Study Information

Title	An International, Prospective Registry Investigating the Natural History of Participants with Achondroplasia
Study Phase	N/A
Protocol number	C4181001
Protocol version identifier	3.0
Date	20 April 2020
Research question and objectives	To investigate the natural history of participants with achondroplasia in terms of: • Anthropometric characteristics; • Achondroplasia-related symptoms, tests, and treatments; • Biomarkers of bone growth.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AGV	Annual Growth Velocity
CHAQ	Childhood Healthcare Assessment Questionnaire
CNP	C-type natriuretic peptide
COM	Chronic Otitis Media
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTX	C-Terminal Telopeptide
CTX-1	C-Terminal Telopeptide -1
CXM	Collagen X Marker
DCT	Data Collection Tool
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDP	Exposure During Pregnancy
EU	European Union
FDA	Food & Drug Administration
FGFR3	Fibroblast Growth Factor Receptor 3
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Council for Harmonisation -
ID	Identification
IEC	Independent Ethics Committee

Abbreviation	Definition
IGF-1	Insulin-like Growth Factor
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NPRB	Natriuretic Peptide Receptor B Pathway
NSAE	Non-Serious Adverse Event
PI	Principle Investigator
proCNP	C-type natriuretic peptide (CNP) amino-terminal propeptide (proCNP)
P1NP	Procollagen type 1 N-terminal propeptide
QoLISSY Brief	Quality of Life in Short Stature youth
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDS	Standard Deviation Score
SEDC	Spondyloepiphyseal Dysplasia Congenital
SLE	Systemic Lupus Erythematosus
SoA	Schedule of Activities
SOC	Standard of Care

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

International Coordinating Investigator

Professor Dr. PPD

Department of Medical Genetics,

PPD

3. SUMMARY

PRODUCT NAME/NUMBER	Not applicable; no investigational treatment will be administered
PROTOCOL NUMBER	C4181001
DEVELOPMENT PHASE	N/A
PROTOCOL TITLE	An International, Prospective Registry Investigating the Natural History of Children with Achondroplasia
INDICATION	Achondroplasia
OBJECTIVES	To investigate the natural history of children with achondroplasia in terms of: • Anthropometric characteristics; • Achondroplasia-related symptoms, tests, and treatments; • Biomarkers of bone growth.
STUDY DESIGN	This is a registry study in children with achondroplasia, age 0-15 years, to be conducted at multiple clinical sites globally. Children's information will be collected in the registry at baseline and at every 3-month interval visits, for a maximum of 5 years. There will be a visit at Screening, Baseline, 3-month intervals, yearly (±3 weeks) and an end of study Visit. The end of this study is defined as the date of the last visit of the last child participating in the study.
PLANNED NUMBER OF PARTICIPANTS	The total number of participants planned to be enrolled across all sites is approximately 300.
STUDY ENTRY CRITERIA	Inclusion criteria: The following criteria must be met for study inclusion: 1. Written informed consent/assent is obtained from the participant and/or parent(s)/legal guardian(s) before any study-related activity is carried out. 2. The participant/parent(s)/legal guardian(s) is able to provide written informed assent, where this is required according to national legislation, before any study-related activity is carried out. 3. The participant has been diagnosed as having achondroplasia documented by clinical diagnosis. 4. The participant is between 0 years and 15 years of age, up to day before 15th birthday, on the date of consent/assent. 5. The investigator has considered the family and prospective participating child being able to comply with the study procedures. Evidence of a personally signed and dated informed consent/assent document indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study. Participants who are willing and able to comply with scheduled visits, laboratory tests and other study procedures.

	Exclusion criteria: The following criteria exclude participation: 1. The participant has a diagnosis of hypochondroplasia or any short stature condition other than achondroplasia (eg, spondyloepiphyseal dysplasia congenital [SEDC], pseudo achondroplasia, trisomy 21). 2. The participant has any medical condition that may impact growth or where the treatment is known to impact growth, such as but not limited to hypothyroidism or hyperthyroidism, insulin-requiring diabetes mellitus, autoimmune inflammatory disease (including celiac disease, systemic lupus erthematosus (SLE), juvenile dermatomyositis, scleroderma, and others), autonomic neuropathy, or inflammatory bowel disease. 3. Treatment in the previous 12 months prior to consent/assent with growth hormone, insulin-like growth factor 1 (IGF-1), anabolic steroids, or any other drug expected to affect growth velocity. 4. Any surgery that affects the growth plate of the long bones that is planned, or has occurred in the past 18 months. 5. Participation in any interventional study (investigational product or device) for treatment of achondroplasia or short stature. 6. Has had bone-related surgery impacting assessment of anthropometric measurements or is expected to have it during the study period. Participants with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to the date of consent/assent and healing is complete without sequelae as determined by the investigator. 7. Has any condition or circumstance that in the view of the investigator places the child at high risk of poor compliance with the visit schedule or of not completing the study. 8. Any concurrent disease or condition that in the view of the investigator would interfere with study participation.
PLANNED STUDY SITES	There will be a total of approximately 35 study sites globally.
CRITERIA FOR EVALUATION	Anthropometric measurements will be the primary assessments, including but not limited to Annual Growth Velocity (AGV). Clinical course of children with achondroplasia with focus on achondroplasia-related symptoms, tests and treatments.
STATISTICAL METHODS	A detailed master Statistical Analysis Plan (SAP) will be developed covering the analytical principles and statistical techniques to be employed both for interim and final analyses. This study plans a primary master SAP, as well as supplemental SAPs. An advantage of this study design is its ability to answer questions that emerge during the study. Subsequent and supplemental SAPs - triggered by new research questions emerging after the initial master SAP is developed or needed because the registry may evolve - can be developed when enough data become available to analyze a research question not included in the master SAP.

	The main purpose of this study is descriptive. Generally, descriptive statistics will be reported for all measured variables captured in this study. Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, number of missing values, mean and 95% confidence interval, standard deviation, median, minimum, and maximum. Continuous variables may be classed into groups and analyzed as a categorical variable when appropriate. Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the category or each possible value. Event data will generally be listed. In case of frequent events, tabulations might be considered. All analyses will be conducted on all enrolled participant. Data after procedures or treatments that may affect growth velocity will be excluded from the analysis of anthropometric parameters. Interim analyses will be performed regularly.
CCI [redacted]	[redacted]
STUDY DURATION	The overall study period is foreseen to be 5 years. The participant may continue study participation until any of the following criteria is met: • Growth plates are considered to have fused, defined as standing height gain less than 1 cm within the last 6 months; • The participant has reached end of puberty (Tanner Stage V); • The participant is enrolled in any interventional study; • The participant is diagnosed or develops any of the coniditions related to exclusion crtieria 1, 2 & 6; • The participant is to receive any growth hormone, insulin-like growth factor 1 (IGF-1), anabolic steroids, or any other drug expected to affect growth velocity; • The participant has participated in the study for 5 years; • The participant is considered lost to follow-up.

4. AMENDMENTS AND UPDATES

Document History

Document	Version Date	Substantial or Administrative Amendment	Protocol section(s) changed	Rationale
3.0	20-Apr-2020	Substantial	N/A	Change of Sponsor from Therachon to Pfizer due to acquisition. Addition of China and Japan to enrich the size of the database collected by enrolling participants in different regions. Additional biomarkers of interest were added. Demography- Month & Year of birth to be collected. To allow for analyzing growth parameters Achondroplasia in natural history against population growth charts. Revised number of participants to approximately enrich the size of the database collected. Addition of QoLISSY Brief tool (HRQoL) & Childhood Health Assessment (CHAQ) as an assessment of quality of life. Addition of optional physical activity tracking and wearability questionnaire. Addition of optional gait walking assessments.
2.0	31-Jan-2019	Substantial	N/A	Clarify that those performed at 3 monthly visits are also required at the yearly visit.

Document	Version Date	Substantial or Administrative Amendment	Protocol section(s) changed	Rationale
				Remove waist circumference (already included in anthropometric measurements). Amend footnotes. Amended trial age up to 15 years to expand range of data collected by the study. Stratification by age was added to better reflect the age range of participants that will be enrolled in interventional trials with TA-46 and the paucity of data in the youngest participants with achondroplasia who have the most severe complications. Australia added as Additional region now added to the study. Clarification of lost to follow up criteria as Minimum of 3 attempted contacts over 1 year to be considered lost to follow up. Add the specific list of measurements to be undertaken to remove the need to submit the anthropometric manual which now only serves as a manual of the specific techniques to be used in measurement. Remove metabolic system from physical examination since it is unclear what a metabolic system examination involves and information is captures

Document	Version Date	Substantial or Administrative Amendment	Protocol section(s) changed	Rationale
				elsewhere (eg, chest/waist circumference, weight). Amend fasting criteria from "are required to" to "should'. Acknowledge that some facets of sampling are not feasible in young participants and whilst all efforts should be made to adhere to sampling guidelines, this is not always possible. Addition of derived anthropometric measurements.
Original	14-Mar-2018	N/A	N/A	N/A

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

5. SCHEDULE OF ACTIVITIES

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 participant.

Procedure/Assessment	**Screening Visit[a]**	**Baseline Visit[b]**	**Every 3 Months[c] (±3 weeks)**	**End of Study Visit[d] (±3 weeks)**
Informed Consent & Assent (as applicable)	X			
Eligibility criteria	X	X		
Demographics	X			
Specific Medical & Surgical History	X	X		
Physical Examination		X	X	X
Genetic Confirmation of Achondroplasia[e]		X		
Anthropometric Measurements		X	X	X
Achondroplasia-related complications, tests & treatments		X	X	X
Non-achondroplasia-related important medical conditions and treatments[f]		X[f]	X[f]	X
Tanner Stage of Puberty[g]		X[g]	X[g]	X
Collection of Biomarker Blood Sample[h]		X	(X) Every 12 Months	
Concomitant treatments	X		X	→
Adverse event monitoring	X	X	→	→
QoLISSY Brief tool (HRQoL)		X	X	X
Childhood Health Assessment Questionnaire (CHAQ)		X	X	X
Physical activity via accelerometry (digital wearable sensors)[i] (selected sites only)	X	X	X	X
Gait walking assessment[j] (selected sites only)	X	X	X	X
Wearability Questionnaire of digital sensors[k] (selected sites only)	X	X	X	X

Abbreviations: → = ongoing/continuous event.

a. Screening may be scheduled within 1 month prior to the Baseline visit.

b. Screening visit and Baseline visit can be combined, if applicable.

c. Three-month follow-up visits are scheduled relative to the date the Baseline Visit was conducted.

d. The End of study visit is conducted if any one of the termination criteria listed are met or after a decision is made by the investigator to withdraw the participant from the study. The end of study visit may be combined with a three-monthly visit.

e. If not available in medical records, then the result of genetic testing should become available as soon as possible, but not later than prior to end of study visit.

f. Any important non-achondroplasia related important medical condition (s) that may potentially jeopardize the participant's health and any treatment based on the medical judgment of the investigator that may affect the participant's growth trajectory (see Section 11.3).

g. Tanner Stage of Puberty: Only for participants ≥7 years of age (providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty).

h. Fasting 8-hour blood sample for biomarker analyses should be drawn in the morning. A less than 8-hour prior to biomarker analysis should be recorded in the source notes.

i. Physical activity: This assessment is optional for participants and will be performed at selected sites. Wrist and lumbar digital wearable sensors will be provided to the participant and worn continuously for 14 days after each three-month visit. The sensors will be returned by the participant to the site via a self-addressed stamped envelope after the 14-day period of data collection. Only for participants ≥2 years who can walk independently. Participants with any skin nickel allergy or silicone or adhesive allergy as well as participants with any implanted medical device (ie, pacemaker or electric pumps) should excluded from participation in the physical activity assessments.

j. Walking Assessment: This assessment is optional for participants and will be performed at selected sites. The walking assessment will be performed once per participant during any given in-clinic visit.
Only for participants ≥2 years who can walk independently. Participants with any skin nickel allergy or silicone or adhesive allergy as well as participants with any implanted medical device (ie, pacemaker or electric pumps) should excluded from participation in the physical activity assessments.

k. Wearability Questionnaire: This assessment is only required for participants who are performing the optional physical activity activity. The participant/caregiver will rate the overall comfort of the wrist and lumbar devices at the conclusion of the 14 days of wearing the sensors. This will be returned to the site via self-addressed stamped envelope along with the sensors.

6. RATIONALE AND BACKGROUND

Achondroplasia is a heritable autosomal dominant disorder and is the most common form of short-limbed dwarfism in humans. Achondroplasia is caused by a single-point gain-of-function mutation in the gene encoding the fibroblast growth factor receptor 3 (FGFR3). FGFR3 is a key inhibitory regulator of endochondrial ossification and its over-activation interferes with normal chondrocyte maturation and causes shorter long bones and changes in flat bones such as the occipital bone and vertebrae.

In addition to the compromised average height in adult men and woman with achondroplasia (ie, 131±5.6 cm and 124±5.9 cm, respectively),[1,2] the most severe, potentially debilitating and life-threatening complications are associated with respiratory difficulties with prolonged periods of intermittent hypoxia due to obstructive sleep apnoea and neurological impairments resulting in episodes of central sleep apnoea and other severe cervico-medullary compression syndromes.[3,4] These achondroplasia manifestations occur with a relatively high frequency and severity in the youngest group of participants.[5] Respiratory difficulties and neurological compression syndromes correlate to dysplasia of the basioccipital, exoccipital bone, and craniovertebral junction which lead to contraction of the skull base and facial underdevelopment.[6]

In addition, a narrow trunk, shortened extremities, particularly proximally, shortened fingers, restricted elbow range of motion, limited hip extension, genu varum, and lumbar hyperlordosis and thoracolumbar kyphosis contribute to delay in developmental milestones and longer-term complications such as osteoarticular problems, chronic pain and stiffness and spinal stenosis.

There are relatively few data available on the actual types, rates and timing of achondroplasia-related symptoms and complications in the youngest subset of participants. Evidence of the natural history of the disease course in relation to symptoms and development of complications, the level of actual disease burden over time due to tests and treatments, as well as data to support identification of possible risk factors, is lacking.

The design of future interventional trials with potentially disease-modifying therapies to treat the underlying morphological disproportions of the skull and skeletal system will benefit from a better understanding of the natural history of the disease course in the youngest group of participants, where final skeletal and morphological proportions are being established prior to entering the final longitudinal growth phase during later stages of childhood and adolescents.

The rationale for the prospective, longitudinal registry design to collect information about important achondroplasia-related symptoms, tests and treatments is the aim to characterize the natural history of the disease course in the youngest participants in relation to symptoms and development of complications, the level of actual disease burden over time due to tests and treatments, as well as data to support identification of possible risk factors.

Despite its importance as a key parameter, growth velocity is difficult to determine in real time in achondroplasia, because skeletal growth is slow and clinical tools to accurately detect very small increments of growth do not exist. During development, bone is created by a process called endochondral ossification, which results in the production of a fragment of type X collagen. Endochondral ossification also occurs during long bone growth and fracture healing.

Recently, Coghlan et al. discovered that the type X collagen fragment could be isolated from blood and its concentration correlated with skeletal growth velocity (Coghlan 2017).[8]

Fragment concentration was inversely correlated with age and fluctuated during fracture healing in adults. The authors developed an assay to quantify the fragment that could be useful as a real-time marker of skeletal growth in participants and for monitoring response to treatment for growth and bone disorders. Recently, the same authors established that type X collagen fragment corresponds to the rate of linear bone growth at time of measurement. Serum concentrations of Collagen X Marker (CXM) plotted against age show a pattern similar to well-established height growth velocity curves and correlate with height growth velocity calculated from incremental height measurements in this study. Hence, CXM testing may be useful for monitoring growth in the pediatric population, especially responses of infants and participants with genetic and acquired growth disorders to interventions that target the underlying growth disturbances, such as currently planned studies in participants with achondroplasia.

In this clinical study, CXM testing as well as measurement of C-type natriuretic peptide (CNP) and its amino-terminal propeptide (proCNP) will be done. The rationale for also assessing CNP/proCNP, P1NP and CTX is to establish whether treatment with a ligand trap may lead to normalization of CNP levels due to restoration of the physiological signalling pathway or changes in associated biomarkers of growth plate metabolism.

The Tanner Stage of puberty will not be required in participants under 7 years of age, providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty.

The rationale for the termination criteria is the consideration that once growth plates have fused, the participant will not be considered eligible for participation in future clinical trials.

The potential risks of study participation include risks of medical evaluation, anthropometric measurements and venepuncture. The risks associated with participation in this study are considered minimal, since the nature of the anthropometric assessments and medical observations tracked and documented are all considered to be established as part of current standard of care (SOC). The extent of repeated anthropometric measurements as well as repeated venepuncture may not be considered SOC at all sites; however, the frequency is considered acceptable to be associated with a minimal risk. There is no direct benefit to the participant, their parent(s) or the health care providers other than being able to track the participating participant's development compared to their peers, something that will be

increasingly important with disease-modifying therapies being developed targeting the consequences of the mutation of the FGFR3 on the human body.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective(s):	**Primary Endpoint(s):**
• Collection of longitudinal anthropometric and disease-related complication data in children with achondroplasia.	Standing height, sitting height, knee height, head circumference, arm span, length of the legs (calculated as the difference between standing and sitting height)and achondroplasia related AEs.
Secondary Objective(s):	**Secondary Endpoint(s):**
• Investigation of potential serum biomarkers in children with achondroplasia.	• Baseline and post-baseline measurements of serum collagen X marker.
CCI [redacted]	[redacted]
[redacted]	[redacted]

7.1. Achondroplasia Complications, Tests & Treatments

Achondroplasia related complications, tests and treatments will be collected in a prospective and standardized fashion to allow characterization of the natural history of the disease course in the youngest participants in relation to symptoms and development of complications, the level of actual disease burden over time due to tests and treatments, as well as data to support identification of possible risk factors.

7.2. Anthropometric Parameters

Anthropometric data will be collected in a prospective and standardized fashion to allow correlation to disease severity and serve as baseline data for future interventional clinical trials. Standing height is most commonly used measure of growth in participants. As one of the morphological characteristics of participant with achondroplasia is the shorter limbs, any biomarker used for the study of these participants should be able to reflect this impaired growth.

The arm span and the length of the legs (calculated as the difference between standing and sitting height) will be used as robust measures of the growth of the limbs. All other measurements collected are considered CCI in nature and may be used to support further endpoints in later development trials.

7.3. Biomarkers

Blood samples will be collected to investigate potential biomarkers of bone growth that can be used to improve efficacy assessment and dose finding in future therapeutic trials for RECIFERCEPT. To minimize the burden of the blood sampling, it is estimated that it will be limited to once yearly in this study.

7.3.1. Collagen X

Collagen X Marker (CXM), is a degradation by-product of endochondral ossification that is released into the circulation in proportion to overall growth plate activity. This marker corresponds to the rate of linear bone growth at time of measurement as recently demonstrated in children of normal average growth. Serum concentrations of CXM plotted against age showed a pattern similar to well-established height growth velocity curves and correlated with height growth velocity calculated from incremental height measurements in this study (Coghlan 2017, Olney 2012).[8,9] This study will be the first time the CXM will be studied in the achondroplasia population. The study will provide important new data to understand the circulating levels of a chondrocytic differentiation marker in children with achondroplasia.

7.3.2. CNP/proCNP

C-type natriuretic peptide (CNP) and its amino-terminal propeptide (proCNP) are known biomarkers for chondrocyte activity related to growth (Olney 2012)[9] and have been shown to be expressed in elevated levels in children with achondroplasia suggesting a desensitization to CNP/proCNP in this population (Olney 2015).[10] Only very limited longitudinal CNP/proCNP data are available in children with achondroplasia. This study will generate data to confirm and support the earlier finding. Our interest to understand the mechanism of achondroplasia requires that we establish additional data on the levels of CNP/proCNP in achondroplasia children of different ages. This data will provide further insight into the pathophysiology of the condition and help to understand whether the CNP/natriuretic peptide receptor B(NPRB) pathway contributes to the regulation of linear bone growth in achondroplasia children.

7.3.3. Additional Bloods Biomarkers

Additional biomarkers such as P1NP and CTX will be analysed. These analyses will be limited to biomarkers known to be related to bone growth, potential markers for treatment response or to the pathology of Achondroplasia.

CTX-1 is a crosslink peptide sequence of type I collagen, found, among other tissues, in bone. This specific peptide sequence relates to bone turnover because it is the portion that is cleaved by osteoclasts during bone resorption, and its serum levels are therefore proportional to osteoclastic activity.

P1NP is derived from type I procollagen cleavage during collagen synthesis and is a widely used bone formation marker representing osteoblast activity. Both markers are included in the ongoing Pfizer Achondroplasia Natural History studies and are strong candidate biomarkers to measure the efficacy of recifercept treatment in particular on bone growth.

7.4. Physical Activity Assessments

Physical activity assessments will be collected using wrist and lumbar sensors and will provide data to support assessment of daily activity and gait characteristics in children with achondroplasia. This may support future trial endpoints around daily functioning.

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, registry study, to be conducted at multiple clinical centers globally, in which participants with achondroplasia will be followed over a five-year period with respect to achondroplasia symptoms, tests & treatments, anthropometric parameters and biomarkers of bone growth collagen X, CNP/proCNP, CTX and P1NP. No study drug will be administered, and no other type of therapy will be provided.

There will be a Screening visit, a Baseline visit, 3-month interval visits (±3 weeks) including an annual visit every 12 months and an end of study visit. The end of study visit will be scheduled (or a given visit will be considered the end of study visit) as soon as any of the following criteria is met:

- Growth plates are considered to have fused, defined as standing height gain less than 1 cm within the last 6 months;
- The participant has reached end of puberty (Tanner Stage V);
- The participant is enrolled in any interventional study;
- The participant is diagnosed or develops any of the coniditions related to exclusion crtieria 1, 2 & 6;
- The participant is to receive any growth hormone, insulin-like growth factor 1 (IGF-1), anabolic steroids, or any other drug expected to affect growth velocity;
- The participant has participated in the study for 5 years;

- The participant is considered lost to follow-up.

The end of this study is defined as the date of the last visit of the last child participating in the study.

The study will enroll participants in the following approximate proportions:

- 40% 0-5y;
- 40% 5-10y;
- 20% 10-15y.

Any treatment received during the study in relation to important medical events and any treatment based on the medical judgment of the investigator that may affect the participant's growth trajectory must be recorded in the eCRF:

- Description of the treatment (for medical treatment: route of administration, frequency and dose);
- Indication;
- Start and stop date.

Treatment is defined as any medical, surgical or other intervention to treat the underlying condition.

The rationale for the study design is summarised as follows:

A prospective longitudinal design is selected to collect blood samples and anthropometric data simultaneously in a standardized fashion, and thereby allowing for estimation of between and within participant variability laboratory parameters as well as testing for possible correlations between laboratory parameters and growth.

A five-year data collection period is chosen to allow detection of substantial growth as measured by the anthropometric endpoints, in order to enhance the strength of a possible correlation.

Fasting prior to blood sampling is required to avoid variability due to impact of the digestive process on circulating levels of metabolic proteins related to bone growth. The fluctuation in bone metabolism markers after eating has been documented in other studies.

The age range 0 - 15 years is chosen to provide a broad knowledge of the serum-levels of collagen X during different stages of growth in childhood.

Information on Tanner Stage of Puberty will be collected in participants at 7 years of age and above to capture signs of initiation of puberty, which may affect growth.

Laboratory assays will be applied for the analysis of collagen X & other associated biomarkers based on venous blood draws.

Health related quality of life measures will be collected to provide information about the quality of life of children, families and caregivers of children with achondroplasia.

Physical activity monitoring will be collected in participants at 2 years of age and above to capture activities of daily living 'in the real world' by using digital accelerometery sensors.

8.1.1. Inclusion Criteria

Participants must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Written informed consent/assent is obtained from the participant and/or parent(s)/legal guardian(s) before any study-related activity is carried out.

2. The participant/parent(s)/legal guardian(s) is able to provide written informed assent, where this is required according to national legislation, before any study-related activity is carried out.

3. The participant has been diagnosed as having achondroplasia documented by clinical diagnosis.

4. The participant is between 0 years and 15 years of age, up to day before 15th birthday, on the date of consent/assent.

5. The investigator has considered the family and prospective participating participant being able to comply with the study procedures.

Evidence of a personally signed and dated informed consent/assent document indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

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

8.1.2. Exclusion Criteria

Participants meeting any of the following criteria will not be included in the study:

1. The participant has a diagnosis of hypochondroplasia or any short stature condition other than achondroplasia (eg, spondyloepiphyseal dysplasia congenital [SEDC], pseudo-achondroplasia, trisomy 21).

2. The participant has any medical condition that may impact growth or where the treatment is known to impact growth, such as but not limited to hypothyroidism or hyperthyroidism, insulin-requiring diabetes mellitus, autoimmune inflammatory disease (including celiac disease, lupus [SLE], juvenile dermatomyositis, scleroderma, and others), autonomic neuropathy or inflammatory bowel disease.

3. Treatment in the previous 12 months prior to consent/assent with growth hormone, insulin-like growth factor 1 (IGF-1), anabolic steroids, or any other drug expected to affect growth velocity.

4. Any surgery that affects the growth plate of the long bones that is planned, or has occurred in the past 18 months.

5. Participation in any interventional study (investigational product or device) for treatment of achondroplasia or short stature.

6. Has had bone-related surgery impacting assessment of anthropometric measurements or is expected to have it during the study period. Participants with previous limb-lengthening surgery may enroll if surgery occurred at least 18 months prior to the date of consent/assent and healing is complete without sequelae as determined by the investigator.

7. Has any condition or circumstance that in the view of the investigator places the child at high risk of poor compliance with the visit schedule or of not completing the study.

8. Any concurrent disease or condition that, in the view of the investigator, would interfere with study participation.

8.1.3. Variables

Variable	Role	Data source(s)	Operational definition
Anthropometric Measurements	Analysis of growth parameters	Anthropometric measurements	Collection every 3 months & End of Study
Tanner Staging	Assess stage of sexual development	Physical Examination	Collection every 3 months & End of Study
Achondroplasia related complications, tests & treatments	Characterize treatments for Achondroplasia	Medical Records	Collection every 3 months & End of Study
Non-Achondroplasia	Characterize medical	Medical records	Collection every 3 months

Variable	Role	Data source(s)	Operational definition
co-morbidities and treatments	history		& End of Study
Biomarker Blood Sample	Analysis for potential biomarkers of bone growth	Blood sample	Blood sample every 12 months & End of Study
Activity Tracker & Gait Measurement	Analysis of daily activity & gait when walking	Activity Tracker & Gait Mat	Collection every 3 months & End of Study
Quality of Life	Assess Quality of Life in Participant & families with Achondroplasia	Questionnaire	Collection every 3 months & End of Study

8.1.3.1. Data Sources

Source documents provide evidence for the existence of the participating child and substantiate the integrity of the data collected. Source documents are filed at the investigator's study site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents and the discrepancies must be explained. The investigator may need to request medical records from other healthcare professionals, if appropriate. Also, current medical records must be available. The use of electronic source data is described in FDA, EU Chinese and Japanese Guidance for Industry – Electronic Source Data in Clinical Investigations (2013).

All study data must be verifiable by source documents. Additionally, the following data entered into the eCRF, should be verifiable by source documents in the participant's medical record, or other records, at the study site, as applicable:

- Details of study participation (study ID and unique identifier);
- Date(s) of informed consent of parent(s)/legal guardian(s);
- Date of informed assent of participant;
- Date of each study visit including signature and/or initials of person(s) conducting the study visit;
- The participant's date of birth, or – as per local regulations – the month and year of birth relative to the date of the signing of consent/assent;
- Confirmation by genetic testing, documenting the diagnosis of achondroplasia;
- Results of anthropometric measurements.

Information recorded in the eCRF system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, and memoranda.

Clinical laboratory data for the biomarkers required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee.

Confirmation of genetic testing should be available as source documents from the local laboratory when the testing is performed. Results should be available and recorded in the eCRF prior to the end of study visit.

9. STUDY PROCEDURES

As applicable, all visits and their timings must occur within the predefined windows outlined in this protocol in the Schedule of Activities (Section 5).

After signature of the informed consent/assent, all screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.1. Demographics

At the Screening Visit, the following information will be obtained and reported in the eCRF:

- Date of birth, or – the age at the date of consenting (years and months of age MUST be provided);
- Gender;
- Race (American Indian or Alaska native, Asian, black or African American, native Hawaiian or other pacific islander, White, Other);
- Height of (biological) parent(s);
- (Biological) Parent(s) have/do not have achondroplasia.

Since one of the primary objectives of this study is to document the natural history of growth in achondroplasia, it is essential that the age of participants is accurately recorded. Thus, it is necessary to collect at least the Month & Year of birth of the study participant.

9.2. Medical and Surgical History

At the Screening and Baseline visit, information on any relevant prior or current condition/procedure will be obtained and reported in the eCRF system.

9.3. Physical Examination

At the Baseline Visit and at 3-month interval visits thereafter, a physical examination of the participant will be done, which will include general appearance and examination of the following body systems: Respiratory system, neurological system, musculoskeletal system, cardiovascular system, other.

Only findings not recorded elsewhere in the eCRF system should be recorded in the Physical Examination eCRF system.

9.4. Assessment of Obesity

Waist circumference will be measured at the Baseline Visit, yearly and at the End of study visit as described in the Anthropometric Measurement Manual.

9.5. Tanner Stage of Puberty

For participants 7 years and older, at the Baseline Visit and at the 3-monthly interval visits thereafter, the Tanner Stage of puberty will be recorded in the eCRF system as stage I-V for both external genitalia, testes and pubic hair (males) and for breast development and pubic hair (females). Participants under 7 years of age do not require this assessment, providing the investigator confirms there is no suspicion of a diagnosis of precocious puberty.

9.6. Achondroplasia-related Interventions

Investigators should record relevant surgeries, procedures and interventions related to achondroplasia at baseline and on an ongoing basis during the study.

9.6.1. Follow-up of Achondroplasia-related Complications

After the initial report on an important medical symptom, test or treatment, the investigator should follow-up on the severity status of the medical symptoms, determine whether the symptom is ongoing or is resolved and assess the outcome of a potential treatment via contacts with relevant treating personnel and/or via communication with the participant and the participant's parent(s)/legal guardian(s) at subsequent study visits, as applicable. The investigator should continue follow-up on the symptoms until the participant's participation in the study has ended.

9.7. Non-achondroplasia-related Conditions of Medical Significance

Information concerning the diagnosis of any non-achondroplasia related conditions of medical significance, including start and stop dates, should be reported. Details will be collected at baseline and on an ongoing basis during the study. Information may be provided by parent(s)/legal guardian(s) or by the participant if this is applicable.

9.8. Achondroplasia-related Complications

Details will be collected on achondroplasia-related complications. In particular, the following complications and details will be collected at baseline and on an ongoing basis during the study.

9.8.1. Sleep Disordered Breathing

- Has the participant ever been diagnosed with sleep-disordered breathing?
- Results of sleep tests/polysomnography including:
  - Date of test.
  - Conclusion/diagnosis of test.
  - Apnoea-hypopnoea index.
  - Was the test conducted on/off oxygen?
  - Was the test conducted on CPAP?
  - Is the test post-adenotonsillectomy (date of surgery if performed)?

9.8.2. Otitis Media

- Has the participant ever been diagnosed with chronic otitis media (COM)?
- Were tympanostomy tubes (grommets) ever inserted (dates of insertions).
- Has the participant had hearing loss as a result of COM (including date start/end and severity)?
- Does the participant require hearing aids as a result of COM-induced hearing loss?

9.8.3. Orthopaedic Complications

- Imaging of the bones or knees.
- Tibial bowing including the dates of any surgery for.
  - Osteotomy.
  - 8-plates.
- Kyphoscoliosis including the presence of wedging on imaging and need for surgery.
- Lumbar lordosis.
  - Diagnosis of lordosis.
  - Presence of neurological signs in legs.
  - Impaired walking.

- Any surgical intervention.

9.8.4. Neurological

- Is there a history of upper cervical compression including?
  - Neurological examination findings.
  - MRI results.
  - Need for decompression surgery (including dates and nature of procedures).
    - Whether there are any persistent findings on neurological examination post-surgery.
- Hydrocephalus and need for shunting.
- Presence of any neurodevelopmental delay.

With respect to other complications not listed above, the investigator should record the relevant complication and make an assessment of the intensity according to the following categories:

- *Mild*: A symptom that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- *Moderate*: A symptom that causes sufficient discomfort for the participant and interferes with normal everyday activities.
- *Severe*: A symptom that prevents normal everyday activities for the participant.

9.9. Anthropometric Measurements

Anthropometric measurements will be done at all 3 monthly visits and measurement results will be reported in the eCRF. Anthropometric measurements will be performed according to a study-specific Anthropometric Measurement Manual, which will be provided to the investigational sites. This manual will contain a detailed description on the following:

1. Which measurements to undertake.
2. The tools/instruments to be used, as well as their calibration.
3. Standard procedure for undertaking these measurements.

The measurements to be taken on a 3-monthly basis are:

- Standing height (or length for participants <2y);

- Sitting height (or crown: rump length for participants <2y);
- Knee height;
- Head circumference;
- Arm span;
- Body weight;
- Elbow extension angle;
- Knee extension angle;
- Cranial dimensions (occipito-frontal, occipito-nasal lengths);
- Waist and chest circumference (annually).

For each participating participant, measurements will have to be performed by the same site personnel, trained according to the contents of the study-specific Anthropometric Measurement Manual.

Information concerning any achondroplasia-related complications, tests and treatments, eg, respiratory difficulties, neurological signs and symptoms, hospitalization, and treatment (surgical, medical, pharmaceutical), should be reported at every visit. Information may be provided by parent(s)/legal guardian(s) (eg, through a parent-specific notebook) or by the participant if this is applicable.

For the anthropometric parameters, only trained site staff will be allowed to perform the anthropometric measurements on participants in this study. The measurer must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, training and standardization exercises may be conducted, and written and signed documentation will be provided by the qualification vendor for each rater's certification. Recertification is required as needed during the study. The site staff who administer specific study assessments will be documented in the site study documentation during the conduct of the study.

9.10. Study Treatments

No study treatment will be administered.

9.11. Concomitant Treatments

During the study participation, the participant will continue receiving his/her usual treatment(s).

Any concomitant medical treatment received that, based on the investigator's judgment, may affect the child's growth trajectory will be recorded in the case report form.

9.12. Prohibited Treatments

Participation in any interventional drug trial is strictly prohibited in this trial. Other treatments such as growth hormone are strictly prohibited whilst participating in the study. If the investigator wishes to treat a participant with any growth hormone, insulin-like growth factor 1 (IGF-1), anabolic steroids, or any other drug expected to affect growth velocity the participant must be withdrawn from the study and complete the final study visit.

9.13. Health-related Quality of Life (HRQoL) Measures

9.13.1. Childhood Health Assessment Questionnaire (CHAQ)

The Childhood Health Assessment Questionnaire (CHAQ) is a 37-item measure of health status and physical function. Subjects aged 1-19 years of age will have the CHAQ completed at designated study visits. The parent-report version will be completed for children aged 1-7 years old. The self-report version will be completed for children aged 8-19 years old. Children will start on the age appropriate version and continue with that version throughout the study. For younger ages, the caregiver completes and continues to complete throughout the study; the children can also complete the self-report version when they are old enough.

Subjects or their caregivers will be asked to provide responses to questions designed to assess function in 8 areas/domains in addition to: 2 visual analogue scales (pain and well-being), the use of aids and devices, and the requirement for help with the functional areas. The 8 functional domains are: Dressing and Grooming (4 items); Arising (2 items); Eating (3 items); Walking (2 items); Hygiene (4 items); Reach (4 items); Grip (5 items); and Activities (5 items). The CHAQ has a recall period of 'over the past week.' A 5-point Likert Scale is utilized ranging from 'without any difficulty' to 'unable to do' and a 'not applicable option.' Lower scores indicate better functioning/health-related quality of life.

This will be administered every 3 months.

9.13.2. Quality of Life in Short Stature Youth (QoLISSY) Brief

Subjects aged 4-18 years of age will complete the Quality of Life Short Stature Youth Brief (QoLISSY Brief) tool. QoLISSY Brief measures health-related quality of life (HRQoL) in children 4-18 years old from the patient and parent perspectives. The parent-report version will be completed for children aged 4-7 years old. The self-report version will be completed for children aged 8-18 years old. Children will start on the age appropriate version and continue with that version throughout the study. For younger ages, the caregiver completes but the children can also complete when they are old enough. There are 9-items that were selected from the full QoLISSY physical, social and emotional HRQoL dimensions. The

QoLISSY Brief questions ask the patient or caregiver about their status currently. Intended for children or caregivers of children, the instrument uses a 5-point Likert Scale ranging from 'not at all/never' to 'extremely/always.'

This will be administered every 3 months.

9.14. Sample Collection

Samples will be collected at the time points specified in the Schedule of Activities (see Section 5). A maximum of 10 mL from each participant will be drawn once yearly for biomarker assays. Fasting blood samples for biomarker analyses should be drawn in the morning. If the participant has been fasted for less than 8 hours, this will be recorded on the sampling documentation. The samples will be sent to a central laboratory contracted for this study purpose. These samples will be stored no longer than 1 year after the final clinical study report (CSR) has been written.

Additionally, if genetic confirmation of the achondroplasia diagnosis is not available in the medical records, then the result of genetic testing should become available as soon as possible, but prior to the end of study visit. The assessment can be done at a local laboratory. The confirmation of the genetic testing should be reported in the eCRF.

Residuals from the biomarker samples will be kept at the central laboratory for no longer than 1 year after the final Clinical Study Report has been written. They will be used to investigate potential biomarkers of bone growth that can be used to assess efficacy in future therapeutic trials and to improve precision in any dose-finding elements of these trials.

9.15. Physical Activity (Accelerometery)

In selected sites, participants >2 years and who are able to walk independently will be asked to participate in an optional assessment of monitoring of their daily physical activity. The continuous monitoring of physical activity via accelerometry will be done by wearable digital wristwatch & lumbar sensors. The digital sensors will be worn continuously for approximately 14 days as specified in the SoA.

One sensor will be placed on the lumbar region and one sensor will be placed on the non-dominant wrist. Participants will be asked to wear the sensor on the wrist continuously (including at night to monitor sleep metrics), and the lumbar sensor during waking hours only. Participants will be asked to return the sensors back to the site via self-addressed stamped envelope after the 14 days of data collection. A technical training manual will be provided separately to site, it will include the Edinburgh Handedness Inventory – Short Form to determine the non-dominant wrist as reference, if required.

9.16. Wearability Questionnaire

In sites participating in the physical activity monitoring optional assessment, a wearability questionnaire will be provided to the participant or their caregiver to complete at the end of each 14-day wearing period. Participants or their caregivers will be asked to rate the overall comfort of wrist & lumbar devices using a scale. Site staff will be required to transcribe the information from the questionnaire into the eCRF system.

9.17. Gait Walking Assessment

In selected sites, participants >2 years and who are able to walk independently will be asked to participate in an optional assessment of monitoring of their gait while walking on a specialized GAITRite walking mat of at least 8 meters (16 feet). The assessment will be performed whilst wearing the digital sensors (wrist and lumbar) at least once and a maximum of three times.

GAITRite technical training guide will be provided separately to the site.

10. ASSESSMENTS

10.1. Additional Research

Not Applicable.

10.2. Assessment of Suicidal Ideation and Behaviour *(If Applicable)*

Not Applicable.

10.3. Biological Samples

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

10.4. Imaging Assessments

Not Applicable.

10.5. Management of Incidental Findings

Not Applicable.

10.6. Rater Qualifications

Not Applicable.

11. DATA ANALYSIS/STATISTICAL METHODS

11.1. Study Size

The sample size was not formally calculated. CCI [redacted]

All analyses will be conducted on all enrolled participants.

11.2. Data Management

The standard procedures for handling and processing records will be followed per GCP in addition to Sponsor & Premier Research's standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated CRF, eCRF completion guidelines, pre-entry review list, self-evident correction conventions, query contacts, coding requirements, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review and must provide his or her electronic signature to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the Clinical Monitoring Plan for CRAs monitoring the conduct of the study and the eCRF data.

11.3. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF[/DCT] 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[/DCT] is required and should be completed for each included participant. The completed original CRFs[/DCTs] 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 form and will be password protected 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[/DCTs] 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. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents and the discrepancies must be explained. The investigator may need to request medical records from other healthcare professionals, if appropriate. Also, current medical records must be available. The use of electronic source data is described in FDA, EU Chinese and Japanese Guidance for Industry – Electronic Source Data in Clinical Investigations (2013).

All study data must be verifiable by source documents. Additionally, the following data entered into the eCRF, should be verifiable by source documents in the participant's medical record, or other records, at the study site, as applicable:

- Details of study participation (study ID and unique identifier);
- Date(s) of informed consent of parent(s)/legal guardian(s);
- Date of informed assent of participant;
- Date of each study visit including signature and/or initials of person(s) conducting the study visit;
- The participant's date of birth, or – as per local regulations – the month and year of birth relative to the date of the signing of consent/assent;
- Confirmation by genetic testing, documenting the diagnosis of achondroplasia;
- Results of anthropometric measurements.

Information recorded in the eCRF system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, and memoranda.

Clinical laboratory data for the biomarkers required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee.

Confirmation of genetic testing should be available as source documents from the local laboratory when the testing is performed. Results should be available and recorded in the eCRF prior to the end of study visit.

The CRFs[/DCTs] must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs[/DCTs] are true. Any corrections to entries made in the CRFs[/DCTs] or source documents must be dated, initialled 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[/DCTs] must match those charts. Source documents provide evidence for the existence of the participating child and substantiate the integrity of the data collected. Source documents are filed at the investigator's study site.

In some cases, the CRF[/DCT] 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[/DCT], and for which the CRF[/DCT] will stand as the source document.

11.4. 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 participants (sufficient information to link records, eg, CRFs[/DCTs] and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs[/DCTs], 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 Council for 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 25 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.

11.5. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

As the main purpose of this study is to collect data to be used as reference for future interventional clinical studies, no hypothesis testing will be made.

A detailed master statistical analysis plan (SAP) will be developed covering the analytical principles and statistical techniques to be employed both for interim and final analysis. This study plans a primary master SAP, as well as supplemental SAPs. An advantage of this study design is its ability to answer questions that emerge during the study.

Subsequent and supplemental SAPs - triggered by new research questions emerging after the initial master SAP is developed or needed because the registry may evolve - can be developed when enough data become available to analyze a particular research question not included in the master SAP.

The main purpose of this study is descriptive.

Generally, descriptive statistics will be reported for all measured variables captured in this study. Derived Anthropometric measurements include:

- Annual Growth Velocity (AGV);
- Height Standard Deviation Score (SDS) with reference to normal population;
- Height SDS with reference to achondroplasia population;
- Sitting height/standing height (%) (or length: crown-rump length);
- Difference or ratio of Arm span/standing height/length (%);
- Knee height: lower segment length (lower segment=standing height – sitting height);
- Ratios between the cranial measurements taken.

Continuous (quantitative) variable summaries will include the number of participants (n) with non-missing values, number of missing values, mean and 95% confidence interval, standard deviation, median, minimum, and maximum.

Continuous variables may be classed into groups and analyzed as a categorical variable when appropriate. Categorical (qualitative) variable summaries will include the frequency and percentage of participants who are in the particular category or each possible value.

Event data will generally be listed. In case of frequent events tabulations might be considered.

Interim analyses will be performed on a regular basis.

Data following procedures or treatments that may affect growth velocity will be excluded from the analysis of anthropometric parameters.

Subgroup analysis should be made by gender, age groups, and the combination of gender and age group.

Biomarker CCI [redacted] will be described in a separate SAP and presented separately from the main CSR.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) and/or Good Pharmacoepidemiology Practices (GPP), as relevant, are being followed. The monitors may review source documents to confirm that the data recorded on CRFs [/data collection tools (DCTs)] 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 participant to review by the IRB/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 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 between the study data and the participant's medical records. 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.

For studies conducted at non-Pfizer investigator sites, 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.

13. LIMITATIONS OF THE RESEARCH METHODS

The study design is limited by pragmatic considerations around available participants, minimizing burden on young participants and the[redacted] nature of many of the growth biomarkers.

14. PROTECTION OF HUMAN PARTICIPANTS

14.1. Participant 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 participant personal data. Such measures will include omitting participant names or other directly identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or 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, participant names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. The investigator site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participant's personal data consistent with the clinical study agreement (CSA) and applicable privacy laws.

The informed consent[/assent] documents and any participant 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 participant 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 participant[,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 participant's personal data. The investigator further must ensure that each study participant [,or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a participant's [legally acceptable representative/parent(s) or legal guardian], the participant's assent (affirmative agreement) must subsequently be obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant'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 participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own consent, the source documents must record why the participant did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the participant's legally acceptable representative, the consent signer's relationship to the study participant (eg, parent, spouse), and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor participants who reach the age of majority during the study, as recognized under local law, they must reconsent 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 participant [or the participant's legally acceptable representative, parent(s), or legal guardian and the participant'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 participant's signed consent/assent document.

14.1.1. Screen Failures

A participant who fail inclusion and/or exclusion criteria may be rescreened for the study. The re-screening can occur at a time interval considered appropriate by the investigator. If a participant is eligible to enter the study after having previously failed screening, they will be assigned a new identification number. However, participants who are withdrawn from the study will not be replaced.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

14.2. Participant Withdrawal

Participants 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, behavioural, or administrative reasons. In any circumstance, every effort should be made to document participant outcome, if applicable. The investigator should inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved adverse events.

If the participant 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.

14.2.1. Lost to Follow-up

The study site personnel must attempt to contact the participant's parent(s)/legal guardian(s) and counsel the parent(s)/legal guardian(s) on the assigned visit schedule and ascertain whether or not the participant and the parent(s)/legal guardian(s) wish study participation to continue.

A participating participant will be considered lost to follow-up in case a 1-year period has passed without return for scheduled visits and if the parent(s)/legal guardian(s) are unable to be contacted by the study site personnel on 3 occasions.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the parent(s)/legal guardian(s) in the form of (where possible) 3 telephone calls and, if necessary, a certified letter to the parent(s)/legal guardian(s) last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record.

Should the parent(s)/legal guardian(s) continue to be unreachable, the participant will be considered as withdrawn from the study with the reason category "lost to follow-up."

14.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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

14.4. 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 Participants (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

15. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

This study includes qualifying diagnostic or monitoring procedures required per protocol to collect clinical data needed to meet the study objectives, which are not standard-of-care but that do not pose more than a minimal risk or burden to the study participant. The qualifying procedures in this study are:

Qualifying diagnostic or monitoring procedure(s)	Recording Time Period
Biomarker Blood Sample (Venous)	**12 hours**

15.1. Adverse Events (AE)

An AE is defined as any untoward medical occurrence and can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the participant's participation in the study.

Any AE that occurs from the time the participant consents to the clinical research through and including 12 hours after completion of the qualifying procedure must be recorded.

The investigator is required to assess whether the AE may be related to the participant'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.

15.2. Research-Related Injury

Should a participant, 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 inparticipant 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 participant 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

The table below summarizes the requirements for recording safety events on the eCRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report form. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious adverse events (NSAE) (as applicable); and (3) scenarios involving exposure to a Pfizer product, including exposure during pregnancy or breast feeding, medication error, lack of efficacy, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of Safety Events."

Safety event	Recorded on the case report form	Reported on the CT SAE Report Form Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	Only SAEs determined by the investigator to be related to a Pfizer product
Non-serious AE	All	None

Safety event	Recorded on the case report form	Reported on the CT SAE Report Form Report Form to Pfizer Safety within 24 hours of awareness
Scenarios **involving exposure to a Pfizer product**, including exposure during pregnancy or breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure	All involving exposure to a Pfizer product (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) involving exposure to a Pfizer product **Note**: Any associated adverse event (either serious or non-serious) is reported together with the exposure scenario

Safety events as specified in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe.

For each AE, 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 SAE (see section "Serious Adverse Events" below).

In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

All AEs (ie, serious and non-serious, including those attributed to qualifying assessments identified as research-related injury) are collected in the clinical study database.

Reporting period

For each participant, the safety event reporting period begins at the time of the participant's informed consent, which is obtained prior to the participant's enrollment in the study, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation *or* failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient. If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to a Pfizer product, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to a Pfizer product, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that a Pfizer product caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether a Pfizer product caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that a Pfizer product did not cause the event, this should be clearly documented on the eCRF and the CT SAE Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a participant administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. The same definition is applied for medical devices and nutritional products (including infant and toddler formulas [hereinafter "pediatric formulas"]).

Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

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

Serious adverse events

A serious adverse event is any untoward medical occurrence in a participant administered a medicinal or nutritional product (including pediatric formulas) at any dose using a medical device that:

- Results in death;

- Is life-threatening;

- Requires inparticipant hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);

- 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above, 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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

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

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, participant has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) a Pfizer product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to a Pfizer product (maternal exposure).

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, either due to treatment or environmental exposure to a Pfizer product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective, and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed. When exposure during pregnancy is associated with an adverse event, it is reported to Safety regardless of the seriousness criterion associated with that adverse event.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with a Pfizer product, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, must be submitted using the CT SAE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to a Pfizer product, in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the CT SAE Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

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, in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. 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 (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE (either serious or non-serious) associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or participant harm while in the control of the healthcare professional, participant, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including: prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use.

Medication errors include:

- Near misses, involving or not involving a participant directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labelling or prescription on the part of the healthcare provider or the participant/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving participant exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a participant directly (eg, potential medication errors or near misses). When a medication error does not involve participant exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter;

    - A suspect product;

    - The event medication error.

When the medication error is associated with an adverse event, it is reported to Safety regardless of the seriousness criterion associated with that the adverse event.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

When the overdose, misuse, and extravasation is associated with an adverse event, it is reported to Safety regardless of the seriousness criterion associated with that adverse event.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

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 Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated AE. When the occupational exposure is associated with an adverse event, it is reported to Safety regardless of the seriousness criterion associated with that adverse event.

Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

16. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

16.1. 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 regulatory 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

16.2. 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 multicentre 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, participant 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 participants, and the CSA will control as to all other issues.

17. REFERENCES

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18. LIST OF TABLES

Not applicable.

19. LIST OF FIGURES

Not applicable.

20. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
	v1.0	12-Feb-20	English-USA-Qolissy Shortform (Children)-v1.0-12-Feb-20 English-USA-Qolissy Shortform (Parents)-v1.0-12-Feb-20
	Original	1990	CHAQ Version 1990 Original version Singh G et al.

21. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.