A NATURAL HISTORY STUDY IN CHINESE MALE PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Therapeutic Area (TA): Rare Diseases

Protocol Number: C3391004

Document History

Document	Version Date
Amendment 2	16 Jun 2022
Amendment 1	14-Sep-2020
Original protocol	15 May 2018

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 2 (16 Jun 2022)

Overall Rationale for the Amendment: Modify the study endpoints/objective without any change to the data that have been collected: The assessment of some endpoints in previous version of protocol are not quite appropriate, some of them may not reflect the disease progress and disease characteristic in an accurate manner. Amendment 2 is to make the endpoints reflect the disease progression and disease characteristic.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 2. Study objective and endpoints	Changed the primary endpoints for time to run/walk 10 meters and time to rise from floor to 10-meter run/walk velocity and rise from floor velocity (supine to stand), respectively, and moved them down to the third primary endpoint. Modified the wording of the assessment timepoints.	To appropriately include participants in the analysis who are not able to perform the activity and can be assigned a value of zero velocity	Substantial
	Changed the primary endpoint Forced Expiratory Volume in one Second (FEV_1) to percent predicted Forced Expiratory	Using %pFEV_1 rather than absolute FEV_1 allows for continuous assessment across a broad range of ages in which growth impacts the absolute FEV_1 and	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	Volume in one Second (%pFEV$_1$)	will aid contextualizing the findings with other studies.	
	Changed the secondary objective of quality of life from study the relationship between disease characteristics and quality of life to characterize the quality of life in Chinese DMD patients.	Characterize the quality of life is usually the primary objective of QoL assessment.	Substantial
	Removed the secondary objective of identify disease characteristics that could predict disease progression and the endpoints under this objective.	To measure disease progression with descriptive summary of YES/No is less meaningful to be an endpoint; the objective could be considered in PMAP modeling which is also one part of the study.	Substantial
	Modified the secondary endpoint of mutation types from large deletion, large duplication, small insertion/deletion, and point mutation to exon deletion, exon duplication, point mutation, small deletion, small insertion, and others.	This is to make it align with the data collected in CRF.	Substantial
	Changed the secondary endpoint of proportion of subjects with mutations involving key high frequency mutation sites to the proportion of each	• To summarize the proportion of each affected exons by mutation types is to characterize Chinese population's mutation, it is the	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	affected exons by mutation types, and the proportion of subjects with any mutation affecting any exon between exon 9 and exon 13, inclusive, or a deletion that affects both exon 29 and exon 30.	process ahead of identifying the high frequency mutation sites. • Population with any mutation affecting any exon between exon 9 and exon 13, inclusive, or a deletion that affects both exon 29 and exon 30, were at high risk of receiving gene therapy.	
Section 9.2 Efficacy analysis	Updated endpoints assessment according to the changes on objective and endpoints.	To reflect the changes on endpoints.	Substantial
Section 2. Study objective and endpoints	Clarified the primary endpoint assessments on time to life-altering clinical milestones are: age at failure to walk, age at failure to stand and age at failure to self-feed.	Age at failure to walk/stand/self-feed reflects the disease course accurately.	Nonsubstantial
	Clarified the primary endpoint of NSAA assessment is NSAA total score for ambulatory children aged ≥ 3 years and the PUL assessment is for total score and moved them up to the second primary endpoint. Modified the wording of the assessment timepoints.	To make the assessment clear and accurate.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	Clarified the primary endpoint assessment for strength of muscle is for the subjects aged ≥ 5 years and modified the wording of assessment timepoints.	To make the assessment clear and accurate.	Nonsubstantial
	Modified the wording of primary endpoint assessment timepoints for ROM.	To make the assessment clear and accurate.	Nonsubstantial
	Clarified the secondary objective of assess the health care utilization to characterize the health care utilization.	To make the description accurate.	Nonsubstantial
	Moved the EQ-5D-Y and EQ-5D-3L up to the right criteria of quality-of-life endpoints from health care utilization endpoints.	To make the description accurate.	Nonsubstantial
	Clarified the secondary endpoints assessments for EQ-5D-Y, EQ-5D-3L, HRU and WPAI:CG.	To make the assessments clear and accurate.	Nonsubstantial
Section 4.1 Inclusion Criteria	Clarified the definition of "stable GC (glucocorticoid) regimen" and the overall requirement on GC background treatment.	To make the statement more detailed and accurate, aligned with global studies and all previous eligible activities in this study to comply with this definition. This is not a change to this criteria, it is a clarification.	Nonsubstantial
Section 6. Study procedures	Modified the description on assessment for ambulatory and non-ambulatory in Section	To avoid misunderstanding for the required assessments	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	6 (including section 6.1, 6.2 and 6.3).		
Section 7.4 12-Lead Electrocardiograms	Removed the ECG variables list and stated the investigator should review ECG and assess the clinical significance of ECG abnormalities .	• ECG is for safety monitoring follows local clinical practice and the ECG variables will not be analyzed. • There is no impact on investigators' judgement on patients' safety.	Nonsubstantial
Section 7.5	Removed total neutrophils (Abs) and allowed to collect either absolute or percentage for neutrophils, Eosinophils, Monocytes, Basophils, Lymphocytes.	To avoid duplicate data collection. In lab library, total neutrophils (Abs) is same as Absolute neutrophils.	Nonsubstantial
Appendix1 to 5.	Removed questionnaires from appendix 1 to 5 and to provide in independent documents without any change to the version and contents.	The questionnaires are copyrighted and were removed from protocol to avoid any issues when the protocol is publicly disclosed.	Nonsubstantial
Document history	Moved amendment 1 information to Appendix 1 Protocol amendment history	To meet the requirement in new protocol template.	Nonsubstantial
Throughout the protocol	Corrected typographical errors where necessary.	NA	Nonsubstantial

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APPENDICES

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to 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 in the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	**Visit 1/ Baseline[a]**	**Visit 2/ Month 6 (Phone contact allowed for non-ambulatory boys)**	**Visit 3/ Month 12**	**Visit 4/ Month 18 (Phone contact allowed for non-ambulatory boys)**	**Visit 5/ Month 24[b]**	**Visit 6/ Month 30/ End of Study[b] (Phone contact allowed for non-ambulatory boys)**
Visit Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**
Informed consent/Assent[c]	X					
Inclusion/exclusion criteria	X					
General/DMD medical history & family history	X					
Mutation type of DMD	X					
Prior medication use[d]	X					
Demographics	X					
Age of life-altering events	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Anthropometrics	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
Pulmonary Function Assessment[e]						
FVC and FEV_1	X		X		X	X
MIP/MEP	X		X		X	X
Peak cough flow	X		X		X	X
Motor Function Assessment[f]						
NSAA	X	X	X	X	X	X
Passive range of motion[g]	X	X	X	X	X	X
Myometry[h]	X	X	X	X	X	X
PUL 2.0[i]	X	X	X	X	X	X
Echocardiogram	X		X		X	X
12-lead ECG	X		X		X	X
WISC[j]	X				X	

Visit Identifier	Visit 1/ Baseline[a]	Visit 2/ Month 6 (Phone contact allowed for non-ambulatory boys)	Visit 3/ Month 12	Visit 4/ Month 18 (Phone contact allowed for non-ambulatory boys)	Visit 5/ Month 24[b]	Visit 6/ Month 30/ End of Study[b] (Phone contact allowed for non-ambulatory boys)
Visit Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**
Subject and Caregiver Outcome Measures						
EQ-5D-3L/EQ-5D-Y[k]	X		X		X	X
HRU questionnaire	X		X		X	X
WPAI:CG	X		X		X	X
PODCI	X	X	X	X	X	X
Laboratory						
Hematology	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X
Concomitant Treatment(s)		X	→	→	→	X
AE and research related injury monitoring	X	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; CK = Creatine Kinase; DMD = Duchenne Muscular Dystrophy; ECG = Electrocardiogram; EQ-5D-3L = EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y = EuroQoL 5 Dimensions - Youth; FEV_1 = Forced Expiratory Volume in One Second; FVC = Forced Vital Capacity; HRU = Healthcare Resource Utilization questionnaire; NSAA = North-Star Ambulatory Assessment; MEP = Maximum Expiratory Pressure; MIP = Maximum Inspiratory Pressure; PODCI = Pediatric Outcomes Data Collection Instrument; PUL 2.0 = Performance of Upper Limb 2.0; WISC = Wechsler Intelligence Scale for Children; WPAI:CG = Work Productivity and Activity Impairment Questionnaire adapted for Caregiving.

a. The day on which Baseline is conducted will be considered as Day 1.

b. The study will complete 24 months after the last subject is enrolled such that all subjects have data through at least 24 months. All subjects will remain enrolled until the study completion date, such that some will have data collected after Month 24. Subjects who complete Visit 5/Month 24 at least 6 months prior to study completion, will be asked to complete an additional visit at Month 30. For any individual subject, the last study visit prior to study completion will be considered as the end of study (EoS) visit.

c. Informed consent must be provided by the subject's caregiver (parent or legal guardian) for subjects aged <18 years. Subjects age ≥6 years and <18 years are required to provide signed assent. For those who are learning to read or who are illiterate, the assent form must be read to them and verbal assent obtained and documented on the assent form.

d. The medication history includes prior use of glucocorticosteroids (GC) since the initiation of GC treatment and all other medication used in one year prior to signing consent form.

e. The pulmonary function assessments will be performed in subjects age ≥6 years.

f. Should subjects become non-ambulatory during the study, the NSAA will not be collected after that time. In addition, young subjects may not be able to perform the NSAA or myometry. But once a subject is deemed capable of performing a measure, it will be performed at all subsequent visits. Please find in Section 7 for details about the age above which the assessment is required to start.

Visit Identifier	Visit 1/ Baseline[a]	Visit 2/ Month 6 (Phone contact allowed for non-ambulatory boys)	Visit 3/ Month 12	Visit 4/ Month 18 (Phone contact allowed for non-ambulatory boys)	Visit 5/ Month 24[b]	Visit 6/ Month 30/ End of Study[b] (Phone contact allowed for non-ambulatory boys)
Visit Window		**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**

g. Range of motion will be evaluated by using goniometry to record any occurrences of elbow and ankle contractures.

h. Myometry will be used to evaluate the muscle strength of the following muscle groups: knee extension, elbow flexion, elbow extension and shoulder abduction.

i. PUL 2.0 will be assessed in subjects ≥10 years.

j. The WISC scale will be performed in subjects age ≥6 years to ≤16 years old who are still ambulatory at time measurement.

k. EQ-5D-3L will be completed by subjects who are aged ≥16 years, EQ-5D-Y will be completed by subjects who are aged <16 years and able to read and complete the questionnaire.

1. INTRODUCTION AND RATIONALE

Duchenne Muscular Dystrophy (DMD), the most common type of muscular dystrophy, is an X-linked recessive genetic disorder caused by mutations in the gene for dystrophin that result in progressive loss of muscle fibers.[1] The disabling and life-threatening disease is characterized by weakness, with stereotypic functional consequences affecting mobility, progressive musculoskeletal deformities, upper limb impairment, impaired airway clearance and ventilation, cardiomyopathy, and premature death.[2] While the epidemiology data from large scale studies is limited in the Chinese population, the incidence of DMD has been estimated at 1 in 3,500 – 5,000 or 2 - 2.9 per 10,000 male births in western countries and the existing literature supports the conclusion that incidence does not vary significantly by racial, ethnic, or geographical origins.[3,4]

There are several reasons to obtain natural history from a current cohort of patients. The overall natural history of DMD has changed significantly in over the past 20-30 years. With the introduction glucocorticoid (GC) therapy systematic implementation of the standards of care, loss of ambulation is occurring several years later.[5-7] It is now recognized that the course of DMD can be influenced by the age at which GC therapy is started and by the GC regimen.[8,9] Aggressive respiratory care and the use of mechanical ventilation has caused a significant increase in life expectancy.[10,11] In addition, mutation-specific therapeutic approaches have generated the need for understanding the natural progression of the targeted genotype subgroups, especially if it differs from the overall DMD population. It is recognized, for example, that some patients with mutations skippable by exon 44 or 45 may present a phenotype intermediate between DMD and Becker Muscular Dystrophy (BMD), due to an elevated number of revertant fibres and residual dystrophin expression.[12,13]

In addition, although several recent studies provide insight into the natural history of DMD, they are primarily focused on the progression of lower extremity motor function, and particularly on ambulation.[5,18] Fewer have been published characterizing the progression of upper extremity weakness or pulmonary disease.[19,20] Although there are cross-sectional evaluations of the disease state in younger boys (eg, <6 years old), there are no published accounts of longitudinal studies in this population. There are ongoing efforts by multiple groups to identify predictors of disease progression, but very few of these have been published.[21] These gaps in our understanding of the natural history are impediments to adequately planning interventional clinical trials for the entire DMD population.

The natural history of DMD remains unclear in the current Chinese patient population as limited data is available. In China, although GC therapy has been recommended by the guideline for DMD patients, the proportion of patients who receive it remained as low as 26.29%.[14] In the same study, it was also observed that <50% and <20% of the patients received cardiac and pulmonary function monitoring, respectively. A few studies have observed that the genotypes of DMD in Chinese patients are similar to those observed in western countries.[14-16]

This natural history study will not only offer a description of the progression of the condition according to current standards of care in Chinese population, it can also meaningfully inform

the design of clinical trials in terms of endpoints and patient populations that meet the specific needs of Pfizer programs:

- The study design and proposed analyses can align with the mechanism of action of specific compounds in development and with anticipated studies included in the Clinical Development Plans;
- Multiple analyses can be performed by altering specific variables so as to explore future trial designs and to conduct the relevant power analyses;
- Analyses can be conducted on the same populations and endpoints as utilized in interventional studies with results included in regulatory documents to provide context for the findings of the interventional trial.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoints:

To characterize the natural history of Chinese DMD patients.	• Time to life-altering clinical milestones due to DMD disease progression, including:
	  • Age at Failure to walk;
	  • Age at Failure to stand;
	  • Age at Failure to self-feed.
	• Change from Baseline at each post-baseline visit in clinical evaluator (CE) determined scales:
	  • Northstar Ambulatory Assessment (NSAA) total score (ambulatory children aged ≥3 years);
	  • Performance of Upper limb 2.0 (PUL 2.0) total score (subjects aged ≥10 years).
	• Change from Baseline at each post-baseline visit in timed motor functions (Ambulatory subjects) , including:
	  • Rise from floor velocity (supine to stand);*
	  • 10 meter walk/run velocity;*
	• Change from Baseline at each post-baseline visit in strength of muscle groups (subjects aged ≥ 5 years):
	  • Knee extension;
	  • Elbow flexion;
	  • Elbow extension;
	  • Shoulder abduction.
	• Change from Baseline at each post-baseline visit in range of motion (ROM) at bilateral ankles and elbows.
	• Change from Baseline in pulmonary function tests (subjects aged ≥ 6 years) at Months 12, 24, and 30, including:
	  • Percent predicted Forced Vital Capacity (%pFVC);
	  • Percent predicted Forced Expiratory Volume in one Second (%pFEV_1);
	  • Maximum Inspiratory Pressure (MIP);
	  • Maximum Expiratory Pressure (MEP);
	  • Peak cough flow.

	• Change from Baseline in cardiac functions at Months 12, 24, and 30, including: • Left ventricular ejection fraction (LVEF). • Change from Baseline in Wechsler Intelligence Scale for Children (WISC) score at Month 24 (ambulatory subjects aged ≥6 years to ≤16 years).
Secondary Objectives:	**Secondary Endpoints:**
To characterize the prevalence of mutation types in Chinese DMD patients.	• DMD Mutation Type Endpoints: • Proportion of subjects with mutation of exon deletion, exon duplication, point mutation, small insertion, small deletion, and others. • The proportion of each affected exon by mutation types. • The proportion of subjects with any mutation affecting any exon between exon 9 and exon 13, inclusive, or a deletion that affects both exon 29 and exon 30.

To characterize the quality of life in Chinese DMD patients.	• Quality of life endpoints:
	  • Change from Baseline in Pediatric Outcomes Data Collection Instrument (PODCI) Global Functioning Scale and each subscale scores at each post-baseline visit.
	  • Response to each of the 5 dimensions of EuroQoL 5 Dimension 3 Level (EQ-5D-3L)/ EuroQoL 5 Dimension Youth (EQ-5D-Y) and change from baseline in EQ-5D-3L/EQ-5D-Y（including VAS scores and index scores）at Months 12, 24, *and* 30.

To characterize the health care utilization in Chinese DMD patients.	• Health care utilization endpoints:
	  • Change from Baseline in Healthcare Resource Utilization (HRU) survey responses (including the number of office visits, out-of-pocket expenses, visits to the emergency room, and number of nights stayed in the hospital) at Months 12, 24, and 30.
	  • Change from Baseline in Work Productivity and Activity Impairment Questionnaire adapted for Caregiving (WPAI:CG) questionnaire scores (including absenteeism, presenteeism, work productivity loss, and activity impairment) at Months 12, 24, and 30.

Note:
*The assessments rise from floor and walk/run 10 meters will be performed as part of NSAA assessment.

3. STUDY DESIGN

This is a multicenter, prospective, single cohort study designed to describe the natural history of DMD in Chinese male patients. The study is planned to be conducted in 6-8 sites in

China. A total of approximately 330 subjects will be enrolled with the target number of subjects in each group as below:

- Group 1, Ambulatory subjects aged <6 years, approximately 100 subjects;
- Group 2, Ambulatory subjects aged ≥6 years, approximately 180 subjects;
- Group 3, Non-ambulatory subjects, approximately 50 subjects.

Subjects will be enrolled in parallel for all age groups. Subjects who are too young to develop the ambulant ability will be considered ambulatory. Each subject will be observed for at least 24 months, ie, the study will be ended 24 months after the last subject is enrolled such that all subjects have data through at least 24 months. All subjects will remain enrolled until the study completion date, such that some will have data collected after Month 24. Data collected during the first visit will be considered the Baseline assessments. The subjects will subsequently be assessed at Months 6, 12, 18, and 24. Subjects, who complete Visit 5/Month 24 at least 6 months prior to study completion, will be asked to complete an additional visit at Month 30. The end of study (EoS) Visit will be the last completed visit at Month 24 or 30. For any individual subject, the last study visit prior to study completion will be considered the end of study visit. During visit at Months 24, it will be determined whether the subjects will be able to attend the visit at Month 30, based on the projected study completion date.

No investigational drug is being studied or provided to subjects in this study. Subjects will be allowed to take medications prescribed by their physicians, which will constitute the standard of care (SOC). Subjects who are ≥ 4 years of age must be receiving GC for 6 months with at least 3 months on stable dose prior to study entry. Subjects who are aged <4 years will be exempt from this requirement; those not taking GC will be eligible if the initiation of GC treatment in these subjects is considered inappropriate in the opinion of Investigators. There is no restriction regarding other therapies for DMD or for concomitant conditions.

4. SUBJECT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria

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

1. Chinese males of any age, 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. Results must confirm the presence of a mutation in the dystrophin gene which is consistent with the diagnosis of DMD.

2. Evidence of a personally signed and dated informed consent and assent (where appropriate) document indicating that the subject and parent(s) have been informed of all pertinent aspects of the study. Subjects will be required to provide assent in compliance with local regulations and Institutional Review Board (IRB) requirements.

3. For subjects ≥ 4 years old, they must be receiving GC for a minimum of 6 months including a stable regimen of GC for at least 3 months prior to signing informed consent. To be considered a stable regimen, there should be no significant change (change >0.2 mg/kg in daily dose) in dosage or dose regimen other than that related to body weight change for at least 3 months immediately prior to signing the informed consent. Subjects who are aged <4 years will be exempt from this requirement; those not taking GC will be eligible if the initiation of GC treatment in these subjects is considered inappropriate in the opinion of Investigators.

4. Subjects who are willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

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

1. 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.

2. Presence or history of other musculoskeletal or neurologic disease or somatic disorders not related to DMD including pulmonary, cardiac, and cognitive diseases.

3. Subjects ≥4 years old who have not completed the varicella vaccination.

4. Subjects who are investigator 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 Pfizer employees, including their family members, directly involved in the conduct of the study.

5. Participation in other studies involving investigational drug(s) within 90 days prior to study entry and/or during study participation.

4.3. Caregiver(s)

The parent(s) or legal guardian(s) of the subject aged <18 years will actively participate as caregiver in this study. Caregivers of adult subjects are those who take care of the subjects while not paid for their caregiving. The caregiver(s) will not only provide informed consent, but will also actively participate in the study, including attendance at study visits, wellness follow-up calls and completion of patient-reported questionnaires on behalf of the subject as well as themselves. The caregiver(s) will also communicate observed safety information to the investigator or designee as appropriate.

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

1. Aged ≥18 years of age and has demonstrated responsibility as a legal caregiver(s) through monitoring the subject and reporting any observed adverse events (AEs);

2. Willingness and ability to provide written informed consent on behalf of the subject;

3. Ability to accompany the subject to the clinic visits;

4. Ability to follow instructions.

4.4. 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 supporting study documentation.

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: 1) protocol identifiers, 2) subject study numbers, 3) contact information for the investigator site, and 4) contact details in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator 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 investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator 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 investigator site.

5. STUDY TREATMENTS

No investigational medicine will be given to subjects in this study.

Subjects who are being treated with GC are encouraged to continue the treatment during the study. The GC should be given according to the SOC, either daily or intermittently (eg, prednisolone 10 days on and then 10 days off or alternate days). Dose reduction will be allowed if the subject experiences intolerable adverse side-effects or becomes non-ambulatory during the study.

For those subjects who are GC-naïve at study entry, the timing of initiation of GC therapy should be decided individually based on functional state, age, and pre-existing risk factors for adverse side-effects. In all cases, the varicella vaccination should be completed before GC treatment is started. The completion of the varicella immunity must be documented on the corresponding case report form (CRF).

Other concomitant medicines that are prescribed for treatment of DMD, physical therapy, and rehabilitation and/or psychosocial interventions will be prescribed by the treating physician as needed.

There is no limitation to therapies for concomitant conditions such as pulmonary infection and cardiac failure. Such concomitant therapies, including the hospitalizations, surgeries, and new or changed devices will be reported on the CRF.

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, when the functional assessments and clinical laboratory assessments are scheduled to be completed at the same visit, these may be completed on two consecutive days within the visit window. Every effort will be made to have the functional assessments performed at approximately the same time of day for all visits.

The first visit will be considered the Baseline visit. During this visit, screening will be conducted first, and if a subject is enrolled, the Baseline assessments will then be performed on that same visit. The visit window for all follow-up visits is ±4 weeks. Functional assessments should be routinely collected when the subject is rested and well-fed.

Should subjects become non-ambulatory during the study, the NSAA will not continue to be collected. In addition, young subjects may not be able to perform the NSAA or myometry. But once a subject is deemed capable of performing a measure, it will be performed at all subsequent visits. Please find in Section 7 for details about the age above which the assessment is required to start. The motor and pulmonary functional assessments will not be performed if the subjects are too young to reliably perform the assessments, at the discretion of Investigators. For these subjects, the functional assessments will start to be performed when they develop the required capacity in the judgement of Investigators.

6.1. Visit 1/Baseline

During the Baseline visit, subjects will be assessed for study eligibility through review of genetic testing results, medical history, and medication history. The day on which Baseline is conducted will be considered as Day 1.

- The report of genetic testing for the diagnosis of DMD as obtained from an appropriate regulated laboratory using a clinically validated genetic test will be reviewed. Results must confirm the presence of a mutation in the dystrophin gene which is consistent with the diagnosis of DMD. The mutation type will be recorded in the CRF as exon deletion, exon duplication, point mutation, small insertion, small deletion, and others.

- A comprehensive medical history and medication history review will be performed for each subject for eligibility confirmation. This will include review of any significant past medical history and concurrent illnesses that are specified in the exclusion criteria. Complete medication history will include all prescription and

nonprescription drugs, and dietary and herbal supplements taken within 1 year prior to signing informed consent. The history of GC treatment will include dosage and dose regimens from the initiation of the treatment, if available.

- Written informed consent will be obtained from subjects who are ≥18 years old prior to initiation of any screening activities. For subjects who are younger than 18 years of age, the caregiver(s) (parent or legal guardian) must sign the informed consent. Subjects aged ≥6 years and <18 years are required to provide signed assent, while for those who are learning to read or who are illiterate, the assent form will be read to them and then verbal assent will be obtained and documented on the assent form. Assent is not required for subjects who are aged <6 years.

Once the subject is confirmed as eligible and consent/assent has been obtained, the following Baseline assessments will be performed.

This initial visit might be conducted within 2 consecutive days at some investigator sites. The motor function assessments should be conducted on a single visit day whenever possible.

- Family history.
- Age of life-altering events including failure to walk, failure to stand, and/or failure to self-feed will be collected.

  The status of "Non-ambulatory" will be recorded in this study when it meets the following definition: 1) full-time wheelchair use or being unable to complete daily activities (such as going to bathroom) by walking independently, based on reported performance at home by subject or caregiver AND 2) verification by trained CE with the inability to perform the 10-meter run/walk assessment.
- Demographic information including date of birth, ethnicity, province of residence, and urban or rural area of residence.
- Physical examination including spine deformity evaluation.
- Vital signs including supine blood pressure, pulse rate, and respiratory rate.
- Anthropometric measures: height, ulnar length, and weight.
- Motor and pulmonary functional assessments: <u>in the following order (omitting any that are not applicable based on subject's age and the status of ambulant or not)</u>:
  - FVC, FEV_1, MIP/MEP, peak cough flow;
  - NSAA;
  - ROM;
  - Muscle strength assessment by myometry;

- PUL.

- Cardiac function assessments:
  - Echocardiogram.
- 12-lead electrocardiograms (ECGs).
- Wechsler Intelligence Scale for Children.
- Subject and caregiver outcome measures:
  - PODCI;
  - EQ-5D-3L/EQ-5D-Y;
  - HRU questionnaire;
  - WPAI:CG questionnaire.
- Blood samples for hematology and chemistry.
- AE and research related injury monitoring.

6.2. Visits 2 and 4 (Months 6 and 18)

The visits should be completed within 2 consecutive days, all assessments should be conducted at approximately the same time of day. Phone contact is allowed for the subjects who are assessed as non-ambulatory at last visit or earlier. Those subjects who are ambulatory at last visit must visit the study site for assessments.

- Physical examination including spine deformity evaluation.
- Vital signs including supine blood pressure, pulse rate, and respiratory rate.
- Anthropometric measures: height, ulnar length, and weight.
- Motor and pulmonary functional assessments: in the following order (omitting any that are not required based on subject's age and the status of ambulant or not):
  - NSAA;
  - ROM;
  - Strength assessment by myometry;
  - PUL.

- PODCI.
- Blood samples for hematology and chemistry.
- Interval occurrence of life-altering events including failure to walk, failure to stand, and/or failure to self-feed.
- Concomitant treatment monitoring.
- AE and research related injury monitoring.

6.3. Visits 3, 5, and 6 (Months 12, 24, and 30)

These visits *may* be conducted within 2 consecutive days, as determined by the site. All assessments should be conducted at approximately the same time of day.

The date of EoS will have been determined before Visit 5/Month 24 for all subjects; therefore, the Investigator should make the determination at Visits 5 for each subject whether the study will be ended before the next visit.

For Visit 6/Month 30, phone contact is allowed for the subjects who are assessed as non-ambulatory at Visit 5/Month 24 or earlier. Those subjects who are ambulatory at Visit 5/Month 24 must visit the study site for assessments.

- Physical examination including spine deformity evaluation.
- Vital signs including supine blood pressure, pulse rate, and respiratory rate.
- Anthropometric measures: height, ulnar length, and weight.
- Motor and pulmonary functional assessments: in the following order (omitting any that are not required based on subject's age and the status of ambulant or not):
  - FVC, FEV_1, MIP/MEP, peak cough flow;
  - NSAA;
  - ROM;
  - Strength assessment by myometry;
  - PUL.
- Cardiac function assessments:
  - Echocardiogram.
- 12-lead ECG.

- Wechsler Intelligence Scale for Children, only at Visit 5/Month 24.
- Subject and caregiver outcome measures:
  - PODCI;
  - EQ-5D-3L/EQ-5D-Y;
  - HRU questionnaire;
  - WPAI:CG questionnaire.
- Blood samples for hematology and chemistry.
- Disease progression in life-altering events including failure to walk, failure to stand, and/or failure to self-feed.
- Concomitant treatment monitoring.
- AE and research related injury monitoring.

6.4. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see below) 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

6.4.1. Withdrawal of Consent:

Subjects who discontinue GC treatment will remain in the study and will continue to adhere to protocol-specified procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or persons previously authorized by the subject to provide this information. Subjects or his legal guardian(s) should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from study procedures and/or 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 assessed publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.5. 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. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, and request that the subject return for a final visit, if applicable. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible 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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Physical Examinations

Physical examinations will be conducted by a physician. The physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.

7.2. Vital Signs

Vital signs (supine blood pressure, pulse rate, and respiratory rate) will be measured at times specified in Schedule of Activities section of this protocol.

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.

7.3. Anthropometrics

Height and weight will be measured at times defined in the Schedule of Activities section of this protocol.

If the subject is unable to stand independently for an appropriate standing height measure, the calculated height as derived from the ulnar measure will be used. The method developed by LM Gauld 2004[22] will be used for this estimation. The subject must be seated comfortably with the right arm positioned at his side and the elbow positioned at 90 degrees of flexion.

The measured or calculated standing height will be recorded to the one-tenth of a centimeter on the worksheet.

Body weight will also be measured by weight scale which is used in clinical practice in the study site. Calibration of the weight scale must be performed before the first measurement at each site.

7.4. 12-Lead Electrocardiograms

12-lead ECGs will be performed as described in Schedule of Activities.

A 12–lead ECG should be recorded after subjects have been resting at least 5 minutes in the supine position in a quiet environment. ECG will be recorded and reviewed by the clinical site, and the clinical significance of ECG abnormalities will be assessed by the Investigator.

7.5. Clinical Laboratory

The following laboratory tests will be performed at times defined in the Schedule of Activities section of this protocol. Unscheduled clinical labs or repeating testing may be obtained at any time as deemed necessary per Investigators during the study. The blood tests for chemistry and hematology will be performed at the local laboratory at study site.

Chemistry	Hematology
Sodium Potassium Calcium Chloride Bicarbonate (Actional bicarbonate ($HCO3^-$)) Glucose (non fasting) Blood Urea Nitrogen (BUN) or Urea (If BUN is not available) Creatinine Total and direct bilirubin Alkaline Phosphatase Total protein Albumin Serum phosphorus Uric acid Cystatin C 25-OH-VD3 Aspartate transaminase (AST) Alanine transaminase (ALT) Lactate dehydrogenase (LDH) High density lipoprotein (HDL) Low density lipoprotein (LDL) Creatine kinase (CK) Cardiac Troponin I or Cardiac Troponin T (If Cardiac Troponin I is not available)	Hemoglobin Hematocrit RBC count Platelet count WBC count (and morphology as applicable) Neutrophils (Absolute or %) Eosinophils (Abs or %) Monocytes (Abs or %) Basophils (Abs or %) Lymphocytes (Abs or %)

7.6. 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, 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 NSAA will not continue to be collected. The motor and pulmonary functional assessments will not be performed if the subjects are too young to reliably perform the assessments, at the discretion of Investigators and CEs. However, for these subjects, the functional assessments will start to be performed when they develop the required capacity in the judgement of Investigators. The age above which each assessment is required to start is specified below.

All functional assessments will be conducted by a trained physiotherapist (or exercise physiologist). Throughout the study they will be referred to as CEs. Training and confirmation that the functional assessments are performed reliably 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 at each site 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 requirements for training and ongoing quality control will be described in the Functional Assessment manual.

7.6.1. Pulmonary Function Assessments

Pulmonary function testing will be completed to evaluate the maximal lung function using spirometry. The maneuvers tested include FVC, FEV_1, MIP, MEP, and peak cough flow. The best (largest) FVC and FEV_1 values will be used to calculate %pFVC and %p FEV_1 according to age, height, race, and gender[23], %pFVC was recommended as an endpoint in DMD studies by experts in the DMD field.[24] Using %pFVC and %p FEV_1 rather than absolute FVC and FEV_1 allows for continuous assessment across a broad range of ages in which growth impacts the absolute FVC and FEV_1, and will aid contextualizing the findings with other studies. The pulmonary function assessments will be performed in subjects ≥6 years old.

Calibration of the spirometer must be performed before each assessment according to the system instructions. A difference in actual versus recorded volume of 3% or less will be acceptable. If more than one assessment is conducted on the same day, it is only required to calibrate the device once each day.

The test environment must be set up prior to subject arrival and must be free of any and all distractions. The subject may take a practice test to become familiarized with the equipment. The test should be repeated at least three times making sure that the subject has recovered between attempts. The **best (largest) of 3** attempts will be documented on the CRF.

More details regarding calibration of the spirometer can be found in the Function Assessment manual.

7.6.2. Motor Functional Assessments

7.6.2.1. Northstar Ambulatory Assessment

The NSAA is a 17-item test that grades performance of various functional skills using the following scale: 0 (unable to perform), 1 (completes independently but with modifications), or 2 (complete without compensation).[25] The NSAA also includes 2 timed function tests: rise from floor and run 10 meters. The NSAA has been found to correlate with other functional outcomes in boys with DMD.[26] The NSAA will be performed in ambulatory children ≥3 years old.

7.6.2.2. Range of Motion

Range of motion will be evaluated by using goniometry to record any occurrences of elbow and ankle contractures.

7.6.2.3. Strength Assessment

Muscle strength will be quantified by means of a handheld myometry. The following muscle groups will be evaluated: knee extension, elbow flexion, elbow extension and shoulder abduction. Muscle strength will be assessed by myometry in subjects ≥ 5 years old. Those who are younger than 5 years may also be assessed if they are able to provide reliable measurements, as determined at the discretion of the Investigators.

7.6.2.4. Performance of Upper Limb 2.0

The PUL 2.0 scale has been devised to assess motor performance of the upper limb for individuals with dystrophinopathies (Becker and Duchenne muscular dystrophy).[27] The purpose of an upper limb scale for use in dystrophinopathy 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, contractures and maturational development (puberty) and the scale aims to incorporate performance of shoulder, elbow, wrist and hand function. The PUL will be administered in subjects ≥10 years old.

7.6.3. Echocardiogram

Echocardiograms should be collected at times specified in the Schedule of Activities section of this protocol. Echocardiogram should be performed using a 2-D imaging collection method. It will be performed in subjects ≥6 years old.

Echocardiogram will be read locally at each site. A qualified individual at the investigator site will evaluate the echocardiogram for left atrial 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.

7.6.4. Cognitive Function Assessment

The WISC will be used to assess the intelligence of subjects at times specified in the Schedule of Activities section of the protocol.

The WISC scale will be performed in subjects age ≥6 years to ≤16 years old who are still ambulatory at time measurement.

The WISC is individually administered intelligence test for children between ages of 6 and 16. It generates a Full Scale Intelligence Quotient (IQ) (formerly known as an intelligence quotient or IQ score) that represents a child's general intellectual ability. It also provides four primary index scores: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index. These indices represent a child's abilities in discrete cognitive domains. It usually takes 45-65 minutes to administer.

7.7. Patient Reported Outcomes (PROs)

7.7.1. EuroQoL 5 Dimension (EQ-5D-3L/EQ-5D-Y)

The EQ-5D-3L is a questionnaire completed by the subject, designed to assess the subject's current health and translate that score into an index value or utility score, providing a mechanism for conducting cost-effectiveness and cost-utility analyses.[28] There are two components to the EQ-5D-3L: a Health State Profile and a visual analog scale (VAS) item. The Health State Profile is described in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular ED-5D dimension and are calculated to form a single index value. The EQ-5D-Y is a newly developed generic instrument measuring health-related quality of life in children and adolescents younger than 16 years old. It was adapted from the EQ-5D original questionnaire (http://www.euroqol.org/about-eq-5d.html).

Both the EQ-5D-3L and EQ-5D-Y will be administered as paper questionnaires. EQ-5D-3L will be completed by subjects who *are* aged ≥16 years. EQ-5D-Y will be completed by subjects who *are* aged <16 years and able to read and complete the questionnaire.

7.7.2. Healthcare Resource Utilization Questionnaire

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

7.7.3. Work Productivity and Activity Impairment Questionnaire adapted for Caregiving

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

- Percent work time missed – a measure of absenteeism, calculated as work time missed due to health problem as a proportion of hours actually worked (Question 4).
- Percent impairment while working – a measure of presenteeism, the degree to which health problem impacted work.
- Percent overall work impairment – a measure of overall work productivity loss due to health problem, combining absenteeism plus presenteeism.

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

In this study, the WPAI:CG will measure the impact of a subject with DMD on a caregiver's work productivity and regular activities. It will be administered as paper questionnaire.

7.7.4. Pediatric Outcomes Data Collection Instrument

In order to evaluate a 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 is intended for completion by parents or caregivers of children ≤10 years old. The adolescent versions will be completed by subjects 11-18 years old and also by their parents or caregivers. 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 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 using a paper questionnaire when the subjects visit the study site.

7.8. Rater Qualifications

For specific assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Functional Assessment manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administers ratings will be verified in the site study documentation during the conduct of the study.

8. SAFETY

8.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Any AE that occurs from the time the participant consenting to the clinical research through and including 12 hours following the participant's last visit must be recorded. The investigator is required to assess whether the AE may be related to the subject's participation in the study. All AEs (ie, serious and non-serious, including those attributed to qualifying procedure identified as research-related injury) are collected in the clinical study database.

The investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a research related injury requiring immediate notification to Pfizer as described below.

8.2. Research Related Injury

Should a subject, in the investigator's opinion, suffer a medically important research-related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately.

A medically important research-related injury is any untoward medical occurrence that:

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

Medical and scientific judgment is exercised in determining whether an injury 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 outcomes listed in the definition above, the important medical event should be reported as a research-related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury 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 treatments, 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.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

No formal statistical sample size computation based on hypothesis testing and power is performed for this study. Total sample size of this study is 330, drop out is estimated to be 10%, and this sample size is acceptable for analyses of DMD natural history.

The target enrollment for each of the 3 groups and corresponding anticipated precision for estimates of key outcome measures based on literature are listed below:

- Group 1, Ambulatory subjects aged <6 years: approximately 100 subjects. There will be ≥90 subjects following anticipated drop out.
- Group 2, Ambulatory patients aged ≥6 years: approximately 180 subjects. There will be ≥162 subjects following anticipated drop out.
- Group 3, Non-ambulatory subjects: approximately 50 subjects. There will be ≥45 subjects following anticipated drop out.

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

To characterize the natural history of Chinese DMD subjects, all efficacy endpoints listed in Section 2 for this objective will be analyzed as follows:

- For continuous endpoints: descriptive statistics using sample size, mean, standard deviation, median, minimum and maximum.
- For categorical endpoints: descriptive statistics using count and percentage.
- For time-to-event endpoints: estimates of median event-free time and survival probabilities by Kaplan-Meier method.

Additional disease progression modeling will be performed to quantify the time course of changes for the selected relevant endpoints, including their correlations with each other and their relationship with the time-to-event endpoints. Detailed methodology for the disease progression modelling will be documented in a Population Modelling and Analysis Plan (PMAP), which will be dated, filed and maintained by the sponsor. Results will be reported in a Population Modelling and Analysis Report (PMAR).

9.2.2. Analysis of Secondary Endpoints

To characterize the prevalence of mutation types in Chinese DMD subjects, descriptive statistics will be reported for the proportion of subjects with mutation of exon deletions, exon duplications, point mutation, small insertion, small deletion, andothers. The propportion of each affected exon by mutation types will also be reported, along with the proportion of subjects with any mutation affecting any exon between exon 9 and exon 13, inclusive, or a deletion that affects both exon 29 and exon 30.

To characterize the quality of life in Chinese DMD patients, quality of life endpoints will be summarized by descriptive statistics..

To assess the health care utilization in Chinese DMD subjects, health care utility endpoints will be summarized by descriptive statistics.

9.3. Safety Analysis

All safety endpoints collected in this study will be reported using the Pfizer Data Standard.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study.

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 study conduct and/or after study completion, the investigator site may be subject to review by the RB/Ethics Committee (EC) and/or 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 and/or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified. 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/Data Collection Tools/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 shall ensure that the CRFs[/DCTs] are securely stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to prevent access by unauthorized third parties.

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

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the International Conference on Harmonisation (ICH) guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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 to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and paper form and will be secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system define by Pfizer subject. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject's personal data, consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials 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 and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection. The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, , including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or his legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his right to access and correct his personal data and to withdraw consent for the processing of his personal data.

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

13. PUBLICATIONS BY INVESTIGATORS

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 investigator sites, and that any subsequent publications by the PI 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. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Document	Version Date	Summary of Changes and Rationale
Amendment 1	14-Sep-2020	1. Removed Expanded Hammersmith Functional Motor Scale and related endpoints. • HFMSE is not an appropriate motor functional assessment for DMD patients. 2. Removed 4 Stair Climb (4SC) and related endpoints. • 4SC is unlikely to change significantly with approximately 1 to 2 years of observation based on results from a completed Pfizer Phase 2 DMD study. 3. Removed Six Minute Walk Test (6MWT) and related endpoints. • The 10 meter walk/run test (part of the NSAA) is a more appropriate measure of ambulatory function than the 6MWT for patients with DMD. 4. Changed the primary endpoint forced vital capacity (FVC) to percent predicted forced vital capacity (%pFVC) • %pFVC was recommended as an endpoint in DMD studies by experts in the DMD field. Using %pFVC rather than absolute FVC allows for continuous assessment across a broad range of ages in which growth impacts the absolute FVC and will aid contextualizing the findings with other studies. 5. Modified subgroup enrollment criteria to keep enrollment plan consistent with data analysis plan of ambulatory or non-

Document	Version Date	Summary of Changes and Rationale
		ambulatory and inalignment with clinical practice. 6. Removed rationale of sample size justification. 7. Updated age requirement of Performance of Upper Limb 2.0 (PUL 2.0) to be in subjects ≥10 years old. • PUL 2.0 is unlikely to change significantly in subjects younger than 10 years old based on published natural history data. 8. Removed ventricular systolic pressure as not used for clinical monitoring in DMD patients and cannot be obtained accurately via Echocardiogram. 9. Allowed to collect Urea if Blood Urea Nitrogen (BUN) is not available. 10. Clarified the age requirements on EQ-5D-Y and EQ-5D-3L. 11. Included all changes in previous Protocol Administrative Changes Letters. • Corrected the mistake of involving Month 36 visit on Quality of Life variables and related endpoints, includes Pediatric Outcomes Data Collection Instrument (PODCI), EuroQoL 5 Dimension 3 Level (EQ-5D-3L)/EuroQoL 5 Dimension Youth (EQ-5D-Y), Healthcare Resource Utilization (HRU), and Work Productivity and Activity Impairment Questionnaire adapted for Caregiving (WPAI:CG). • Updated and clarifiedthe definition and requirements of Caregiver and related text. • Updated the instruction text of Wechsler Intelligence Scale for Children (WISC) to

Document	Version Date	Summary of Changes and Rationale
		allow use *of* WISC version IV instead of version V, as there is no available version V in Chinese. • Provided correct Appendix 2 EQ-5D-Y. • Allow to collect Cardiac Troponin T if Cardiac Troponin I is not available. • Clarified the requirement in Section 6.2 to complete all assessments within 2 consecutive days and at approximately the same time of day. Section 6, 6.1, 6.3 were also updated accordingly to ensure consistency. • Revised the exclusion criteria and the related text by removing requirement of completing the recommended national immunization schedule to comply with local requirements. • Corrected and clarified that"Actional bicarbonate ($HCO3^-$)" is the component to be collected for Bicarbonate assessment. • Updated the appendix of Healthcare Resource Utilization Questionnaire to use latest version. 12. Updated Section 6.4 and Section 8.1 to incorporate latest requirement on participant discontinuation/withdrawal and safety, corresponding to Section 7.2 and Section 8.3.1 in latest methodology study protocol template. 13. Provided clarifying text where necessary. 14. Updated SOA to reflect corrections, changes and updates to assessments. 15. Updated Appendix 6. Abbreviations to reflect changes.

Document	Version Date	Summary of Changes and Rationale
		16. Original reference #23 was removed (due to removal of 6MWT) and added new references as #23 and #24 (due to the endpoint of FVC was changed to %pFVC), making original reference #24, #25, #26 and #27 now reference #25, #26, #27 and #28, and the original references #28, #29, #30 and #31 were removed (due to removal of sample size justification). 17. Corrected typographical errors.
Original protocol	15 May 2018	Not applicable (N/A)

Appendix 2. Abbreviations

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

Abbreviation	Term
%pFVC	Percent predicted forced vital capacity
%p FEV_1	Percent predicted forced expiratory volume in one second
AE	adverse event
BMD	Becker muscular dystrophy
CE	clinical evaluator
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
DMD	Duchenne muscular dystrophy
EC	ethics committee
ECG	electrocardiogram
EQ-5D-3L	EuroQoL 5 Dimensions 3 Levels
EQ-5D-Y	EuroQoL 5 Dimensions – Youth
FEV_1	forced expiratory volume in one second
EoS	end of study
FVC	forced vital capacity
GC	glucocorticoid
GCP	Good Clinical Practice
HR	heart rate
HRU	Healthcare Resource Utilization
ICH	International Conference on Harmonisation
IQ	intelligence quotient
IRB	institutional review board
LVEF	left ventricular ejection fraction
N/A	not applicable
NSAA	North-Star Ambulatory Assessment
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
MP	master physiotherapist
PI	principal investigator
PMAP	Population Modelling and Analysis Plan
PMAR	Population Modelling and Analysis report
PODCI	Pediatric Outcomes Data Collection Instrument
PRO	Patient Reported Outcome
PUL	Performance of Upper Limb
ROM	range of motion
SAP	statistical analysis plan
SOC	standard of care
TA	therapeutic area
VAS	visual analog scale

Abbreviation	Term
WISC	Wechsler Intelligence Scale for Children
WPAI:CG	Work Productivity and Activity Impairment Questionnaire adapted for Caregiving