A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-06252616 IN AMBULATORY 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:	2014-002072-92
Protocol Number:	B5161002
Phase:	2

[redacted]

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	15 August 2016	• Incorporation of Protocol Administrative letters issued on 01DEC2015, 07JAN2016, 08FEB2016 and 09MAR2016. • Schedule of Actives and carried out throughout protocol where appropriate. • Removed 6 hour PK and PD collection by the time of implementation of Amendment 2 a sufficient amount of 6-hour PK and PD samples will have been collected to characterize PK and PD. Removal of the timepoint will remove the burden to patients for this testing while maintaining the ability to achieve the PK and PD objectives. • Vital signs moved to align with pre and post dosing collection. • Revised the requirements for weight collection from either the current visit or prior month's visit. • Clarified window for fecal occult blood test. • Revised the timing for collection of thigh MRI and Functional assessments to provide flexibility while attempting to mitigate potential variability that may be introduced inconsistent testing. • Clarified requirements for functional testing in non-ambulatory patients. • Clarified the data to be considered by the E-DMC for reduction in liver monitoring frequency. • Modified the window for investigational product administration to align with the

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		observed various site practices. Clarified the delivery to include the flush time. • Added allowance to stop monitoring for Tanner Stage, testicular volume, hormone and X-ray, should boys reach sexual maturity during the study. • Added DXA-Whole body to Early Termination visit as it was missing from prior protocol version. • Section 1.6 Toxicology-revisions made to reflect IB language. • Section 1.7 Clinical Experience-revisions made to reflect IB language. • Section 1.8.2 Immunogenicity-revisions made to reflect IB language. • Added provision to allow the E-DMC to permit the results from the liver MRI and iron indices to be provided to the team and sites following their review of data which indicate these data are not unblinding to the study treatment assignment. • Section 1.11.3 remove the requirement for monitoring Tanner staging for boys who reach sexual maturity during the study. • Section 2 Objectives/Endpoints: Added secondary objectives to 1) permit evaluation of long-term treatment and 2) evaluation of functional assessments in sub-group of subjects. Added description of endpoints to meet new objectives. Corrected timepoints for endpoints. Removed strength testing by the MRC scale to reduce the burden of testing on subjects. Subjects will still undergo myometry testing for strength. • Section 3 Clarified the length of follow-up required for subjects who may be enrolling in the OLE study. Clarified the duration of the study which has been extended due to longer than anticipated time to enroll.

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		Clarified that additional subjects may be enrolled if the study is full recruited before the interim analysis is completed and no safety issues have been observed. Clarified the timing for the E-DMC to consider if the study can move to an automated dose-escalation rather than a manual process and/or reduce the liver MRI monitoring frequency. Clarified that the E-DMC may determine if the liver MRI results and serum iron indice data may be shared with the study team if a determination can be made that the data are not unblinding as to the treatment assignment. • Section 4-Expanded the age to include boys up to <16 years of age, clarified screening results for fecal occult blood test and in exclusion item 10, added current or prior treatment with anti-myostatin and clarified prior utrophin modifier exposure exclusion requirements (PACLs 07 Jan 2016 and 06 Mar 2016). • Section 5 updated to reflect the use of an Investigational Product Manual. Updated the requirements to allow the previous month's weight to be used for dose calculation for visits occurring after Day 1. Modified the masking to include the in-line filter of the infusion set. This was added due to the potential of higher concentrations of the investigational drug produce which may be required for older subjects who are receiving the higher dose levels. Provided guidance on compliance with dosing. Clarified the infusion time (PACL 08 Feb 2016). • Section 6 updated to reflect changes noted in the Schedule of Activities. • Section 7 clarified reporting of abnormal findings from physical exams, clarified monitoring for sexual maturity, and removed the strength testing by MRC scale

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		to reduce the burden of testing on subjects. • Section 9, added the intention of continued recruitment if the study completes enrollment prior to the time of the IA and there are no safety issues identified. Added a description of historic control group to evaluate with subjects in sequence Group 1 who have been treated for 2 years. • Section 9.4, Revised the gamma for futility to ($\gamma \leq -1$). • Various administrative changes made throughout protocol.
Amendment 1	18 May 2015	• Abbreviations-added GLDH, removed PESC and UTN. • Schedule of Activities (SoA) revised to move Day 1 activities into a separate column to help clarify the procedures that will occur at baseline versus those that will occur on Day 1. • SOA-Revised the visit window for Screening and Baseline to allow for additional days at Baseline and removed window for Day 1. • SOA corrected Immunogenicity sample at baseline (it was previously noted in Section 6 but not on the SOA). • SOA added "testicular volume" after Tanner Staging for clarity of collection of this data. • Clarified the window for vital signs at 6 hours post dose. • SOA removed the requirements for thigh MRI visit 449 and 561 in Period 2. • SOA separated DXA to whole body and spine for clarity of which DXA is to be performed at which visit. • SOA updated footnotes; added GLDH for lab tests and observation time required following investigational product

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		administration, clarified the following: collection of stool sample at screening, assessments needed for randomization, the subject observation time post dosing and for the 6 hour PK collection • SOA and Section 5 clarified Dose Administration window for administration (±15 minutes) and requirements for administration outside of visit window. • Section 1, clarified investigational product appearance, added GLDH to be used as a biomarker for hepatic injury. • Section 2, added GLDH in the list of primary clinical laboratory endpoints for safety assessment of liver injury; clarified collection of the exploratory endpoints for T2-mapping and Dixon methods to be collected at sites with capabilities. Clarified the assessments for GDF-8 parameters. • Section 3, clarified the process for confirmation of exposure in the first 12 subjects enrolled, removed the E-DMC decision at the time of IA to reduce the number of thigh MRIs instead the protocol will prospectively be changed to only collect thigh MRI annually in Period 2. • Section 3 Dose Adjustment-added a requirement to confirm the number of doses received at each dose level, updated table for dose adjustment to removed % Transferrin Saturation as criteria for dose adjustment, clarified that criteria applied to all subjects (active and placebo), clarified information to be communicated to assure blind is maintained, clarified dose adjustment in Sequence Period 2. • Section 3 Changed the Pfizer Executive Steering Committee to "sponsor management" to align with the E-DMC charter. • Section 4 Inclusion criteria- clarified criteria for 4SC to be ≤1.6 stairs/second (or

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		≥2.5 seconds), clarified the criteria for serum iron (≤1.2 x ULN), serum ferritin (≤140 ng/mL), % transferrin saturation ≤50%) and results fecal occult blood testing to be negative at screening. • Section 4 Exclusion criteria- clarified prior "lower limb" fractures, LVEF <55% (normal range at screening), concomitant medications (permitted and not permitted) and additives for the investigational product. • Section 4 Randomization, clarified that eligibility is based on the 4 SC at screening while randomization requires the baseline 4SC to stratify subjects. • Section 4 Screen Failures, added criteria for allowing re-screening for screen failures who fail the 4SC criteria only. • Section 4 Lifestyle clarified caffeine use within 24 hours of study visits. • Section 4 Lifestyle removed iron supplements to align with the other section of the protocol. • Section 4 Lifestyle added dietary guidelines for fecal occult blood test and clarified dietary preparation for DXA scan. • Section 4 Contraception clarified to align with updated protocol template language. • Section 4 Caregiver clarified that they will be responsible for completing the C-SSRs at each visit. • Section 4 Sponsor Qualified Medical Personnel clarified to align with updated protocol template language. • Section 4.7.3 Clinical Evaluators clarified the requirements for reliability to align with the Functional Assessment manual. • Section 5 Study Treatment, updated with protocol template language and clarified, the window for investigational product

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		administration (±15 minutes), the decrease in infusion rate following an infusion site reaction, guidance for dosing outside of the visit window, added the 1 hour observation post administration, clarified the Investigational Product Storage and added a section on destruction of investigational drug product, clarified the DAI calculations and dose preparation double verification requirements and blinding procedures if more than 2 subjects are dosed at the same time. • Section Concomitant medication- clarified permitted and prohibited medications. Added ARB and aldosterone blocker/thiazide diuretic as permitted. Added bisphosphonates as permitted. Added utrophin and treatment with an iron supplement and idebenone as prohibited. Noted that subjects may be discontinued who receive prohibited therapies. • Section 6 Study Procedures updated to align with revisions made to the SOA and to clarify procedures required for re-screening subjects. • Section 7 Blood Collection added an option of an IV cannula for serial blood collection, updated the estimated laboratory blood volumes and added GLDH to list of clinical tests, clarified resuls for WBC and ANC and collection of serum for liver biomarker; and clarified timing for hormone testing. • Section 7 Electrocardiogram clarified the use of reporting results with the Fridericia correction. • Section 7 Cardiac MRI/Echocardiogram, clarified preferred method is cardiac MRI, data provided by the central imaging vendor for cardiac MRI. Clarified method and data parameters to be collected for echocardiogram. • Section 7 C-SSRs clarified to be conducted

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		via parent proxy at each visit. • Section 7 Liver MRI, clarified who will calculate the R2* value for the liver MRI and quality of liver MRI. • Section 7 Thigh MRI, clarified not to be done after exercise. • Section 7 Additional Research, added information about additional research that may be performed with imaging assessments. • Section 7 Functional Assessments, clarified the training for the functional assessments and the ongoing quality control measures. • Section 7 4SC, clarified that the method is with or without use of hand rails. • Section 7 Trigger- Removed trigger for potential accelerated sexual development • Section 7 Trigger- Added trigger for spine compression or fracture. • Section 7 PODCI added information about the PODCI which had previously been omitted. • Section 8 Updates to align with protocol template language. • Section 9 Analysis, clarified the IA and handling of missing data for efficacy analysis • Sections 10-15 updates made to align with protocol template language. • Appendices, removed PODCIs for 11-18 year olds. • Various administrative changes made throughout protocol.
Original protocol	18 July 2014	N/A

This amendment incorporates all revisions to date including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

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Abbreviations

This is a list of abbreviations that may be used in the protocol.	
Abbreviation	**Term**
4SC	four stair climb
6MWD	six minute walk distance
6MWT	six minute walk test
ACE	angiotensin-converting-enzyme
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferace
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMD	bone mineral density
BMP/TGFβ	bone morphogenetic protein transforming growth factor-β
CDC	Center for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
CHMP	Committee for Medicinal Product for Human Use
CL	clearance
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DILI	drug-induced liver injury
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DU	dispensable unit
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)
EF	ejection fraction
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle stimulating hormone
FVC	forced vital capacity

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

GCP	Good Clinical Practice
GDF-8	growth differentiation factor 8
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	Identification
IgG1	immunoglobulin G1
IND	investigational new drug application
INR	international normalized ratio
IP	intraperitoneal
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IVR	interactive voice response
IWR	interactive web response
LBM	lean body mass
LC/MS	liquid chromatography/mass spectrometry
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of normal
LSLV	last subject last visit
MHP	mental health provider
MRC	Medical Research Council
MRI	magnetic resonance imaging
MSW	Master's level Clinical Social Workers
N	number
N/A	not applicable
Nab	neutralizing antibodies
NHP	non-human primate
NOAEL	no observed adverse effect levels
NSAA	Northstar Ambulatory Assessment
OLE	open label extension
PCD	primary completion date
PK/PD	pharmacokinetic/pharmacodynamics
PNP	psychiatric Nurse Practitioners
PODCI	Pediatric Data Outcomes Collection Instrument
POM	proof of mechanism
PPV-23	pneumococcal polysaccharide vaccine
PT	prothrombin time

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PUL	Performance of Upper Limb
RBC	red blood cell
RNA	ribonucleic acid
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	Standard deviation
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject's identification
SWFI	sterile water for injection
T4	thyroxine
TEAEs	treatment emergent AEs
TIBC	total iron binding capacity
TK	toxicokinetic
TMDD	Target mediated drug disposition
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
ULN	upper limit of normal
US	United States
USPI	United States package insert

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PROTOCOL SUMMARY

Background and Rationale

The investigational product PF-06252616, a humanized anti-myostatin (GDF-8) monoclonal antibody that neutralizes myostatin (GDF-8) is in development for the treatment of Duchenne muscular dystrophy (DMD) to preserve and/or improve muscle function. Other potential indications for PF-06252616 include other muscular dystrophies, muscle frailty conditions such as cancer cachexia and sarcopenia and rehabilitation of muscle strength.

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

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)[4,12] 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. Most boys lose the ability to walk between the ages of 10 and 14 (Lamperti & Moggio, 2010).[11] Progressive cardiac problems manifest in the second decade. Death occurs in the late teens or early twenties (Manzur et al, 2008).[12]

Protocol B5161002 is a first-in-patient study with PF-06252616. This study will provide the initial clinical assessment of the safety, efficacy, PK and PD of PF-06252616 following repeat IV doses in ambulatory boys with DMD.

Objectives and Endpoints

Primary Safety and Efficacy

- To determine the safety and tolerability of multiple ascending repeat IV doses of PF-06252616 in ambulatory boys with DMD. Safety will be based on incidence of abnormal and clinically relevant laboratory findings, physical examinations, weight, vital signs, electrocardiogram (ECG), left ventricular ejection fraction (LVEF) by cardiac magnetic resonance imaging (MRI) with gadolinium or echocardiogram (if cardiac MRI is not available at the site), liver MRI, dual energy x-ray absorptiometry (DXA) (bone mineral density), x-ray (bone age) and Columbia Suicide Severity Rating Scale (C-SSRS) parameters by Week 49. Cardiac MRI with gadolinium is the preferred method for cardiac imaging. If the subject has a contraindication to gadolinium, cardiac MRI without gadolinium will be acceptable. Echocardiogram may be substituted if it is not possible to perform cardiac MRI (if cardiac MRI is not available at the site).

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- To demonstrate the efficacy of treatment with IV doses of PF-06252616 based on an observed mean change from baseline on function (4 Stair Climb) as compared to placebo following 49 weeks of treatment.

Secondary

- To characterize the effects of PF-06252616 on muscle strength and other functional assessments (Forced Vital Capacity [FVC], Northstar Ambulatory Assessment [NSAA], range of motion [ROM], Performance of Upper Limb [PUL], six minute walk distance [6MWD]) compared to placebo.

- To evaluate the PD activity of PF-06252616 based on the percent change of muscle volume as measured on MRI from baseline as compared to placebo.

- To evaluate the PD profile of PF-06252616 based on GDF-8 (myostatin) modulation in blood.

- To characterize the PK profile of PF-06252616.

- To evaluate the immunogenicity (anti-drug antibodies [ADA] and neutralizing antibodies [NAb]) of PF-06252616.

- To characterize the long-term effects following approximately 2-years of treatment with PF-06252616 on functional assessments compared to historical control.

- To characterize the effects of PF-06252616 on muscle strength and functional assessments compared to placebo in a subset of subjects who may demonstrate a rapid disease decline and with relatively low variability over a one-year period.

Exploratory

- To evaluate biomarkers (lean body mass [LBM] by DXA, muscle quality by MRI, quantification of blood biomarkers) that may be informative in demonstrating the pharmacologic effect of PF-06252616.

- To evaluate biomarkers that may be informative for monitoring hepatic liver injury in the setting of dystrophic muscle.

- To evaluate the Functional Health Status (Pediatric Data Outcomes Collection Instrument [PODCI] questionnaire).

- To evaluate long term safety of PF-06252616 in subjects treated for >1 year.

- To evaluate duration of treatment response following withdrawal and/or continuation of treatment for >1 year.

- To evaluate response in a delayed treatment group.

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Study Design

This is a Phase 2 randomized, 2-period, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, PK and PD of PF-06252616 administered to ambulatory boys diagnosed with DMD. Three IV infused dose levels (5, 20 and 40 mg/kg) administered every 28 days will be investigated in a within subject dose escalating fashion.

Approximately 105 eligible subjects will be randomly assigned to 1 of 3 sequence groups and receive investigational product for approximately 96 weeks (2 treatment periods of approximately 48 weeks each) stratified by their baseline time to complete the 4 stair climb (either ≤ or >8 seconds).

Sequence 1 (n=35):
Period 1: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)
Period 2: Active treatment (PF-06252616) at the maximum tolerated dose in Period 1

Sequence 2 (n=35):
Period 1: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)
Period 2: Placebo

Sequence 3 (n=35):
Period 1: Placebo
Period 2: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)

Each dose level will be explored in a dose escalating fashion within subjects, starting with the lowest dose. At each dose level, dosing will be administered over a 2-hour IV infusion every 4 weeks for a total of 16 weeks (4 doses). Dose escalation within a subject will occur following the planned fourth dose within each dose level. Subjects will move from Period 1 to Period 2 without a pause between periods.

Individual dose escalation decisions will be conducted for each subject by the Investigator, sponsor Medical Monitor and a Designated Reviewer. This process will occur from time of the first subject being enrolled and continue until the time of the IA. At the time of IA (or sooner as determined by the External Data monitoring committee's review of unblinded data), if adequate safety has been demonstrated at each dose level as determined by an External Data Monitoring Committee (E-DMC), subsequent dose escalation will occur without confirmation of the individual safety data prior to dose escalation.

From the time of study initiation through completion of the study, the sponsor will conduct routine safety monitoring of the blinded data per the safety review plans. In addition, the E-DMC will review unblinded safety data. The E-DMC may determine if it is necessary to close or adjust a dose level within the study or continue with individual level dose escalation review.

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In the event that the E-DMC determines that adequate safety has been established at each dose level (following the IA or sooner), they will also consider if the requirement for liver MRI can be reduced to an annual safety assessment (based on normal findings on the liver MRI).

The individual subject dose adjustment will be determined by three parties including the Investigator, sponsor Medical Monitor and a Designated Reviewer. Following the planned fourth dose within each dose level, all available safety data for an individual subject will be reviewed by the Investigator, sponsor Medical Monitor and Designated Reviewer to determine the appropriate dose adjustment.

Dose adjustment criteria will be used to determine if the dosing or dose level should be:

- Escalated to the next dose level.
- Maintained at the current dose level.
- Reduced to a lower dose level, or
- Stop dosing.

Subjects who complete this study may be invited to participate in an open label extension study.

Investigational Product Administration

Subjects will be treated with IV infused PF-06252616 or placebo in this double-blind, placebo controlled study. Allocation of subjects to the sequence groups (treatment assignment) will proceed through the use of an Interactive Response Technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR) system] by the unblinded dispensing personnel.

PF-06252616 will be provided by Pfizer as a lyophilized powder for injection in single use, sterile glass vials. Each vial will be sealed with a coated stopper and an aluminum overseal and labeled according to local regulatory requirements. The drug product must be reconstituted with sterile water for injection (SWFI) for IV infusion. The reconstituted PF-06252616 drug product is a clear to slightly opalescent solution and colorless to slightly colored in appearance.

The placebo will be provided by Pfizer as a solution for injection. The placebo is supplied in a glass vial sealed with a coated chlorobutyl serum stopper and an aluminum overseal and labeled according to local regulatory requirements.

The placebo does not match the active drug product and therefore, the supplies are provided as open label vials. Trained unblinded site staff personnel who are appropriately qualified (eg, pharmacist, pharmacist technician) are required to prepare the investigational product.

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

Following preparation of the investigational product (PF-06252616 or placebo) by the unblinded site staff personnel, the prepared product will be provided to blinded staff personnel for administration.

At the time of investigational product administration, topical anesthetics (eg, topical lidocaine at the site of infusion) may be administered to subjects, consistent with institutional guidelines.

The IV infusion should be administered by qualified healthcare professionals trained to detect any infusion related issues. Infusion times, rates, any infusion interruptions or infusion rate reduction, will be recorded. The study drug should be infused over a 2-hour period where time 0 is the beginning of the infusion and include the flush time. Subjects should be observed for 1-hour following completion of the investigational product administration.

Statistical Method for Primary Efficacy

The sample size is based on the primary endpoint of demonstrating efficacy of change from baseline on a 4 stair climb timed function test as compared to placebo at 49 weeks. To detect a 2.5 second difference in change from baseline in 4 stair climb based on a difference between the active treatment and the placebo treatment in Period 1 assuming a standard deviation of 4.0 with 80% power at α=0.05 (two-sided), a 2:1 treatment allocation and one IA, a total of 96 subjects should complete 49 weeks of dosing for this assessment. Assuming a 10% attrition rate, approximately 105 subjects should be enrolled (70 subjects receiving PF-06252616 and 35 subjects receiving placebo) in order to ensure a sufficient number of subjects will complete this assessment. If there are no safety issues and enrollment has completed, additional subjects may be enrolled prior to the time of the interim analysis. These additional subjects may help off-set any unforeseen variability that may occur outside the presumed standard deviation for this age group.

One IA is planned to evaluate futility and efficacy after approximately 50% of the subjects have completed through Week 49. Alpha- and beta-spending functions will be used to determine the cutoffs for efficacy and futility at the interim based on the observed number of subjects in the IA. The gamma family spending functions will be used to appropriately account for error spending and adjust for the observed information at the time of the IA and conservative boundaries ($\gamma \leq -1$) will be used to define the futility and efficacy boundaries. The cutoff used at the IA will be calculated based on the percentage of subjects included at the IA to ensure appropriate protection of the type I error. Further details regarding the IA and simulations are included in the statistical analysis plan (SAP).

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At the time of the IA if the E-DMC makes a recommendation to the sponsor management to modify or terminate the study based on establishing efficacy and safety of PF-06252616, the sponsor management will review the recommendation with regulatory agencies prior to making any changes to the study design, including termination of the study.

Continuous variables will be summarized by the number (N), mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by percent and counts. All summaries will be displayed by treatment group and/or period depending on the endpoint. Efficacy data will be listed, tabulated and graphically represented, as appropriate. Model assumptions will be tested using appropriate statistical or graphical techniques.

All analyses will be based on the full analysis set (FAS) which includes all randomized subjects who have received at least one dose of study drug. Additionally analyses based on a per protocol analysis set may also be performed.

Change from baseline in 4 stair climb will be analyzed using a longitudinal mixed effects model. The baseline result, treatment, time and treatment by time interaction will be included as fixed effects in the model. Subject will be included as a random effect and the model will be fit with an unstructured covariance for the repeated measures. The distribution of the time to climb 4 stairs is assumed to be right skewed. Transformations of the time to climb 4 stairs (including the log transformation) will be evaluated to ensure the normality assumption is met. Contrasts will be created to estimate the differences in change from baseline time in 4 stair climb at the end of each dose treatment levels for Period 1 (Week 17, Week 33 and Week 49). The final analysis of the primary endpoint will be performed at Week 49, though data will continue to be collected through Week 97. Additionally, non-Gaussian models may be explored in the case of non-normal data for the time to climb 4 stairs.

Missing data will be handled using maximum likelihood techniques for a mixed effects model. This analysis is unbiased under the assumption of missing at random when the model assumptions hold. Subjects who lose the ability to climb 4 stairs and/or ambulate will be missing not at random. Additional imputation methods to assess the sensitivity of the analysis to missing not at random data will also be performed. A completer analysis will also be conducted as a sensitivity analysis.

A sensitivity analysis of the time to climb 4 stairs will be based on the velocity (defined as the reciprocal of time). This analysis will use the same longitudinal model, but subjects who can no longer ambulate will be analyzed with a velocity of 0 instead of a missing time to climb 4 stairs at that time point, as specified above. Thus the missing data will no longer be handled by the maximum likelihood techniques under the missing at random assumption for subjects who can longer complete the 4 stair climb. Based on the number of subjects who cannot complete the function test at Week 49, a zero inflation model may also be explored for the velocity endpoint.

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Additionally, a non-parametric sensitivity analysis may be performed on the Week 49 data if there is a large number of subjects who can no longer ambulate. The proportion of subjects who can no longer complete the test will also be compared between the two treatment groups at the Week 49 time point along with a time to failure analysis comparing the two treatment groups based on the ability to complete the test.

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SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures for Period 1, 2 and Early Withdrawal. In order to accommodate the scheduling, assessments may be conducted on separate days within the visit window; however the order of completion of assessments must be adhered to. Refer to the STUDY 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 Period 1

Period 1																
Visit Number/*Treatment Week)*[a]	***1***	***2***	**3 / (*1 wk*)**		**9 / *(17 wk)* 15 / *(33 wk)***		**4 / *(2 wk)*[a] 10 / *(18 wk)*[a] 16 / *(34 wk)*[a]**	**5 / (*5 wk*) 11 / (*21 wk*) 17 / (*37 wk*)**		**6 / (*9 wk*) 12 / (*25 wk*) 18 / (*41 wk*)**		**7 / (*13 wk*) 13/ (*29 wk*) 19 / (*45 wk*)**		**8 / (14 wk)[a] 14 / *(30 wk)*[a] 20 / *(46 wk)*[a]**	
Study Day/Visit Window[b]	**Screening -42 to -5**	**Baseline -4 to -1**	**1[p]**		**113 ±3 225 ±3**		**8 ±1 120 ±1 232 ±1**	**29 ±3[p] 141 ±3 253 ±3**		**57 ±3 169 ±3 281 ±3**		**85 ±3 197 ±3 309 ±3**		**92 ±1 204 ±1 316 ±1**	
Hours Post Dose			Pre	2	Pre	2		Pre	2	Pre	2	Pre	2		
Entry/Safety Assessments/Questionnaire															
Informed consent/Assent[c]	X														
Demography	X														
Medical History[d]	X														
Medication History	X														
Inclusion/Exclusion Review	X	X													
Physical Examination[e]	X	X			X			X		X		X			
Tanner Stage and Testicular Volume[s]		X			X										
Height[f]		X			X										
Weight[g]	X	X[g]			X			X		X		X			
Vital Signs[h]	X	X	X	X	X	X		X	X	X	X	X	X		
Triplicate ECG	X	X			X										
Cardiac MRI (or Echocardiogram)[i]	X														

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Period 1									
Visit Number/*Treatment Week)*[a]	***1***	***2***	**3 / (*1 wk*)**	**9 / *(17 wk)* 15 / *(33 wk)***	**4 / *(2 wk)*[a] 10 / *(18 wk)*[a] 16 / *(34 wk)*[a]**	**5 / (*5 wk*) 11 / (*21 wk*) 17 / (*37 wk*)**	**6 / (*9 wk*) 12 / (*25 wk*) 18 / (*41 wk*)**	**7 / (*13 wk*) 13/ (*29 wk*) 19 / (*45 wk*)**	**8 / (14 wk)[a] 14 / *(30 wk)*[a] 20 / *(46 wk)*[a]**
Study Day/Visit Window[b]	**Screening -42 to -5**	**Baseline -4 to -1**	**1[p]**	**113 ±3 225 ±3**	**8 ±1 120 ±1 232 ±1**	**29 ±3[p] 141 ±3 253 ±3**	**57 ±3 169 ±3 281 ±3**	**85 ±3 197 ±3 309 ±3**	**92 ±1 204 ±1 316 ±1**
Hours Post Dose			Pre 2	Pre 2		Pre 2	Pre 2	Pre 2	
Clinical Laboratory Tests[j]	X	X		X	X[a]	X	X	X	X[a]
Serum Ferritin, Serum Iron, TIBC, % Transferrin Saturation[j]	X	X		X		X	X	X	
Hormones (LH, FSH, T4, TSH, androstenedione, testosterone)[f,s]		X		X					
Fecal Occult Blood[k]	X	X		X		X	X	X	
PODCI Questionnaire	X	X		X			X		
C-SSRS[l]	X	X		X		X	X	X	
Randomization[m]		X							
Imaging Assessments									
MRI-Liver	X							X[n]	
MRI-Thigh	X[n]			X[n]					
DXA-Spine[i]	X								
DXA-Whole Body	X			X					
X-ray (hand and wrist)[s]	X			X					
Functional Assessments									
FVC	X[n]	X		X[n]			X		
4 Stair Climb	X[n]	X		X[n]			X		
Northstar Ambulatory Assessment	X[n]	X		X[n]			X		
Range of Motion	X[n]	X		X[n]			X		
Strength Assessment	X[n]	X		X[n]			X		
PUL	X[n]	X		X[n]			X		
6MWT	X[n]	X		X[n]			X		
Investigational Product Administration									
Investigational Product administration[o]			X	X		X	X	X	

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Period 1															
Visit Number/*Treatment Week)*[a]	***1***	***2***	**3 / (*1 wk*)**		**9 / (*17 wk*) 15 / (*33 wk*)**		**4 / (*2 wk*)[a] 10 / (*18 wk*) [a] 16 / (*34 wk*) [a]**	**5 / (*5 wk*) 11 / (*21 wk*) 17 / (*37 wk*)**		**6 / (*9 wk*) 12 / (*25 wk*) 18 / (*41 wk*)**		**7 / (*13 wk*) 13/ (*29 wk*) 19 / (*45 wk*)**		**8 / (14 wk)[a] 14 / (*30 wk*)[a] 20 / (*46 wk*)[a]**
Study Day/Visit Window[b]	**Screening -42 to -5**	**Baseline -4 to -1**	**1[p]**		**113 ±3 225 ±3**		**8 ±1 120 ±1 232 ±1**	**29 ±3[p] 141 ±3 253 ±3**		**57 ±3 169 ±3 281 ±3**		**85 ±3 197 ±3 309 ±3**		**92 ±1 204 ±1 316 ±1**
Hours Post Dose			Pre	2	Pre	2		Pre	2	Pre	2	Pre	2	
PK/PD/Biomarker/Immunogenicity														
PK sample[q]			X	X	X	X	X[a]	X	X	X	X	X	X	X[a]
PD sample (Total GDF-8) [q]			X	X	X	X		X	X	X	X	X	X	
Biomarker Sample Group 1 (Prep D1.5)	X													
Biomarker Sample Group 2 (Prep B1.5, B2.5)[j]	X	X			X									
Biomarker Sample Group 3 (Prep R1, Cell-free RNA)	X													
Biomarker Sample Liver	X	X			X		X	X		X		X		X
Immunogenicity		X			X			X		X		X		
Wellness Phone Check[r]			X		X			X		X		X		
Infusion Site Reaction monitoring			X		X		X	X		X		X		X
Adverse event monitoring			X		→		→	→		→		→		→
Concomitant medication			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; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; GDF-8=growth differentiation factor 8; LH= Luteinizing hormone; MRI=magnetic resonance image; PD=Pharmcodynamics, PK=Pharmocokinetics, PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance of Upper Limb, T4 =thyroxine; TIBC=Total iron binding capacity, TSH=thyroid stimulating hormone.

a. The first 12 subjects will be required to complete 6 additional visits including Visit 4, 8, 10, 14, 16 and 20 (Day 8, 92, 120, 204, 232 and 316) to provide clinical laboratory and PK samples in Period 1. Subjects enrolled after the first 12 subjects will not be required to complete these additional visits.

b. Assessments should be conducted on the Study Day within the visit window. In order to assure consistency in assessment collection, at visits where functional assessments and imaging assessments are collected at the same visit, subjects will be required to be assessed over a 2 day period. Please see Section 6 for additional details.

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

d. Medical history will include confirmation by genetic testing of the diagnosis of Duchenne muscular dystrophy (DMD) as obtained from an approved laboratory. Results must confirm the presence of a mutation in the dystrophin gene(s) which is clinically consistent with the diagnosis of DMD.

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

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

g. Weight must be collected at each visit prior to dosing. For the dosing on Day 1, the weight from the baseline visit will be used to calculate the dose on Day 1. At subsequent visits after Day 1, either the current visit or the prior month's weigh may be used to calculate the dose.

h. Vital sign evaluations will include supine blood pressure, pulse rate, respiratory rate and oral temperature. At each dosing visit, vital signs will be taken pre and post-dosing. The post-dosing vitals will be taken upon completion of the investigational product administration during the 1-hour observational period post-dose.

i. After the screening assessments are conducted, DXA-spine and cardiac MRI (or echocardiogram) assessments will only be conducted at Visit 21 and 33 (Day 337 and 673) and Early Withdrawal. 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 should be used consistently within a single subject. Cardiac MRI with gadolinium should only be performed after all other imaging assessments are completed.

j. Clinical laboratory tests include hematology, chemistry, gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (PT), activated partial thromboplastin time (aPTT), creatine kinase, amylase, cardiac troponin I and urinalysis. Cardiac troponin I will be collected at Baseline, Visits 9, 15, 21, 25, 29 and 33 (Days, 113, 225, 337, 449, 561, 673) and EarlyWithdrawal. The samples for Biomarker Group 2, serum ferritin, serum iron, TIBC and % transferrin saturation should be collected following and 8 hour fast. See Section 7.3 for description on Biospecimen sample collection.

k. If a stool sample is unable to be collected during 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, a stool sample will be collected at home within *approximately* 1 week prior to the scheduled visit. Note that the collection may fall outside of the visit window.

l. The "Children's Baseline/Screening" C-SSRS will be administered at screening. At all other visits the "Children's Since Last Visit" assessment will be performed.

m. Randomization will occur after all screening evaluations and baseline C-SSRs are complete and subjects are confirmed to be eligible to participate in the study. All baseline evaluations should also be completed prior to the randomization, as the weight and 4SC results from baseline are needed at the time of registration in the randomization system.

n. At visits when both imaging (MRI-thigh) and functional assessments are being conducted, these assessments should be conducted on separate days. Functional assessments should routinely be collected in the morning when the subject is rested and well fed. The MRI-thigh should routinely be collected at approximately the same time of day throughout the study. Functional assessments must be conducted in the order presented within the schedule of activities. Should subjects become non-ambulatory during the study, the 4SC, NSAA and 6MWT will not continue to be collected. Following the interim analysis (or at an earlier time point as determined by the E-DMC upon their review of unblinded data), if the E-DMC determines that monitoring frequency for the liver is able to be reduced, the liver MRI will then only be conducted at Screening and on Visit 19 and 32 (Days 309 and 645).

o. Investigational product should be delivered in a 2 hour window -15 or +30 minutes including the flush time. Subjects are required to be observed for 1 hour after the infusion of the investigational product is completed. If a dosing visit cannot be conducted within the visit window, attempts should be made to

bring the subject back for dosing as soon as possible; however the dosing **must not occur** within 2 weeks prior to the next scheduled dose. If the subject cannot return in this timeframe, the dose should be missed and the next visit should be conducted per the schedule of activities.

p. Per the local requirements in Japan, all Japanese subjects will be hospitalized for an overnight observation following the first and second treatment on Day 1 and Day 29.

q. The window for the PK/PD assessments post dosing at 2 hours is +30 minutes. If the infusion rate is decreased (following an infusion site reaction) the PK/PD assessments should be collected at the time of infusion completion (within a +30 minute window).

r. Approximately 1 week following each dosing visit, the site will call the caregiver to verify if there are any adverse events which have emerged since dosing.

s. For subjects who may be sexually mature at the onset of study (as assessed at the baseline visit) or reach sexual maturity during the trial, as indicated by a Tanner Stage V rating, the Tanner Stage, testicular volume, hormone and X-ray (hand and wrist) will no longer required to be collected to assess for signs of precocious puberty.

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Study Flowchart Period 2 and Early Withdrawal

Period 2												Early Withdrawal
Visit Number/ (*Treatment Week*)	**21 / *(49 wk)* 25 / *(65 wk)* 29 / *(81 wk)***		**22 / *(53 wk)* 26 / *(69 wk)* 30 / *(85 wk)***		**23 / *(57 wk)* 27 / *(73 wk)* 31 / *(89 wk)***		**24 / *(61 wk)* 28 / *(77 wk)* 32 / *(93 wk)***		**33 / (*97 wk*)**	**34 / (*105 wk*)**	
Study Day/Visit Window[a]	**337 ±3 449 ±3 561 ±3**		**365 ±3 477 ±3 589 ±3**		**393 ±3 505 ±3 617 ±3**		**421 ±3 533 ±3 645 ±3**		**673 ±3**	**729 ±3**[b]	
Hours Post Dose	Pre	2	Pre	2	Pre	2	Pre	2			
Safety Assessments/Questionnaire											
Physical Examination[c]	X		X		X		X		X		X
Tanner Stage and Testicular Volume[p]	X								X		X
Height[d]	X								X		X
Weight[e]	X		X		X		X		X		X
Vital Signs[f]	X	X	X	X	X	X	X	X	X		X
Triplicate ECG	X								X		X
Cardiac MRI or Echocardiogram[g]	X[g]								X[g]		X
Clinical Laboratory Tests[h]	X		X		X		X		X		X
Serum Ferritin, Serum Iron, TIBC, % Transferrin Saturation[h]	X		X		X		X		X		X
Hormones (LH, FSH, T4, TSH, androstenedione, testosterone)[d,p]	X								X		X
Fecal Occult Blood[i]	X		X		X		X		X		X
PODCI Questionnaire	X				X				X		X
C-SSRS)[j]	X		X		X		X		X		X
Imaging Assessments											
MRI-Liver[l]							X				X
MRI-Thigh[k]	X								X		X
DXA-Spine[g]	X[g]								X[g]		X
DXA-Whole Body	X								X		X
X-ray (hand and wrist)[p]	X								X		X
Functional Assessments[k]											
FVC	X[k]				X				X[k]		X
4 Stair Climb	X[k]				X				X[k]		X
Northstar Ambulatory Assessment	X[k]				X				X[k]		X
Range of Motion	X[k]				X				X[k]		X
Strength Assessment	X[k]				X				X[k]		X

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Period 2												Early Withdrawal
Visit Number/ (*Treatment Week*)	**21 / *(49 wk)* 25 / *(65 wk)* 29 / *(81 wk)***		**22 / *(53 wk)* 26 / *(69 wk)* 30 / *(85 wk)***		**23 / *(57 wk)* 27 / *(73 wk)* 31 / *(89 wk)***		**24 / *(61 wk)* 28 / *(77 wk)* 32 / *(93 wk)***		**33 / (*97 wk*)**	**34 / (*105 wk*)**	
Study Day/Visit Window[a]	**337 ±3 449 ±3 561 ±3**		**365 ±3 477 ±3 589 ±3**		**393 ±3 505 ±3 617 ±3**		**421 ±3 533 ±3 645 ±3**		**673 ±3**	**729 ±3**[b]	
Hours Post Dose	Pre	2	Pre	2	Pre	2	Pre	2			
PUL	X[k]				X				X[k]		X
6MWT	X[k]				X				X[k]		X
Investigational Product Administration											
Investigational Product administration[m]	X		X		X		X				
PK/PD/Biomarker/Immunogenicity											
PK sample[n]	X	X	X	X	X	X	X	X			X
PD sample (Total GDF-8)[o]	X	X	X	X	X	X	X	X			X
Biomarker Sample Group 2(Prep B1.5, B2.5)[h]	X								X		X
Biomarker Sample Group 3(Prep R1, Cell-free RNA)	X								X		X
Biomarker Sample Liver	X		X		X		X		X		X
Immunogenicity	X		X		X		X		X		X
Wellness Phone Check[o]	X		X		X		X				
Infusion Site Reaction monitoring	X		X		X		X		X		X
Adverse event monitoring	X		→		→		→		→	X	X
Concomitant medication	X		→		→		→		→	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; FSH= Follicle stimulating hormone; FVC=Forced vital capacity; GDF-8=growth differentiation factor 8; LH= Luteinizing hormone; MRI=magnetic resonance image; PD-Pharmacodynamics, PK=Pharmacokinetics, PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance of Upper Limb; T4=thyroxine; TIBC=Total iron binding capacity, TSH=thyroid stimulating hormone.

a. Assessments should be conducted on the Study Day within the visit window. In order to assure consistency in assessment collection, at visits where functional assessments and imaging assessments are collected at the same visit, subjects will be required to be assessed over a 2 day period. Please see Section 6 for additional details.

b. At the final study Visit 34 (Day 729) any ongoing adverse events and concomitant medications will be reviewed. This visit can be conducted by phone.

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

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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

e. Weight must be collected at each visit prior to dosing. At subsequent visits after Day 1, either the current visit or the prior month's weight may be used to calculate the dose.

f. Vital sign evaluations will include supine blood pressure, pulse rate, respiratory rate and oral temperature. At each dosing visit, vital signs will be taken pre and post-dosing. The post-dosing vitals will be taken upon completion of the investigational product administration during the 1-hour observational period post-dose.

g. After the screening assessments are conducted, DXA-spine and cardiac MRI or echocardiogram will only be conducted at Visit 21 and 33 (Day 337 and 673) and Early Withdrawal. If it is not possible to perform cardiac MRI (eg, not the available at the site) echocardiogram will be acceptable. The same method of cardiac imaging should be used consistently within a single subject. Cardiac MRI with gadolinium should only be performed after all other imaging assessments are completed.

h. Clinical laboratory tests include hematology, chemistry, GGT GLDH, PT, aPTT, creatine kinase, amylase, cardiac troponin I, and urinalysis. Cardiac troponin I will be collected at Baseline, Visits 9, 15, 21, 25, 29 and 33 (Days, 113, 225, 337, 449, 561 673) and Early Withdrawal. The samples for Biomarker Sample Group 2, serum ferritin, serum iron, TIBC and % transferrin saturation should be collected in the morning following an 8 hour fast. See Section 7.3 for description on Biospecimen sample collection.

i. A stool sample will be collected at home within *approximately* 1 week prior to the scheduled visit. Note that the collection may fall outside of the visit window.

j. The "Children's Baseline/Screening" C-SSRS will be administered at screening. At all other visits the "Children's Since Last Visit" assessment will be performed.

k. At visits when both imaging (MRI-thigh) and functional assessments are being conducted, the assessments should be conducted on separate days. Functional assessments should routinely be collected in the morning when subject is rested and well fed. The MRI-thigh should routinely be collected at approximately the same time of day throughout the study. In Period 2, the MRI-thigh will only be conducted at Visit 21 and 33 (Days 337 and 673). Functional assessments must be conducted in the order presented within the schedule of activities. Should subjects become non-ambulatory during the study, the 4SC, NSAA and 6MWT will not continue to be collected.

l. Following the interim analysis (or at an earlier time point as determined by the E-DMC upon their review of unblinded data), if the E-DMC determines that the monitoring frequency for liver MRI can be reduced, it will only be conducted at Screening and on Visit 19 and 32 (Days 309 and 645).

m. Investigational product should be delivered in a 2 hour window -15 or +30 minutes including the flush time. Subjects are required to be observed for 1 hour after the infusion of the investigational product is completed. If a dosing visit cannot be conducted within the visit window, attempts should be made to bring the subject back for dosing as soon as possible; however the dosing **must not occur** within 2 weeks prior to the next scheduled dose. If the subject cannot return in this timeframe, the dose should be missed and the next visit should be conducted per the schedule of activities.

n. The window for the PK/PD assessments post dosing at 2 hours is +30 minutes. If the infusion rate is decreased (following an infusion site reaction) the PK/PD assessments should be collected at the time of infusion completion (within a +30 minute window).

o. Approximately 1 week following each dosing visit, the site will call the caregiver to verify if there are any adverse events which have emerged since dosing.

p. For subjects who may be sexually mature at the onset of the study (as assessed during the baseline visit) or reach sexual maturity during the trial, as indicated by a Tanner Stage V rating, the Tanner Stage, testicular volume, hormone and X-ray (hand and wrist) will no longer be required to be collected to assess for signs of precocious puberty.

TABLE OF CONTENTS

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

LIST OF TABLES

APPENDICES

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

1. INTRODUCTION

1.1. Mechanism of Action/Indication

The investigational product PF-06252616, a humanized anti-myostatin (GDF-8) monoclonal antibody that neutralizes myostatin (GDF-8) is in development for the treatment of Duchenne muscular dystrophy (DMD) to preserve and/or improve muscle function. Other potential indications for PF-06252616 include other muscular dystrophies, muscle frailty conditions such as cancer cachexia and sarcopenia and rehabilitation of muscle strength.

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

Protocol B5161002 is a first-in-patient study with PF-06252616. This study will provide the initial clinical assessment of the safety, efficacy, PK and PD of PF-06252616 following repeat IV doses in ambulatory boys with DMD.

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

1.2. Background and Rationale

1.2.1. Myostatin Role in Muscle Regulation

Myostatin or growth and differentiation factor 8 (GDF-8) is a member of the bone morphogenetic protein transforming growth factor-β (BMP/TGFβ) superfamily of secreted differentiation factors (McNally, 2004).[23] The muscle specific negative regulator role of GDF-8 is well conserved between zebrafish, dogs, cattle, mice and humans. GDF-8 has been best studied in skeletal muscle where GDF-8 -/- 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).[24] 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).[23] One case of a human has been reported with a homozygous mutation of the GDF-8 gene, associated with an absence of GDF-8 protein, increased muscle strength and, by age 4, no apparent untoward health effects (Schuelke et al, 2004).[27] Pharmacologic inhibition of GDF-8 activity in rodents results in increased muscle mass and improved muscle function in both normal and dystrophic animals (Bradley et al, 2008).[3] 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.

1.3. 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)[4,12] which is absent from the muscle of boys with DMD. DMD is the most severe of all muscular dystrophies and is

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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).[11] Progressive cardiac problems manifest in the second decade. Death occurs in the late teens or early twenties (Manzur et al, 2008).[12] Although girls don't usually experience the full effects of DMD or the milder Becker muscular dystrophy a minority of females with the mutation are manifesting carriers, who have a mild form of the disorder (Lamperti & Moggio, 2010).[11]

There is no specific approved treatment that can stop or reverse the progression of DMD. 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 (Manzur et al, 2008)[12] 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.

A key therapeutic goal is to make DMD symptoms into milder Becker muscular dystrophy symptoms, but there is no satisfactory symptomatic or disease-modifying treatment at present. Only limited and inadequate approaches such as chronic glucocorticoid use are currently available. Thus, glucocorticoid off-label use in DMD may improve muscle strength for a period of time and perhaps delay the course of the disease, (Mendell et al, 1989; Bonifati et al, 2000),[25,2] but glucocorticoid use is associated with well-known adverse events such as weight gain and broad hypothalamic-pituitary-adrenal axis effects.

1.3.1. PF-06252616

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

1.4. Nonclinical Pharmacodynamics

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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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

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1.7. Clinical Experience with PF-06252616

The clinical program for PF-06252616 was initiated in June 2012 with a Phase 1 first in human, randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled study (B5161001) evaluating the safety, tolerability, PK, PD, and pharmacologic (anabolic) effects of escalating single doses of PF-06252616 in healthy adult subjects. The study completed enrollment with 73 subjects at a single site. Doses of 1, 3, 10, 20, and 40 mg/kg administered by IV and 3 mg/kg administered by SC, 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.

PF-06252616 serum concentrations in Study B5161001 were measured using a validated enzyme-linked immunosorbent assay (ELISA) method. The PK serum profiles following the single and repeat dose administrations were analyzed. Following either single or repeat IV infused doses, peak concentrations were generally observed within 2 hours after the end of infusion (median T_{max} was 4 hours after the start of the 2-hour infusion). Concentrations declined relatively rapidly for the first 1 to 2 weeks and more slowly thereafter over a period of months. Following SC administration, C_{max} was observed at about 1 week (median T_{max} of 7 days [168 hours]) and concentrations subsequently declined slowly over a period of months. Mean apparent terminal elimination $t_{½}$ was roughly 2 weeks (14 days) overall but appeared to increase with dose, from 12 to 13 days at the lower doses up to 18 to 19 days for the higher doses. Serum C_{max} generally appears to increase proportionally with dose following IV administration of 1 mg/kg to 40 mg/kg. The apparent bioavailability of the 3 mg/kg SC injection was 61% based on comparison of geometric mean AUC_{inf} values for 3 mg/kg SC and IV.

The PD activity of PF-06252616 was evaluated in Study B5161001, by measuring total serum myostatin levels using a validated liquid chromatography/mass spectrometry (LC/MS) method. Following the PF-06252616 serum concentration levels, total serum myostatin levels were noted to be modulated at all dose levels. After single dose administration, the median time to maximum total serum myostatin levels was generally between 11 and 30 days. The extent of modulation generally increased between 1 and 10 mg/kg IV doses and seemed to reach a plateau by the 20 mg/kg IV dose. In the repeat dose cohort, the median myostatin baseline level was 3.1 mg/mL on Day 1 and following

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10 mg/kg IV dosing, the median myostatin concentration increased to 18.6 ng/mL after the third dose. The median C_{max} (myostatin) after 10 mg/kg single and repeat dose were 24.5 and 24.9 ng/mL respectively.

One of the secondary objectives of Study B5161001 was to demonstrate proof of mechanism (POM) for evidence of a pharmacologic effect based on a percentage change in lean body mass (LBM) as measured in dual-energy x-ray absorptiometry (DXA) in the repeat dose cohort (10 mg/kg IV every 2 weeks for 1 month). Per the analysis criteria, the percent change in LBM in the repeat dose cohort did not reach significance at any time point evaluated. The criteria were then applied in an exploratory analysis to the magnetic resonance imaging (MRI) measurements of thigh muscle volume and T2-mapping of measures at each time point. On the thigh muscle volume measurement, an increase in muscle volume at Day 113 was demonstrated, at which time a mean 4.48% difference from baseline, relative to placebo, was observed. The T2-mapping analysis further supported the observation of an increase of lean muscle in PF-06252616 treated subjects relative to placebo in an exploratory analysis.

Study B5161002 is an ongoing first-in-patient, Phase 2, randomized, 2-period, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, PK and PD of PF-0652616 administered to ambulatory boys with DMD. The study was initiated in November 2014. Information for this study may be found in the Investigator's Brochure.

1.8. Immunogenicity Risk Assessments

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1.8.2. Immunogenicity Results B5161001

The immunogenicity assessment population included all 53 subjects who received the active study drug (PF-06252616) with at least 1 post-treatment anti-drug antibody (ADA) determination. The impact of ADAs and neutralizing antibodies (NAb) on PK and PD were also evaluated graphically with no apparent differences in PK and PD profiles between ADA positive subjects and ADA negative subjects.

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In subjects receiving active PF-06252616, ADAs were detected early on Day 15 of the study. Overall incidence of ADA was noted in 6 out of 53 subjects who received active treatment (PF-06252616) in the following cohorts; 1 subject in 1 mg/kg, 10 mg/kg (single IV), 10 mg/kg (repeat dose) and 20 mg/kg IV dose cohorts; 2 subjects in 3 mg/kg SC dose cohort. The confirmed incidence rate was 11.3%. There were 14 subjects who were considered inconclusive and the inconclusive subject-adjusted incidence rate excluding these subjects was 15.4% (6 out of 39 subjects). Samples which tested positive for ADA were further tested for NAb. A total of 5 samples from 4 subjects showed NAb titer ≥1.3 in the following cohorts: 1 each in the 1 mg/kg, 10 mg/kg (repeat), 20 mg/kg IV, and 3 mg/kg SC group. Although these samples were positive in the NAb assay, all were determined to have 'inconclusive' results for neutralizing activity due to potential interference from PF-06252616 levels in these samples.

In summary, for Study B5161001, there was a confirmed ADA incidence rate of 11.3% but without any obvious impact on the PF-06252616 PK or myostatin modulation.

1.9. Rationale for Dosage Selection and Method of Administration

For Study B5161002, 5 mg/kg administered over two hours and every 4 weeks is being proposed as the starting dose as it is expected to show median GDF-8 serum coverage over 80%, and therefore may show pharmacology as well as further provide a safety multiple of 17 and 28.6 for C_{max} and C_{av} at steady state respectively. 20 mg/kg administered over two hours and every 4 weeks is being proposed as the dose that would provide target coverage similar to the 10 mg/kg Q 2 week dose in Study B5161001, which produced MRI signal changes in healthy volunteers. 40 mg/kg administered over two hours and every 4 weeks is being proposed as the highest dose as it will provide additional safety coverage for future studies and it maximizes the potential for efficacy, especially considering that the target engagement of PF-06252616 in muscles is unclear. IV was chosen as the route of administration to support the large volume of the dose that will be required to obtain the targeted GDF-8 coverage as well as for subject adherence. 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.

To arrive at the above doses and regimens PK and PK/PD approaches were considered using the data previously generated within the program. As prior PF-06252616 PK data has been derived in an adult population, a literature review was conducted to determine the CL and V_{ss} parameters of monoclonal antibodies administered to both an adult and a pediatric population. This meta-analysis suggested that both parameters were similar between the adults and children, especially when both populations received a body weight based (mg/kg) dosing. To confirm allometry for the current monoclonal antibody, allometric scaling of non-compartmental PK parameters (CL and V_{ss}) determined in mice, rat, monkey and adult humans (Study B5161001) were scaled with body weight. The exponents obtained were 0.79 and 0.94 for CL and V_{ss} respectively suggesting that PF-06252616 is similar to other monoclonal antibodies and that the PK parameters scale allometrically.

Predicted CL and V_{ss} parameters were generated across the population using both the allometrically scaled non-compartmental parameters and allometrically scaled (using a fixed

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0.75 exponent) population PK model; both methods gave similar results where the 5th, 50th and 95th percentile CL and V_{ss} values using the different methods were <30% different and within the normal variability observed for monoclonal antibodies. These simulations considered the range of body weights that are expected in the current study (DMD subjects, ages 6 to 10 years old) based on literature values (pooled mean and standard deviations) and assessed the appropriateness of administering the same dose (mg/kg) to all subjects. The weight distribution simulation suggested the difference between the lightest (5th percentile of age 6) and heaviest (95th percentile of age 10) DMD subject is approximately 36 kg. However if dosed per body weight, the corresponding CL values at the above weight extremes were approximately 13%.

From a PK/PD consideration, a target mediated drug disposition model (TMDD) was developed to simulate PF-06252616 exposures and corresponding GDF-8 coverage. For Study B5161002 PK and GDF-8 simulations, it was assumed that that the weight normalized population PK parameters and the GDF-8 binding parameters are similar between healthy adult volunteers and DMD subjects 6 to 10 years old. These parameters were used to simulate both the expected PK profile (to compare to toxicology exposure margins) and the expected PD profile (considering target coverage in serum). These simulations suggest that 5 mg/kg PF-06252616 when administered over a 2-hour infusion duration and every 4 weeks provides a median (50th percentile) GDF-8 coverage of approximately 85% with a lower end prediction (5th percentile of the trough) of 61% coverage at steady state. This dose was determined to be a suitable starting dose in Study B5161002 as an impact on the pharmacology may be expected and there are wide safety margins to the toxicology limits (Table 1). Similarly, simulations suggest that 20 mg/kg PF-06252616 when administered over a 2-hour infusion duration and every 4 weeks may provide a median target coverage of approximately 95% with the lower end of the prediction (5th percentile of the trough) of 87% at steady state. These values are very similar to the estimated GDF-8 coverage for the 10 mg/kg dose administered every 2 weeks in Study B5161001 which produced a MRI signal on Day 113. Finally, simulations suggest that a 40 mg/kg dose administered every 4 weeks will provide median target coverage of approximately 97% with a lower end (5th percentile of the trough) of around 93% at steady state. At the highest dose, it is anticipated that a 2-fold safety margin to the toxicology limits will be maintained (Table 1).

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

IV Dose (mg/kg)	Predicted C_{max} (μg/mL)	Safety margin to toxicology limit (C_{max})	Predicted C_{av}	Safety margin to toxicology limit (C_{av})
5	158	17	65	28.6
20	598	4.5	265	7.1
40	1214	2.2	550	3.4

[a.] Toxicology limit set by the NOAEL of 26 week non-human primate juvenile study at 50 mg/kg [C_{max} = 2690 μg/mL, $C_{av,ss}$=1870 μg/mL].
The toxicology AUC_{168} 314,000 μg•hr/mL was converted to C_{av} as follows: 314000 ÷ 168 = Cav. The predicted human AUC_{672} 369298 μg•hr/mL was converted to C_{av} as follows: 369298 ÷ 672 = 550 μg/mL
C_{max} = maximum concentration at steady state; C_{av} = average concentration at steady state.

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1.10. Study Design Rationale

The four stair climb (4SC) has been selected as the primary endpoint for this study based on results of prior oral steroid clinical trials in DMD. The 4SC has been measured for more than 20 years in DMD, widely used as an outcome in clinical trials, deemed as a reliable measure of motor function (Bushby et al 2011; McDonald et al 2013),[5,21] can be "bench-marked" by a meaningful improvement with steroids (Manzur et al, 2008)[13] and is a meaningful indicator of DMD boys' lower limb function in a one year study.

Oral steroids are the only treatment demonstrated in randomized controlled trials to improve DMD boys' strength and function. (Griggs et al 1991; Mendell et al, 1989).[7,25] Functional improvements were measured as the time required to walk or run 9 meters or to climb 4 stairs after six months of daily steroids. In a pooled analysis of three separate steroid studies, the magnitude of six month functional improvement compared to placebo group was larger as measured by the stair climb test (-3.69 sec 95% CI [-4.71 to -2.67 sec]) than the walk/run test (-2.64 sec 95% CI [-3.70 to -1.58]) (Manzur et al, 2008).[13] Clinically, propelling oneself up stairs requires more proximal leg strength than walking on a flat surface. This is supported by the natural history of DMD in that boys lose the ability to climb stairs prior to the loss of ambulation (Bushby et al, 2011; McDonald et al, 1995).[5,18] In addition, there is data to support that a prolonged 4SC >8 seconds time is associated with loss of ambulation in 12 months (McDonald et al, 2013).[20] There is a stronger correlation between knee extensor strength, a key lower limb muscle to maintain ambulation, and 4SC (r=0.74) than time to walk/run (r=0.70) and distance walked in six minutes (r=0.64) (McDonald et al, 2013).[21] A recent industry sponsored trial from PTC Therapeutics (placebo group) demonstrated that DMD boys treated with steroids and ≥7 years of age demonstrated a mean change of 4.7 sec ±7.5 sec over 12 months (McDonald et al, 2013).[20] Therefore, ability to improve time to climb 4 stairs in a 12 month study while boys receive standard of care steroid treatment is a pertinent functional endpoint.

The six minute walk test (6MWT) has been used as the primary outcome measure in recent industry sponsored clinical trials for therapies to improve dystrophin expression in the muscle of boys with DMD. However in these clinical studies as well as in natural history studies 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, 2013).[17,8,20] An absolute change in the 6MWD may not be a reliable measurement of function in a one-year study of DMD boys for the primary endpoint, and therefore the 6MWD will be evaluated as a secondary endpoint.

B5161002 is a Phase 2 randomized, 2-period, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, PK and PD of PF-06252616 in ambulatory boys with DMD. The study design is intended to mitigate the bias of treatment effect while balancing the opportunity for subjects to receive active drug for a rare and fatal disorder. The study will be conducted in two periods. In each period the majority of subjects will be on active treatment according to the randomization plan (2 active:1 placebo). In Period 2, subjects who received placebo in Period 1 will be assigned active drug. In order to

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mitigate the potential heterogeneity in response and because efficacy has not been established at any dose level, each subject will have an opportunity to dose escalate to receive all drug levels while being monitored for safety. Based on the publication by McDonald et al 2013,[20] subjects who complete a 4SC in >8 seconds may be at higher risk for loss of ambulation in the following 12 months. To balance this potential difference, stratification on the 4 SC at baseline will be utilized.

1.11. Anticipated Risks and Safety Monitoring

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

Anticipated risks are based on clinical and toxicology data.

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

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1.11.6. Radiation

Possible risks related to subject's undergoing evaluation with DXA and bone age include 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. The expected total radiation dose for 7 whole body DXA exams, 3 spine scans and 7 hand x-rays for bone age assessment is not expected to exceed 0.75 mSv. This is less than 1 year of natural background radiation which is approximately 3.0 mSv per year (EHS Radiation Risk; Blake et al, 2006).[10,1]

1.11.7. Other Risks

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

1.11.8. 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], glutamate dyhydrogenase [GLDH], prothrombin time/activated partial thromboplastin time [PT/aPTT], creatine kinase, amylase, and chemistry) and Columbia Suicide Severity Rating Scale (C-SSRS). Laboratory monitoring will also be performed to detect ADA and NAb.

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1.12. Summary of Risk Benefit

Study B5161002 is the first therapeutic study being conducted in pediatric subjects with DMD. The drug may demonstrate pharmacologic activity in subjects.

In view of the initial clinical evidence of safety and the monitorable nature of key nonclinical toxicological findings, data support an acceptable risk profile for PF-06252616 in the current study and support a favorable benefit-risk profile in the indication of 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 Safety and Efficacy

- To determine the safety and tolerability of multiple ascending repeat IV doses of PF-06252616 in ambulatory boys with DMD.
- To demonstrate the efficacy of treatment with IV doses of PF-06252616 based on an observed mean change from baseline on function (4 Stair Climb) as compared to placebo following 49 weeks of treatment.

2.1.2. Secondary

- To characterize the effects of PF-06252616 on muscle strength and other functional assessments compared to placebo.
- To evaluate the PD activity of PF-06252616 based on the percent change of muscle volume from baseline as compared to placebo.
- To evaluate the PD profile of PF-06252616 based on GDF-8 (myostatin) modulation in blood.
- To characterize the PK profile of PF-06252616.
- To evaluate the immunogenicity of PF-06252616.
- To characterize the long-term effects following approximately 2-years of treatment with PF-06252616 on functional assessments compared to historical control.
- To characterize the effects of PF-06252616 on muscle strength and functional assessments compared to placebo in subset of subjects who may demonstrate a rapid disease decline and with relatively low variability over a one-year period.

2.1.3. Exploratory

- To evaluate biomarkers that may be informative in demonstrating the pharmacologic effect of PF-06252616.

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- To evaluate biomarkers that may be informative for monitoring hepatic liver injury in the setting of dystrophic muscle.
- To evaluate the Functional Health Status.
- To evaluate long term safety of PF-06252616 in subjects treated for >1 year.
- To evaluate duration of treatment response following withdrawal and/or continuation of treatment for >1 year.
- To evaluate response in a delayed treatment group (Sequence Group 3, Period 2).

2.2. Endpoints

2.2.1. Primary Safety-Based on Data from Period 1

- Incidence of dose limiting or intolerability treatment related AEs by Week 49.
- Incidence, severity and causal relationship of treatment emergent AEs (TEAEs) and withdrawals due to TEAEs by Week 49.
- 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 and urinalysis) by Week 49.
- Abnormal and clinically relevant changes in liver MRI by Week 45 and physical examinations (including nose and throat mucosal exam and Tanner stage), weight, vital signs, ECG, cardiac MRI or echocardiogram measured LVEF (and other exploratory cardiac endpoints), DXA-spine (bone mineral density), x-ray (hand and wrist for bone age evaluation) and C-SSRS (See Appendix 1 and Appendix 2) parameters by Week 49. Cardiac MRI with gadolinium is the preferred method for cardiac imaging. If the subject has a contraindication to gadolinium, cardiac MRI without gadolinium will be acceptable. Echocardiogram may be substituted if it is not possible to perform cardiac MRI.

2.2.2. Primary Efficacy-Based on Data from Period 1

- Mean change from baseline on the 4SC as compared to placebo by Week 49.

2.2.3. Secondary Endpoints-Based on Data from Period 1 and 2

2.2.3.1. Strength and Function

- Mean change from baseline as compared to placebo on function tests including, Forced Vital Capacity (FVC), Northstar Ambulatory Assessment (NSAA), range of motion (ROM), Performance of Upper Limb (PUL), 6MWD at Week 17, 33 and 49. Mean change from baseline as compared to placebo on the 4 SC at Week 17 and 33.

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- Mean change from baseline as compared to placebo on muscle strength by myometry at Week 17, 33 and 49.

- In subject randomized to Sequence 1, mean change from baseline as compared to historical control on functional tests including, 4SC, 6MWD, FVC, NSAA at Week 97.

- In a pre-specified subset of subjects who may demonstrate a rapid disease decline and with relatively low variability, the mean change from baseline as compared to placebo on function tests including, 4SC, FVC, NSAA, PUL, 6MWD at Week 17, 33 and 49. The definition of this subgroup will be detailed in the Statistical Analysis Plan (SAP).

- In a pre-specified subset of subjects who may demonstrate a rapid disease decline, the mean change from baseline as compared to placebo on muscle strength at Week 17, 33 and 49.

2.2.3.2. Pharmacodynamic

- Mean percent change as compared to placebo in thigh muscle volume as measured on MRI by Week 17, 33 and 49. Within subject change from baseline in thigh muscle volume through Week 97.

- Noncompartmental GDF-8 parameters such as $AUC_{\tau(GDF\text{-}8)}$, $C_{GDF\text{-}8(0)}$, $C_{max\ (GDF\text{-}8)}$, $T_{max(GDF\text{-}8)}$, $C_{trough\ (GDF\text{-}8)}$, and $C_{av\ (GDF\text{-}8)}$, may be determined.

2.2.3.3. Pharmacokinetic

Noncompartmental PK parameters will be derived from serum PF-06252616 concentration data for the following subjects and visits.

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

- All subjects receiving active drug in Period 1 followed by placebo in Period 2 (Sequence 2): terminal t½ for Visit 19 (last dose in Period 1) using concentration data from samples collected during placebo treatment in Period 2.

- Subjects with additional PK sampling receiving active drug in Period 1: AUC_{τ} and C_{av} for Visits 3, 9, and 15 (first dose of each dose escalation level); AUC_{τ}, C_{av}, and CL for Visits 7, 13, and 19 (last dose of each dose escalation level); for subjects in Sequence 2, also V_{ss} for Visit 19.

2.2.3.4. Immunogenicity

Incidence of ADA and NAb development by Week 97.

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2.2.4. Exploratory Endpoint-Based on Data from Period 1 and 2

2.2.4.1. Pharmacologic

- Mean percent change from baseline as compared to placebo in lean body mass by whole body DXA by Week 17, 33 and 49. Within subject change from baseline in lean body mass through Week 97.

- Changes from baseline in muscle quality and fat fraction as compared to placebo as measured by T2-mapping and Dixon MRI Week 17, 33 and 49. Within subject change from baseline in T2-mapping and Dixon MRI through Week 97. Depending on the imaging capabilities at each site, this data may only be collected at a subset of sites.

- Quantification of changes as measured by blood biomarkers (pharmacogenomic and liver).

2.2.4.2. Functional Health Status

Changes from baseline in the Pediatric Data Outcomes Collection Instrument (PODCI) score as compared to placebo by Week 17, 33 and 49. Within subject change from baseline in the PODCI through Week 97. See Appendix 3.

2.2.4.3. Long Term Safety-Based on Data from Period 2

In subjects randomized to Sequence 1, long term safety will be evaluated within subjects as compared to baseline for all safety endpoints previously described through Week 97.

2.2.4.4. Duration of Treatment Response-Based on Data from Period 2

In subjects randomized to Sequences 1 and 2, duration of treatment response will be evaluated within subjects as compared to baseline for all efficacy (function and strength), pharmacologic and PD endpoints previously described through Week 97.

2.2.4.5. Response in a Delayed Treatment Group-Based on Data from Period 2

In subjects randomized to Sequence 3, treatment response will be evaluated within subjects as compared to baseline for all efficacy (function and strength), pharmacologic and PD endpoints previously described through Week 97.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2 randomized, 2-period, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, PK and PD of PF-06252616 administered to ambulatory boys diagnosed with DMD. Three IV infused dose levels will be investigated in a within subject dose escalating fashion.

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PF-06252616 dose levels:

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

Depending on safety and PK data availability, alternative dose levels will be available and may be evaluated instead of or in addition to the planned dose levels. In Period 2, dosing may be adjusted based on the emerging safety and/or efficacy data.

Approximately 105 eligible subjects will be randomly assigned to 1 of 3 sequence groups and receive investigational product for approximately 96 weeks (2 treatment periods of approximately 48 weeks each) stratified by their baseline time to complete the 4 SC (either ≤ or >8 seconds).

Sequence 1 (n=35):
Period 1: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)
Period 2: Active treatment (PF-06252616) at the maximum tolerated dose in Period 1

Sequence 2 (n=35):
Period 1: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)
Period 2: Placebo

Sequence 3 (n=35):
Period 1: Placebo
Period 2: Active treatment (PF-06252616) within subject dose escalation (5, 20 and 40 mg/kg)

Each dose level will be explored in a dose escalating fashion within subjects, starting with the lowest dose. At each dose level, dosing will be administered over a 2-hour IV infusion every 4 weeks for a total of 16 weeks (4 doses). Dose escalation within a subject will occur following review of all available safety data through the planned fourth dose within each dose level. For example, in Period 1, there are three times when individual safety data will be reviewed for a determination of dose adjustment, at Week 13, Week 29 and Week 45 (every 4 months). In Period 2, there are two times when individual safety data are reviewed for a determination of dose adjustment, at Weeks 61 and 77 (every 4 months). Subjects will move from Period 1 to Period 2 without a pause between periods.

Subjects who complete this study through Week 97 may be invited to participate in an open-label-extension (OLE) study. Subjects, who have had a positive test result for ADA at any point during the study, *may* be asked to complete additional immunogenicity testing if warranted by other clinical safety findings prior to joining an extension study.

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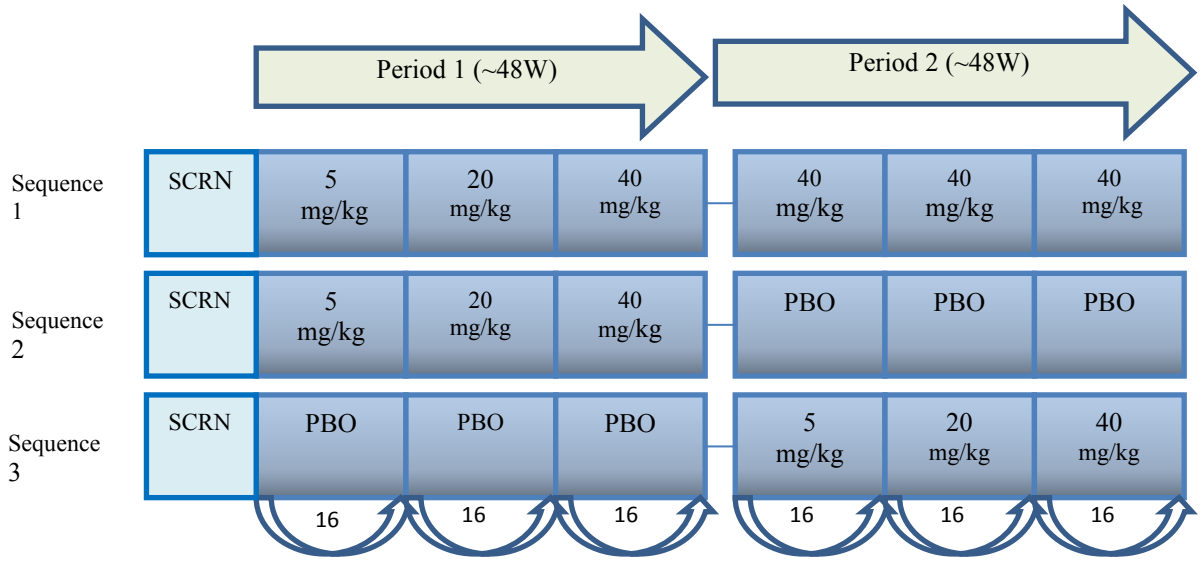
During the study, additional visits will be required to fully characterize PK and safety when subjects would not otherwise be returning for study drug administration. In order to limit the burden of the additional PK/safety assessments, only the first 12 subjects enrolled in the study will be asked to complete these additional PK visits. At each dose level, the first 12 subjects will be asked to return for testing 1 week after the first dose within each level and once again at 1 week after the last dose at each dose level. The additional PK/safety assessments will occur 6 times in Period 1. No additional visits would be required for these subjects in Period 2.

Exposure from the first 12 subjects will be reviewed to confirm that the exposure in the pediatric population is consistent with model predictions from the healthy adult volunteer study. This will occur following at least one dose at the 5 mg/kg dose level and will occur again following at least one dose at 20 mg/kg dose level. Should there be any clinically relevant differences in exposure versus those predicted; a dose adjustment may be made as agreed with the E-DMC. This analysis will be performed by a group of unblinded Clinical Pharmacology scientists not directly involved in the day to day conduct of the study. It is planned that recruitment would continue during this evaluation period.

The study will remain double-blinded until the time of the primary analysis for safety and efficacy (after the last enrolled subject completes 49 weeks). At that time, a limited number of study team members will be unblinded to the treatment assignments. The sites (with the exception of unblinded site personnel eg, the pharmacist) and the subjects will remain blinded to their study treatment through the conclusion of the study.

The following is a schematic of the study design.



Note: Sequence 1, Period 2 demonstrates subjects continuing on the maximum tolerated dose from Period 1 for each individual subject, as per the dose adjustment criteria (Table 2). SCRN=Screening, PBO=Placebo, W=Weeks

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3.2. Duration of Subject Participation

Subjects' participation will begin during the screening period (up to 6 weeks) followed by two dosing periods (48 weeks each) and 2 final study visits (ending 12 weeks after the last study dose). Subjects, who are enrolling in the OLE study, will only be required to return for 1 final study visit at Week 97. Subjects will return to the site monthly for study drug administration (24 visits) as well as completion of safety and efficacy assessments.

For the first 12 subjects enrolled who are undergoing the additional PK testing, a total of 34 visits are required. The remaining subjects will be expected to attend 28 visits. The total time on study for all subjects will be approximately 105 weeks (26 months including screening).

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

Per the local requirements in Japan, all Japanese subjects will be hospitalized for an overnight observation following the first and second treatment (Day 1 and 29).

3.3. Approximate Duration of Study

The study is estimated to complete in approximately 5 years allowing for 30 months of enrollment and 26 months on study.

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.

3.4. Planned Number of Subjects

A minimum of 105 randomized subjects will participate in multiple centers and countries worldwide. In order to assure adequate enrollment, a sufficient number of subjects may be screened. If there are no safety issues, additional subjects may be enrolled prior to the time of the interim analysis. These additional subjects may help off-set any unforeseen variability that may occur outside the presumed standard deviation for this age group.

3.5. Safety Monitoring, Individual Dose Escalation and the E-DMC

Individual dose escalation decisions will be conducted for each subject by the Investigator, sponsor Medical Monitor and a Designated Reviewer. This process will occur from time of the first subject being enrolled and continue until the time of the IA (or sooner as determined by the E-DMC's review of unblinded data). At that time, if adequate safety has been demonstrated at each dose level as determined by an External Data Monitoring Committee (E-DMC), subsequent dose escalation will occur without confirmation of the individual safety data prior to dose escalation.

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From the time of study initiation through completion of the study, the sponsor will conduct routine safety monitoring of the blinded data per the safety review plans. In addition, the E-DMC will review unblinded safety data. The E-DMC may determine if it is necessary to close or adjust a dose level within the study or continue with individual level dose escalation review.

In the event that the E-DMC determines that adequate safety has been established at each dose level (following the IA or sooner), they will also consider if the requirement for liver MRI can be reduced to an annual safety assessment (based on normal findings on the liver MRI).

Following the interim analysis, if the E-DMC makes a recommendation to the sponsor management to modify or terminate the study based on establishing the efficacy and safety of PF-06252616, the sponsor management will review the recommendation with regulatory agencies prior to making any changes to the study design, including termination of the study.

3.5.1. Individual Subject Dose Adjustment and Stopping Rules

The individual dose adjustment will be determined by three parties including the Investigator, sponsor Medical Monitor and a Designated Reviewer.

The dose adjustment criteria described in Table 2 will be used to determine if the dosing or dose level should be:

- Escalated to the next dose level
- Maintained at the current dose level
- Reduced to a lower dose level, or
- Stop dosing.

Following the planned fourth dose within each dose level, all available safety data for an individual subject will be reviewed to determine the appropriate dose adjustment. The Investigator will confirm the number of doses received within the dose level and review all the available safety data along with the sponsor Medical Monitor with the exception of the serum iron indices (serum iron, serum ferritin, TIBC, % transferrin saturation) and the liver MRI results. Findings from the serum iron indices and the liver MRI may inadvertently unblind the Investigator and the sponsor Medical Monitor to the subject's treatment assignment, therefore results from these tests will not be available to the sites or sponsor Medical Monitor for review. Instead, an unblinded Designated Reviewer will review the liver MRI results to monitor for potential iron accumulation. The E-DMC will be unblinded to the serum iron indices and liver MRI results to provide an ongoing safety review of these data.

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The Investigator and sponsor Medical Monitor, if necessary will meet to discuss any safety issues and then provide a single recommendation to the unblinded Designated Reviewer who will be separately monitoring the liver MRI results. The Designated Reviewer will collect the safety confirmation from the Investigator and sponsor Medical Monitor and apply the criteria from Table 2 to determine the dose adjustment action. The dose adjustment will then be applied to the subject's assigned treatment, accordingly.

Table 2. Criteria to Determine Dose Adjustment within Individual Subjects

Dose Adjustment Decision	Criteria
Increase Dose Level	E-DMC has not closed the next higher dose level **and** Subject received ≥3 doses within a the current dose level **and** Investigator and sponsor Medical Monitor indicate that the current dose level is safe **and** Designated Reviewer indicates that the liver iron content estimate as determined by R2* value is within the normal range[a,d].
Maintain Dose Level	E-DMC indicates that the next higher dose level is closed **and/or** Subject received <3 doses received within a dose level **and** Investigator and sponsor Medical Monitor indicate that the current dose level is safe **and** Designated Reviewer indicates that the liver iron content estimate as determined by R2* is in the normal range[a,d].
Reduce Dose Level	E-DMC indicates that the current dose level is closed **and** the subject is not at the lowest dose level **or** Subject is *not* at the lowest dose level **and** Investigator and sponsor Medical Monitor indicate that the current dose is safe **and** Designated Reviewer indicates that the liver iron content estimate as determined by R2* value is *above* the *normal range* [b,d].
Stop Dosing	E-DMC indicates that the current dose level is closed **and** the subject is at the lowest dose level **or** Investigator and sponsor Medical Monitor indicate that the current dose is *not safe* **or** Designated Reviewer indicates that the liver iron content estimate as determined by R2* value is *above* the *normal range* [b,d] and the subject is at the lowest dose level **or** Designated Reviewer indicates that the liver iron content estimate as determined by R2* value is *within mild overload range*[c,d].

a. R2* normal range is ≤75 Hz at 1.5 T or R2*≤139 Hz at 3.0 T
b. R2* above normal range is >75 Hz and ≤190 Hz at 1.5 T or R2* is >139 Hz and ≤369 Hz at 3.0 T
c. R2* mild overload range is R2* >190 Hz at 1.5 T or R2* >369 Hz at 3.0 T
d. Storey et al, 2007; Wood et al, 2005; Hankins et al, 2009]).[28,29,9]

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In order to maintain the treatment blind, all subjects regardless of treatment assignment will undergo review for dose adjustment. Subjects who are receiving placebo will have the decision criteria applied, as if they are at the lowest dose level.

The results of the dose adjustment decision (increase, maintain or reduce) *will not* be communicated to the investigator or sponsor medical monitor at any time.

If the Designated Reviewer determines that the subject must stop dosing, he/she will notify the sponsor Medical Monitor who will be responsible for informing the Investigator. In this case, the Designated Reviewer may provide the results of the liver MRI (or iron indices) to the sponsor Medical Monitor. The treatment assignment however, will not be provided.

If dosing is stopped, subjects will continue to be followed for resolution of the safety finding or until a new baseline is established. At any time during the study, either the Investigator and/or sponsor Medical Monitor may determine a safety issue has occurred and it is in the best interest of the subject to stop dosing. In this case, the sponsor Medical Monitor may not overrule the Investigator's decision, nor will the Investigator overrule the sponsor Medical Monitor's decision.

If the E-DMC determines that a dose level should be closed, following their unblinded review of all safety data, no other subjects will be escalated to that dose level. Subjects who are currently dosing within that dose level will be advised by the E-DMC to reduce their dose level.

Subjects in Sequence 2, Period 2, and Sequence 3 Period 1 (who are assigned to placebo), will have dosing terminated should they meet any of the criteria described in Table 2 for "Stop Dosing".

Subjects in Sequence 1 will be treated with their maximum tolerated dose level from Period 1 when they enter Period 2. They will not be escalated to additional higher dose levels in Period 2. For example, if in Period 1, a subject's maximum tolerated dose is 20 mg/kg, they will not be escalated up to 40 mg/kg in Period 2. Although they will not escalate in Period 2, they may have their dose reduced or stop dosing based on the criteria in Table 2.

Subjects, who plan to enroll in the OLE study, will have their *maximum tolerated dose* from study B5161002 be provided by the Designated Reviewer following Week 93 in order to continue on the same dose level in the OLE study without unblinding their treatment assignment in the B5161002 study.

3.5.2. 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 include a Hepatic Expert to review any cases of potential liver toxicity. A patient advocate will also be included on the E-DMC if an appropriately qualified individual can be identified as agreed upon by the E-DMC chairperson. The E-DMC will also include a Cardiology Expert to provide expert interpretation of cardiac MRI or echocardiogram results (as needed). The

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E-DMC will be responsible for ongoing unblinded efficacy and safety monitoring (including the liver MRI and iron indices whose results are blinded to the site and study team) per the E-DMC charter from the initiation of the study through the final study visit. Reviews will include aggregate unblinded safety, targeted medical events of special interest including liver toxicity, and serious AE data. The E-DMC may also complete ad hoc safety reviews as described in the E-DMC charter. PK data will be provided to confirm that the exposure in the pediatric population does not exceed the predicted PK stopping limits described below. Ad hoc PK data may be provided to the E-DMC as requested. In addition to the safety reviews, the E-DMC will review the unblinded study data for futility and efficacy at the time of the IA.

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, terminate a dose level, reduce the liver MRI assessment to annually, remove the manual process for individual dose escalation steps and allow an automated dose-escalation, permit the liver MRI and iron indices data to be provided to the site and blinded study team), 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.

The E-DMC will consider the following safety criteria during their safety review:

- The number of subjects who have severe AEs or serious AEs in the same organ system which are determined to be related to study medication (active treatment, not placebo).

- The exposure within a dose level which approximately reaches or exceeds the PK stopping limits of predicted C_{av} of 2690 mg/mL and C_{max} of 1870 mg/mL (exposures obtained at the monkey NOAEL dose of 50 mg/kg). Modified doses may be considered if they are not expected to exceed PK stopping criteria.

- Other findings that may indicate that a dose level should be closed.

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 non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

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4.1. Inclusion Criteria

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

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

1. Ambulatory boys age 6 to <16 years old (at the time of randomization), diagnosed with DMD. Diagnosis must be confirmed in subject's medical history and by genetic testing obtained during routine clinical care for diagnostic purposes as reported from an appropriate regulated laboratory using a clinically validated genetic test (genetic testing is not provided by the sponsor). Results must confirm the presence of a mutation in the dystrophin gene(s) which is clinically consistent with the diagnosis of DMD.

2. Subjects who are able to perform the 4 stair climb in ≥0.33 but ≤1.6 stairs/second at screening.*****

3. Evidence of a personally signed and dated informed consent and assent (where appropriate) document indicating that the subject and a legally acceptable representative/parent(s)/legal guardian have been informed of all pertinent aspects of the study.

4. Subjects and their legal guardians who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Subjects will be required to provide assent in compliance with local regulations and IRB requirements.

5. Subjects must be receiving glucocorticosteroids for a minimum of 6 months prior to signing informed consent. There should be no significant change (>0.2 mg/kg) in dosage or dose regimen (not related to body weight change) for at least 3 months immediately prior to signing the informed consent and a reasonable expectation that dosage and dosing regimen will not change significantly for the duration of the study.

6. Adequate hepatic and renal function on screening laboratory assessments:

   - GGT ≤ upper limit of normal (ULN).
   - Alkaline phosphatase ≤ ULN.
   - Total Bilirubin ≤ ULN.
   - Serum Albumin ≥ LLN.
   - Serum creatinine ≤ ULN.

7. No underlying disposition for iron accumulation on screening laboratory assessments:

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- Serum Iron ≤1.2 x ULN.
- Serum Ferritin ≤140 ng/mL.
- % Transferrin Saturation ≤50%.

8. No underlying disposition for bleeding disorder on screening laboratory assessments:
   - PT/INR ≤1.25 x ULN.
   - aPTT ≤1.25x ULN.
   - Fecal occult blood is negative. If the fecal occult blood is positive due to known pre-exiting medical condition (eg, any cause of rectal bleeding; hemorrhoids, anal fissure) that is not considered to be clinically significant by the investigator, the subject may be included.
9. Iron content estimate on the screening liver MRI is within the normal range as determined by R2* value (R2*≤75 Hz at 1.5 T or R2*≤139 Hz at 3.0 T).

CCI [redacted]

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects with known cognitive impairment or behavioral issues that would impede the ability to follow instructions.
2. History of major surgical procedure within 6 weeks of signing the informed consent or planned surgery during the study.
3. Any injury which may impact functional testing. Previous injuries must be fully healed prior to consenting. Prior lower limb fractures must be fully healed and at least 3 months from injury date.
4. Presence or history of other musculoskeletal or neurologic disease or somatic disorder not related to DMD including pulmonary and cardiac disease.
5. Compromised cardiac function (left ventricular ejection fraction <55% as determined on a screening cardiac MRI or echocardiogram). Subjects may be receiving ACE (angiotensin-converting-enzyme) inhibitors, β blockers, ARB (angiotensin II receptor

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blocker) or aldosterone blocker/thiazide diuretic; however they must have initiated treatment more than 3 months prior to screening to ensure stable therapy.

6. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular (including uncontrolled hypertension), hepatic, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

7. Documented history of iron overload including hemochromatosis, beta thalassemia major, beta thalassemia intermedia or hemolytic anemia.

8. Unwilling or unable (eg, metal implants, requires sedation) to undergo examination with closed MRI without sedation.

9. Participation in other studies involving investigational drug(s) 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.

10. Current or prior treatment with anti-myostatin, exon skipping, nonsense mutation targeted therapies ever or more than 30 days of treatment with utrophin modifiers and treatment with utrophin modifiers within 30 days prior to signing the informed consent and/or during study participation.

11. Current or prior treatment within the past 3 months with androgens or human growth hormone.

12. Current treatment with immunosuppressant therapies (other than glucocorticoid steroids), aminoglycosides (eg, gentamicin), multi-vitamins with iron and iron supplements and other investigational therapies (including idebenone).

13. 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).

14. Have suicidal ideation and behavior associated with actual intent and/or method and/or plan and/or action (eg, self-harming behaviors) in the past 6 months based on the Columbia-Suicide Severity Rating Scale (C-SSRS Children's Baseline/Screening Appendix 1) or at baseline (C-SSRS Children's Since Last Visit Appendix 2).

15. Subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active who are unwilling or unable to use a condom to prevent potential transfer of exposure to drug through semen; male subjects of childbearing potential, with their female partners at risk for pregnancy, who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol (in addition to the condom to prevent potential transfer of drug through semen) for the duration of the study and through completion on final study visit.

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16. 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.

17. 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.

Note: Screening 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. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. During the randomization, the results of the 4 SC from the baseline visit will be provided for stratification. Subjects will be stratified into two groups, those completing the 4 stair climb in ≤8 seconds and those completing in >8 seconds. Results from the *screening* 4 SC (not the baseline 4SC) will be used to determine subject's eligibility. The baseline 4SC will be used for all analysis.

4.3.1. Screen Failures

Subjects who do not meet the inclusion criteria for the 4SC only will be allowed to re-screen one time during the study, while enrollment remains open. In this case the subject number they are assigned at the initial screening will be documented as a screen failure for the 4 SC and they will be issued a new subject number for the re-screen. Re-screen subjects will re-consent and depending on the length of time from initial screening to re-screen certain screening assessments will need to be repeated. This information is provided in STUDY PROCEDURES Section.

If subjects are screen failures for any other criteria (other than the 4SC) they will not be re-screened.

4.4. Lifestyle Guidelines

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

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

- Subjects should abstain from large amounts of caffeine within 24 hours of study visits. Negligible amounts (eg, found in chocolate) are not of concern.

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- 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 and Biomarker sample Group 2.

- 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 testing, *whenever possible*, subjects should refrain from eating red meat, turnips, horseradish, or medications containing aspirin or vitamin C. It is recommended that subjects consume small amounts of chicken, canned tuna fish, peanuts, popcorn, bran cereal, vegetables and fruit.

4.4.2. Activity

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

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

4.4.3. Contraception

All male subjects who, in the opinion of the investigator, are biologically capable of having 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, 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. 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 will identify the permitted contraception methods as outlined in the protocol. 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.

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:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the subject plans to remain on the

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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, this option is not appropriate.

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 questionnaire and being interviewed for the C-SSRS on behalf of the subject. They will be responsible for collection of the fecal sample and providing feedback during the wellness calls. 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.
- Is available to accompany the subject to the clinic visits.
- Can follow instructions.
- 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 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

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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.

The C-SSRS will be completed by the subject's care giver/legal guardian throughout the study.

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

4.7.2. Tanner Stage

Tanner staging 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.

4.7.3. Clinical Evaluators

Functional assessments including the FVC, 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. Details of the assessments, training, reliability and ongoing quality control are provided in the Functional Assessment manual.

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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 or placebo 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. Refer to the Investigational Product Manual and the Administration Card for details regarding the preparation and administration of this investigational product.

Subjects will be treated with IV infused PF-06252616 or placebo in this double-blind, placebo controlled study. Please refer to the dosage and administration instruction in the Investigational Product Manual for complete information on storage, stability, preparation and administration of both investigational drug products (PF-06252616 and placebo).

This study is a 3-sequence group, double-blind, placebo controlled, randomized clinical trial. Subjects will be randomized to one of 3 sequence groups and will receive treatment on a 28 day schedule, per the Schedule of Activities. Each subject will have the opportunity to receive a total of four doses of each dose level every four weeks. The dose will be calculated based on the subject weight, which will be obtained at each visit prior to each infusion. Either the current weight or the prior month's weight may be used to provide this calculation with the exception of Day 1. At Day 1 the weight from the Baseline visit should be used to calculate Day 1 dose. The following tables depict the dosing schedule in Period 1 and 2 for each Sequence group.

Table 3. Period 1 Dosing Schedule

Dosing Week	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**
Sequence 1 PF-06252616 Dose	5 mg/kg once every 4 weeks				20 mg/kg once every 4 weeks				40 mg/kg once every 4 weeks			
Sequence 2 PF-06252616 Dose	5 mg/kg once every 4 weeks				20 mg/kg once every 4 weeks				40 mg/kg once every 4 weeks			
Sequence 3 Placebo Dose	0 mg/kg once every 4 weeks											

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Table 4. Period 2 Dosing Schedule

Dosing Week	49	53	57	61	65	69	73	77	81	85	89	93
Sequence 1 PF-06252616 Dose	40 mg/kg (or maximum tolerated dose per each subject) once every 4 weeks											
Sequence 2 Placebo Dose	0 mg/kg once every 4 weeks											
Sequence 3 PF-06252616 Dose	5 mg/kg once every 4 weeks				20 mg/kg once every 4 weeks				40 mg/kg once every 4 weeks			

Note: Sequence 1 in this example shows all subjects tolerating the maximum dose level.

Following demonstration of tolerance at a lower dose, if subjects are unable to tolerate higher doses, their dose level may be reduced by a level at the time of dose escalation. Subjects in Sequence 1 will be treated at their maximum tolerated dose level from Period 1 when they enter Period 2 and they will not be escalated to additional higher doses during Period 2. Subjects in Sequence 3 will receive active drug in Period 2 in accordance with the dose adjustment criteria.

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.

5.1. Allocation to Treatment

Allocation of subjects to the sequence groups (treatment assignment) will proceed through the use of an Interactive Response Technology (IRT) System [Interactive Web Response (IWR)/Interactive Voice Response (IVR) system] by the unblinded dispensing personnel.

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 randomization number and container number assignment from the IRT system. The randomization number and the date on which the randomization number was assigned will be recorded on the case report form (CRF). Once subject screening numbers, container numbers, and randomization numbers have been assigned, they cannot be reassigned.

The unblinded 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 unblinded dispenser will be provided with a

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sequence group assignment and 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 unblinded dispenser in the unblinded 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 of Site Personnel

In this observer-blinded study, the study staff preparing and dispensing investigational products (PF-06252616 and placebo) will be unblinded, but all other site study personnel, including the principal investigator and the subject, will be blinded. The investigator will assign the responsibility of unblinded dispenser to persons who will not participate in the evaluation of any study subject. More than 1 unblinded dispenser must be assigned per site.

A member of the clinic pharmacy should fulfill the role of unblinded dispenser. Contact between the unblinded dispenser and study subjects should be kept to a minimum. The investigator, study coordinator, and any site staff (other than the unblinded dispenser) must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the investigational product container contents.

5.3. Blinding of Sponsor

All study team members and laboratory personnel will remain blinded to drug product assigned/received throughout the study. Separate from the study team members, there will be an unblinded sponsor-Designated Reviewer who will verify the criteria for dose adjustment. The unblinding process for the purpose of the continuous safety review by sponsor personnel not involved in the conduct of the study will be described in the Study Blinding Plan.

5.4. Breaking the Blind

This study is intended to be conducted as double-blind. The subject, investigator and sponsor will be blinded to the randomized study treatments. The Designate Reviewer (described in Section 3.5) and the pharmacists will be identified as unblinded as they will need to communicate regarding subject dose level adjustments. The unblinded pharmacist will receive and prepare study drug. Other unblinded individuals (eg, site monitors, clinical pharmacology, E-DMC) will be prospectively identified with their study roles.

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the PF-06252616 study team. Under this plan a group of Statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to aid in analyzing the PK and PD data as well as to initiate the building of statistical models of the PK, as well as exposure/response analysis models and conduct associated simulations.

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The aim of this work will be to facilitate review of PK/PD data for a fuller interpretation of the study upon completion (or at appropriate milestones). This group will not serve on the study team while the study is fully blinded prior to the primary analysis being performed. The details of the procedures will be described in the PK/PD unblinding Plan for Modeling and Simulation for Study B5161002.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

The study site pharmacists should not release unblinding information to the other study staff, instead the formal IRT procedure should be used. Aside from such emergent subject safety situations, information of study treatment including sequence group, subject dose level and randomized study treatment will be kept confidential and will not be released to the investigator/study staff until the conclusion of the study.

5.5. Compliance

Study treatment will be administered under the supervision of investigator site personnel. Significant medication errors will be considered doses received that are less than 80% or greater than 120% of the planned total dose. These will be reported as significant quality events.

5.6. Drug Supplies

5.6.1. Dosage Form(s) and Packaging

PF-06252616 will be provided by Pfizer as a lyophilized powder for injection in single use, sterile glass vials. Each vial will be sealed with a coated stopper and an aluminum overseal 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.

The placebo will be provided by Pfizer as a solution for injection. The placebo is supplied in a glass vial sealed with a coated chlorobutyl serum stopper and an aluminum overseal and labeled according to local regulatory requirements.

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

The placebo does not match the active drug product and therefore, the supplies are provided as open label vials. An unblinded pharmacist is required to prepare the investigational product. In order to maintain the blind, a separate area must be used for study drug preparation.

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PF-06252616 and placebo will be packaged as open-label supplies. The external packaging (carton) for both products will describe its contents indicating them as active drug product or placebo. Each carton will contain a single vial of study medication or placebo, and each carton is identified with a unique container number. Therefore, it is very important that blinded staff do not receive or handle the investigational product. 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.

5.6.2. Preparation and Dispensing

See the dosage and administration instructions section in the Investigational Product Manual on how to prepare the investigational product for administration.

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

Unblinded site 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. No information concerning subject treatment assignments will be communicated from the unblinded site personnel to investigators, site study staff, sponsor's study staff, or study subjects.

Subject's body weight will be measured at each time point where study drug is administered and used to calculate the dose for that visit. Either the current or the prior month's weight may be used to provide this calculation with the exception of Day 1. At Day 1 the weight from the Baseline visit should be used to calculate Day 1 dose.

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

5.7. Investigational Product Administration

Following preparation of the study treatment investigational product (PF-06252616 or placebo) by the unblinded site personnel (eg, pharmacist or pharmacist technician), the prepared product together with the administration card will be provided to the blinded administrator. The site will take all necessary precautions to maintain the blind of the investigator and site personnel including masking the IV bag, the drip chamber and in-line filter of infusion set given the potential difference in appearance of the product solution (eg, slightly yellow color of PF-06252616 versus clear color of placebo). If more than one subject (participating in either the B5161002 study or the open label extension study) will be

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infused at the same time in the same room, the use of a curtain or screen between each subject with sufficient coverage to block the view of the IV bag/pump between chairs/beds is required. A curtain or screen would not be required if subjects are being infused in a private room with no other subjects present.

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 (-15 or +30 minutes) where time 0 is the beginning of the infusion and includes the flush time. The time to infuse the investigational product and the flush will be recorded.

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 window for delivery (-15 or +30 minutes) will not be applied. Should the infusion rate be decreased, the PK will be collected per the Schedule of Activities. The duration of the treatment interruption should not exceed the limits of in-use shelf-life of the drug product solution per the dosage and administration instructions 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.

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

5.8. Investigational Product Storage

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

Upon receipt at the study site, the investigational products (PF-06252616 or placebo) 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 single reference safety document (SRSD) (ie, Investigator's Brochure [IB]) will be superseded by the storage conditions stated in the labeling.

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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.

5.9. Investigational Product Accountability

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

5.9.1. 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.

5.10. 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.

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

5.10.1. Permitted Therapies

- Subjects will be required to be receiving glucocorticosteroids (ie, deflazacort, prednisolone, and prednisone) for at least 6 months prior to signing the informed consent and with no significant changes (>0.2 mg/kg) in the dose regimen (not related to body weight adjustments) for at least 3 months prior to signing the informed consent. During the study, the dose regimen should remain stable unless adjustments are required for weight. If subjects are schedule to receive their glucorticodsteroids 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 blocker) or aldosterone blocker/thiazide diuretic; however, subjects must have initiated treatment more than 3 months prior to screening and plan to remain on a stable dose during the study.

- Supplements such as vitamin D, coenzyme Q10, carnitine, aminoacids (glutamine, arginine), anti-inflammatory/anti-oxidants (eg, fish oil, vitamin E, green-tea extract) are permitted. Calcium is permitted but should not be taken with 24 hours prior to a DXA scan. 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.

5.10.2. Prohibited Therapies

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

- Immunosuppressant therapy (other than glucocorticosteroids).

- Other investigational therapies (including idebenone).

- Anti-myostatin, exon skipping, nonsense mutation targeted therapies and utrophin modifiers.

- 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.

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- Sedation prior to undergo imaging assessments. In the event that a subject becomes intolerant to MRI scanning after the screening visit and during the study, the subject may be separately consented to be administered sedation in order to complete the liver MRI (and/or cardiac MRI) only.

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

5.10.3. Rescue Medication

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

6. STUDY PROCEDURES

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

The Screening and Baseline visit windows are described below. The visit window for the additional PK visits on Day 8, 92, 120, 204, 232 and 316 is ±1 Day. For all other visits, the window is ±3 days. The window for the PK/PD assessments post dosing at 2 hours is +30 minutes. If the infusion rate is decreased (following an infusion site reaction) the PK/PD assessments should be collected at the time of infusion completion and flush (within a +30 minute window). Subjects are required to be observed for 1 hour after the administration of the investigational product is completed. The post-dosing vital sign will be taken upon completion of the investigational product administration during the 1-hour observation period.

At visits when both MRI-thigh and functional assessments are being conducted, these assessments should be conducted on *separate* days. Functional assessments should routinely be collected in the morning when the subject is rested and well-fed. The MRI-thigh should routinely be collected at approximately the same time of day throughout the study. Should subjects become non-ambulatory during the study, the 4SC, NSAA and 6MWT will not continue to be collected.

If a stool sample is unable to be collected during 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, a stool sample will be collected at home within approximately 1 week prior to the scheduled visit. Note that the collection may fall outside of the visit window.

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For subjects who may be sexual mature at the onset of the study (as assessed during the baseline visit) or reach sexual maturity during the trial, as indicated by a Tanner Stage V rating, the Tanner Stage, testicular volume, hormone and X-ray (hand and wrist) will no longer be required to be collected during the study to assess for signs of precocious puberty.

6.1. Visit 1 (Screening Day -42 to -5)

This visit will be conducted over a minimum of 2 days to separate the days when the MRI-thigh and functional assessments are conducted. Sites may choose to extend this beyond 2 days to accommodate the logistics of completing all testing.

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 randomized 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 randomized to assure an adequate baseline image has been acquired. If the image is determined to be of poor quality, it will be repeated. The visit window (Day -42 to -5) for screening is to allow for the analysis of laboratory testing, assurance of imaging quality and to provide multiple days to perform the assessments in the order described below. The screening assessments should be conducted as consecutive days whenever possible.

Please note that eligibility confirmation also requires the baseline C-SSRS is completed. As soon as these assessments are completed and a subject's eligibility has been confirmed, he may be randomized into the study.

If a subject becomes a screen failure, and meets the criteria for re-screening as described in Section Screen Failures, they must re-consent. The sponsor must be notified that subject is re-screening. All screening assessments must be repeated with the following exceptions:

Repeat the following imaging assessment only if more than 6 months have passed since the initial screening image was acquired:

- Liver MRI
- Cardiac MRI (or echocardiogram)
- X-ray (hand and wrist).

All other screening assessments must be repeated if the subject is re-screening.

6.1.1. 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.

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- **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 will also 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 nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose. The date of initiation of glucocorticoid steroids will be collected.

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

- **Fecal occult blood.** If a stool sample is unable to be collected during 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.

- **Weight.**

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

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

- **Triplicate ECG.**

- **Cardiac MRI** (with or without gadolinium) or **Echocardiogram** (the modality used to monitor LVEF should be consistent throughout the study for each subject, if cardiac MRI with gadolinium is used, the imaging may only performed following all other imaging at the study visit).

- **PODCI** questionnaire.

- **C-SSRS**: Children's Baseline/Screening (Version 6/23/10).

Clinical laboratory testing:

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

- **Blood samples** for Biomarkers: Group 1, Group 2 (fasting collection), Group 3 and Liver.

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- **Blood samples** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase and amylase.
- **Urine sample** for urinalysis.

Imaging assessments:

- **Fasting Dual-energy x-ray absorptiometry (DXA)**: whole body and spine.
- **Magnetic resonance imaging (MRI)**: thigh and liver.
- **X-ray**: non-dominant hand and wrist.

- **Functional assessments**: <u>All functional assessments in the following order</u>:
  - **FVC.**
  - **4SC** Used to determine eligibility.
  - **NSAA**.
  - **ROM**.
  - **Strength assessment**.
  - **PUL**.
  - **6MWT**.

6.2. Visit 2 (Baseline Day -4 up to -1 prior to dosing on Day 1)

This visit *may* be conducted over 1 or 2 days as determined by the site.

Clinical laboratory testing:

- **Fasting blood collection**: serum ferritin, serum iron, TIBC and % transferrin saturation
- **Fasting blood collection** for Biomarker: Group 2.
- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Blood collection for hormones should be done in the morning.
- **Blood sample** for Biomarker: Liver.
- **Blood sample** for hematology, blood chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase, cardiac troponin I and hormones (LH, FSH, T4, TSH

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androstenedione, testosterone). Blood collection for hormones should be done in the morning.

- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.

- **Weight**: The subject's weight is required when randomizing the subject.
- **Height**: Height should be measured in the morning.
- **Functional Assessments** should be assessed in the morning: Must be conducted in the following order: FVC, 4SC, NSAA, ROM, strength assessment, PUL, 6MWT. Note: The time to complete the 4SC at baseline is required to stratify subjects at the time of randomization, however it is the 4SC at screening which will qualify them for the study.
- **Fecal occult blood:** Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.
- **Physical Examination**: including nose and throat mucosal exam.
- **Tanner Stage** and **testicular volume**.
- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Triplicate ECG**.
- **PODCI** questionnaire.
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10). <u>This evaluation is required at baseline to confirm subject's eligibility.</u>
- **Inclusion/Exclusion Criteria**: Subject eligibility will be confirmed against inclusion and exclusion criteria.
- **Randomization**: Randomization will occur after all screening evaluations are complete. Subject's eligibility is based on the screening assessments and the baseline C-SSRS. At the time of randomization, the baseline 4SC and weight are required to be entered into the IRT system. Subjects may be randomized once these assessments are complete and subject if determined to be eligible.

6.3. Visit 3 (Day 1)

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

- **Blood samples** for PK.

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- **Blood samples** for PD.
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

Dosing:

- **Investigational product administration**.

After dosing, the following procedures will be completed:

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

Blood samples for:

- **PK**: Collected following the completion of infusion and flush (hour 2).
- **PD**: Collected following the completion of infusion and flush (hour 2).

- **Infusion site reaction monitoring.**
- **Adverse event (AE) monitoring.**
- **Concomitant medication monitoring.**
- **Wellness phone check**: Approximately 1 week following each dosing visit, the site will call caregiver to verify if there are any AEs that have emerged since dosing.

6.4. Visit 4, 8, 10, 14, 16, 20 (Day 8, 92, 120, 204, 232, 316) Additional PK visits

The first 12 subjects enrolled in the study will be required to complete 6 additional visits to further characterize the PK profile of the study drug. Subjects enrolled after the first 12 subjects will not be required to complete these additional visits.

Clinical Laboratory testing:

- **Blood samples** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase and amylase.
- **Blood sample** for Biomarker: Liver.
- **Blood sample** for PK.
- **Urine sample** for urinalysis.

- **Infusion site reaction monitoring.**
- **AE monitoring.**

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

- **Concomitant medication monitoring.**

6.5. Visits 5, 11, 17, 22, 26, 30 (Days 29, 141, 253, 365, 477, 589)

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.

- **C-SSRS**: Children's Since Last Visit (Version 6/23/10).

Prior to dosing, the following procedures will be completed:

Clinical laboratory sample collection:

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

- **Blood sample** for Biomarker: Liver.

- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase and amylase.

- **Blood sample** for immunogenicity.

- **Urine** for urinalysis.

- **Blood sample** for PK.

- **Blood sample** for PD.

- **Weight:** Weight must be collected at each visit prior to dosing.

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

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

Dosing

- **Investigational product administration**.

After dosing, the following procedures will be completed:

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

- **Blood sample for PK**: Collected following the completion of infusion and flush (hour 2).

- **Blood sample for PD**: Collected following the completion of infusion and flush (hour 2).

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- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**
- **Wellness phone check**: Approximately 1 week following each dosing visit, the site will call caregiver to verify if there are any AEs that have emerged since dosing.

6.6. Visits 6, 12, 18, 23, 27, 31 (Days 57, 169, 281, 393, 505, 617)

This visit may be completed on the same day if logistics are permissive.

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10).
- PODCI Questionnaire.

Prior to dosing, the following procedures will be completed:

Clinical laboratory testing:

- **Fasting blood collection**: serum ferritin, serum iron, TIBC and % transferrin saturation.
- **Blood for Biomarker**: Liver.
- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase and amylase.
- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.
- **Blood sample** for PK.
- **Blood sample** for PD.

- **Weight:** Weight must be collected at each visit prior to dosing.
- **Functional Assessments:** Must be conducted in the following order: FVC, 4SC, NSAA, ROM, strength assessment, PUL, 6MWT.
- **Physical Examination**, including nose and throat mucosal exam.
- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

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Dosing

- **Investigational product administration.**

After dosing, the following procedures will be completed:

- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Blood sample** for PK: Collected following the completion of infusion and flush (hour 2).
- **Blood sample** for PD: Collected following the completion of infusion and flush (hour 2).
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring**.
- **Wellness phone check**: Approximately 1 week following each dosing visit, the site will call caregiver to verify if there are any AEs that have emerged since dosing.

6.7. Visits 7, 13, 19, 24, 28, 32 (Days 85, 197, 309, 421, 533, 645)

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.
- **C-SSRS:** Children's Since Last Visit (Version 6/23/10).

Imaging assessments:

- **MRI:** liver (Is able to be conducted at any time during the visit). If the E-DMC determines that the liver MRI monitoring is able to be reduced, it will then only be conducted at Visit 19 and 32 (Days 309 and 645).

Prior to dosing, the following procedures will be completed:

Clinical laboratory testing:

- **Fasting blood collection**: serum ferritin, serum iron, TIBC, % transferrin saturation.
- **Blood sample** for Biomarker: Liver.
- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT creatine kinase and amylase.

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- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.
- **Blood sample** for PK.
- **Blood sample** for PD.

- **Weight:** Weight must be collected at each visit prior to dosing.
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Physical Examination**, including nose and throat mucosal exam.

Dosing

- **Investigational product administration**.

After dosing, the following procedures will be completed:

- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Blood sample** for PK: Collected following the completion of infusion and flush (hour 2).
- **Blood sample** for PD: Collected following completion of infusion and flush (hour 2).
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**
- **Wellness phone check**: Approximately 1 week following each dosing visit, the site will call caregiver to verify if there are any AEs that have emerged since dosing.

6.8. Visits 9, 15, 21, 25, 29 (Days 113, 225, 337, 449, 561)

A two day visit will be required to complete assessments at this visit. MRI-thigh and functional assessments should be collected on separate days. Functional assessments should routinely be collected in the morning when the subject is rested and well fed. The MRI-thigh should routinely be collected at approximately the same time of day throughout the study.

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10).

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- **PODCI** questionnaire.

Imaging assessments:

- **DXA:** whole body (following 2 hour fast).
- **DXA:** spine Visit 21 (Day 337) only.
- **MRI:** thigh Visit 9, 15, 21 (Days 113, 225 and 337) only.
- **X-ray**: non-dominant hand and wrist.

- **Cardiac MRI** (with or without gadolinium) or **Echocardiogram** Visit 21 (Day 337) only. The modality used to monitor LVEF should be consistent throughout the study for each subject, if cardiac MRI with gadolinium is used, the imaging may only performed following all other imaging at the study visit.
- **Triplicate ECG**.
- **Tanner Stage** and **testicular volume**.
- **Functional assessments**: Must be conducted in the following order: FVC, 4SC, NSAA, ROM, strength assessment, PUL, 6MWT.

Prior to dosing, the following procedures will be completed:

Clinical laboratory testing:

- **Fasting blood collection**: serum ferritin, serum iron, TIBC and % transferrin saturation.
- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Blood collection for hormones should be done in the morning.
- **Fasting blood** collection for Biomarker: Group 2.
- **Blood sample** for Biomarker: Group 3 at Visit 21 (Day 337) only.
- **Blood sample** Biomarker: Liver.
- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase and cardiac Troponin I.
- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.

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- **Blood sample** for PK.
- **Blood sample** for PD.

- **Weight:** Weight must be collected at each visit prior to dosing.
- **Height:** Height should be measured in the morning.
- **Physical Examination**, including nose and throat mucosal exam.
- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

Dosing

- **Investigational product administration**.

After dosing, the following procedures will be completed:

- **Blood sample for PK**: Collected following the completion of infusion and flush (hour 2).
- **Blood sample for PD**: Collected following the completion of infusion and flush (hour 2).
- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring**.
- **Wellness phone check**: Approximately 1 week following each dosing visit, the site will call caregiver to verify if there are any AEs that have emerged since dosing.

6.9. Visits 33 (Follow-up Day 673)

A two day visit will be required to complete assessments at this visit. MRI-thigh and functional assessments should be collected on separate days. Functional assessments should routinely be collected in the morning when the subject is rested and well fed. The MRI-thigh should routinely be collected at approximately the same time of day throughout the study.

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10).
- **PODCI** questionnaire.

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Clinical laboratory testing:

- **Fasting blood** collection: serum ferritin, serum iron, TIBC and % transferrin saturation.
- **Fasting blood** collection Biomarker Sample: Group 2
- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Blood collection for hormones should be done in the morning.
- **Blood** collection Biomarker: Group 3 and Liver.
- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase and cardiac Troponin I.
- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.

Imaging assessments:

- **DXA**: whole body (following 2 hour fast).
- **DXA:** spine.
- MRI: thigh.
- **X-ray**: non-dominant hand and wrist.

- **Weight:** Weight must be collected at each visit prior to dosing.
- **Height**: Height should be measured in the morning.
- **Cardiac MRI** (with or without gadolinium) or **Echocardiogram**. The modality used to monitor LVEF should be consistent throughout the study for each subject, if cardiac MRI with gadolinium is used; the imaging may only performed following all other imaging at the study visit.
- **Triplicate ECG**.
- **Physical Examination**, including nose and throat mucosal exam.
- **Tanner Stage** and **testicular volume**.
- **Vital signs**: Supine blood pressure, pulse rate, respiratory rate, and oral temperature.

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- **Functional assessments**: Must be conducted in the following order: FVC, 4SC, NSAA, ROM, strength assessment, PUL, 6MWT.
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**

6.10. Visit 34 (Follow-up Day 729)

Visit may be conducted by phone.

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

6.11. Unscheduled Visits

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

- **Fecal occult blood.**
- **Weight.**
- **Physical Examination, including nose and throat mucosal exam.**
- **Vital Signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Triplicate ECG.**
- **Cardiac MRI (with or without gadolinium) or Echocardiogram** (the modality used to monitor LVEF should be consistent throughout the study for each subject, 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 sample** for hematology, chemistry, GGT, PT, aPTT, creatine kinase, amylase and cardiac Troponin I.

- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Should be collected in the morning.

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- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.
- **Blood sample for PK.**
- **Blood sample for PD.**

Imaging assessments:

- **MRI:** liver.

- **Infusion site reaction monitoring.**
- **Adverse event (AE) monitoring.**
- **Concomitant medication monitoring.**

6.12. Subject Withdrawal

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

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

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record (see Section 6.13). In any circumstance, every effort should be made to document subject outcome, if possible. The investigator

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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.

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

Assessments may include:

- **Fecal occult blood**: Fecal sample is to be collected at home within approximately 1 week prior to scheduled visit.

Clinical laboratory sample collection:

- **Fasting blood** collection: serum ferritin, serum iron, TIBC and % transferrin saturation.
- **Blood sample** for hormones (LH, FSH, T4, TSH, androstenedione, testosterone). Should be collected in the morning.
- **Biomarker sample collection**: Group 2 (fasting collection), Group 3, Liver.
- **Blood sample** for hematology, chemistry, GGT, GLDH, PT, aPTT, creatine kinase, amylase and cardiac Troponin I.
- **Blood sample** for immunogenicity.
- **Urine sample** for urinalysis.
- **Blood sample for PK.**
- **Blood sample for PD.**

- **Height:** Height should be measured in the morning.
- **Weight.**
- **Physical Examination,** including nose and throat mucosal exam.
- **Tanner Stage** and **testicular volume.**
- **Vital signs:** Supine blood pressure, pulse rate, respiratory rate, and oral temperature.
- **Triplicate ECG.**
- **Cardiac MRI (with or without gadolinium) or Echocardiogram** (the modality used to monitor LVEF should be consistent throughout the study for each subject, if

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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

- **PODCI** questionnaire**.**
- **C-SSRS**: Children's Since Last Visit (Version 6/23/10).

Imaging assessments:

- **DXA:** whole body (following 2 hour fast).
- **DXA:** spine.
- **MRI:** thigh.
- **MRI:** liver.
- **X-ray:** non-dominant hand and wrist.

- **Functional assessments:** Must be conducted in the following order: FVC, 4SC, NSAA, ROM, strength assessment, PUL, 6MWT.
- **Infusion site reaction monitoring.**
- **AE monitoring.**
- **Concomitant medication monitoring.**

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, Assessments. Clinically important suicidality includes but is not limited to:

1. Suicidal behavior (with or without intent of suicide or serious self-harm).
2. 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.
3. Determination of "yes" on question 5 (Active Suicidal Ideation with Specific Plan and Intent) for the Suicidal Ideation section of the C-SSRS.
4. 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.

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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

6.13. Subject Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or emails 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. In the event that a subject becomes intolerant to MRI scanning after the screening visit and during the study, the subject may be separately consented to be administered sedation in order to complete the liver and cardiac MRI only.

Per the sites local standard operating procedures for blood collection, an IV cannula may be placed in the contralateral arm (from the arm where the IV infusion is being administered) to obtain serial blood samples. Samples should *never* be drawn from the same arm as the investigational product is administered as this will confound the PK results. 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

To minimize the volume of blood collected in this pediatric study, the Center for Disease Control and Prevention (CDC) growth chart was used to estimate the lower end weight in a healthy boy which would be approximately 15 kg (10^{th} percentile weight). Based on this weight, the total blood volume per month will not exceed approximately 45 mL.

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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

Period	Visit	Total Volume (mL) At Each Visit
Period 1	Screening	28
	Baseline, Day 1	35
	Day 8, 92, 120, 204, 232, 316 (Additional PK)	8
	Day 29, 57, 85, 141, 169, 197, 253, 281, 309	24
	Day 113, 225	35
	Total Volume Period 1, including additional PK*	**396**
	Total Volume Period 1, excluding additional PK	**347**
Period 2	Day 337	47
	Day 449, 562	35
	Day 365, 393, 421, 477, 505, 533, 589, 617, 645	24
	Day 673	35
	Total Volume Period 2	**366**
	Early Withdrawal	***39***

*Additional PK visit to be conducted in the first 12 subjects enrolled.

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.

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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 and 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 Serum for Liver Biomarker Cardiac Troponin I Serum Ferritin[c] Serum Iron[c] Total Iron Binding[c] Capacity (TIBC)[c] Unsaturated Binding capacity[c], % Transferrin Saturation[c] Hormones (LH, FSH, T4 (total and free), TSH, androstenedione, testosterone) [d]	Fecal Occult
	Additional Tests[b]			
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT GLDH PT INR			

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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. For subjects who may reach sexual maturity, hormone testing will no longer be required.

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.

Abnormal findings will be further characterized as "clinically significant" or "not clinically significant" for the purposes of reporting as adverse events.

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 (Marshall &Tanner 1970).[14] In addition to the Tanner staging, a measurement of testicular size (volume) using orchidometer beads will be documented.

For subjects who may reach sexual maturity during the trial, as indicated by a Tanner Stage V rating, the Tanner Stage, testicular volume, hormone and X-ray (hand and wrist) will no longer be required to be collected to assess for signs of precocious puberty.

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. Whenever possible, the same arm (preferably the dominant arm) should be used throughout the study.

Wherever possible, the same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. 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.

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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

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

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

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, please use the formula below to calculate.

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

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 QTc 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.

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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 the left ventricular ejection fraction (LVEF) will be provided to sites. Sites will be provided with a scanning and image transmittal guide for collection of the cardiac MRI.

If cardiac MRI is utilized, it will be read by a central imaging vendor.

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 ventricular systolic pressure, 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 Baseline/Screening (Version 6/23/10) (Appendix 1) of the C-SSRS should be completed at the Screening Visit (Visit 1). At all study visits following the Screening Visit, the Children's Since Last Visit (Version 6/23/10) (Appendix 2) of the C-SSRS should be utilized. The Since Last Visit version refers to the subject's experience since their last visit.

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

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

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

Risk Assessment: In the event that a subject endorses a 4 or 5 on the C-SSRS ideation section or reports any suicidality behavior, an evaluation of suicide risk (risk assessment) will be completed as part of the psychiatric evaluation and assessment of subject safety to participate will be performed by the following child and adolescent mental health provide: In the United States: 1) Child and Adolescent Pyschiatrists (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,

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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 pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in 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 informed consent document/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 informed consent document/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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 2-mL blood biospecimen**(Biomarker Group 1) Prep D1.5 (K_2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis)** will be collected at the Screening visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Additional biospecimens in biomarker Group 2 will be collected in the morning following an 8 hour fast to be retained for exploratory analyses in this study include the following:

Biomarker Sample Group 2:

- **Prep B1.5 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis):** A 2-mL blood biospecimen will be collected at Visits 1(Screening), 2 (Baseline), 9, 15, 21, 25, 29, 33 or at Early Withdrawal, if applicable.

- **Prep B2.5 (serum collection optimized for biomarker/ proteomics/metabonomic analysis):** A 2-mL blood biospecimen will be collected at Visits, 1 (Screening), 2 (Baseline), 9, 15, 21, 25, 29, 33 or at Early Withdrawal, if applicable.

Biomarker Sample Group 3:

- **Prep R1 (PAXGene whole blood collection optimized for RNA analysis):** A 2.5-mL blood biospecimen will be collected at Visits 1 (Screening), 21 and 33 and Early Withdrawal, if applicable.

- **Prep P4 (Cell-free RNA):** A 5-mL blood biospecimen will be collected at Visits 1 (Screening), 21, 33, or at Early Withdrawal, if applicable.

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 informed consent document/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:

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

- 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 (7.3.1) 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)

During all study periods, 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 at the exact nominal time relative to dosing 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)

During all study periods, 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 at the exact nominal time relative 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.

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

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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.

7.6. Pharmacodynamics/Serum for Total GDF-8

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

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

The PD samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD 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 pharmacodynamics of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

Blood samples (2 mL) to provide serum will be collected into appropriately labeled tubes (silica coated, no additives). Blood samples will be collected for the analysis of total GDF-8 at times specified in the Schedule of Activities.

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

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. The independent central radiologist will be blinded to the study treatment assignment. In order to maintain the study blind, the investigator and the sponsor will be blinded to the liver MRI findings, except for those from

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screening so that the investigator may confirm eligibility. Select sponsor study team members may have access to the liver MRI results however they will not have access to the associated subject numbers. The Designated Reviewer will be unblinded to MRI results and will review results per the dose adjustment criteria described in Section 3. The R2* value should not be calculated by the study site as this may unblind site personnel to the treatment assignment. If the site reviews MRI scans for general safety, the site radiologist should review individual images and not reconstructed R2* maps. Site imaging or radiology staff should not report suspicion of iron overload or R2* values to the investigator.

At the initiation of the study, the post-screening liver MRI and liver iron indices results (serum iron, serum ferritin, total iron-binding capacity and % transferrin saturation) will not be provided to the site or blinded study team members as these data may be unblinding to the assigned treatment. Should the E-DMC agree during their continuous review of the unblinded data that these data are not unblinding, the results may be provided to sites and the study team during the remainder of the study.

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. Thigh MRI

Single thigh MRI will be obtained according to the Schedule of Activities to measure the percent change in muscle volume. Additional measurements may include evaluation of muscle quality through T2-mapping and/or Dixon imaging sequences to evaluate fat fraction. The standard procedure to obtain serial MRIs will be described in an Image Acquisition manual which will be provided to the site. Ideally, thigh MRIs will be taken at approximately the same time of day (morning) to provide optimal testing conditions and consistency in endpoint measurements. MRIs should not be acquired after exercise or strenuous activity as this could impact the study results.

The site will be trained on all aspects of obtaining quality MRIs. MRIs will be sent to an independent central radiology imaging facility for analysis of the study endpoints. The independent central radiologist will be blinded to the study treatment assignment.

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 thigh MRI.

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

7.7.3.1. DXA

DXA scans will be obtained according to the Schedule of Activities to measure the percent change in lean body mass (LBM) over time and to evaluate bone mineral density (BMD) on the spine and whole body without head. The standard procedure to obtain serial DXA whole body and spine analysis 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

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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 lean body mass measure. Calcium should be avoided for 24 hours as it may not absorb and will affect the measure of bone mineral density and lean body mass.

7.7.3.2. 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. 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 analysis bone age. 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.

For subjects who may reach sexual maturity during the trial, as indicated by a Tanner Stage V rating, the Tanner Stage, testicular volume, hormone and X-ray (hand and wrist) will no longer be required to be collected to assess for signs of precocious puberty.

7.7.3.3. 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. The expected total radiation dose for 7 whole body DXA exams, 3 spine scans and 7 hand x-rays for bone age assessment is not expected to exceed 0.75 mSv. This is less than 1 year of natural background radiation which is approximately 3.0 mSv per year (EHS Radiation Risk; Blake et al, 2006).[10,1]

7.7.4. Additional Research with Imaging Assessments

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the images collected in this study to also be used to further study the disease/condition or to gain further understanding of the imaging methods.

Subjects may still participate in the clinical study if they elect not to allow their images to be used for the additional purposes described in this section.

7.8. Functional Assessments

Functional assessments will be obtained according to the Schedule of Activities. In order to provide optimal testing conditions and consistency in endpoint measurements, the functional assessments should be completed at approximately the same time of day and in the morning

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when the subject is rested and well-fed. The order for completing all testing will be detailed in a functional assessment manual.

Should subjects become non-ambulatory during the study, the 4SC, NSAA and 6MWT will not continue to be collected.

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 will 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 described in Section Record Retention.

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

7.8.1. Forced Vital Capacity (FVC)

Pulmonary function testing will be completed to evaluate the maximal lung function utilizing the FVC maneuver by spirometry.

7.8.2. 4 Stair Climb (4 SC)

The primary efficacy endpoint will be based on the 4 SC (with or without the use of hand rails). 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.

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).[15] 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).[16]

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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.

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 dsytrophinopathy is to assess change that occurs in motor performance of the upper limb overtime from when a boy is still ambulant 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).[19] 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, 2013).[17,8,20]

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.

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7.11. 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. 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 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. Scores may be reported as standardized, or they may be converted to normative scores based on the scores reported in a large, healthy population.

The PODCI will be collected electronically on a tablet device.

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.

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- AEs (serious and nonserious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of 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);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength.

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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 advese event (SAE) is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

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- 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:

1. Loss of mobility or ambulation.

2. Muscle weakness.

3. Symptoms related to spinal deformity.

4. Respiratory muscle weakness/Hypoxia.

5. Fracture.

6. 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 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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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 (x ULN) concurrent with a total bilirubin value ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 x ULN or not available;

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

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

    Concurrent with

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

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

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, 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.

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

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

8.8. Severity Assessment

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

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

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product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

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

2. 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 a 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 pre-procedure 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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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's parent/legal guardian/ legally acceptable representative. In addition, each study subject's parent/ 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.

As noted in the Protocol-Specified Serious Adverse Events section, should an investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

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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

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

9.1. Sample Size Determination

The sample size is based on the primary endpoint of demonstrating efficacy of change from baseline on a 4 stair climb timed function test as compared to placebo at 49 weeks. To detect a 2.5 second difference in change from baseline in 4 stair climb based on a difference between the active treatment and the placebo treatment in Period 1 assuming a common

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standard deviation of 4.0 with 80% power at α=0.05 (two-sided), a 2:1 treatment allocation and one interim analysis a total of 96 subjects should complete 49 weeks of dosing for this assessment. Assuming a 10% attrition rate, approximately 105 subjects should be enrolled (70 subjects receiving PF-06252616 and 35 subjects receiving placebo) in order to ensure sufficient number of subjects will complete this assessment. If there are no safety issues and enrollment has completed, additional subjects may be enrolled prior to the time of the interim analysis. These additional subjects may help off-set any unforeseen variability that may occur outside the presumed standard deviation for this age group.

One interim analysis is planned to evaluate futility and efficacy after approximately 50% of the subjects have completed through Week 49. Alpha- and beta-spending functions will be used to determine the cutoffs for efficacy and futility at the interim based on the observed number of subjects in the interim analysis. The gamma family spending functions will be used to appropriately account for error spending and adjust for the observed information at the time of the interim analysis and conservative boundaries ($\gamma \leq -1$) will be used to define the futility and efficacy boundaries. The cutoff used at the interim analysis will be calculated based on the percentage of subjects included at the interim analysis to ensure appropriate protection of the type I error. Further details regarding the interim analysis and simulations are included in the SAP.

9.2. Efficacy Analysis

Continuous variables will be summarized by the N, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by percent and counts. All summaries will be displayed by treatment group and/or period depending on the endpoint. Efficacy data will be listed, tabulated and graphically represented, as appropriate. Model assumptions will be tested using appropriate statistical or graphical techniques.

All analyses will be based on the full analysis set (FAS) which includes all randomized subjects who have received at least one dose of study drug. Additionally analyses based on a per protocol analysis set may also be performed.

9.2.1. Analysis of the Primary Endpoint

Change from baseline in 4 stair climb will be analyzed using a longitudinal mixed effects model. The baseline result, treatment, time and treatment by time interaction will be included as fixed effects in the model. Subject will be included as a random effect and the model will be fit with an unstructured covariance for the repeated measures. The distribution of the time to climb 4 stairs is assumed to be right skewed. Transformations of the time to climb 4 stairs (including the log transformation) will be evaluated to ensure the normality assumption is met. Contrasts will be created to estimate the differences in change from baseline time in 4 stair climb at the end of each dose treatment levels for Period 1 (Week 17, Week 33 and Week 49). The final analysis of the primary endpoint will be performed at Week 49, though data will continue to be collected through Week 97. Additionally, non-Gaussian models may be explored in the case of non-normal data for the time to climb 4 stairs.

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Missing data will be handled using maximum likelihood techniques for a mixed effects model. This analysis is unbiased under the assumption of missing at random when the model assumptions hold. Subjects who lose the ability to climb 4 stairs and/or ambulate will be missing not at random. Additional imputation methods to assess the sensitivity of the analysis to missing not at random data will also be performed. A completer analysis will also be conducted as a sensitivity analysis.

A sensitivity analysis of the time to climb 4 stairs will be based on the velocity (defined as the reciprocal of time). This analysis will use the same longitudinal model, but subjects who can no longer ambulate will be analyzed with a velocity of 0 instead of a missing time to climb 4 stairs at that time point, as specified above. Thus the missing data will no longer be handled by the maximum likelihood techniques under the missing at random assumption for subjects who can longer complete the 4 stair climb. Based on the number of subjects who cannot complete the function test at Week 49, a zero inflation model may also be explored for the velocity endpoint.

Additionally, a non-parametric sensitivity analysis may be performed on the Week 49 data if there is a large number of subjects who can no longer ambulate. The proportion of subjects who can no longer complete the test will also be compared between the two treatment groups at the Week 49 time point along with a time to failure analysis comparing the two treatment groups based on the ability to complete the test.

9.2.2. Analysis of the Secondary Endpoints

Secondary endpoints of change from baseline in FVC, NSAA, ROM, PUL, 6MWD, myometry based strength assessments, and MRI volume endpoints will be analyzed using the same longitudinal mixed model as described for the primary analysis. Transformation of the data will also be considered if model assumptions are not met.

Additionally, a sensitivity analysis based on velocity may also be performed as described for the primary analysis for timed function tests.

In a pre-specified subset of subjects who may demonstrate a rapid disease decline and with relatively low variablity , the mean change from baseline as compared to placebo on functional testing (4SC, FVC, NSAA, PUL, 6MWD will be evaluated.

9.2.2.1. Historic Control

In keeping with global guidance (eg, Food and Drug Administration's Guidance from 2015: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment and Eurpoean Medicinal Agency[EMA]/Committee for Medicinal Product for Human Use [CHMP] Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Duchenne and Becker muscular dystrophy, 2016) and related advice received from regulators, the long-term effects on functional assessments following approximately 2-years of treatment with PF-06252616 will be characterized compared to a historical control group.

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9.2.3. Analysis of the Exploratory Endpoints

All exploratory endpoints, including the pharmacologic and health outcome endpoints, will be summarized by treatment group and period. Additional analyses may be performed to understand the relationship between these endpoints and treatment. Analyses of the primary and secondary endpoints during Period 2 will be considered exploratory. These endpoints will be summarized by period and additional analyses may be performed.

9.2.4. Analysis of Pharmacokinetics

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

PK parameters for PF-06252616 following administration of PF-06252616 will be derived from the concentration-time profiles as described in the following table. For subjects in Sequence 2, PK samples collected during placebo treatment in Period 2 will be used to estimate t½ following the last dose of active treatment in Period 1.

PK parameters for PF-06252616 following administration of PF-06252616 will be derived from the concentration-time profiles as described.

Parameter	Definition	Method of Determination
C_{max}	Maximum serum concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data
C_{trough}	Trough (predose) serum concentration	Observed directly from data
AUC_{τ}	Area under the serum concentration-time curve over the dosing interval τ, where τ=4 week (672 hours)	Linear/Log trapezoidal method
C_{av}	Average serum concentration over the dosing interval	AUC_{τ}/τ
$t_{½}$ [a]	Terminal elimination half-life	$Log_e(2)/k_el$, where k_el is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in regression
CL	Clearance	$Dose/AUC_{\tau}$
V_{SS} [a]	Volume of distribution at steady state	CL * MRT, where MRT is the mean residence time

[a] If data permit

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

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

subject and median profiles of the serum concentration time data will be plotted for subjects with additional PK sampling.

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

Parameter	Summary statistics
C_{max}, AUC_{τ}, C_{av} $C_{trough,}$ CL, V_{SS}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean, geometric CV%
$t_{½}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

Any population PK analysis if conducted will be reported separately.

9.2.5. Analysis of Pharmacodynamics

The GDF-8 concentration population is defined as all enrolled subjects in whom at least 1 concentration value is reported. The GDF-8 parameter analysis population is defined as all enrolled subjects who received at least 1 dose of PF-0625616 and in whom at least 1 of the parameters of interest is calculated.

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

Parameter	Definition	Method of Determination
$AUC_{\tau(GDF\text{-}8)}$	Area under GDF-8 curve over the 4-week dosing interval for PF-06252616	Linear trapezoidal method
$C_{max(GDF\text{-}8)}$	Maximum concentration of GDF-8	Observed directly from data
$T_{max(GDF\text{-}8)}$	Time to maximum GDF-8 concentration	Observed directly from data
$C_{GDF\text{-}8(0)}$	Baseline GDF-8 (Day 1 predose)	Observed directly from data
$C_{trough,(GDF\text{-}8)}$	Trough (predose) serum	Observed directly from data
$C_{av\ (GDF\text{-}8)}$	Average GDF-8 concentration over dosing interval	$AUC\tau_{(GDF\text{-}8)}/\ \tau$

The GDF-8 parameters will be summarized by treatment and will include the set of summary statistics as specified in the table below:

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

Parameter	Summary statistics
$AUC_{\tau(GDF-8),}$ $C_{max(GDF-8),}$ $T_{max(GDF-8),}$ $C_{GDF-8(0),}$ $C_{trough,(GDF-8),}$ $C_{av\ (GDF-8)}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean
T_{max}	N, median, minimum, maximum

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

Additionally, data permitting relationships between PF-06252616 PK, GDF-8, imaging data (DXA, MRI), 4 stair climb, immunogenicity and any safety signals may be explored.

9.3. Safety Analysis

Safety analyses will be based on the full analysis set.

9.3.1. Vital Signs

Vital signs will be listed and tabulated by dose group and week with descriptive statistics. Change from baseline will also be summarized using the same descriptive statistics by dose group and month.

9.3.2. Electrocardiogram

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

Baseline and change from baseline for QT, QTcF, heart rate, QRS, PR and RR will be summarized using descriptive statistics by treatment and study week. The baseline for ECG parameters will be the average of the triplicate pre-dose measurements at Week 0. Any triplicate measurements will be averaged prior to the calculation of summary statistics. For QTcF a classification of absolute values and increase from baseline will be used.

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

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

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9.3.3. Cardiac MRI/Echocardiogram

The mean absolute and percent change from baseline in LVEF will be evaluated as compared to placebo. Exploratory analyses comparing left ventricular wall thickness, ventricular wall strain and cardiac fibrosis against placebo will be performed where data from cardiac MRI are available.

9.3.4. Liver MRI

The mean absolute and percent change from baseline in the R2* value will be tabulated for each subject. Other exploratory analyses may be performed to compare the treatments.

9.3.5. Other Safety

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

Other safety data will be listed.

9.4. Interim Analysis

An interim analysis will be conducted after approximately 50% of the subjects have completed assessments at Week 49. The futility and efficacy boundaries will be calculated based on the gamma family alpha- and beta-spending and conservative stopping boundaries ($\gamma \leq -1$) will be implemented for the futility and efficacy boundaries. The cutoff used at the interim analysis will be calculated based on the percentage of subjects included at the interim analysis to ensure appropriate protection of the type I error. A statistical and programming team independent from the study team will conduct all unblinded analyses to be forwarded to the external data monitoring committee (E-DMC) and will maintain the study blind per Pfizer's SOPs. Further details of the interim analysis will be included in the final SAP. This analysis plan will be approved prior to the unblinding of the independent statistical and programming team.

9.5. Data Monitoring Committee

This study will use an E-DMC.

The E-DMC will be responsible for ongoing monitoring of safety and the efficacy at the interim analysis and 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. See Section 3.5.2 for additional information.

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10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during the 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 the study conduct and/or after 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.

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.

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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 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 (IRB)/Ethics Committee (EC)

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

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 use of initials should be avoided. The study site will maintain a confidential list of subjects who participated in the study linking each subject's numerical code to the 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 if a minor, 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 legeally 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.

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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

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

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

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).

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14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, 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 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results 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 (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.

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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 a principal investigator of the results of the study based on information collected or generated by the 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.

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Appendix 1. Columbia-Suicide Severity Rating Scale (C-SSRS), Children's Baseline/Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

PPD

Disclaimer:

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

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

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

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____	____

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

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

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Appendix 2. Columbia-Suicide Severity Rating Scale (C-SSRS), Children's Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

PPD

Disclaimer:

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

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

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

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself) - like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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Appendix 3. Pediatric Outcomes Data Collection Instrument (PODCI)
Age 2-10-Completed by Parent

Pediatric

Outcomes Questionnaire

Developed by:

American Academy of Orthopaedic Surgeons®

Pediatric Orthopaedic Society of North America

American Academy of Pediatrics

Shriner's Hospitals

To be completed by the parent for children 2 – 10 years old

Based on the Version 2.0 Pediatrics-Parent/Child Outcomes Instrument

Also commonly referred to as the PODCI ("Pediatric Outcomes Data Collection Instrument")

Revised, renumbered, reformatted August 2005

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Today's Date / /

Thank you for completing this questionnaire!

This questionnaire will help us to better understand your general health and any problems related to bone and muscle conditions.

Your completion of this questionnaire is completely voluntary and your responses will be held in the strictest confidence.

Please answer every question. Some questions may look like others, but each one is different.

There are no right or wrong answers. If you are not sure how to answer a question, just give the best answer you can. You can make comments in the margin. We do read all your comments, so feel free to make as many as you wish.

Your Child's Birth Date / /

Your Child's Social Security Number _____

Your Social Security Number _____

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Some kind of problems can make it hard to do many activities, such as eating, bathing, school work, and playing with friends. We would like to find out how your child is doing. (Circle one response on each line.)

During the **last week** was it easy or hard for your child to:

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
1.	Lift heavy books?	1	2	3	4	5
2.	Pour a half gallon of milk?	1	2	3	4	5
3.	Open a jar that has been opened before?	1	2	3	4	5
4.	Use a fork and spoon?	1	2	3	4	5
5.	Comb his/her hair?	1	2	3	4	5
6.	Button buttons?	1	2	3	4	5
7.	Put on his/her coat?	1	2	3	4	5
8.	Write with a pencil?	1	2	3	4	5

9. On average, **over the last 12 months,** how often did your child miss school (preschool, day care, camp, etc.) because of his/her health?

1. Rarely
2. Once a month
3. Two or three times a month
4. Once a week
5. More than once a week
6. Does not attend school, etc.

During the **last week** how happy has your child been with: (Circle one response on each line.)

		Very happy	Somewhat happy	Not sure	Somewhat unhappy	Very unhappy	Child is too young
10.	How he/she looks?	1	2	3	4	5	6
11.	His/her body?	1	2	3	4	5	6
12.	What clothes or shoes he/she can wear?	1	2	3	4	5	6
13.	His/her ability to do the same things his/her friends do?	1	2	3	4	5	6
14.	His/her health in general?	1	2	3	4	5	6

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During the **last week**, how much of the time:

(Circle one response on each line.)

		Most of the time	Some of the time	A little of the time	None of the time
15.	Did your child feel sick and tired?	1	2	3	4
16.	Was your child full of pep and energy?	1	2	3	4
17.	Did pain or discomfort interfere with your child's activities?	1	2	3	4

During the **last week,** has it been easy or hard for your child to:
(Circle one response on each line.)

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
18.	Run short distances?	1	2	3	4	5
19.	Bicycle or tricycle?	1	2	3	4	5
20.	Climb three flights of stairs?	1	2	3	4	5
21.	Climb one flight of stairs?	1	2	3	4	5
22.	Walk more than a mile?	1	2	3	4	5
23.	Walk three blocks?	1	2	3	4	5
24.	Walk one block?	1	2	3	4	5
25.	Get on and off a bus?	1	2	3	4	5

26. How often does your child need help from another person for walking and climbing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

27. How often does your child use assistive devices (such as braces, crutches, or wheelchair) for walking and climbing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

During the **last week,** has it been easy or hard for your child to:
(Circle one response on each line.)

		Easy	A little hard	Very hard	Can't do at all	Too young for this activity
28.	Stand while washing his/her hands and face at a sink?	1	2	3	4	5
29.	Sit in a regular chair without holding on?	1	2	3	4	5
30.	Get on and off a toilet or chair?	1	2	3	4	5
31.	Get in and out of bed?	1	2	3	4	5
32.	Turn door knobs?	1	2	3	4	5
33.	Bend over from a standing position and pick up something off the floor?	1	2	3	4	5

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34. How often does your child need help from another person for sitting and standing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

35. How often does your child use assistive devices (such as braces, crutches, or wheelchair) for sitting and standing? (Circle one response.)

1 Never 2 Sometimes 3 About half the time 4 Often 5 All the time

36. Can your child participate in **recreational outdoor activities** with other children the same age? (For example: bicycling, tricycling, skating, hiking, jogging) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 36 above, was your child's activity limited by: (Circle yes to all that apply)

		Yes
37.	Pain?	1
38.	General Health?	1
39.	Doctor or parent instructions?	1
40.	Fear the other kids won't like him/her?	1
41.	Dislike of recreational outdoor activities?	1
42.	Too young?	1
43.	Activity not in season?	1

44. Can your child participate in **pickup games or sports** with other children the same age? (For example: tag, dodge ball, basketball, soccer, catch, jump rope, touch football, hop scotch) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 44 above, was your child's activity limited by: (Circle yes to all that apply)

		Yes
45.	Pain?	1
46.	General Health?	1
47.	Doctor or parent instructions?	1
48.	Fear the other kids won't like him/her?	1
49.	Dislike of pickup games or sports?	1
50.	Too young?	1
51.	Activity not in season?	1

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52. Can your child participate in **competitive level sports** with other children the same age? (For example: hockey, basketball, soccer, football, baseball, swimming, running [track or cross country], gymnastics, or dance) (Circle one response.)

1 Yes, easily 2 Yes, but a little hard 3 Yes, but very hard 4 No

If you answered "no" to Question 52 above, was your child's activity limited by: (Circle yes to all that apply)

		Yes
53.	Pain?	1
54.	General Health?	1
55.	Doctor or parent instructions?	1
56.	Fear the other kids won't like him/her?	1
57.	Dislike of pickup games or sports?	1
58.	Too young?	1
59.	Activity not in season?	1

60. How often in the **last week** did your child get together and do things with friends? (Circle one response.)

1 Often 2 Sometimes 3 Never or rarely

If you answered "sometimes" or "never or rarely" to Question 60 above, was your child's activity limited by: (Circle yes to all that apply)

		Yes
61.	Pain?	1
62.	General Health?	1
63.	Doctor or parent instructions?	1
64.	Fear the other kids won't like him/her?	1
65.	Friends not around?	1

66. How often in the **last week** did your child participate in **gym/recess**? (Circle one response.)

1 Often 2 Sometimes 3 Never or rarely 4 No gym or recess

If you answered "sometimes" or "never or rarely" to Question 66 above, was your child's activity limited by: (Circle yes to all that apply)

		Yes
67.	Pain?	1
68.	General Health?	1
69.	Doctor or parent instructions?	1
70.	Fear the other kids won't like him/her?	1
71.	Dislike of gym/recess?	1
72.	School not in session?	1
73.	Does not attend school?	1

090177e1909dc770\Approved\Approved On: 25-Mar-2019 05:50 (GMT)

74. Is it easy or hard for your child to make friends with children his/her own age? (Circle one response.)

1 Usually easy 2 Sometimes easy 3 Sometimes hard 4 Usually hard

75. How much pain has your child had during the **last week**? (Circle one response.)

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

76. During the **last week**, how much did pain interfere with your child's normal activities (including at home, outside of the home, and at school)? (Circle one response.)

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

What expectations do you have for your child's treatment?
As a result of my child's treatment, I expect my child:
(Circle one response on each line.)

		Definitely yes	Probably yes	Not sure	Probably not	Definitely not
77.	To have pain relief.	1	2	3	4	5
78.	To look better.	1	2	3	4	5
79.	To feel better about himself/herself.	1	2	3	4	5
80.	To sleep more comfortably.	1	2	3	4	5
81.	To be able to do activities at home.	1	2	3	4	5
82.	To be able to do more at school.	1	2	3	4	5
83.	To be able to do more play or recreational activities (biking, walking, doing things with friends).	1	2	3	4	5
84.	To be able to do more sports.	1	2	3	4	5
85.	To be free from pain or disability as an adult.	1	2	3	4	5

86. If your child had to spend the rest of his/her life with his/her bone and muscle condition **as it is right now**, how would you feel about it? (Circle one response.)

1 Very satisfied 2 Somewhat satisfied 3 Neutral 4 Somewhat dissatisfied 5 Very dissatisfied

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