Title Page

A PHASE 3 MULTICENTER, OPEN LABEL, MULTI COHORT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SOMATROPIN IN JAPANESE PARTICIPANTS WITH PRADER-WILLI SYNDROME (PWS)

Study Intervention Number:	PNU-180307
Study Intervention Name:	somatropin
US IND Number:	N/A
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT04697381
Protocol Number:	A6281323
Phase:	3

Brief Title: Phase 3 study of the efficacy and safety of somatropin in Japanese participants with PWS

Document History

Document	Version Date
Amendment 1	13 December 2021
Original protocol	21 August 2020

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

Protocol Amendment Summary of Changes Table

Amendment 1 (13-December-2021)

Overall Rationale for the Amendment: This protocol amendment enables study participants to complete study visits during extension period by utilizing Decentralized Clinical Trial component (Home health visit and Telehealth) deemed appropriate based on the participant's preference and the investigator's discretion.

Section # and Name	Description of Change	Brief Rationale
Overall	Minor corrections, clarifications to text, and correction of typographical errors have been made throughout the protocol to improve overall readability.	Not applicable
1.1. Synopsis, 6.1.1 Administration	Text for Adult cohort was updated to correct typographical error; Dose increase should occur at Month 1 visit.	To reflect changes made by PACL#1 dated 27-Oct-2020
1.3 Schedule of Activities	Month 42 is added to header row to clarify and write down all specific visit timing in the case the extension period continues for 36 months (ie, Month 48 visit).	To reflect changes made by PACL#1 dated 27-Oct-2020
1.3 Schedule of Activities	Reference date for each protocol required visit was added for clarification.	To reflect changes made by PACL#5 dated 21-Jul-2021
1.3 Schedule of Activities	Footnote j was updated to clarify DEXA scan performed within 7 days before Day 1 visit is acceptable.	To reflect changes made by PACL#1 dated 27-Oct-2020
1.3 Schedule of Activities	Footnote k was added to clarify Follow-up visit (28 days after EOS visit) can be done as telephone visit.	To reflect changes made by PACL#1 dated 27-Oct-2020
1.3 Schedule of Activities	Footnote l was added to clarify that protocol specified visits for Extension period can be done by utilizing Telehealth/Home health	To allow participant to utilize one of Decentralized Clinical

	visit, instead of conventional on-site visit when deemed appropriate based on the participant's preference and the investigator's discretion.	Trial component in this study
1.3 Schedule of Activities	Footnote m was added to clarify assessments for Height (pediatric participants only where required), BMI, and BIA can be exempted if a participant utilizes Telehealth/Home health visit for each protocol specified visit during Extension Period.	To allow participant to utilize one of Decentralized Clinical Trial component in this study
4.1 Overall Design	Screening period was updated to "up to 28 days" to make sure consistency with visit window for screening.	To reflect changes made by PACL#1 dated 27-Oct-2020
6.1.3 Shipment and Collection of Study Intervention	New section added to clarify Study intervention shipment/collection by an appropriate third-party courier can be utilized in this study.	To reflect changes made by PACL#6 dated 09-Sep-2021
6.8 Concomitant Therapy	Text was updated to clarify non-drug treatments are within scope of the requirements for concomitant therapy.	To reflect changes made by PACL#7 dated 02-Dec-2021
6.8.2 Permitted During the Study	Text was updated to clarify if the investigator judges that the dose change will fall within the expected range of dose adjustment, then the dose change is permitted.	To reflect changes made by PACL#2 dated 15-Jan-2021
7.1 Discontinuation of Study Intervention	In response to the ongoing global pandemic COVID-19 and the increasing restrictions and concerns on public health, text was added to clarify alternative solutions to accommodate study procedures during the COVID-19 pandemic.	To reflect changes made by PACL#3 dated 19-Feb-2021
9.2 Analysis Sets	Text was updated to maintain consistency across sections.	To reflect changes made by PACL#7 dated 02-Dec-2021
10.2 Appendix 2: Clinical Laboratory Tests	Text for footnote a. was updated to clarify a serum hCG testing can be selected as an alternative to a serum β-hCG when clinically appropriate at the discretion of the investigator.	To reflect changes made by PACL#4 dated 28-May-2021

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Phase 3 study of the efficacy and safety of somatropin in Japanese participants with PWS

Rationale

Somatropin is a recombinant human growth hormone (r-hGH) indicated for the long-term treatment of children with growth disturbance due to various conditions and replacement therapy in AGHD.

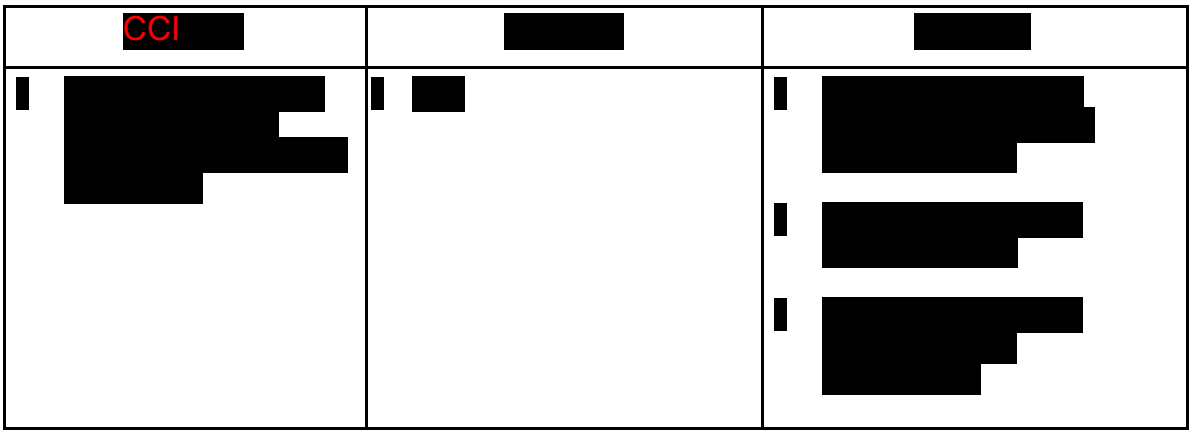
GH replacement therapy is recommended for both pediatric and adult patients with PWS. In Japan, GH replacement therapy is approved for short stature associated with PWS in 2002 but not approved for the use of maintaining or improving body composition in pediatric PWS patients or any use in adults with PWS.

Somatropin for the indication "improvement of body composition in pediatric and adult PWS" was officially judged as drug/indication in high medical needs at the “MHLW committee on unapproved/off-label used drugs”. The present study is to evaluate the efficacy and safety of somatropin in Japanese patients with PWS in response to the MHLW development request issued [redacted]

Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the efficacy of somatropin in participants with PWS.	• Population: Japanese participants with PWS in each cohort; • Variable: Change from baseline to Month 12 in lean body mass (%) measured by DEXA; • Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of study, etc.), if collected, will not be considered; • Population level summary: Mean (GH naïve pediatric and	• Change from baseline to Month 12 in lean body mass (%) measured by DEXA.

Objectives	Estimands	Endpoints
	GH treated pediatric cohort) or LS mean (adult cohort).	
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the effects of somatropin on other body composition parameters.	• Population: Japanese participants with PWS syndrome in each cohort; • Variable: Each secondary endpoint; • Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of study, etc.), if collected, will not be considered; • Population level summary: Mean (GH naïve pediatric and GH treated pediatric cohort) or mean/LS mean (adult cohort).	• [KEY SECONDARY] Change from baseline to Month 12 in lean body mass (%) measured by BIA; • Change from baseline to Month 12 in body fat (%) measured by DEXA; • Change from baseline to Month 12 in adipose tissue distribution measured by abdominal CT; • Change from baseline to Month 6 in lean body mass (%) measured by DEXA (adult cohort only).
• To evaluate the safety and tolerability of somatropin.	• N/A.	• AE. • SAE. • Clinical laboratory values. • Bone maturation.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



Overall Design

Brief Summary

This is a multicenter, open label, multi cohort study of participants with PWS. This study has 3 cohorts (GH naïve pediatric cohort, GH treated pediatric cohort and adult cohort) and all participants will receive somatropin.

Number of Participants

Approximately 30 Japanese participants (5 GH naïve pediatric participants, 5 GH treated pediatric participants and 20 adult participants) will be enrolled to study intervention.

Intervention Groups and Duration

The study consists of a screening period, treatment period of 12 months and extension period which continues for 36 months or until regulatory approval, whichever occurs first. Upon commencement of active treatment with somatropin, participants will be dosed 6 or 7 times in a week, subcutaneously.

Dose regimens in each of the cohorts are as below (the weekly dose should be divided into 6 or 7 subcutaneous injections):

- GH naïve pediatric cohort: 0.245 mg/kg/week;
- GH treated pediatric cohort: 0.084 mg/kg/week. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels but should not exceed 1.6 mg/day;
- Adult cohort: starting with 0.042 mg/kg/week, then titrated up to 0.084 mg/kg/week from Month 1 visit. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels but should not exceed 1.6 mg/day.

Data Monitoring Committee or Other Independent Oversight Committee: No

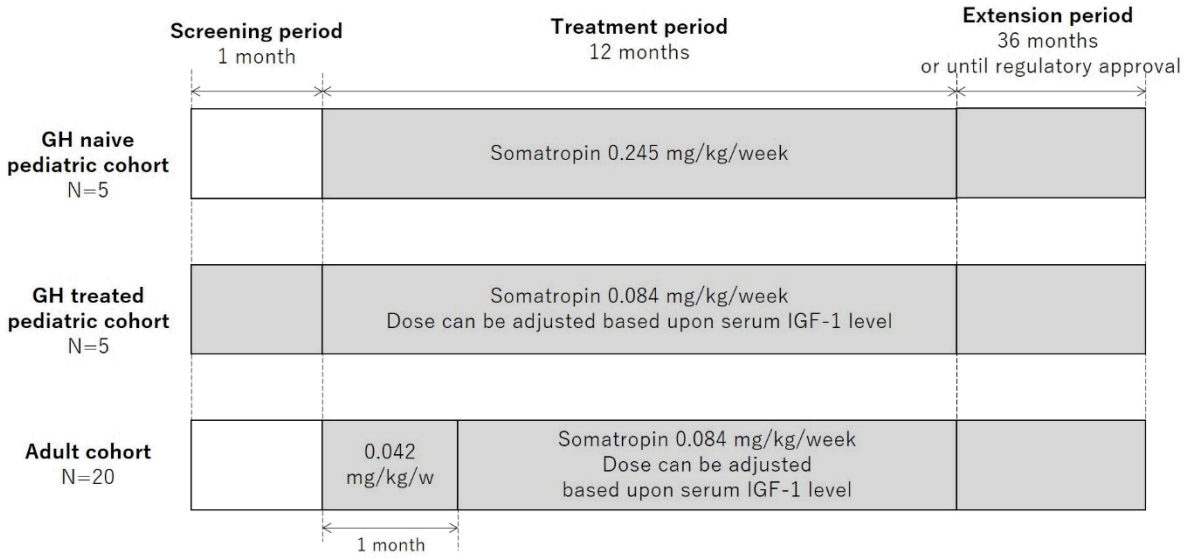
Statistical Methods

Statistical hypothesis testing will not be performed.

Data will be evaluated individually and descriptively for each cohort.

For adult cohort, the least squares (LS) mean and its 95% CI of change from baseline to Month 6 and 12 in lean body mass (%) measured by dual energy X-ray absorptiometry (DEXA) or in other secondary efficacy endpoints will be estimated based on a Mixed-effects Models for Repeated Measures (MMRM).

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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 SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

	Screening Period	Treatment Period							Extension Period[l]	End of Study	Follow-up
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11	**Screening**	**Day 1**[h]	**Month 1 Week 4**	**Month 2**[b] **Week 8**	**Month 3 Week 12**	**Month 6 Week 26**	**Month 9 Week 39**	**Month 12 Week 52**	**Month 18/24/30/36/42 Week 78/104/130/156/182**	**End of Study/Early Termination/ Discontinuation**	**28 days after EOS visit**[k]
Visit Window	**Day -28 to -1**	**N/A**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±14d**		**+7d**
Informed consent/assent	X										
Registration	X										
Inclusion/exclusion criteria	X	X									
Medical history	X	X									
Demographics	X	X									
Physical examination, including behavioral and mental health status	X	X									
Vital signs	X	X	X	X[b]	X	X	X	X	X	X	
Diet/exercise management compliance check	X	X	X		X	X	X	X	X		
Weight, BMI	X	X	X		X	X	X	X	X[m]	X	
Height[i]	X	X[c]	X[c]		X[c]	X[c]	X[c]	X	X[c, m]	X	
Bone age[c]		X						X		X[d]	
Assessment of childbearing potential	X										
Pregnancy testing (WOCBP only)	X					X		X	X	X	

	Screening Period	Treatment Period							Extension Period[l]	End of Study	Follow-up
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11	**Screening**	**Day 1**[h]	**Month 1 Week 4**	**Month 2**[b] **Week 8**	**Month 3 Week 12**	**Month 6 Week 26**	**Month 9 Week 39**	**Month 12 Week 52**	**Month 18/24/30/36/42 Week 78/104/130/156/182**	**End of Study/Early Termination/ Discontinuation**	**28 days after EOS visit**[k]
Visit Window	**Day -28 to -1**	**N/A**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±14d**		**+7d**
Contraception check (WOCBP only)		X	X		X	X	X	X	X	X	X
Study intervention											
Dispense study intervention		X	X		X	X	X	X	X[f]		
Review injection diary			X		X	X	X	X	X	X	
Assessments											
Efficacy											
Body composition (DEXA)[j]		X				X[e]		X		X[d]	
Abdominal CT[j]		X						X		X[d]	
Body composition (BIA)		X	X		X	X	X	X	X[m]	X	
Waist circumference		X						X		X[d]	
Safety											
Concomitant treatment(s)		X	→	→	→	→	→	→	→	→	X
Serious and nonserious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	X
Laboratory[g]											
Blood count	X	X			X	X		X	X	X	
Blood chemistry	X	X			X	X		X	X	X	
IGF-1, IGF-1 SDS	X	X	X		X	X		X	X	X	
Thyroid function (TSH, FT4)	X	X	X		X	X		X	X	X	
Cortisol	X	X	X		X	X		X	X	X	
Gonadal function (LH, FSH, E2, testosterone)	X	X				X		X	X	X	
HbA1c	X	X	X	X[b]	X	X	X	X	X	X	
Casual blood glucose		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Lipid profile	X	X			X	X		X	X	X	

	Screening Period	Treatment Period							Extension Period[l]	End of Study	Follow-up
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 11	**Screening**	**Day 1**[h]	**Month 1 Week 4**	**Month 2**[b] **Week 8**	**Month 3 Week 12**	**Month 6 Week 26**	**Month 9 Week 39**	**Month 12 Week 52**	**Month 18/24/30/36/42 Week 78/104/130/156/182**	**End of Study/Early Termination/ Discontinuation**	**28 days after EOS visit**[k]
Visit Window	**Day -28 to -1**	**N/A**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±14d**		**+7d**

a. Day relative to start of study intervention (Day 1).
b. Applicable only for participants with diabetes.
c. For pediatric cohorts only. If the participant reaches bone age of 17 for boys and 15 for girls, the assessment is not necessary after that.
d. Applicable only for early termination before Month 12.
e. For adult cohort only.
f. For extension period, study intervention can be dispensed every 3 months in case a participant cannot bring home a 6-month drug supply at once. If a participant chooses to receive drug supply every 3 months, safety assessment (at least but not limited to: AE/SAE, concomitant treatment) should be confirmed via physical site visit or telehealth before dispensing for the remaining 3 months. If a participant choose a 6-month drug supply, he/she will come back to the site for next protocol specified visits and complete assessments according to protocol.
g. All laboratory testing can be performed locally at the site. Fasting is not required for any of lab tests in this study.
h. Laboratory test result at Screening can be used for Day 1 if the test was performed within 7 days before Day 1 visit.
i. Height measurement at Screening can be used for Day 1 if the measurement was performed within 14 days before Day 1 visit.
j. DEXA/Abdominal CT scan prior to Day 1 visit is acceptable if the evaluation was performed within 7 days before Day 1 visit.
k. Follow-up visit may become telephone visit at investigator's discretion.
l. Protocol specified visits for Extension period can be done by utilizing Telehealth/Home health visit, instead of conventional on-site visit when deemed appropriate based on the participant's preference and the investigator's discretion.
m. Assessments for Height (pediatric participants only where required), BMI, and BIA can be exempted if a participant utilizes Telehealth/Home health visit for each protocol specified visit during Extension Period.

2. INTRODUCTION

Somatropin is a r-hGH currently being investigated in participants with PWS.

2.1. Study Rationale

The purpose of the study is to evaluate the efficacy and safety of somatropin in a cohort of Japanese participants with PWS.

This study is planned to support a supplemental new drug application in Japan in response to the official development request issued by Research and Development Division, Health Policy Bureau and Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW.

2.2. Background

Somatropin is indicated for the long-term treatment of children with growth disturbance due to various conditions and replacement therapy in AGHD and marketed in more than 100 countries over 30 years.

GH replacement therapy is recommended for both pediatric and adult patients with PWS[1] and somatropin is approved for pediatric PWS regardless of stature in European countries and for adult PWS in New Zealand. In Japan GH replacement has been approved since 2002 for "short stature without epiphyseal closure associated with PWS", and is not approved for the use of improving body composition in pediatric patients and any use in adult patients with PWS.

A nation-wide patient advocacy group submitted a petition for somatropin for the indication "improvement of body composition in pediatric and adult PWS" and the requested indication was judged as a high medical need at the 39th MHLW Committee on Unapproved/Off-label used Drugs on 26 Aug 2019. Thereafter the official development request was issued to Pfizer Japan on CCI [redacted] by Research and Development Division, Health Policy Bureau and Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW.

The outline of the study was agreed upon with the Pharmaceuticals and Medical Devices Agency (PMDA) on CCI [redacted]

2.2.1. Clinical Overview

The safety and efficacy of somatropin in the treatment of pediatric participants with PWS were evaluated in two randomized, open-label, controlled clinical trials.[2] No Japanese participants were enrolled to these studies. Participants received either somatropin or no treatment for the first year of the studies, while all participants received somatropin during the second year. In Study 1, the treatment group received somatropin at a dose of 0.24 mg/kg/week during the entire study. During the second year, the control group received somatropin at a dose of 0.48 mg/kg/week. In Study 2, the treatment group received

somatropin at a dose of 0.36 mg/kg/week during the entire study. During the second year, the control group received somatropin at a dose of 0.36 mg/kg/week.

In both of these studies, participants who received somatropin showed significant increases in linear growth during the first year of study, compared with participants who received no treatment. Linear growth continued to increase in the second year, when both groups received treatment with somatropin. Changes in body composition were also observed in the participants receiving somatropin. These changes included a decrease in the amount of fat mass, and increases in the amount of lean body mass and the ratio of lean-to-fat tissue, while changes in body weight were similar to those seen in participants who received no treatment. Treatment with somatropin did not accelerate bone age, compared with participants who received no treatment.

There has been no clinical study conducted in Japanese PWS patients evaluating improvement in body composition as a primary endpoint. Approval in Japan for the indication "short stature associated with PWS" was based on the randomized studies mentioned above. Post marketing surveillance for the indication was conducted in pediatric PWS population and no new safety issues were identified. The re-evaluation process was completed based on the result from the surveillance.

The efficacy and safety of GH for adult PWS has been shown in several clinical studies.[3,4,5,6,7] A meta-analysis[8] also supports the effectiveness of GH in improving the body composition in PWS patients.

Although the evidence in Japanese PWS patients is limited, the efficacy and safety of GH has been shown in many studies with both pediatric and adult PWS populations.

2.3. Benefit/Risk Assessment

There are data regarding clear benefits to GH treatment in PWS populations. At the same time there have been reports of AEs associated with the use of GH in several conditions and therefore eligibility criteria for this study have been selected to ensure that only appropriate participants are included in the study. More detailed information about the known and expected benefits and risks and reasonably expected AEs of somatropin may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) somatropin		
Potential risks associated with somatropin include the following: fatalities due to upper airway obstruction, myositis, type 2 diabetes mellitus, hyperthyroidism, hypoadrenalism, slipped epiphyses of the hip, benign intracranial hypertension, scoliosis.	The potential risks are based on product labeling for somatropin which is based on data from clinical trials and pharmacovigilance activities.	• Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). • More intensive monitoring is required for participants with preexisting diabetes.

2.3.2. Benefit Assessment

Treatment with somatropin in this study is anticipated to improve participants' body composition.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with somatropin are justified by the anticipated benefits that may be afforded to participants with PWS.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To evaluate the efficacy of somatropin in participants with PWS.	• Population: Japanese participants with PWS in each cohort; • Variable: Change from baseline to Month 12 in lean body mass (%) measured by DEXA; • Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of study, etc.), if collected, will not be considered; • Population level summary: Mean (GH naïve pediatric and GH treated pediatric cohort) or LS mean (adult cohort).	• Change from baseline to Month 12 in lean body mass (%) measured by DEXA.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the effects of somatropin on other body composition parameters.	• Population: Japanese participants with PWS syndrome in each cohort; • Variable: Each secondary endpoint; • Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of	• [KEY SECONDARY] Change from baseline to Month 12 in lean body mass (%) measured by BIA; • Change from baseline to Month 12 in body fat (%) measured by DEXA; • Change from baseline to Month 12 in adipose tissue

Objectives	Estimands	Endpoints
	study, etc.), if collected, will not be considered; • Population level summary: Mean (GH naïve pediatric and GH treated pediatric cohort) or mean/LS mean (adult cohort).	distribution measured by abdominal CT; • Change from baseline to Month 6 in lean body mass (%) measured by DEXA (adult cohort only).
• To evaluate the safety and tolerability of somatropin.	• N/A.	• AE. • SAE. • Clinical laboratory values. • Bone maturation.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, open label, multi cohort study to evaluate the efficacy and safety of somatropin in Japanese participants with PWS. This study has 3 cohorts (GH naïve pediatric cohort, GH treated pediatric cohort and adult cohort) and all participants will receive somatropin.

The durations of the study periods are listed below:

- Screening Period up to 28 days;

- Treatment Period: 12 months;
- Extension Period: 36 months or until regulatory approval, whichever is sooner.

4.2. Scientific Rationale for Study Design

An open-label study design was chosen. Rarity of disease necessitated a single arm study and the high unmet need required an efficient design.

4.2.1. Participant Input Into Design

Protocol design and schedules of activities were shared and discussed with patients/caregivers with PWS at the web-based advisory board meeting and confirmed as acceptable.

4.2.2. Choice of Contraception/Barrier Requirements

Somatropin is approved for use in treatment of children with growth disturbance due to various conditions and replacement therapy in AGHD without any contraceptive precautions. There is no suspicion of human teratogenicity based on the intended pharmacology. See Appendix 4 for contraceptive requirements.

4.3. Justification for Dose

The planned somatropin doses in this study are as below (the weekly dose should be divided into 6 or 7 subcutaneous injections):

- **GH naïve pediatric cohort:** 0.245 mg/kg/week.

  Rationale: (1)dose identical to the current approved dose for short stature associated with PWS in Japan; (2)dose identical to the approved dose for pediatric PWS (regardless of their stature) in European countries; (3)consistent with the recommendation in the Consensus Guideline[1].

- **GH treated pediatric cohort:** 0.084 mg/kg/week. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels but should not exceed 1.6 mg/day.

  Rationale: (1)similarities between PWS and AGHD in clinical characteristics; (2)dose identical to the maximum approved dose for AGHD in Japan; (3)dose used in the study is about three times lower than the dose participants have received; (4)dose adjustment based on IGF-1 level and maximum dose of 1.6 mg/day are consistent with the recommendation in the Consensus Guideline.

- **Adult cohort:** starting with 0.042 mg/kg/week, then titrated up to 0.084 mg/kg/week from Month 1 visit. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels but should not exceed 1.6 mg/day.

Rationale: (1)similarities between PWS and AGHD in clinical characteristics; (2)dose identical to the maximum approved dose for AGHD in Japan; (3)initiate treatment at a lower dose to ensure participants' safety; (4)dose adjustment based on IGF-1 level and maximum dose of 1.6 mg/day are consistent with the recommendation in the Consensus Guideline.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit which is defined as the follow-up telephone call 28 days from EOS or the Termination visit.

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics:

1. Male or female participants with documentation of genetically confirmed diagnosis of PWS.

2. No plan to initiate a new treatment that may affect the body composition, such as gonadal hormone replacement therapy.

3. Currently on appropriate diet and exercise programs and willing to continue throughout the study period at the discretion of the investigator.

4. Participants, and if required by local/site regulations their parent(s)/legal guardian(s) must be willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Informed Consent:

5. Evidence of a personally signed and dated ICD (and written assent where applicable based on age and country regulation) indicating that the participant or a legally

acceptable representative/parent(s)/legal guardian has been informed of all pertinent aspects of the study. Refer to Appendix 1 for the detailed process of obtaining consent.

For inclusion of GH naïve pediatric cohort, participants must meet criteria 6 to 8:

6. 18 years or younger.
7. Naïve to GH treatment.
8. Tanner stage 1 (for testes in males, for breasts in females).

For inclusion of GH treated pediatric cohort, participants must meet criteria 9 and 10:

9. Continued GH treatment for at least 2 years with stable dose for the last 6 months and being on GH at time of inclusion. The recent dose should be higher than 0.084 mg/kg/week.
10. Participants who are about to complete GH treatment for his/her short stature (eg, due to meeting the treatment stopping criteria defined as a height SDS more than -2.5 for Japanese adult standards).

For inclusion of adult cohort, participants must meet criteria 11 to 13:

11. 18 years of chronological age or older at Day 1 visit.
12. Off from GH treatment for at least 1 year.
13. Serum IGF-1 level within +2 SDS, adjusted for age and sex.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Participants with uncontrolled diabetes at the discretion of the investigator.
2. Participants with malignant tumors.
3. Participants with severe obesity or serious respiratory impairment.
4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concurrent Clinical Study Experience:

5. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Other Exclusions:

6. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

It is important that participants continue their typical dietary habits and physical activity throughout the study period. Participants will be asked not to change their diet and their exercise routine.

5.3.1. Contraception (WOCBP Only)

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to somatropin.

6.1. Study Intervention(s) Administered

Intervention Name	Somatropin
ARM Name (group of participants receiving a specific treatment or no treatment)	Somatropin
Type	Biologic
Dose Formulation	Device
Unit Dose Strength(s)	5.3 mg, 12 mg
Dosage Level(s)	For GH naïve pediatric cohort: 0.245 mg/kg/week For GH treated pediatric cohort: 0.084 mg/kg/week For adult cohort: 0.042 → 0.084 mg/kg/week
Route of Administration	Subcutaneously
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in container. Each container will be labeled as required per country requirement.

6.1.1. Administration

Dose regimens in each cohorts are as below (the weekly dose should be divided into 6 or 7 subcutaneous injections):

- GH naïve pediatric cohort: 0.245 mg/kg/week;
- GH treated pediatric cohort: 0.084 mg/kg/week. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose can be increased but should not exceed 1.6 mg/day;
- Adult cohort: starting with 0.042 mg/kg/week, then titrated up to 0.084 mg/kg/week from Month 1 visit. The dosage may be adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose can be increased but should not exceed 1.6 mg/day.

Site personnel will instruct the participant or designated person on the proper sterile technique to administer a subcutaneous injection when using the pen device at home. During the baseline visit, the initial dose of study intervention must be administered in the office by study personnel, while the participant or participant's caregiver observes.

6.1.2. Medical Devices

1. The sponsor-manufactured medical devices (or devices manufactured for sponsor by a third party) provided for use in this study are Genotropin GoQuick 5.3 mg or 12 mg.
2. Instructions for medical device use are provided in the IP manual.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.1.3. Shipment and Collection of Study Intervention

Study intervention may be shipped by an appropriate third-party courier to study participants (or be collected by an appropriate third-party courier from study participants) if permitted by local regulations and in accordance with storage and transportation requirements for Study intervention. Pfizer does not permit the shipment of Study intervention by mail. The tracking record of shipments and the chain of custody of Study intervention must be kept in the participant's source documents/medical records. Study intervention can continue to be administered at home in accordance with the protocol.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All somatropin that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

Somatropin will be provided as pen devices packaged and dispensed in cartons with tamper-evident seals. A qualified staff member will dispense the study intervention using an IRT drug management system via unique container numbers in the cartons provided, and in quantities appropriate to the SoA. A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the study intervention is to be administered.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned devices during the site visits (or upon receipt of study intervention from study participants in case they utilize third-party courier for the collection of study drug) and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of somatropin pen devices dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.5. Dose Modification

The dose in this study will be based on the participant's weight. The investigator should review participants' weight at every protocol-specified visit and recalculate the prescribed dose if necessary.

For GH treated pediatric and adult cohorts, dose modification is permitted according to the participant's symptoms and serum IGF-1 levels at the discretion of the investigator, in addition to the modification based on their weight. The weekly dose can be increased but should not exceed 1.6 mg/day (see Section 6.1.1).

6.6. Continued Access to Study Intervention After the End of the Study

This extension period of the study continues for 36 months or until regulatory approval whichever occurs first. No intervention will be provided to study participants at the end of the study.

6.7. Treatment of Overdose

For this study, any dose of somatropin greater than prescribed dose will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Medications/treatments that are taken in the screening period as well as any medications/treatments taken for the management of PWS will be documented as prior medications/treatments. Medications/treatments taken after the first dose of study intervention has been administered will be documented as concomitant medications/treatments.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use;
- Dates of administration;
- Dosage information.

6.8.1. Prohibited During the Study

The following medications and treatments are prohibited for use during the study. If medically necessary, the investigator should consult with the sponsor in advance.

- Newly initiated medications/non-drug treatments which could affect body composition, such as hormonal replacement therapy, medications for hyperlipidemia, anti-obesity medication, and surgery accompanied with metal implants.
- Growth hormone products other than study intervention and investigational drugs.

6.8.2. Permitted During the Study

Medications and treatments for conditions associated with PWS which are optimized and stable treatment regimen, as determined by the investigator, for at least 3 months prior to Day 1, are permitted. Participants should remain on stable dosages/treatment regimens required to maintain stability of conditions associated with PWS during the study period. If dose modification or any other changes are medically necessary, the investigator should consult with the sponsor in advance. However, if the investigator judges that the dose change will fall within the expected range of dose adjustment, then the dose change is permitted.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study

intervention include the following: refused further follow-up, lost to follow-up, death, study terminated by sponsor.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study treatment/intervention must be considered. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic including SARS-CoV-2 infection or quarantine related to SARS-CoV-2 exposure, enter "COVID-19" in the "Specify Status" field.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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.

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

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

The total blood sampling volume for individual participants in this study is approximately 430 mL. The actual collection times of blood sampling may change.

8.1. Efficacy Assessments

Refer to the SoA table for required procedures for each visit.

8.1.1. Body Composition Measured by DEXA

Body fat and lean body mass will be measured by DEXA. All scans for the same participant are made on same machine, with regular quality assurance at the site throughout the study. Regular quality assurance should include calibration following site's standard operational procedure.

8.1.2. Body Composition Measured by BIA

Body fat and lean body mass will be measured by BIA. All scans for the same participant are made on same machine, with regular quality assurance at the site throughout the study. Regular quality assurance should include calibration following site's standard operational procedure.

8.1.3. Adipose Tissue Distribution by Abdominal CT

The areas of subcutaneous adipose tissue (cm^2), visceral adipose tissue (cm^2) will be measured at the level of the umbilicus by abdominal CT. All scans for the same participant are made on same machine, with regular quality assurance at the site throughout the study. Regular quality assurance should include calibration following site's standard operational procedure.

8.1.4. Waist Circumference

Waist circumference will be measured at the level of the umbilicus.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical and Auxological Examinations

A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Assessments of the behavioral/mental health status will also be included. Investigators should pay special attention to clinical signs related to previous serious illnesses. Any abnormal findings at Screening visit should be recorded as Medical History. Study participants who have any abnormal findings related to behavioral/mental health status must also be followed by a PWS multispecialty team that includes at least a primary physician and/or a mental health specialist.

Height and weight will also be measured and recorded. Bone age will be assessed only in pediatric participants by an X-ray picture of the left hand and wrist. If the participant reaches bone age of 17 for boys and 15 for girls, the assessment is not necessary after that.

8.2.2. Vital Signs

Vital signs will be measured with the participant in a sitting position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

8.2.3. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

For participants with preexisting diabetes, casual blood glucose tests are to be performed in addition to HbA1c at the specified visits to make sure the participants' blood glucose level is maintained within acceptable range. Last mealtime before blood draw should be recorded along with the casual glucose tests.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.4. Diet/Exercise Management Compliance Check

The investigator will confirm the diet and exercise programs which the individual participant is currently on and needs to continue throughout the study period at Screening visit. At time points indicated in the SoA, the investigator will inform the participant of the need to continue diet/exercise programs consistently and correctly and document the participant’s confirmation in the participant’s chart.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/parent will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any 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 Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The

information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so 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.

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 SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE.**

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or non-serious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the CT SAE Report Form as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

CCI [redacted]

8.5. Genetics

8.5.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

CCI [redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

In this study, no formal hypothesis testing will be conducted.

The efficacy will be evaluated comprehensively based on individual data and summary statistics in each cohort for the primary, secondary, CCI [redacted] In addition, it will be confirmed in adult cohort that the point estimate of the least squares (LS) mean of the primary endpoint is above 0.

9.1.1. Estimands

1. The estimand for the primary endpoint is the hypothetical estimand, which estimates the effect if all participants maintain their treatment and adhere to the protocol. It includes the following 4 attributes:

    - Population: Japanese participants with PWS in each cohort;

    - Variable: Change from baseline to Month 12 in lean body mass (%) measured by DEXA;

- Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of study, etc.), if collected, will not be considered;

- Population level summary: Mean (GH naïve pediatric and GH treated pediatric cohort) or LS mean (adult cohort).

2. The estimand for secondary endpoints is the hypothetical estimand, which estimates the effect if all participants maintain their treatment and adhere to the protocol. It includes the following 4 attributes:

    - Population: Japanese participants with PWS in each cohort;

    - Variable: Each secondary endpoint;

    - Intercurrent events: All data after an intercurrent event (major deviation of diet/exercise, discontinuation of treatment, discontinuation of study, etc.), if collected, will not be considered;

    - Population level summary: Mean (for GH naïve pediatric and GH treated pediatric cohort) or mean/LS mean (for adult cohort).

For change from baseline endpoints, it would require that a participant have a baseline value and at least 1 post baseline value to be included in the analysis for that endpoint.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full Analysis Set (FAS)	All participants assigned to study intervention and who take at least one dose of study intervention.
Efficacy Evaluable Set	All participants assigned to study intervention and who take at least one dose of study intervention and have at least one efficacy evaluation.

Defined Analysis Set	Description
Adherence to protocol regimen	For participants who experience major deviation of diet/exercise or other major protocol deviation and/or discontinuation of treatment or study withdrawal, all data after the major deviation or discontinuation will not be considered.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

All efficacy analyses will be performed on the efficacy evaluable set and all safety analyses will be performed on the FAS. All listings will be generated on the FAS.

Descriptive statistics consists of measures such as N, counts and percentages for categorical variables and N, mean, SD, median, range, min, max for continuous variables.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary endpoint for the study is change from baseline to Month 12 in lean body mass (%) measured by DEXA.

Data will be evaluated individually and descriptively for each cohort.

For adult cohort, the least squares (LS) mean and its 95% CI of change from baseline to Month 6 and 12 in lean body mass (%) measured by DEXA will be estimated based on a Mixed-effects Models for Repeated Measures (MMRM). The model will include fixed effects for visit as a categorical variable, and baseline lean body mass value (%) and interaction between baseline lean body mass value (%) and visit as a continuous variable.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

The secondary endpoints for the study are as follows.

- [KEY SECONDARY] Change from baseline to Month 12 in lean body mass (%) measured by BIA.
- Change from baseline to Month 12 in body fat (%) measured by DEXA.
- Change from baseline to Month 12 in adipose tissue distribution measured by abdominal CT.
- Change from baseline to Month 6 in lean body mass (%) measured by DEXA (adult cohort only).

Data will be evaluated individually and descriptively for each cohort.

For adult cohort, excluding adipose tissue distribution measured by abdominal CT, the least squares (LS) mean and its 95% CI of change from baseline to Month 6 and Month 12 in each variable will be estimated based on a Mixed-effects Models for Repeated Measures

(MMRM). The model will include fixed effects for visit as a categorical variable, and baseline each variable value (%) and interaction between baseline each variable value (%) and visit as a continuous variable.

CCI

[redacted]

9.3.5. Other Safety Analyses

AEs and SAEs (including local tolerability), discontinuations, and changes in vital signs, bone maturation, and clinical laboratory parameters will be descriptively summarized, and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data.

9.3.6. Other Analyse(s)

Not Applicable.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

CCI

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.1.1. 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 study intervention, 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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Participants and their legally authorized representative must be informed that their participation is voluntary. Participants and their legally authorized representative will be required to provide a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that legally authorized representative (parent/guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICD was the participant's legally authorized representative (parent/guardian). The authorized person obtaining the informed consent must also sign the ICD.

- Participants and their legally authorized representative (parent/guardian) must be re-consented and re-assented to the most current version of the ICD(s) during their participation in the study.

- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.

- A copy of the ICD(s) must be provided to the participant or the participant's parent/guardian.

- As appropriate, children may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their parent/guardian, unless required by local law.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' 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 will 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 participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study 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 and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the clinical monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at

the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Endocrinology
WBC count	**General condition**	**Pregnancy test**
Hemoglobin	Total protein	β-hCG[a]
Hematocrit	Albumin	
RBC count		**Growth hormone**
MCV	**Lipid**	IGF-1
MCH	Total cholesterol	
MCHC	Triglyceride	**Adrenal glands function**
Platelet count	HDL cholesterol	Cortisol
	LDL cholesterol	
		Thyroid function
	Liver function	TSH
	AST	FT4
	ALT	
	Alkaline phosphatase	**Gonadal function**
	Total bilirubin	LH
		FSH
	Renal function	E2
	BUN	Testosterone
	Creatinine	
	Electrolyte	
	Calcium	
	Sodium	
	Potassium	
	Chloride	
	Glucose metabolism	
	HbA1c	
	Casual blood glucose[b]	

a. Both local serum and urine testing will be acceptable. A urine pregnancy test should have sensitivity of at least 25 mIU/mL. A serum hCG testing can be selected as an alternative to a serum β-hCG when clinically appropriate at the discretion of the investigator.
b. For participants with preexisting diabetes.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a 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 pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding,	All AEs or SAEs associated with exposure during pregnancy or breastfeeding Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

     - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials. Items marked with an asterisk (*) denote contraceptives that are not approved for use in Japan.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.*

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

   - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;

- Intravaginal*;
- Transdermal*;
- Injectable*.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:
   - Oral*;
   - Injectable*.
8. Sexual abstinence:
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.*
10. Male or female* condom with or without spermicide*.
11. Cervical cap*, diaphragm*, or sponge with spermicide*.
12. A combination of male condom with either cervical cap*, diaphragm*, or sponge with spermicide* (double-barrier methods).

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition

- A USADE is a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.8.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for

recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occuring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the product information in his/her assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.8.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-Specific Requirements

10.9.1. Japan

10.9.1.1. Definitions of Serious Adverse Event, Serious Adverse Event Caused by Medical Device, and Unanticipated Serious Adverse Event Caused by Medical Device

Definition of Serious Adverse Event Caused by Medical Device

A serious adverse event caused by medical device is defined as an adverse event caused by a medical device which led to an outcome characteristic to serious adverse events, or a device-related incident whose recurrence might lead to death or serious deterioration in health.

10.10. Appendix 10: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally or specific location(s) and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.10.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing (if available). Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.10.2.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.10.2. Alternative Facilities for Safety Assessments

10.10.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- All protocol required lab draws as defined in Section 10.2.
  - Hematology panel.

- Chemistry panel.
- Endocrinology panel, including pregnancy testing (for WOCBP).

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.10.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Somatropin may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of somatropin by mail. The tracking record of shipments and the chain of custody of somatropin must be kept in the participant's source documents/medical records.

10.10.4. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- All protocol required lab draws as defined in Section 10.2.
  - Hematology panel.
  - Chemistry panel.
  - Endocrinology panel, including pregnancy testing (for WOCBP).
- Vital signs.

- Weight.

10.10.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.10.6. Efficacy Assessments

Efficacy assessments listed in Section 8.1 are only to be collected during on-site visits.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AGHD	adult growth hormone deficiency
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BIA	bioelectrical impedance analysis
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CT SAE	clinical trial serious adverse event (report form)
DEXA	dual energy X-ray absorptiometry
DILI	drug-induced liver injury
DMC	data monitoring committee
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOS	end of study
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c

Abbreviation	Term
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGF-1	insulin-like growth factor 1
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
LDL	low-density lipoprotein
LFT	liver function test
LH	luteinizing hormone
LS	least squares
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MHLW	Ministry of Health, Labour and Welfare
MMRM	mixed-effects models for repeated measures
N/A	not applicable
NIMP	noninvestigational medicinal product
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
PWS	Prader-Willi syndrome
RBC	red blood cell
r-hGH	recombinant human growth hormone
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDS	standard deviation score
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TBili	total bilirubin
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
WBC	white blood cell
WOCBP	woman of childbearing potential

11. REFERENCES

[1] Deal CL, et al. Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome. J Clin Endocrinol Metab 2013;98(6):E1072-87.

[2] Genotropin USPI.

[3] Höybye C, et al. Growth hormone treatment improves body composition in adults with Prader-Willi syndrome. Clin Endocrinol (Oxf) 2003;58(5):653-61.

[4] Mogul HR, et al. Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. J Clin Endocrinol Metab 2008;93(4):1238-45.

[5] Sode-Carlsen R, et al. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. J Clin Endocrinol Metab 2010;95(11):4943-50.

[6] Sode-Carlsen R, et al. Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. Growth Horm IGF Res 2011;21(4):185-90.

[7] Kuppens RJ, et al. Beneficial Effects of GH in Young Adults With Prader-Willi Syndrome: A 2-Year Crossover Trial. J Clin Endocrinol Metab 2016;101(11):4110-6.

[8] Sanchez-Ortiga R, et al. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis. Clin Endocrinol (Oxf) 2012;77(1):86-93.

Document Approval Record

Document Name:	A6281323 Study Protocol Amendment 1
Document Title:	A6281323 Study Protocol Amendment 1

Signed By:	Date(GMT)	Signing Capacity
PPD	13-Dec-2021 05:31:42	Final Approval
PPD	13-Dec-2021 06:31:33	Final Approval