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SYNOPSIS

Study Title: 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 Number: A6281323

Regulatory Agency or Public Disclosure Identifier Number: NCT04697381

Study Phase: 3

Name of Study Intervention: PNU-180307

Name of Sponsor/Company: Pfizer Japan Inc.

CSR Version and Report Date: v1.0 and 10 Mar 2023

Number of Study Center(s) and Investigator(s):

A total of 33 participants were enrolled at 5 sites in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not applicable

Study Period:

The study initiation date was 09 Feb 2021 and the primary completion date was 06 Dec 2022.

This study was neither discontinued nor interrupted.

Rationale:

Somatropin is a 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 without epiphyseal closure associated with PWS in 2002 but is not approved for the use of 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

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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. The purpose of the present study was to evaluate the efficacy and safety of somatropin in Japanese patients with PWS in response to the MHLW development request issued on 19 Sep 2019.

Objectives, Endpoints, and Statistical Methods:

Table S1. Objectives, Estimands and Endpoints

Type and Objective	Estimands	Endpoints
Primary		
• Efficacy • 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 LBM (%) 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, was not 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 LBM (%) measured by DEXA.
Secondary:		
• To evaluate the effects of somatropin on other body composition parameters	• 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, was not 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 LBM (%) 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 LBM (%) measured by DEXA (adult cohort only).
Exploratory		
• To evaluate the effect of somatropin on IGFlevel over time	• N/A.	• Change from baseline to each visit in IGF-1 SDS.

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• To evaluate the effect of somatropin on other parameters related to body composition.	• N/A.	• Change from baseline to Month 1,3,6,9 and 12 in body fat (%) measured by BIA. • Change from baseline to Month 1, 3, 6, 9, and 12 in BMI. • Change from baseline to Month 12 in waist circumference. • Change from baseline to Month 1, 3, 6, and 9 in LBM (%) measured by BIA. • Change from baseline to Month 6 in body fat (%) measured by DEXA (adult cohort only).
Safety		
• To evaluate the safety and tolerability of somatropin	• N/A.	• AE. • SAE. • Clinical laboratory values. • Bone maturation.

AE = adverse event, BIA = bioelectrical impedance analysis, BMI = body mass index, CT = computed tomography, DEXA = dual-energy X-ray absorptiometry, GH = growth hormone, IGF-1 SDS = insulin-like growth factor-1 standard deviation score, LBM = lean body mass, LS = least square, N/A = not applicable, PWS = Prader-Willi syndrome, SAE = serious adverse event

Methodology:

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

Number of Participants (planned and analyzed):

A total of 33 participants completed the screening phase of the study. None of the participants discontinued during the screening phase or treatment phase.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants were eligible to be included in the study only if all the following criteria applied:

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

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

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

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4. Participants, and if required by local/site regulations their parent(s)/legal guardian(s) were 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 16.1.1, Protocol Section 10.1 for the detailed process of obtaining consent.

For inclusion of GH naïve pediatric cohort, participants met 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 met 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 was higher than 0.084 mg/kg/week.

10. Participants who were 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 met 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.

Participants were excluded from the study if any of the following criteria applied:

Medical conditions:

14. Participants with uncontrolled diabetes at the discretion of the investigator.

15. Participants with malignant tumors.

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16. Participants with severe obesity or serious respiratory impairment.

17. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that could increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concurrent Clinical Study Experience:

18. 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).

19. 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.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Somatropin 12 mg powder for injection (genetic recombination)	CW2351	[redacted]	12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	CY7175		12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	DT3211		12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	FM1234		12 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	DP6458		5.3 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	DR4949		5.3 mg	Commercial product

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Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Somatropin 5.3 mg powder for injection (genetic recombination)	ER3745	[redacted]	5.3 mg	Commercial product

Dose regimens in each cohorts are as below (the weekly dose was 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 was adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose could be increased but should not have exceeded 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 was adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose could be increased but should not have exceeded 1.6 mg/day.

Duration of Study Intervention:

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 was sooner.

Summary of Results:

Demographic and Other Baseline Characteristics:

The percentage of male participants in the GH naïve pediatric cohort was 66.7%, the GH treated cohort was 57.1% and the adult cohort was 35.0%. The mean age of the participants was 5.83, 14.86, and 23.90 years in the GH naïve pediatric cohort, GH treated cohort, and adult cohort, respectively.

Exposure:

The average treatment duration was 51.31 weeks, 51.84 weeks and 51.56 weeks, for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively. The

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average actual administered dosage (mg/kg/week) for the GH naïve pediatric cohort was 0.22, GH treated pediatric cohort was 0.16, and the Adult cohort was 0.07.

Analysis Population:

This study consisted of participant analysis sets (FAS and EES) and defined analysis set (adherence to protocol regimen).

- FAS - All participants assigned to study intervention and who took at least one dose of study intervention.
- EES - All participants assigned to study intervention and who took at least one dose of study intervention and had at least one efficacy evaluation.
- Adherence to protocol regimen - For participants who experienced 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 were not considered.

Efficacy Results:

Primary Efficacy Endpoint

- The primary endpoint was the change from baseline to Month 12 in LBM (%) measured by DEXA. The primary efficacy criterion was met since the LS mean (95% CI) of the primary endpoint was 3.09 (1.85, 4.33) and the point estimate was greater than the pre-specified efficacy criterion of 0 for the adult cohort (least squares [LS] mean and its 95% CI of change from baseline were estimated based on an MMRM. In the model, visit, baseline value, and baseline value-by-visit interaction were included as fixed effects).
- For the GH naïve pediatric cohort and the GH treated pediatric cohort, the mean ± SD of the change from baseline to Month 12 in LBM (%) measured by DEXA were 4.59 ± 4.490 and -1.34 ± 3.238, respectively.
- While the sample size was quite limited, the LBM (%) at Month 12 measured by DEXA numerically increased from baseline for the GH naïve pediatric cohort and decreased slightly for the GH treated pediatric cohort. In the GH treated pediatric cohort, the LBM was clinically maintained despite the low dose of study drug which was approximately one-third of the GH naïve pediatric cohort dose. For the adult cohort, the mean ± SD of the change from baseline to Month 12 in LBM (%) measured by DEXA was 3.08 ± 2.917.

Secondary Efficacy Endpoints

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- **Change From Baseline to Month 12 in LBM (%) Measured by BIA:** The LS mean (95% CI) of the change from baseline to Month 12 of LBM (%) measured by BIA was 2.03 (-0.67, 4.73). The mean ± SD of the change from baseline to Month 12 in LBM (%) measured by BIA was 3.32 ± 3.867, 0.58 ± 4.711, and 2.08 ± 5.474 for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively.

- **Change From Baseline to Month 12 in Body Fat (%) Measured by DEXA:** The LS mean (95% CI) of the change from baseline to Month 12 of body fat (%) measured by DEXA was -3.09 (-4.33, -1.85). The mean ± SD of the change from baseline to Month 12 of body fat (%) measured by DEXA was -4.59 ± 4.490, 1.34 ± 3.238, and -3.08 ± 2.917 for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively.

- **Change From Baseline to Month 12 in Adipose Tissue Distribution Measured by Abdominal CT:** Both the mean SAT (cm^2) and VAT (cm^2) increased in the GH naïve pediatric cohorts at Month 12 compared to baseline. The mean SAT (cm^2) increased whereas the VAT (cm^2) decreased in GH treated pediatric cohorts at Month 12 compared to baseline. In the adult cohort, both the mean SAT (cm^2) and VAT (cm^2) decreased at Month 12 (197.58 and 54.49, respectively).

- **Change From Baseline to Month 6 in LBM (%) Measured by DEXA (Adult Cohort Only):** The LS mean (95% CI) change from baseline to Month 6 in LBM (%) measured by DEXA was 2.38 (1.30, 3.46).

Safety Results:

At least one TEAE was experienced by 5 (83.3%), 5 (71.4%), and 19 (95.0%) participants in the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively. No AEs resulted in discontinuation during 12-month treatment period but 1 participant in the adult cohort discontinued study drug due to a severe unrelated adverse event (sleep apnoea syndrome) and was still in the study up to the cutoff date; however, the event was not related to somatropin. There were no deaths reported during the study. A total of 4 SAEs all not related to study treatment were reported from 3 participants (1 participant in GH treated pediatric cohort and 2 participants in adult cohort). Two (2) (33.3%) participants in the GH naïve pediatric cohort, 1 (14.3%) participant in the GH treated pediatric cohort, and 7 (35.0%) participants in the adult cohort had dose reduced or temporarily discontinued from the study due to AEs.

Conclusions:

Efficacy conclusions:

Primary endpoint

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- The LS mean (95% CI) of the change from baseline to Month 12 in LBM (%) measured by DEXA (i.e., the primary endpoint) in the adult cohort was 3.09 (1.85, 4.33). The primary efficacy criterion was met since the point estimate was greater than the pre specified efficacy criterion of 0 for the adult cohort.

- The study drug resulted in numerical increase in LBM (%) as measured by DEXA from baseline to Month 12 for the GH naïve pediatric cohort (mean ± SD: 4.59 ± 4.490) and remained clinically maintained from baseline for the GH treated pediatric cohort (mean ± SD: -1.34 ± 3.238). The results should be interpreted cautiously due to small sample size.

Secondary endpoints

- The LS mean (95% CI) of the change from baseline to Month 12 of LBM (%) measured by BIA was 2.03 (-0.67, 4.73) for the adult cohort.

- The mean ± SD of the change from baseline to Month 12 of LBM (%) measured by BIA was 3.32 ± 3.867 for the GH naïve pediatric cohort and 0.58 ± 4.711 for the GH treated pediatric cohort.

- The LS mean (95% CI) of the change from baseline to Month 12 of body fat (%) measured by DEXA was -3.09 (-4.33, -1.85) for the adult cohort.

- The mean ±SD of the change from baseline to Month 12 of body fat (%) measured by DEXA was -4.59 ± 4.490) for the GH naïve pediatric cohort and 1.34 ± 3.238) for the GH treated pediatric cohort.

In the adult cohort, the mean SAT (cm^2) and VAT (cm^2) decreased at Month 12 compared to baseline. The mean SAT (cm^2) and VAT (cm^2) increased in the GH naïve pediatric cohort at Month 12 compared to baseline. The mean SAT (cm^2) increased whereas VAT (cm^2) decreased in the GH treated pediatric cohort at Month 12 compared to baseline.Exploratory endpoints

- The results of exploratory endpoints were generally consistent with the overall results of the primary efficacy and secondary endpoints analysis.

Safety conclusions:

- Somatropin administration was generally safe and well-tolerated in Japanese participants with PWS and no new safety signals were identified from the study.

- No deaths were reported during the study.

- No participant was withdrawn from the study due to TEAE in the treatment phase.

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- No treatment-related SAEs were reported.

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SYNOPSIS

Study Title: 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 Number: A6281323

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov Identifier: NCT04697381

Study Phase: Phase 3

Name of Study Intervention: PNU-180307 (Somatropin)

Name of Sponsor/Company: Pfizer Japan Inc.

CSR Version and Report Date: Supplemental CSR Version 1.0 and 22 July 2024

Number of Study Centers and Investigators:

A total of 33 participants were enrolled at 5 sites in Japan. A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: Not Applicable.

Study Period:

Study Initiation Date (First Patient First Visit): 09 February 2021

Study Completion (Last Patient Last Visit) Date: 15 April 2024

This study was neither discontinued nor interrupted.

Rationale:

Refer to the primary completion date (PCD) clinical study report (CSR) synopsis for information on study rationale.

After somatropin was approved by the Ministry of Health, Labour and Welfare in Japan on 22 December 2023, the Phase 3 portion of this study was closed and continued as a post-marketing clinical study until all patients on treatment could access commercial somatropin. After the PCD CSR synopsis at Month 12, the efficacy data of the extension period (Month 18 to Month 36) of the Phase 3 portion and post-marketing clinical study, and safety data of throughout the study were included in the supplemental CSR synopsis.

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Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are summarized in Table S1.

Table S1. Objectives, Estimands, and Endpoints

Type	Objectives	Estimands	Endpoints
Primary			
Efficacy	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 LBM (%) 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, were not 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 LBM (%) measured by DEXA.
Secondary			
Efficacy	To evaluate the effects of somatropin on other body composition parameters.	• 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, were not 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 LBM (%) 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 LBM (%) measured by DEXA (adult cohort only).
Safety	To evaluate the safety and tolerability of somatropin.	• N/A.	• AE. • SAE. • Clinical laboratory values. • Bone maturation.

AE = adverse event, BIA = bioelectrical impedance analysis, CT = computed tomography, DEXA = dual-energy X-ray absorptiometry, GH = growth hormone, LBM = lean body mass, LS = least square, N/A = not applicable, PWS = Prader-Willi syndrome, SAE = serious adverse event.

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Methodology:

Refer to the PCD CSR synopsis for information on study design.

Number of Participants (Planned and Analyzed):

Refer to the PCD CSR synopsis for information on number of participants.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Refer to the PCD CSR synopsis for information on diagnosis and main criteria for inclusion and exclusion.

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

Refer to the PCD CSR synopsis for information on study interventions, dose, and mode of administration and manufacturing lot numbers for the study interventions dispensed in this study until PCD. The study interventions, dose, and mode of administration and manufacturing lot numbers for the study interventions dispensed in this study after PCD are provided in Table S2.

Table S2. Study Interventions Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Somatropin 12 mg powder for injection (genetic recombination)	FM1234	22-AE-00661	12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	GG2539	23-AE-00919	12 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	ER3745	22-AE-00470	5.3 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	FR1729	22-AE-00817	5.3 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	GD8205	23-AE-00920	5.3 mg	Commercial product

Duration of Study Intervention:

Refer to the PCD CSR synopsis for information on duration of study intervention.

Summary of Results:

Demographic and Other Baseline Characteristics:

Refer to the PCD CSR synopsis for the summary of demographic characteristics and there is no further update after PCD in any cohort.

Exposure:

The average treatment duration was 137.69 weeks, 132.76 weeks, and 126.49 weeks for the growth hormone (GH) naïve pediatric cohort, GH treated pediatric cohort, and adult cohort,

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respectively. The average actual administered dosage was 0.21 mg/kg/week, 0.15 mg/kg/week, and 0.07 mg/kg/week for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively.

Analysis Population:

Refer to the PCD CSR synopsis for information on analysis population and there is no further update.

Efficacy Results:

Primary Endpoint Result:

Change From Baseline to Month 12 in Lean Body Mass (%) Measured by Dual-Energy X-ray Absorptiometry:

Refer to the PCD CSR synopsis for the summary of change from baseline to Month 12 in lean body mass (LBM) (%) measured by dual-energy X-ray absorptiometry (DEXA) for each cohort and there is no further update.

Secondary Endpoints Results:

Change From Baseline to Month 12 in LBM (%) Measured by Bioelectrical Impedence Analysis:

Refer to the PCD CSR synopsis for the summary of change from baseline to Month 12 in LBM (%) measured by bioelectrical impedence analysis (BIA) for each cohort and there is no further update.

Change From Baseline to Month 12 in Body Fat (%) Measured by DEXA:

Refer to the PCD CSR synopsis for the summary of change from baseline to Month 12 in body fat (%) measured by DEXA for each cohort and there is no further update.

Change From Baseline to Month 12 in Adipose Tissue Distribution Measured by Abdominal Computed Tomography:

Refer to the PCD CSR synopsis for the summary of change from baseline to Month 12 in adipose tissue distribution measured by abdominal computed tomography for each cohort and there is no further update.

Change From Baseline to Month 6 in LBM (%) Measured by DEXA (Adult Cohort Only):

Refer to the PCD CSR synopsis for the summary of change from baseline to Month 6 in LBM (%) measured by DEXA for adult cohort and there is no further update.

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Safety Results:

There were no deaths reported during the study. Overall, 4 participants reported 7 serious adverse events (SAEs) (3 participants in the adult cohort reported 6 SAEs: 3 SAEs of brain contusion, skull fractured base, sinus node dysfunction in 1 participant; 2 SAEs of hypertension and seizure in 1 participant, and 1 SAE of affect lability in 1 participant; and 1 participant in the GH treated pediatric cohort reported 1 SAE of ankle fracture). There were no treatment-related SAEs in this study. Overall, at least 1 treatment-emergent adverse event (TEAE) was experienced by 5 (83.3%), 7 (100.0%), and 19 (95.0%) participants in the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively. Most of the TEAEs were mild or moderate in severity (unrelated to the study drug) and 4 (20.0%) participants in the adult cohort had severe TEAEs. No TEAEs resulted in discontinuation from study, but 3 (15%) participants in the adult cohort discontinued study drug due to TEAEs (ie, severe unrelated TEAE [sleep apnoea syndrome], moderate unrelated TEAE [Type 2 diabetes mellitus] and mild related TEAE [Type 2 diabetes mellitus]) and were continued in the study. Three (50.0%) participants in the GH naïve pediatric cohort, 2 (28.6%) participants in the GH treated pediatric cohort, and 7 (35.0%) participants in the adult cohort had dose reduced or temporarily discontinued the study drug due to TEAEs.

Refer to the PCD CSR synopsis for details on TEAEs at PCD.

After PCD, in addition to the PCD data 3 new SAEs were reported in adult cohort (2 participants who already experienced SAEs during the PCD CSR also experienced 1 more SAE each [sinus node dysfunction and seizure] and 1 additional participant experienced an SAE of affect lability). All SAE reported after PCD were not related to study drug. There were additional 2 participants in the GH treated pediatric cohort who experienced at least 1 TEAE and there were no updates in the GH naïve pediatric cohort and adult cohort. Two additional participants in the adult cohort had severe TEAEs. Two more participants in the adult cohort discontinued the study drug but continued the study due to moderate unrelated TEAE of Type 2 diabetes mellitus and mild related TEAE of Type 2 diabetes mellitus. One participant each in the GH naïve pediatric cohort and GH treated pediatric cohort had dose reduction or temporary discontinuation from the study due to TEAEs. No additional participant in the adult cohort experienced dose reduction or temporarily discontinuation from the study drug due to TEAEs.

Clinical Laboratory Evaluation:

Overall, 24 participants reported laboratory test abnormalities (5 [83.3%], 3 [42.9%], and 16 [80.0%] participants in the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively).

After PCD, in addition to the PCD data, 1 more participant in the GH treated pediatric cohort had laboratory test abnormalities and there is no update in number of participants with laboratory test abnormalities in the GH naïve pediatric cohort and adult cohort.

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No aspartate aminotransferase related abnormalities were reported in the study. There were no participants in the study who met the Hy's Law criteria.

Vital Signs and Auxological Findings:

No notable changes from baseline in vital signs were found in the study.

Overall, the mean change in height standard deviation score (SDS) from baseline to Month 36 increased in the GH naïve pediatric cohort (mean ± SD: 1.1 ± 0.34) while it was unchanged in the GH treated pediatric cohort and adult cohort (mean ± SD: -0.1 ± 0.26 and 0.0 ± 0.11, respectively). After PCD, changes from baseline in the height SDS remained consistent with the data at PCD.

Physical Examination and Bone Maturation Findings:

Most of the participants had normal physical examination results throughout the study.

Bone maturation at Month 12 was <1.0 in most of the evaluable participants.

Conclusions:

Refer to the PCD CSR synopsis for the conclusions based on data up to PCD. Based on data in extension period/safety follow-up beyond Month 12, the following conclusions are provided:

Efficacy Conclusions:

- The efficacy conclusions in the PCD CSR synopsis remained unchanged despite the addition of results in extension period beyond Month 12, which were generally consistent with the overall results of the primary and secondary efficacy endpoints.

Safety Conclusions:

- The safety conclusions in the PCD CSR synopsis remained unchanged despite addition of results in extension period/safety follow-up beyond Month 12.

- The long-term treatment with somatropin was generally safe and well-tolerated in Japanese participants with PWS and no new safety signals were identified from the study.

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SYNOPSIS

Study Title: 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 Number: A6281323

Regulatory Agency or Public Disclosure Identifier Number: NCT04697381

Study Phase: 3

Name of Study Intervention: PNU-180307

Name of Sponsor/Company: Pfizer Japan Inc.

CSR Version and Report Date: v1.0 and 10 Mar 2023

Number of Study Center(s) and Investigator(s):

A total of 33 participants were enrolled at 5 sites in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not applicable

Study Period:

The study initiation date was 09 Feb 2021 and the primary completion date was 06 Dec 2022.

This study was neither discontinued nor interrupted.

Rationale:

Somatropin is a 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 without epiphyseal closure associated with PWS in 2002 but is not approved for the use of 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

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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. The purpose of the present study was to evaluate the efficacy and safety of somatropin in Japanese patients with PWS in response to the MHLW development request issued on 19 Sep 2019.

Objectives, Endpoints, and Statistical Methods:

Table S1. Objectives, Estimands and Endpoints

Type and Objective	Estimands	Endpoints
Primary		
• Efficacy • 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 LBM (%) 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, was not 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 LBM (%) measured by DEXA.
Secondary:		
• To evaluate the effects of somatropin on other body composition parameters	• 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, was not 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 LBM (%) 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 LBM (%) measured by DEXA (adult cohort only).
CCI		
• CCI	• CCI	• CCI

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• CCI [redacted]	• CCI [redacted]	• CCI [redacted]
Safety		
• To evaluate the safety and tolerability of somatropin	• N/A.	• AE. • SAE. • Clinical laboratory values. • Bone maturation.

AE = adverse event, BIA = bioelectrical impedance analysis, BMI = body mass index, CT = computed tomography, DEXA = dual-energy X-ray absorptiometry, GH = growth hormone, IGF-1 SDS = insulin-like growth factor-1 standard deviation score, LBM = lean body mass, LS = least square, N/A = not applicable, PWS = Prader-Willi syndrome, SAE = serious adverse event

Methodology:

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

Number of Participants (planned and analyzed):

A total of 33 participants completed the screening phase of the study. None of the participants discontinued during the screening phase or treatment phase.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Participants were eligible to be included in the study only if all the following criteria applied:

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

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

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

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4. Participants, and if required by local/site regulations their parent(s)/legal guardian(s) were 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 16.1.1, Protocol Section 10.1 for the detailed process of obtaining consent.

For inclusion of GH naïve pediatric cohort, participants met 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 met 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 was higher than 0.084 mg/kg/week.

10. Participants who were 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 met 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.

Participants were excluded from the study if any of the following criteria applied:

Medical conditions:

14. Participants with uncontrolled diabetes at the discretion of the investigator.

15. Participants with malignant tumors.

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16. Participants with severe obesity or serious respiratory impairment.

17. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that could increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concurrent Clinical Study Experience:

18. 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).

19. 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.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Somatropin 12 mg powder for injection (genetic recombination)	CW2351	20-003817	12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	CY7175	21-000524	12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	DT3211	21-AE-00357	12 mg	Commercial product
Somatropin 12 mg powder for injection (genetic recombination)	FM1234	22-AE-00661	12 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	DP6458	20-003818	5.3 mg	Commercial product
Somatropin 5.3 mg powder for injection (genetic recombination)	DR4949	21-000525	5.3 mg	Commercial product

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Table S2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Somatropin 5.3 mg powder for injection (genetic recombination)	ER3745	22-AE-00470	5.3 mg	Commercial product

Dose regimens in each cohorts are as below (the weekly dose was 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 was adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose could be increased but should not have exceeded 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 was adjusted according to participants' symptoms and serum IGF-1 levels at the discretion of the investigator. The weekly dose could be increased but should not have exceeded 1.6 mg/day.

Duration of Study Intervention:

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 was sooner.

Summary of Results:

Demographic and Other Baseline Characteristics:

The percentage of male participants in the GH naïve pediatric cohort was 66.7%, the GH treated cohort was 57.1% and the adult cohort was 35.0%. The mean age of the participants was 5.83, 14.86, and 23.90 years in the GH naïve pediatric cohort, GH treated cohort, and adult cohort, respectively.

Exposure:

The average treatment duration was 51.31 weeks, 51.84 weeks and 51.56 weeks, for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively. The

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average actual administered dosage (mg/kg/week) for the GH naïve pediatric cohort was 0.22, GH treated pediatric cohort was 0.16, and the Adult cohort was 0.07.

Analysis Population:

This study consisted of participant analysis sets (FAS and EES) and defined analysis set (adherence to protocol regimen).

- FAS - All participants assigned to study intervention and who took at least one dose of study intervention.
- EES - All participants assigned to study intervention and who took at least one dose of study intervention and had at least one efficacy evaluation.
- Adherence to protocol regimen - For participants who experienced 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 were not considered.

Efficacy Results:

Primary Efficacy Endpoint

- The primary endpoint was the change from baseline to Month 12 in LBM (%) measured by DEXA. The primary efficacy criterion was met since the LS mean (95% CI) of the primary endpoint was 3.09 (1.85, 4.33) and the point estimate was greater than the pre-specified efficacy criterion of 0 for the adult cohort (least squares [LS] mean and its 95% CI of change from baseline were estimated based on an MMRM. In the model, visit, baseline value, and baseline value-by-visit interaction were included as fixed effects).
- For the GH naïve pediatric cohort and the GH treated pediatric cohort, the mean ± SD of the change from baseline to Month 12 in LBM (%) measured by DEXA were 4.59 ± 4.490 and -1.34 ± 3.238, respectively.
- While the sample size was quite limited, the LBM (%) at Month 12 measured by DEXA numerically increased from baseline for the GH naïve pediatric cohort and decreased slightly for the GH treated pediatric cohort. In the GH treated pediatric cohort, the LBM was clinically maintained despite the low dose of study drug which was approximately one-third of the GH naïve pediatric cohort dose. For the adult cohort, the mean ± SD of the change from baseline to Month 12 in LBM (%) measured by DEXA was 3.08 ± 2.917.

Secondary Efficacy Endpoints

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- **Change From Baseline to Month 12 in LBM (%) Measured by BIA:** The LS mean (95% CI) of the change from baseline to Month 12 of LBM (%) measured by BIA was 2.03 (-0.67, 4.73). The mean ± SD of the change from baseline to Month 12 in LBM (%) measured by BIA was 3.32 ± 3.867, 0.58 ± 4.711, and 2.08 ± 5.474 for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively.

- **Change From Baseline to Month 12 in Body Fat (%) Measured by DEXA:** The LS mean (95% CI) of the change from baseline to Month 12 of body fat (%) measured by DEXA was -3.09 (-4.33, -1.85). The mean ± SD of the change from baseline to Month 12 of body fat (%) measured by DEXA was -4.59 ± 4.490, 1.34 ± 3.238, and -3.08 ± 2.917 for the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively.

- **Change From Baseline to Month 12 in Adipose Tissue Distribution Measured by Abdominal CT:** Both the mean SAT (cm^2) and VAT (cm^2) increased in the GH naïve pediatric cohorts at Month 12 compared to baseline. The mean SAT (cm^2) increased whereas the VAT (cm^2) decreased in GH treated pediatric cohorts at Month 12 compared to baseline. In the adult cohort, both the mean SAT (cm^2) and VAT (cm^2) decreased at Month 12 (197.58 and 54.49, respectively).

- **Change From Baseline to Month 6 in LBM (%) Measured by DEXA (Adult Cohort Only):** The LS mean (95% CI) change from baseline to Month 6 in LBM (%) measured by DEXA was 2.38 (1.30, 3.46).

Safety Results:

At least one TEAE was experienced by 5 (83.3%), 5 (71.4%), and 19 (95.0%) participants in the GH naïve pediatric cohort, GH treated pediatric cohort, and adult cohort, respectively. No AEs resulted in discontinuation during 12-month treatment period but 1 participant in the adult cohort discontinued study drug due to a severe unrelated adverse event (sleep apnoea syndrome) and was still in the study up to the cutoff date; however, the event was not related to somatropin. There were no deaths reported during the study. A total of 4 SAEs all not related to study treatment were reported from 3 participants (1 participant in GH treated pediatric cohort and 2 participants in adult cohort). Two (2) (33.3%) participants in the GH naïve pediatric cohort, 1 (14.3%) participant in the GH treated pediatric cohort, and 7 (35.0%) participants in the adult cohort had dose reduced or temporarily discontinued from the study due to AEs.

Conclusions:

Efficacy conclusions:

Primary endpoint

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- The LS mean (95% CI) of the change from baseline to Month 12 in LBM (%) measured by DEXA (i.e., the primary endpoint) in the adult cohort was 3.09 (1.85, 4.33). The primary efficacy criterion was met since the point estimate was greater than the pre specified efficacy criterion of 0 for the adult cohort.

- The study drug resulted in numerical increase in LBM (%) as measured by DEXA from baseline to Month 12 for the GH naïve pediatric cohort (mean ± SD: 4.59 ± 4.490) and remained clinically maintained from baseline for the GH treated pediatric cohort (mean ± SD: -1.34 ± 3.238). The results should be interpreted cautiously due to small sample size.

Secondary endpoints

- The LS mean (95% CI) of the change from baseline to Month 12 of LBM (%) measured by BIA was 2.03 (-0.67, 4.73) for the adult cohort.

- The mean ± SD of the change from baseline to Month 12 of LBM (%) measured by BIA was 3.32 ± 3.867 for the GH naïve pediatric cohort and 0.58 ± 4.711 for the GH treated pediatric cohort.

- The LS mean (95% CI) of the change from baseline to Month 12 of body fat (%) measured by DEXA was -3.09 (-4.33, -1.85) for the adult cohort.

- The mean ±SD of the change from baseline to Month 12 of body fat (%) measured by DEXA was -4.59 ± 4.490) for the GH naïve pediatric cohort and 1.34 ± 3.238) for the GH treated pediatric cohort.

In the adult cohort, the mean SAT (cm^2) and VAT (cm^2) decreased at Month 12 compared to baseline. The mean SAT (cm^2) and VAT (cm^2) increased in the GH naïve pediatric cohort at Month 12 compared to baseline. The mean SAT (cm^2) increased whereas VAT (cm^2) decreased in the GH treated pediatric cohort at Month 12 compared to baseline. CCI [redacted]

- CCI [redacted]

Safety conclusions:

- Somatropin administration was generally safe and well-tolerated in Japanese participants with PWS and no new safety signals were identified from the study.

- No deaths were reported during the study.

- No participant was withdrawn from the study due to TEAE in the treatment phase.

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- No treatment-related SAEs were reported.