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Clinical Research Article

Liraglutide for Weight Management in Children and Adolescents With Prader–Willi Syndrome and Obesity

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Abstract

Context: Prader–Willi syndrome (PWS) is characterized by lack of appetite control and hyperphagia, leading to obesity. Pharmacological options for weight management are needed.

Objective: To determine whether liraglutide treatment for weight management is superior to placebo/no treatment in pediatric individuals with PWS.

Methods: This was a multicenter, 52-week, placebo-controlled trial with a 16-week double-blinded period. Adolescents (n = 31, aged 12-17 years; Tanner stage 2-5) and children (n = 24, aged 6-11 years; Tanner stage <2) with PWS and obesity were included. Patients were randomized 2:1 to liraglutide 3.0 mg (or maximum-tolerated dose) or placebo for 16 weeks, after which placebo was stopped. Liraglutide was continued for 52 weeks. All patients followed a structured diet and exercise program throughout the trial. The coprimary endpoints were change in body mass index (BMI) standard deviation score (SDS) from baseline to 16 and 52 weeks. Secondary endpoints included other weight-related parameters, hyperphagia, and safety.

Results: Change in BMI SDS from baseline to weeks 16 and 52 was not significantly different between treatments in adolescents (estimated treatment difference: −0.07 at week 16 and −0.14 at week 52) and children (−0.06 and −0.07, respectively). Changes in other weight-related parameters between treatments were not significant. At week 52, hyperphagia total and drive scores were lower in adolescents treated with liraglutide vs no treatment. The most common adverse events with liraglutide were gastrointestinal disorders.

Conclusion: Although the coprimary endpoints were not met, changes in hyperphagia total and drive scores in adolescents warrant further studies on liraglutide in this population.

Key Words: Prader–Willi Syndrome, obesity, children, adolescents, pediatric population, BMI SDS

Abbreviations: BMI, body mass index; ETD, estimated treatment difference; GH, growth hormone; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, multiple imputation; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9; PWS, Prader–Willi syndrome; SDS, standard deviation score.

Prader–Willi syndrome (PWS), a rare genetic disorder caused by the loss of expression of the genes in locus q11-q13 (PWS region) on paternal chromosome 15, is associated with various developmental and behavioral problems in children, including difficulty in controlling appetite (1). In early childhood, patients with PWS begin displaying obsessive food-seeking behavior and lack of appetite control. Hyperphagia and obesity represent major causes of morbidity and mortality in children and adolescents with this syndrome (2-5). In clinical practice, weight management in patients with PWS is predominantly achieved by diet and exercise with rigorous restriction of food access. However, food restriction may be difficult to implement and can create tension between patients and caregivers, leading to behavioral difficulties (6). Thus, pharmacological options for weight management are needed.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that alters the activity of hypothalamic neurons in the arcuate nucleus directly associated with eating behavior,

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thereby increasing satiety and reducing energy intake, leading to weight loss (7). Liraglutide is approved for weight management at once-daily doses of 3.0 mg in adults with obesity (body mass index [BMI] ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbidity (8-11). In adolescents with obesity, liraglutide 3.0 mg as an adjunct to lifestyle interventions is effective for weight loss (12) and is approved for weight management in patients aged 12-17 years (10, 11). Given its benefits on appetite regulation and weight loss in adults and adolescents, this study aimed to investigate the efficacy and safety of liraglutide in children and adolescents with PWS and obesity vs placebo at 16 weeks, and vs no treatment at 52 weeks as adjunct to a structured diet and exercise program.

Materials and Methods

Study Design and Locations

This 52-week, randomized, placebo-controlled, parallel-group trial included a 16-week double-blind period and 36-week open-label period, with a 2-week off-drug follow-up period (Fig. S1 (13)). The trial was conducted at 20 sites in Australia, Canada, France, Italy, The Netherlands, New Zealand, Turkey, and the United States in accordance with the Declaration of Helsinki. An independent external data monitoring committee oversaw the safety of the participants and evaluated the benefit–risk balance. Written informed consent was obtained from all patients and/or parents or legal representatives; informed assent was obtained from participants if applicable (based on age and local regulation) before the initiation of any trial-related procedures. The sponsor was responsible for the design and conduct of the trial, and for data collection and analysis. The authors had full access to data, participated in drafting and critical revision of the manuscript, made the decision to submit the manuscript for publication, and guarantee the accuracy and completeness of the data and adherence to the trial protocol. Support for drafting the manuscript was provided by a medical writer, funded by the sponsor, under the supervision of the authors.

Patients

Male or female adolescents aged ≥12 to <18 years with pubertal development Tanner stage 2-5 and children aged ≥6 to <12 years with Tanner stage <2 (premature adrenarche permitted) with genetically confirmed PWS were eligible for inclusion if they met the following criteria: obesity, defined as BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points (14) and ≥95th percentile for age and sex; and stable body weight, defined as a self-reported weight change of <10 kg during the 90 days before screening. Key exclusion criteria included diagnosis of type 1 or 2 diabetes, documented or untreated adrenal insufficiency, and suggestive history or significant risk of gastroparesis (eg, marked abdominal bloating postmeal, history of vomiting, severe constipation), as judged by the investigator. Concomitant growth hormone treatment was permitted if initiated prior to randomization and maintained until the end of the open-label period (ie, no starting or stopping therapy; dose adjustments were permitted). Full exclusion criteria are detailed elsewhere (13).

Randomization and Blinding

Patients were randomly assigned using an interactive web voice/web response system. Randomization was stratified according to pubertal status and presence or absence of dysglycemia. At screening, all patients were assigned a unique randomization number that remained the same throughout the trial. Patients and investigators were blinded to the assigned study treatment for the first 16 weeks of treatment. Treatment allocation was unblinded after week 16.

Treatment Interventions

All patients received individualized dietary and physical activity counseling as a structured program with the goal of achieving weight loss during the trial. Within 2 weeks of screening, patients were randomized 2:1 to liraglutide 3.0 mg (or maximum-tolerated dose) or matched placebo for the initial 16 weeks (double-blind period). From weeks 17 to 52, patients assigned to liraglutide continued receiving their randomized treatment and patients assigned to placebo received no treatment apart from diet and exercise (open-label period) (Fig. S1 (13)). Liraglutide or placebo was administered once daily as subcutaneous injections in the abdomen, thigh, or upper arm. Liraglutide was initiated at 0.6 mg and escalated in weekly increments of 0.6 mg until the target or maximum-tolerated dose was achieved. For children (aged ≥6 to <12 years) with body weight <45 kg, liraglutide was initiated at 0.3 mg up to a maximum dose of 2.4 mg as a precautionary measure due to the difficulty in relying on symptomology to assess tolerability in children with PWS.

Outcomes

The coprimary efficacy endpoints were change in BMI standard deviation score (BMI SDS) from baseline to 16 weeks and to 52 weeks. BMI SDS is a measure of the number of SDs from the population mean BMI, matched for age and sex. Key supportive secondary endpoints included the proportion of patients achieving ≥5% and ≥10% reduction in baseline BMI at weeks 16 and 52; proportion of patients with no increase in baseline BMI SDS at weeks 16 and 52; changes from baseline to week 16 and week 52 in BMI, body weight (%, kg), waist circumference, waist-to-hip circumference ratio, hyperphagia score (total score, hyperphagic behavior, drive, and severity scores, assessed using Dykens original 13-item questionnaire (15)), high sensitivity C-reactive protein, fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, very-low-density lipoprotein cholesterol, triglycerides, and free fatty acids), systolic and diastolic blood pressure, and glucose metabolism parameters (glycated hemoglobin, fasting plasma glucose, fasting insulin, fasting C-peptide, glycemic category, homeostasis model assessment of beta-cell function, and insulin resistance parameters). Safety endpoints included the number of treatment-emergent adverse events and hypoglycemic episodes reported during the in-trial period (from baseline to week 52). Mental health was assessed in adolescents (aged ≥12 to <18 years) using the Columbia-Suicide Severity Rating Score questionnaire and the Patient Health Questionnaire-9 (PHQ-9). Additional secondary endpoints are detailed elsewhere (13).

Statistical Analysis

This was a superiority study comparing liraglutide with placebo. For the first coprimary endpoint, a sample size of

57 patients was determined to provide the trial with a power of 80% to demonstrate a significant treatment difference between liraglutide and placebo of −0.23 (corresponding to a 5-6% decrease in BMI), with a SD of 0.25 and a withdrawal rate of 10% at week 16.

All randomized patients who received at least 1 dose of the trial product and had postrandomization data were included in the full analysis set. The safety analysis set included all patients exposed to at least 1 dose of the trial product.

For the coprimary endpoints, data were analyzed in the full analysis set according to the intention-to-treat principle, using an analysis of covariance model with randomized treatment, sex, region, Tanner stage, and baseline glycemic category (presence or absence of dysglycemia) as factors, and baseline age and BMI SDS as covariates. Tanner stage and baseline glycemia were also used as interaction factors for the model. The superiority of liraglutide vs placebo was assessed in hierarchical order starting at 16 weeks before testing superiority at 52 weeks, with superiority at a significance level of 5%. For the secondary endpoints, comparisons were not adjusted for multiplicity. Hypothesis testing was 2-sided, and data are presented as estimated treatment differences (ETDs) with 95% CIs. Missing data were handled by a jump-to-reference multiple imputation method, using all available assessments at the respective landmark visits in the placebo group, under the assumption that patients who discontinued treatment responded as if they had been treated with placebo for the entire trial. Safety data were analyzed descriptively in the safety analysis set. Further details of the statistical methods are provided elsewhere (13). SAS (version 9.4) was used to perform the analysis.

Results

Characteristics of Patients

The trial was initiated on November 9, 2015, and completed on November 19, 2020. A total of 64 patients were screened, of whom 32 adolescents and 24 children were randomized and received study treatment (Fig. 1). One adolescent was excluded from the full analysis set owing to a lack of postbaseline data. In patients randomized to liraglutide, 94.7% of adolescents and 58.8% of children reached the target dose of 3.0 mg. Of those randomized to placebo, 91.7% of adolescents and 71.4% of children reached a target dose of 3.0 mg. Seven children (5 randomized to liraglutide and 2 randomized to placebo) had body weight below 45 kg, and those randomized to liraglutide received liraglutide at the target dose of 2.4 mg (Table S1 (13)). Most baseline patient characteristics were balanced across treatment arms (Table 1 and Table S2 (13)). However, some imbalances were noted. In adolescents randomized to liraglutide vs placebo, 52.6% were female (vs 41.7%), mean BMI was 36.3 kg/m^2 (vs 40.2 kg/m^2), and body weight was 90.1 kg (vs 102.0 kg). In children randomized to liraglutide vs placebo, 64.7% were female (vs 28.6%), mean BMI was 32.4 kg/m^2 (vs 30.3 kg/m^2), and body weight was 57.1 kg (vs 55.5 kg). Mean BMI SDS was 3.35 in adolescents receiving liraglutide and 4.02 in those receiving placebo. In children, BMI SDS was 4.89 and 4.17 in those receiving liraglutide and placebo, respectively. The proportions of adolescents receiving concomitant growth hormone treatment during the study were 42.1% in the liraglutide arm and 50.0% in the placebo arm. The proportions of children receiving growth hormone treatment in the liraglutide and placebo arms were 47.1% and 57.1%, respectively.

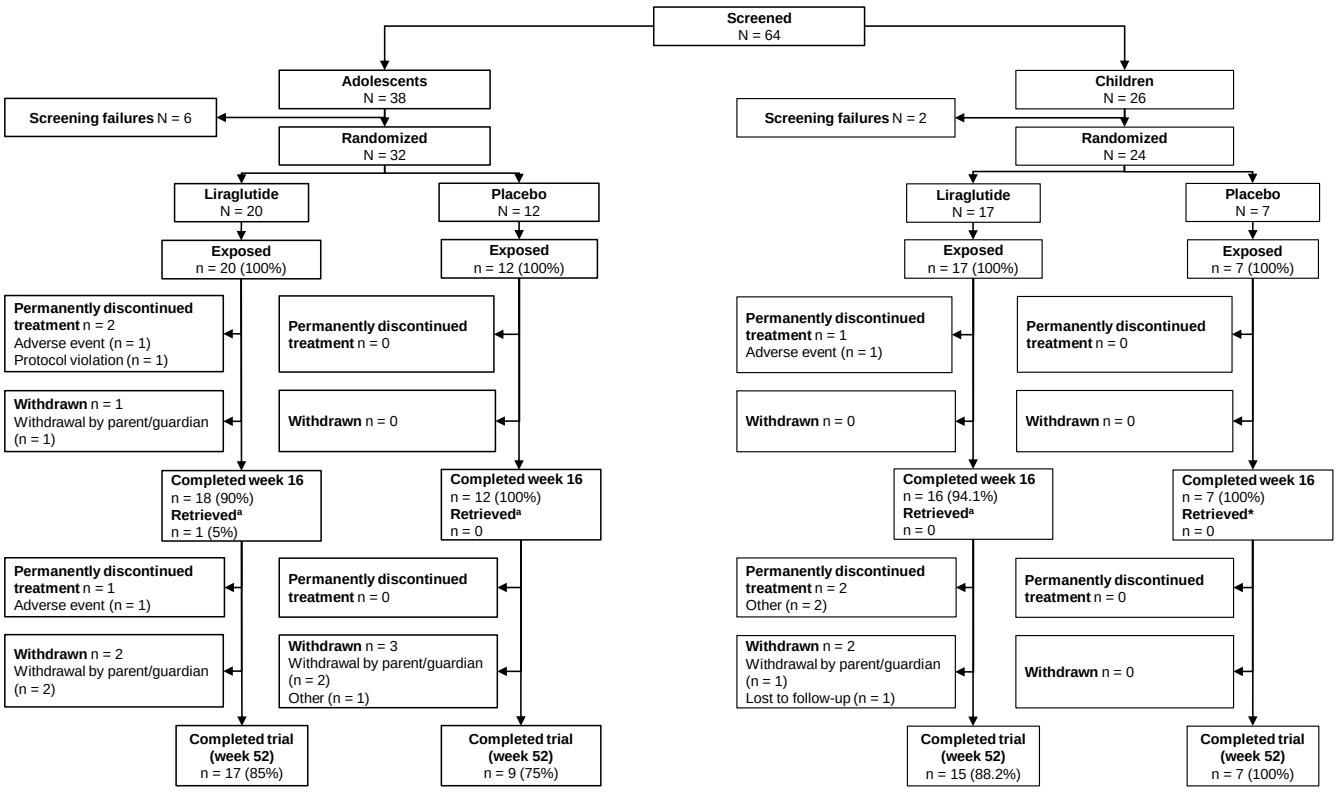

Figure 1. Consolidated standards of reporting trials flowchart. [a]Participants who permanently discontinued treatment but attended week 16 visit.

Table 1. Baseline characteristics of children and adolescents enrolled in the trial (full analysis set)

Parameter	Adolescents			Children		
	Liraglutide (n = 19)	Placebo (n = 12)	Total (n = 31)	Liraglutide (n = 17)	Placebo (n = 7)	Total (n = 24)
Age, years	14.4 ± 1.9	14.1 ± 1.9	14.3 ± 1.9	8.1 ± 1.7	9.4 ± 1.6	8.5 ± 1.8
Female, n (%)	10 (52.6)	5 (41.7)	15 (48.4)	11 (64.7)	2 (28.6)	13 (54.2)
Race, n (%)						
Black or African American	2 (10.5)	0	2 (6.5)	1 (5.9)	0	1 (4.2)
White	11 (57.9)	6 (50.0)	17 (54.8)	10 (58.8)	7 (100)	17 (70.8)
Other	1 (5.3)	2 (16.7)	3 (9.7)	3 (17.6)	0	3 (12.5)
Not applicable[a]	5 (26.3)	4 (33.3)	9 (29.0)	3 (17.6)	0	3 (12.5)
Tanner stage, n (%)						
Stage 1	—	—	—	17 (100)	7 (100)	24 (100)
Stage 2	4 (21.1)	0	4 (12.9)	—	—	—
Stage 3	7 (36.8)	6 (50.0)	13 (41.9)	—	—	—
Stage 4	4 (21.1)	3 (25.0)	7 (22.6)	—	—	—
Stage 5	4 (21.1)	3 (25.0)	7 (22.6)	—	—	—
On GH treatment, n (%)	8 (42.1)	6 (50.0)	14 (45.2)	8 (47.1)	4 (57.1)	12 (50.0)
BMI, kg/m^2	36.3 ± 6.5	40.2 ± 10.7	37.8 ± 8.4	32.4 ± 7.5	30.3 ± 5.5	31.8 ± 6.9
BMI SDS	3.35 ± 1.07	4.02 ± 1.61	3.61 ± 1.32	4.89 ± 2.37	4.17 ± 2.11	4.68 ± 2.28
Hyperphagia total score, (range)	27.9 ± 10.1 (14-49)	30.3 ± 7.98 (20-42)	—	28.2 ± 10.7 (14-46)	29.7 ± 9.79 (20-45)	—
Hyperphagia behavior score, (range)	11.1 ± 4.27 (5-20)	13.0 ± 3.69 (9-20)	—	12.2 ± 4.91 (5-22)	12.4 ± 5.35 (7-22)	—
Hyperphagia drive score, (range)	11.8 ± 4.26 (7-20)	12.1 ± 3.20 (8-18)	—	11.4 ± 4.49 (4-19)	12.7 ± 3.99 (7-17)	—
Hyperphagia severity score, (range)	5.0 ± 2.38 (2-10)	5.3 ± 2.45 (2-10)	—	4.6 ± 2.00 (2-8)	4.6 ± 1.51 (3-7)	—
HbA_{1c}, %	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.6 ± 0.3	5.4 ± 0.3	5.5 ± 0.3
Fasting plasma glucose, mmol/L	4.8 ± 0.6	4.9 ± 0.6	4.9 ± 0.6	4.9 ± 0.4	5.1 ± 0.4	4.9 ± 0.4
Fasting plasma glucose, mg/dL	86.88 ± 10.0	88.60 ± 10.8	87.5 ± 10.1	87.5 ± 7.7	91.4 ± 7.0	88.6 ± 7.6

Data are mean ± SD, unless stated otherwise.
Abbreviations: BMI, body mass index; GH, growth hormone; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SDS, standard deviation score.
[a]Race information was not allowed to be collected from patients recruited from France.

Efficacy

The superiority of liraglutide was not confirmed for the coprimary endpoints, as no statistically significant differences were observed between liraglutide and placebo/no treatment in BMI SDS from baseline for either adolescents (ETD [95% CI] −0.07 [−0.23, 0.09]; $P = .38$ at week 16 and −0.14 [−0.62, 0.34]; $P = .57$ at week 52) or children (−0.06 [−1.06, 0.93]; $P = .90$ at week 16 and −0.07 [−0.89, 0.76]; $P = .88$ at week 52; Table 2 and Fig. 2).

The proportion of patients with a reduction of ≥5% in BMI from baseline at week 16 or 52 did not differ between treatment arms (Table 2 and Fig. S2 (13)). Few patients achieved ≥10% reduction in BMI from baseline at either timepoint (Table 2); thus, this endpoint was not analyzed statistically. The proportion of adolescents with no increase in BMI SDS at weeks 16 and 52 was similar between treatment groups (Fig. S3 (13)). Change in body weight was similar between treatment groups at weeks 16 (ETD [95% CI] −1.39 kg [−5.23, 2.44] in adolescents and −0.16 kg [−5.55, 5.22] in children) and 52 (−2.48 kg [−12.81, 7.86] in adolescents and −1.91 kg [−10.74, 6.93] in children; Fig. S4 and Fig. S5 (13)). No significant changes in other body weight-related parameters were reported between treatment arms at weeks 16 and 52 in either adolescents or children (Fig. S5 (13)). At week 52, reductions in hyperphagia total score (ETD [95% CI] −6.42 [−11.40, −1.45]) and hyperphagia drive score (−3.87 [−7.45, −0.30]) were observed for liraglutide vs no treatment in adolescents; however, the analysis was not controlled for type 1 error (Table 3 and Fig. S6 (13)). Changes from baseline in vital signs, glycemic parameters, and fasting lipids were not significantly different between treatments, except for a reduction in fasting plasma glucose with liraglutide (without type 1 error control) in adolescents observed at week 16 (Fig. S7, Fig. S8, and Table S3 (13)).

Safety Outcomes

The most common adverse events with liraglutide were gastrointestinal disorders (Table 4). Gastrointestinal events were reported throughout the trial, most were mild or moderate in severity, and were more frequently reported with liraglutide than with placebo (55.0% of patients [52 events] vs

Table 2. Primary and selected secondary efficacy outcomes relating to BMI in children and adolescents (full analysis set)

		Adolescents (n = 31)			Children (n = 24)		
		Liraglutide	Placebo	ETD vs placebo/ no treatment (95% CI; *P* value)	Liraglutide	Placebo	ETD vs placebo/ no treatment (95% CI; *P* value)
Change in mean BMI SDS	Week 16	−0.20 ± 0.05	−0.13 ± 0.06	−0.07 (−0.23, 0.09; *P* = .38)	−0.50 ± 0.28	−0.44 ± 0.33	−0.06 (−1.06, 0.93; *P* = .90)
	Week 52	−0.31 ± 0.13	−0.17 ± 0.21	−0.14 (−0.62, 0.34; *P* = .57)	−0.73 ± 0.21	−0.67 ± 0.32	−0.07 (−0.89, 0.76; *P* = .88)
				OR vs placebo/no treatment (95% CI; *P* value)			OR vs placebo/no treatment (95% CI; *P* value)
Estimated proportion (%) of patients with ≥5% BMI reduction	Week 16	23.2	2.5	11.71 (0.45, 305.66; *P* = .14)	34.2	57.2	0.39 (0.04, 3.39; *P* = .39)
	Week 52	30.7	14.1	2.69 (0.32, 22.95; *P* = .36)	33.0	38.4	0.79 (0.08, 7.61; *P* = .84)
Observed proportion (%) of patients with ≥10% BMI reduction	Week 16	0	0	—	1 (6.3)	1 (14.3)	—
	Week 52	2 (11.8)	0	—	2 (14.3)	2 (28.6)	—

Data are estimated means ± standard error, unless otherwise specified.
For secondary endpoints, *P* values were not adjusted for multiplicity.
Abbreviations: BMI, body mass index; ETD, estimated treatment difference; OR, odds ratio; SDS, standard deviation score.

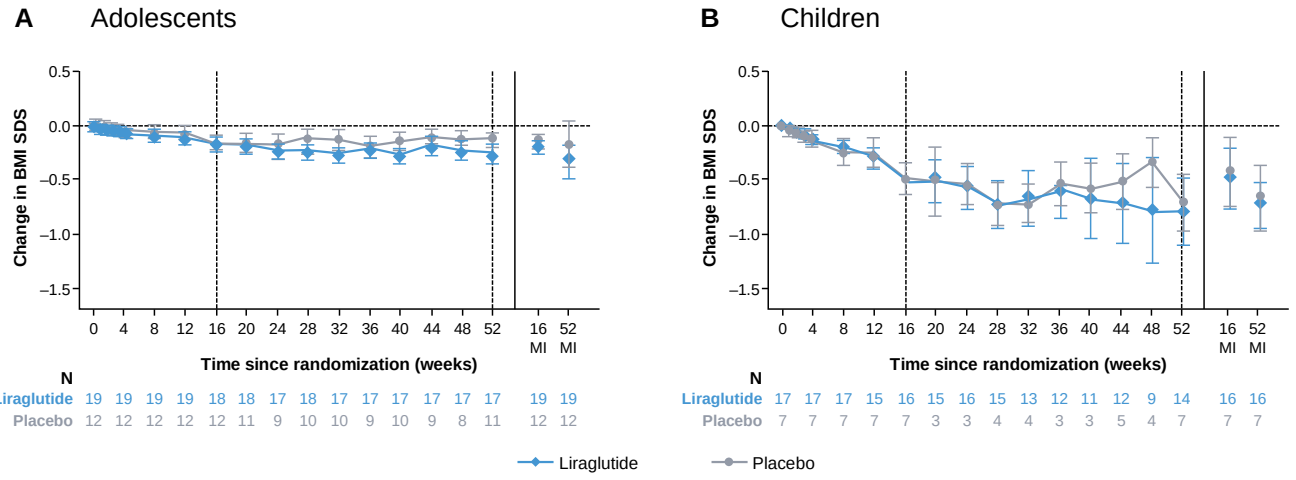

Figure 2. Change in BMI SDS in adolescents and children during the trial (full analysis set). Data are observed mean change in BMI SDS from baseline by treatment week for adolescents (A) and children (B) during the in-trial period. MI represents the estimated change in BMI SDS at week 16 and week 52 using an analysis of covariance model. Error bars are standard error of the mean. Abbreviations: BMI, body mass index; MI, multiple imputation; N, number of patients with available BMI SDS measurements; SDS, standard deviation score.

41.7% [9 events] in adolescents and 58.8% [91 events] vs 28.6% [2 events] in children, with liraglutide and placebo, respectively; Table 4 and Fig. S9 (13)). The most common gastrointestinal disorders were diarrhea and abdominal pain, with more than half of the diarrhea events being reported by 1 child.

Few serious adverse events were reported during the study (Table 4 and Table S4 (13)). All serious adverse events except 1 case of cholelithiasis in the liraglutide group were considered unlikely to be related to the trial product by the investigator and most were resolved (Table S4 (13)).

Treatment-emergent hypoglycemic events were classified according to the American Diabetes Association 2018, International Society for Pediatric and Adolescent Diabetes 2018, and International Hypoglycaemia Study Group 2017 criteria (16-18). Two adolescents treated with liraglutide experienced 1 episode each of clinically significant hypoglycemia (<3.0 mmol/L [54 mg/dL]) (Table S5 (13)). One child treated with liraglutide experienced an episode of severe hypoglycemia. However, this episode (plasma glucose 3.6 mmol/L [65 mg/dL]) did not meet the American Diabetes Association 2018, International Society for Pediatric and Adolescent

Table 3. Hyperphagia outcomes in children and adolescents (full analysis set)

Change in mean hyperphagia questionnaire		Adolescents (N = 31)			Children (N = 24)		
		Liraglutide	Placebo	ETD vs placebo/ no treatment (95% CI; *P* value)	Liraglutide	Placebo	ETD vs placebo/ no treatment (95% CI; *P* value)
Total score	Week 16	−2.87 ± 1.33	−2.13 ± 1.71	−0.74 (−5.42, 3.94; *P* = .75)	−2.63 ± 1.42	−5.47 ± 2.41	2.85 (−3.55, 9.24; *P* = .36)
	Week 52	−4.97 ± 1.42	1.46 ± 2.04	−6.42 (−11.40, −1.45; *P* = .01)	−1.26 ± 2.08	−2.65 ± 3.81	1.38 (−7.58, 10.34; *P* = .76)
Hyperphagia behavior score	Week 16	−1.12 ± 0.73	−1.23 ± 0.94	0.11 (−2.49; 2.71; *P* = .93)	−1.04 ± 0.75	−2.90 ± 1.26	1.85 (−1.48, 5.18; *P* = .26)
	Week 52	−1.35 ± 0.65	0.28 ± 1.08	−1.63 (−4.12, 0.85; *P* = .20)	−0.73 ± 4.38	−1.06 ± 8.14	0.33 (−12.98, 13.65; *P* = .96)
Hyperphagia drive score	Week 16	−1.03 ± 0.57	−0.78 ± 0.73	−0.25 (−2.26, 1.76; *P* = .80)	−1.55 ± 0.61	−2.52 ± 1.04	0.97 (−1.79, 3.74; *P* = .47)
	Week 52	−2.19 ± 0.98	1.68 ± 1.50	−3.87 (−7.45, −0.30; *P* = .03)	−0.54 ± 1.01	−0.47 ± 1.81	−0.08 (−4.38, 4.23; *P* = .97)
Severity score	Week 16	−0.63 ± 0.40	−0.25 ± 0.52	−0.38 (−1.81, 1.05; *P* = .58)	0.01 ± 0.37	−0.17 ± 0.63	0.19 (−1.48, 1.85; *P* = .82)
	Week 52	−1.39 ± 0.56	−0.33 ± 1.10	−1.06 (−3.43, 1.30; *P* = .38)	−0.26 ± 0.76	−1.33 ± 1.34	1.08 (−2.13, 4.28; *P* = .51)

Data are estimated means ± standard error, unless otherwise specified.
P values were not adjusted for multiplicity.
Hyperphagia questionnaire is a 13-item informant measure rated on a 5-point scale, 1 = not a problem to 5 = severe and/or frequent problem.
Abbreviations: ETD, estimated treatment difference.

Diabetes 2018, and International Hypoglycaemia Study Group 2017 criteria for severe hypoglycemia as the child did not have cognitive impairment associated with the event; this classification was used because of the need for assistance due to the patient's young age.

No adolescents reported suicidal ideation of type 4 or 5 with the Columbia-Suicide Severity Rating Score questionnaire (Fig. S10 (13)). No adolescents presented with a PHQ-9 score of ≥15. A shift to a more severe category in PHQ-9 was observed in 2 adolescents in the placebo group at week 16 and in 1 at week 52, and in none treated with liraglutide (Fig. S11 (13)).

There was no apparent effect on growth or pubertal development, based on growth velocity (change in height cm/year) and Tanner stage assessment (breast development/testicular volume and pubic hair) (Table S6 (13)). No clinically relevant changes in biochemistry, hematology, or hormonal parameters were observed, nor any unexpected findings with respect to plasma amylase, lipase, and calcitonin. Some fluctuations were observed in mean resting pulse rate; however, there were no significant differences in the change in pulse rate between treatment arms in either population at week 16 or week 52 (Fig. S12 (13)).

Among patients receiving liraglutide, 4 (10.8%) had antiliraglutide antibodies at a single visit only (2 at week 16 [1 adolescent, 1 child] and 2 at week 54 [2 adolescents]). Two children (5.4% of patients) had antiliraglutide antibodies at 2 visits (1 at week 16 and week 52 and 1 at week 16 and week 54). No patients had neutralizing antibodies (Table S7 (13)).

Discussion

This 52-week trial investigated the effect of liraglutide on weight management in children and adolescents with PWS and obesity. In our trial, BMI SDS was reduced from baseline in both children and adolescents but was not significantly different between liraglutide and placebo at week 16 or with no treatment at week 52. Consistent with the coprimary endpoint findings, no significant differences were seen between liraglutide and placebo/no treatment groups for other weight-related endpoints at 16 or 52 weeks. By comparison, treatment with liraglutide for 56 weeks in adolescents with obesity but without PWS was superior to placebo in reducing BMI SDS, with numerical improvements observed for other weight-related endpoints for liraglutide vs placebo (12). In another study, treatment with liraglutide or exenatide for 24 months in 6 adults with PWS and type 2 diabetes showed a tendency towards decreased BMI and waist circumference (19).

The lack of effect of liraglutide on reducing BMI SDS in this population is not completely understood, but may be related to the underlying hypothalamic dysregulation that characterizes PWS (6), which may hinder the known effect of liraglutide on appetite centers in the hypothalamus (20). However, it should be noted that GLP-1 receptor agonist treatment has been shown to be efficacious in some patients

Table 4. Adverse events reported during the in-trial period (safety analysis set)

	Adolescents						Children					
	Liraglutide (N = 20)			Placebo (N = 12)			Liraglutide (N = 17)			Placebo (N = 7)		
	n (%)	Events	Rate	n (%)	Events	Rate	n (%)	Events	Rate	n (%)	Events	Rate
Adverse event	17 (85.0)	138	7073.5	11 (91.7)	76	5666.5	17 (100)	161	9333.7	5 (71.4)	15	2065.5
Serious adverse event	2 (10.0)	3	153.8	2 (16.7)	3	223.7	2 (11.8)	5	289.9	1 (14.3)	1	137.7
Adverse events leading to premature treatment discontinuation	2 (10.0)	2	102.5	0	—	—	1 (5.9)	1	58.0	0	—	—
Severity												
Severe	4 (20.0)	6	307.5	1 (8.3)	1	74.6	2 (11.8)	5	289.9	0	—	—
Moderate	8 (40.0)	30	1537.7	6 (50.0)	18	1342.1	8 (47.1)	32	1855.1	0	—	—
Mild	16 (80.0)	102	5228.2	11 (91.7)	57	4249.9	17 (100)	124	7188.7	5 (71.4)	15	2065.5
Gastrointestinal adverse events system organ class	11 (55.0)	52	2665.4	5 (41.7)	9	671.0	10 (58.8)	91	5275.6	2 (28.6)	2	275.4
Gastrointestinal adverse events by preferred term[a]												
Diarrhea	10 (50.0)	30	1537.7	2 (16.7)	4	298.2	7 (41.2)	63	3652.3	1 (14.3)	1	137.7
Abdominal pain	6 (30.0)	8	410.1	4 (33.3)	4	298.2	3 (17.6)	12	695.7	0	—	—
Abdominal pain upper	1 (5.0)	1	51.3	0	—	—	3 (17.6)	7	405.8	0	—	—
Vomiting	2 (10.0)	3	153.8	0	—	—	3 (17.6)	4	231.9	0	—	—
Constipation	3 (15.0)	4	205.0	0	—	—	0	—	—	0	—	—

Adverse events were reported in the safety analysis set during the in-trial period (baseline to week 52).
Adverse events leading to trial product discontinuation were abdominal pain and aggressive behavior in adolescents, and behavioral disorder in children. One patient (child) reported 51 episodes of diarrhea.
Abbreviation: N, number of participants experiencing at least 1 event; rate of events per 1000 patient-years of observation.
[a]Gastrointestinal adverse events occurring in ≥3 patients in any treatment arm.

with hypothalamic obesity due to hypothalamic damage, including in those with craniopharyngioma, suggesting GLP-1-induced weight loss may not require a functioning and intact hypothalamus. A case series publication highlighted substantial weight loss in 8 patients with hypothalamic obesity due to tumors treated with a GLP-1 receptor agonist (exenatide or liraglutide), with 5 patients experiencing increased satiation (21). All were adults with the exception of 1 17-year-old patient.

Treatment with once-weekly exenatide for 36 weeks was associated with a significant decrease in body fat, waist circumference, and deposition of adipose tissue in the Energy Balance & Weight Loss in Craniopharyngioma-related or Other Hypothalamic Tumors in Hypothalamic Obesity (ECHO) trial, which enrolled 42 10- to 25-year-olds with hypothalamic injury and obesity following an intracranial tumor (22). Reflecting the observations in our study, no significant difference in percent change in BMI on treatment with exenatide vs placebo was observed in this trial (22). Interestingly, a secondary analysis of the ECHO trial concluded that there were greater reductions in adiposity following exenatide treatment in individuals with a higher degree of hypothalamic damage (23).

A study of 10- to 26-year-olds with hypothalamic obesity with suprasellar tumors reported that exenatide treatment was associated with a decrease in energy intake during an ad libitum buffet meal and a decrease in total energy expenditure that was disproportionate to change in body composition (24).

It is important to acknowledge that in the current study hyperphagia total and drive scores (but not other hyperphagia scores) seemed to reduce in adolescents treated with liraglutide, indicating that liraglutide could have had some effect on appetite. Participation in a trial with a structured diet and physical activity program may also have contributed to the overall improvement in weight, as evidenced by the reductions in BMI SDS observed in the placebo/no treatment group.

At week 52, hyperphagia total and drive scores were reduced in adolescents receiving liraglutide compared with no treatment, although it should be noted that this occurred within the open-label period and was not adjusted for multiplicity. In a pilot study in adult patients with PWS and obesity, exenatide 10 μg (another GLP-1 receptor agonist) increased satiety independently of measured appetite hormones (25). Given the burden related to hyperphagia in PWS (26), a potential reduction in hyperphagia with liraglutide is expected to be beneficial to patients and caregivers.

Overall, treatment with liraglutide was well tolerated. The rate of adverse events was higher with liraglutide than with placebo, although comparisons should account for the small sample size and differences in treatment exposure between liraglutide and placebo. Gastrointestinal disorders were the most common adverse events with liraglutide throughout the trial, consistent with previous liraglutide studies in adult and adolescent populations without PWS (8, 9, 12). All gastrointestinal disorders reported with liraglutide were nonserious and most were mild to moderate in severity. Relatively few events led to premature discontinuation or dose reduction. Diarrhea, abdominal pain, and vomiting were the most frequently reported, although a high proportion of these events occurred in 2 patients. In other studies, nausea and vomiting were more common with liraglutide than with placebo in adolescents with

obesity (12), whereas nausea is generally the most common side effect in adults (9). In PWS, episodes of vomiting and abdominal pain are infrequent and should be carefully monitored due to the patients' high pain threshold and the potential risk of gastric rupture (6). However, history of gastroparesis was an exclusion criterion in this trial and events of abdominal pain were nonserious, mostly mild to moderate in severity, and were resolved.

Adrenal and growth hormone insufficiency in PWS are associated with increased risk of hypoglycemia (27). In our trial, there were more episodes of hypoglycemia with liraglutide than with placebo, including 2 adolescents with clinically significant hypoglycemia and 1 child with severe hypoglycemia requiring assistance (due to the patient's young age).

Limitations

Limitations of this study included the small sample size and the different treatment exposure periods, which should be taken into consideration when interpreting the results and could help to explain the lack of statistical significance observed. Changes in body composition and fat distribution were not captured by BMI SDS evaluations and were not assessed during the study. Hormones involved in the control of appetite, including ghrelin and leptin, were also not evaluated during the trial. PWS is a rare genetic disorder and placebo-controlled clinical trials investigating potential treatment options are valuable in furthering our understanding of the disease and improving patient care. Although no difference was observed between liraglutide and placebo groups with respect to change in BMI SDS in this study, further larger trials of liraglutide in this special population may be warranted.

Conclusions

In conclusion, liraglutide did not result in significantly greater reduction in BMI SDS in children and adolescents with PWS and obesity compared with placebo/no treatment as adjunct to a structured diet and exercise program. However, an apparent improvement in hyperphagia (total score and drive score) in adolescents was seen, which is a key characteristic of PWS. The safety profile of liraglutide in our trial was overall consistent with that observed in other populations. Further research is needed to investigate the potential of GLP-1 receptor agonists in PWS.

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Author Contributions

Concept and design: G.D., P.M.H., C.H.J., M.T. Acquisition, analysis, or interpretation of data: G.D., P.M.H., C.H.J., S.T., M.T. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: C.R.

Conflict of Interest

G.D. declares no conflicts of interest relevant to this publication. M.A. reports participation as a speaker for Novo Nordisk. P.L.H. has no conflicts of interest. P.M.H. and C.H.J. are employees and stockholders of Novo Nordisk. C.R. is an employee of Novo Nordisk. S.T. and A.H-K. declare no conflicts of interest relevant to this publication. M.T. has received fees for participating in scientific board meetings at Merck Serono, Millendo, Novo Nordisk, and Pfizer, has received a research grant from Pfizer, and holds 3 patents for oxytocin-related products in Prader–Willi syndrome.

Data Availability

Data will be shared with bona fide researchers who submit a research proposal approved by an independent review board. Individual patient data will be shared in datasets in a de-identified and anonymized format. Data will be made available after research completion and approval of the product and product use in the EU and the USA. Information about data access request proposals can be found at novonordisk-trials.com.

Trial Registration

NCT02527200 (registered August 18, 2015, https://clinicaltrials.gov/ct2/show/NCT0252 7200).

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