Outcome Assessments (Subject completed)

It is the intent to have all subject questionnaires completed electronically on a tablet or similar hand-held device for convenience of the patient and accurate data capture. However, if the license should in anyway prohibit use, an alternate delivery will be explored such as use of a paper version. If a suitable alternative is not found a questionnaire may be withdrawn from the protocol.

If a subject is unwilling to provide self-reported data, they can still participate in the study.

7.12.1. Pediatric Outcomes Data Collection Instrument (PODCI)

Children will become eligible to complete the Adolescent self-report version of the PODCI questionnaire once they are 11 years of age. The PODCI is a patient-reported assessment of musculoskeletal health intended for use in children and adolescents (Daltroy et al, 1998; http://www.aaos.org/). The instrument contains 83 items and is organized into multiple domains: upper extremity function, transfers and mobility, physical function and sports, comfort (pain free), happiness and satisfaction, and expectations for treatment. Each domain produces an independent score, and a summary total score is also computed. These scores range from 0-100 with lower scores representing higher levels of disability. Scores may be reported as standardized, or they may be converted to normative scores based on the scores reported in a large, healthy population (see Clinical Outcomes Assessment manual).

7.12.2. EuroQol 5 Dimensions - Youth

The EQ-5D-Y is a newly developed generic instrument measuring health-related quality of life in children and adolescents 8 years onwards. It was adapted from the EQ-5D original questionnaire (http://www.euroqol.org/about-eq-5d.html). It consists of a descriptive system (EQ-5D) of health-related quality of life states, consisting of five dimensions including mobility (walking about), self-care (looking after myself), usual activities (doing usual activities), pain/discomfort (having pain or discomfort), and anxiety/depression (feeling worried, sad or unhappy) each of which can take one of three responses. The responses record three levels of severity (no problems, some problems, or a lot of problems) within a particular ED-5D dimension. Additionally, the EQ-5D consists of a standard vertical 20 cm visual analogue scale (EQ VAS) for recording an individual's rating of their current health-related quality of life state on a scale from 0 to 100 with 0 representing the worst and 100 the best health state he or she can imagine. All items refer to the health state "today." Health state utilities will also be calculated (see Clinical Outcomes Assessment manual).

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 a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. 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 or its designated representative 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 84 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 the sponsor 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 investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last 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).
- Medication error.
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, 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 CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor 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 is captured on the medication error version of the 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

A serious adverse event 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 the investigational product 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 of this protocol. These events are anticipated to occur commonly in a population with DMD. 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:

a. Loss of mobility or ambulation.

b. Muscle weakness.

c. Symptoms related to spinal deformity.

d. Respiratory muscle weakness/Hypoxia.

e. Fracture.

f. Steroid related metabolic changes (Hypertension, diabetes).

Should an aggregate analysis indicate that these pre-specified 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 epidemiologial 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 regular basis per internal standard operating procedures and on a quarterly basis by the E-DMC.

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below 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.

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 (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × 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 × ULN, or ≥8 × 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 × ULN or if the value reaches ≥3 × 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, GGT, GLDH, PT/INR, and alkaline phosphatase. 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 of 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 pretreatment 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 non-serious); 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 the 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 both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. 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.

2. 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).

3. A male 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 an SAE report form and an 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 baby, 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 the investigational product.

Additional information regarding the EDP 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 AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the 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 CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

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

Withdrawal due to AEs 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/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/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.

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 EDP, 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's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Due to the open-label design of the study, statistical analyses will be exploratory in nature. The data that will define the baseline for each analysis set will be outlined in the SAP.

9.1. Sample Size Determination

As the number of subjects in this study is limited by the sample size of B5161002 study which has approximately 105 subjects, the sample size will be capped at the number of enrolled subjects from the parent study.

9.2. Safety Analysis

Summary statistics will be performed on the following safety endpoints:

- Incidence and/or rate of intolerability or dose limiting treatment related AEs.
- Incidence and/or rate, severity and causal relationship of TEAEs and withdrawals due to TEAEs.
- Incidence and magnitude of abnormal laboratory findings (clinical laboratory tests: hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase, serum ferritin, serum iron, total iron binding capacity (TIBC), % transferrin saturation. Hormone: [luteinizing hormone [LH], follicle stimulating hormone [FSH], thyroxine [T4], thyroid stimulating hormone [TSH], fecal occult blood, cardiac troponin I and urinalysis).
- Abnormal and clinically relevant changes in liver MRI and physical examinations (including nose and throat mucosal exam and Tanner stage/testicular volume), weight, vitals, electrocardiogram (ECG), cardiac MRI (or echocardiogram) measured LVEF, bone mineral density by DXA, x-ray (hand and wrist for bone age evaluation) and C-SSRS.

9.3. Efficacy Analysis

9.3.1. Analysis of efficacy and PD endpoints

Baseline values, change from baseline to last visit in PFTs, 4SC, NSAA, PUL, 6MWD, muscle strength by myometry and lean body mass by DXA will be described based on summary statistics including minimum, median, mean, maximum, and standard deviation. Change from baseline may also be assessed for any or all intermediate visits.

9.3.2. Analysis of PK and Immunogenicity

- Summary statistics will be provided for trough serum concentrations by dose.
- Incidence of ADA and NAb.

9.4. Exploratory Analyses

9.4.1. Clinical Outcome Assessments

Summary statistics will be presented for the following endpoints by baseline, treatment and time point as applicable. Methodology for any treatment group comparisons will be specified in the SAP.

- Change from baseline in the PODCI Parent-report and Adolescent self-report scores.
- Change from Baseline in the EuroQol 5 Dimension 3 Levels (EQ-5D-3L) Health Questionnaire.
- Change from Baseline the EuroQoL 5 Dimensions – Youth.
- Change from Baseline in the Healthcare Resource Utilization (HRU) questionnaire.
- Change from Baseline in the Zarit Burden Interview (ZBI).
- Change from Baseline in the Work Productivity and Activity Impairment Questionnaire adapted for Caregiving (WPAI:CG) the percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to a child's Duchenne muscular dystrophy.

9.5. Interim Analysis

There is no interim analysis planned for this study.

9.6. Data Monitoring Committee

This study will use an E-DMC.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC in regards to safety or interim efficacy to alter the conduct of the study will be forwarded to the sponsor

management for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Details of the composition of the E-DMC and sponsor management including interactions between them will be further specified in the DMC charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and 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. It should be noted that PODCI and Caregiver burden questionnaires will likely not be captured in the CRF but be completed on a tablet or similar hand held electronic device. Otherwise, a CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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 investigative 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 the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

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/Ethics Committee

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 are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' 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 and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject or his legally acceptable representative, or parent(s) or legal guardian, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide

consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, 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

Subject recruitment efforts are not required for this study because this is an extension study.

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

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries 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, or investigational product 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 24 hours. 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 by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. 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 of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication 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 before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

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.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

Blake GM, Naeem M, Boutros M. Comparison of effective dose to children and adults from dual X-ray absorptiometry examinations. Bone 2006; 38(6):935-42.

Bonifati MD, Ruzza G, Bonometto P, et al. A multicenter, double-blind, randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy. Muscle Nerve 2000; 23(9):1344-7.

Bradley L. Yaworsky PJ, Walsh FS. Myostatin as a therapeutic target for musculoskeletal disease. Cell Mol Life Sci 2008; 65(14):2116-24.

Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010; 9(1):77-93.

Daltroy LH, Liang MH, Fossel AH, et al. The POSNA Pediatric Musculoskeletal Functional Health Questionnaire:report on reliability, validity, and sensitivity to change. J Pediatr Orthop 1998; 18:561-71.

Goemans N, van den Hauwe M, Wilson R, et al. Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. Neuromuscul Disord 2013; 23(8):618-23.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Resp Crit Care Med 1999; 159:179-87.

Lamperti C and Moggio M. Muscular Dystrophies: Histology, immunohistochemistry, molecular genetics and management. Current Pharmaceutical Design 2010; 16(8):978-87.

Manzur AY, Kinali M and Muntoni F. Update on the management of Duchenne muscular dystrophy. Arch Dis Child 2008; 93(11):986-90.

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45(239):13-23.

Mazzone ES, Messina S, Vasco G, et al. Reliability of the North Star Ambulatory Assessment in a multicentric setting. Neuromuscul Disord 2009; 19(7):458-61.

Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. Neuromuscul Disord 2010; 20(11):712-6.

Mazzone ES, Pane M, Sormani MP, et al. 24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy. PloS One 2013; 8(1):e52512.

McNally EM. Powerful genes – myostatin regulation of human muscle mass. New England Journal of Medicine 2004; 350(26):2642-4.

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations. Muscle Nerve 2010; 42(6):966-74.

McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve 2013a; 48(3):343-56.

McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in Duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve 2013b; 48(3):357-68.

McMillan HJ, Gregas M, Darras BT, et al. Serum transaminase levels in boys with Duchenne and Becker muscular dystrophy. Pediatrics 2011; 127(1):e132-6.

McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997; 387(6628):83-90.

Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med.1989; 320(24):1592-7.

Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force: Standardisation of Lung Function Testing. Standardisation of Spirometry Eur Respir J 2005; 26:319-38.

Reily MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment questionnaire. PharmacoEconomics 1993; 4:353-65.

Schuelke M, Wagner KR, Stolz LE, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med 2004; 350(26):2682-8.

Zarit SH, Orr NK, Zarit JM. The hidden victims of Alzheimer's disease: Families under stress New York University Press, New York 1985.

Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: Correlates of feelings of burden. The Gerontologist 1980; 20:649-55.

Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
4SC	four stair climb
6MWD	6 minute walk distance
6MWT	6 minute walk test
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATS/ERS	American Thoracic Society/European Respiratory Society
BMD	bone mineral density
CTA	clinical trial application
CE	Clinical Evaluators
CIOMS	Council for International Organizations of Medical Sciences
COA	Clinical Outcome Assessments
CRF	case report form
CSA	clinical study agreement
C-SSRS	Columbia Suicide Severity Rating Scale
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DXA	dual energy x-ray absorptiometry
EC	ethics committee
ECG	Electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EQ-5D-3L	EuroQoL 5 Dimensions 3 Levels
EQ-5D-Y	EuroQoL 5 Dimensions – Youth
EudraCT	European Clinical Trials Database
FEV_1	forced expiratory volume in one second
FIH	first in human
FIP	first in patient
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDF-8	growth differentiation factor 8
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
HRQL	Health-related quality of life
HRU	Healthcare resource utilization

Abbreviation	Term
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonization
ID	Identification
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	Intravenous
IVR	interactive voice response
IWR	interactive web response
LBM	lean body mass
LVEF	Left ventricular ejection fraction
LH	luteinizing hormone
LSLV	last subject last visit
MRI	magnetic resonance imaging
MSW	Master's level Clinical Social Workers
MTD	maximum tolerated dose
N/A	not applicable
NAb	neutralizing antibodies
NSAA	Northstar Ambulatory Assessment
OLE	open-label extension
PEFR	peak expiratory flow rate
PFTs	pulmonary function tests
PD	Pharmacodynamics
PK	Pharmacokinetic
PNP	psychiatric Nurse Practitioners
PODCI	Pediatric Outcomes Data Collection Instrument
PT	prothrombin time
pQCT	peripheral quantitative computed tomography
PUL	Performance of Upper Limb
PWRD	Pfizer Worldwide Research and Development
RBC	red blood cell
RNA	ribonucleic acid
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject's identification

Abbreviation	Term
SWFI	sterile water for injection
T4	Thyroxine
TEAEs	treatment emergent AEs
TGFβ	Transforming growth factor beta
TIBC	total iron binding capacity
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WPAI:CG	Work Productivity and Activity Impairment questionnaire adapted for Caregiving
ZBI	Zarit Burden Interview