Liraglutide in an Adolescent Population with Obesity: A Randomized, Double-Blind, Placebo-Controlled 5-Week Trial to Assess Safety, Tolerability, and Pharmacokinetics of Liraglutide in Adolescents Aged 12-17 Years

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Objectives To investigate the safety, tolerability, and pharmacokinetics of liraglutide in adolescents with obesity.

Study design This was a randomized, double-blind, placebo-controlled trial. Twenty-one subjects, aged 12-17 years and Tanner stage 2-5, with obesity (body mass index [BMI] corresponding to both a BMI ≥95th percentile for age and sex and to a BMI of ≥30 kg/m^2 for adults; additionally, BMI was ≤45 kg/m^2) were randomized (2:1) to receive 5 weeks of treatment with liraglutide (0.6 mg with weekly dose increase to a maximum of 3.0 mg for the last week) (n = 14) or placebo (n = 7). The primary endpoint was number of treatment-emergent adverse events (TEAEs). Secondary endpoints included safety measures, and pharmacokinetic and pharmacodynamic endpoints.

Results All participants receiving liraglutide, and 4 receiving placebo (57.1%), had at least 1 TEAE. The most common TEAEs were gastrointestinal disorders. No severe TEAEs, TEAE-related withdrawals, or deaths occurred. Twelve hypoglycemic episodes occurred in 8 participants receiving liraglutide and 2 in 1 participant receiving placebo. No severe hypoglycemic episodes were reported. Liraglutide exposure in terms of trough concentration increased with dose, although dose proportionality was confounded by unexpectedly low trough concentration values at the 2.4 mg dose. Exposure in terms of model-derived area under the plasma concentration time curve from 0 to 24 hours after dose in steady state was similar to that in adults with obesity.

Conclusions Liraglutide had a similar safety and tolerability profile compared with adults when administered to adolescents with obesity, with no unexpected safety/tolerability issues. Results suggest that the dosing regimen approved for weight management in adults may be appropriate for use in adolescents. *(J Pediatr 2017;181:146-53).*

Trial registration ClinicalTrials.gov: NCT01789086.

The prevalence of overweight and obesity in children and adolescents has increased over the past 3 decades, reaching approximately 23% in developed countries in 2013, with smaller increases evident in developing countries.[1] Although the figures appear to have plateaued in some countries,[1,2] the general upward trend appears to be continuing.[1] The health complications of pediatric obesity are well documented and include the development of type 2 diabetes (T2D) in adolescents.[3] Because of the potential for the development of severe complications, treatment options including bariatric surgery have been considered as an option even in this young age group.[4] Young people may suffer stigmatization and isolation as a result of obesity,[5,6] and many will remain obese into adulthood.[7]

AUC_{24}	Area under the plasma concentration time curve from 0 to 24 hours after dose in steady state
BMI	Body mass index
CL/F	Apparent clearance
C_{trough}	Trough concentration
FPG	Fasting plasma glucose
ECG	Electrocardiogram
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated hemoglobin A1c
LDH	Lactate dehydrogenase
PG	Plasma glucose
T2D	Type 2 diabetes
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
Vd/F	Apparent volume of distribution

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Sponsored by Novo Nordisk A/S, which was involved in all aspects of the trial, including its design and the collection, analysis, and interpretation of data. The decision to submit the manuscript for publication was made jointly by the authors and sponsor. The final version of the manuscript was reviewed and approved by the authors. T.D. has received speaker honoraria and research support and has consulted for Abbott, Bayer, BMS/AstraZeneca, Boehringer Ingelheim, DexCom, Eli Lilly and Co, Medtronic, Novo Nordisk, Sanofi, and Roche; and is a shareholder of DreaMed Ltd. S.J., L.J. and K.C. are employees and stockholders at Novo Nordisk A/S. P.H. is an employee and stockholder at Novo Nordisk Inc. O.K. has received research support and has consulted for Novo Nordisk and Sanofi; and is a shareholder of DreaMed Ltd. T.B. has received speaker honoraria and research support from Medtronic. O.K. declares no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.10.076

Lifestyle interventions to promote weight loss are unsuccessful for many adolescents.[8] The American Academy of Pediatrics Expert Committee recommends intensive interventions, including a low-calorie diet, medication, and surgery, in children with body mass index (BMI) >99th percentile or >95th percentile with significant comorbidities, who do not respond to multidisciplinary interventions.[9,10] Currently, only orlistat is approved for weight management in adolescents aged ≥12 years in the US. No weight management pharmacotherapies have received regulatory approval for the general adolescent population within Europe. Hence, there is an unmet medical need for treatment options as an adjunct to lifestyle interventions for children and adolescents <18 years of age.

The glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide, has demonstrated efficacy, safety, and tolerability at a dose of 3.0 mg for weight management as an adjunct to diet and exercise in adults with obesity (BMI ≥30 kg/m^2) or who are overweight (BMI ≥27-< 30 kg/m^2 with comorbidities) without a diagnosis of diabetes[11] and also those with diabetes.[12] Liraglutide 3.0 mg has received regulatory approval for weight management in adults in the US, Europe, and other countries.

The safety, pharmacokinetics, and pharmacodynamics of liraglutide at doses up to 1.8 mg have been investigated in a short-term trial in children aged 10-17 years old with T2D. The results demonstrated that the safety, tolerability, and pharmacokinetic profile were similar when compared with adults with T2D. This has not yet been investigated in adolescents with obesity.[13,14] Therefore, the primary aim of this clinical pharmacology trial was to assess the safety and tolerability of liraglutide at doses up to 3.0 mg/day in adolescents with obesity, aged 12-17 years and Tanner stage 2-5, before initiating longer-term safety and efficacy pediatric trials. Pharmacokinetic and exploratory pharmacodynamic properties of liraglutide treatment were also investigated.

Methods

This randomized, double-blind, parallel-group, placebo-controlled trial was conducted at a single center in Germany (ClinicalTrials.gov NCT01789086). The trial was approved by an independent ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants, with their parents or legally acceptable representative, provided written informed consent.

The key inclusion criteria were male or female adolescent (12-17 years); Tanner stage 2-5 pubertal development; BMI corresponding to both a BMI ≥95th percentile for age and sex[15] and to a BMI of ≥30 kg/m^2 for adults by international cut-off points[10] (in addition, BMI had to be ≤45 kg/m^2); and fasting plasma glucose (FPG) <126 mg/dL (7.0 mmol/L). Both sets of BMI criteria were used to satisfy regulatory requirements. Key exclusion criteria included secondary causes of childhood obesity; prepuberty (Tanner stage 1); type 1 diabetes or T2D; previous treatment with a GLP-1 receptor agonist, dipeptidyl peptidase-4 inhibitors, orlistat, or other weight-lowering medication within the previous 3 months; and previous surgical treatment for obesity.

Following screening, participants were randomized 2:1 to 5 weeks of treatment with either liraglutide or matched-volume placebo (**Figure 1**; available at www.jpeds.com). Liraglutide (or corresponding volume of placebo) was administered at a starting dose of 0.6 mg, and the dose was increased by 0.6 mg/week to a maximum of 3.0 mg/day. The dose was not escalated if FPG was <56 mg/dL (3.1 mmol/L) or <70 mg/dL (3.9 mmol/L) with symptoms of hypoglycemia during the previous week, or if the dose was not tolerated. One additional treatment week was allowed in case a participant needed extra time on one dose level prior to dose escalation, giving a total maximum treatment time of 6 weeks.

Both liraglutide and placebo were administered by subcutaneous abdominal injections once daily at 8 a.m. ± 2 hours. The children and parents were trained by an experienced diabetes educator in how to perform the injections and were required to complete a test self-injection with a placebo training pen at the screening visit before enrollment.

Safety and tolerability were assessed throughout the entire trial. Blood sampling for assessment of steady-state liraglutide plasma trough concentration (C_{trough}, measured at the end of a dosing interval at steady state taken directly before next administration) at each dose step was performed prior to participants taking their daily dose of liraglutide or placebo at the end of each week. Participants receiving liraglutide were also randomized to 1 of 6 pharmacokinetic blood-sampling schemes (sparse blood sampling; **Figure 2** available at www.jpeds.com) following the last treatment dose for assessment of model-derived steady-state pharmacokinetic endpoints.

Outcomes

The primary endpoint was the number of treatment-emergent adverse events (TEAEs) from first dose until completion of follow-up. Secondary endpoints included the number of hypoglycemic episodes; the change from baseline to end of treatment in physical examination, electrocardiogram (ECG), vital signs, and clinical laboratory evaluations; and the incidence of antiliraglutide antibodies at follow-up.

Hypoglycemia was defined according to the American Diabetes Association.[16] An additional category of confirmed hypoglycemia was defined by Novo Nordisk, comprising severe or minor (symptoms of hypoglycemia with confirmation by plasma glucose [PG] <56 mg/dL [3.1 mmol/L] and self-handled, or any asymptomatic PG <56 mg/dL [3.1 mmol/L]) episodes.

Pharmacokinetic investigations of liraglutide included C_{trough} plasma concentration measurements, as well as a population pharmacokinetic covariate analysis based on the joint data from adolescents (current trial) and an adult population (previous trial)[17] (see Statistical Analyses section). Adults from the previous trial had a BMI between 30 and 40 kg/m^2, were aged 18-75 years old, and received liraglutide for 5 weeks with a dose escalation to 3.0 mg. This joint analysis investigated the effects of body weight, sex, and age category (adolescent/adult) on liraglutide exposure (area under the plasma concentration time curve from 0 to 24 hours after dose in steady state [AUC_{24}]).

Exploratory pharmacodynamic endpoints included the change from baseline to end of treatment in BMI z score,[18] body weight, FPG, fasting serum insulin, and glycated hemoglobin A1c (HbA1c).

Statistical Analyses

No formal sample size calculations were made. Based on clinical judgment, a sample size of 18 participants (12 on liraglutide and 6 on placebo) was considered sufficient. To account for withdrawals, 21 participants were planned for enrollment.

All randomized participants who received at least 1 dose of the investigational medicinal product were included in the full analysis set. The safety analysis set comprised participants exposed to at least 1 dose of investigational medicinal product.

No formal statistical testing was performed for any of the safety or tolerability endpoints and summary statistics by treatment were the primary mode of statistical presentation of safety data.

Pharmacokinetic endpoints were summarized using descriptive statistics. Liraglutide dose proportionality was based on C_{trough} levels by estimating the slope β in a linear normal regression model with the logarithm of C_{trough} as dependent variable, a common intercept, the logarithm of the dose as fixed covariate, and a participant-specific intercept as a random effect. The estimated dose-proportionality parameter 2^{β} with 95% CI was reported, and the resulting P value represents the test of $2^{\beta} = 2$.

A 1-compartment pharmacokinetic model with first-order absorption and elimination parameters (absorption rate constant [ka], apparent clearance [CL/F], and apparent volume of distribution [Vd/F]) was previously reported to adequately describe liraglutide pharmacokinetic data in adults and pediatric individuals.[13,19] This model was fitted to pooled data from the current trial and the trial in adults. Trial effects were confounded with the effects of age category, and the trial effect was, therefore, not included in the model. Between-participant variability parameters (random effects) were included for CL/F and Vd/F. Residual error was described using a proportional error model. Estimates for steady-state CL/F for each participant and the corresponding maintenance dose level were used to derive the AUC_{24}.

Investigation of the preselected covariates on the joint data set (including data from the current trial in adolescents and the previous adult trial) allowed for simultaneous testing of effects. The change in the mean (90% CI) AUC_{24} relative to a reference individual (100-kg female adult) was assessed for each covariate, and effects were considered relevant if the 90% CIs were outside the range of bioequivalence limits (0.8-1.25). A body weight of 100 kg is the approximate mean body weight for the adult and adolescent populations with obesity in the clinical trials and was, therefore, selected as the reference body weight.

Change from baseline to end of treatment for physical examination, vital signs, laboratory tests, and pharmacodynamic endpoints was analyzed using an ANCOVA model with treatment as fixed factor and baseline value as covariate, with a statistical significance level of 0.05, and no adjustment for multiplicity given the exploratory nature of the study. The null hypothesis was that there was no difference between the 2 groups.

Results

In total, 24 participants were screened between February 7, 2013, and May 26, 2014; of these, 21 were eligible for inclusion and were randomized to treatment (**Figure 3**; available at www.jpeds.com). One participant randomized to liraglutide was withdrawn after 4 days of treatment (because of storage temperature deviation of trial product) and did not provide blood samples for pharmacokinetic analysis and pharmacodynamic endpoints.

Participant characteristics were generally well matched between treatment groups at baseline (**Table I**), although there was a higher proportion of female participants in the liraglutide group compared with the placebo group.

TEAEs

All 14 participants in the liraglutide group and 4 (57.1%) in the placebo group reported at least 1 TEAE during the trial (**Table II**). Most of the TEAEs with liraglutide (96.5%), and all TEAEs in the placebo group were mild. There were no severe or serious TEAEs or deaths, and no withdrawals because of TEAEs in either treatment group.

For placebo, all the reported TEAEs were considered unlikely to be related to treatment. Approximately one-half of the TEAEs in the liraglutide group (51.2%) were considered to be probably or possibly related to treatment. The most common TEAEs judged possibly or probably related to liraglutide treatment by the investigator were gastrointestinal (GI) disorders, including 34 (77%) of the 44 treatment-related TEAEs (**Table III**; available at www.jpeds.com). No clear pattern between liraglutide dose and the timing or duration of GI events was identified (**Figure 4**). In terms of local tolerability, injection site pain and pruritus were seen with liraglutide but not placebo (**Table IV**).

Hypoglycemic Episodes

The total number of all hypoglycemic episodes[16] was higher in the liraglutide group (12 in 8 participants) than in the placebo group (2 in 1 participant) (**Table II**). Five of the 12 episodes with liraglutide occurred after an extended fasting period of more than 10 hours after the last meal; 1 occurred 7 hours after, and 2 occurred between 1 and 4 hours after a meal (timing in relation to last meal was unknown for the remaining 4 episodes). Most hypoglycemic episodes with liraglutide occurred at doses of 0.6 mg and 1.2 mg (**Figure 5**; available at www.jpeds.com).

There were 3 confirmed hypoglycemic episodes (**Table II**) in 2 participants receiving liraglutide; all were minor episodes and were documented symptomatic. No severe hypoglycemic episodes were reported with either treatment.

One participant reached a maximum liraglutide dose of only 2.4 mg; this participant was prescribed liraglutide 1.2 mg for 2 weeks because of low blood glucose concentration

Table II. Summary of treatment-emergent adverse events and hypoglycemic episodes

	Liraglutide* n = 14			Placebo n = 7		
	Participants		Events	Participants		Events
Variables	n	%	n	n	%	n
TEAEs	14	100	86	4	57.1	7
Severity†						
Mild	14	100	83	4	57.1	7
Moderate	3	21.4	3	0	0	0
Relationship to trial product						
Probable/possible	2 / 13	14.3 / 92.9	3 / 41	0 / 0	0 / 0	0 / 0
Unlikely	13	92.9	42	4	57.1	7
Outcome						
Recovered/recovering	14 / 3	100 / 21.4	83 / 3	4 / 0	57.1 / 0	7 / 0
TEAEs by system organ class and preferred term, irrespective of relationship to trial product						
GI disorders	12	85.7	43	2	28.6	3
Nervous system disorders	7	50.0	13	1	14.3	1
Infections and infestations	6	42.9	6	2	28.6	2
General and administration site conditions	5	35.7	7	0	0	0
Musculoskeletal and connective tissue disorders	3	21.4	3	0	0	0
Reproductive system and breast disorders	3	21.4	3	0	0	0
Respiratory, thoracic and mediastinal disorders	2	14.3	5	1	14.3	1
Skin and subcutaneous tissue disorders	2	14.3	2	0	0	0
Injury, poisoning and procedural complications	1	7.1	1	0	0	0
Investigations	1	7.1	1	0	0	0
Vascular disorders	1	7.1	2	0	0	0
Hypoglycemic episodes						
Confirmed‡	2	14.3	3	0	0	0
ADA§	8	57.1	12	1	14.3	2
Severe	0	0	0	0	0	0
Documented symptomatic	2	14.3	4	0	0	0
Asymptomatic	4	28.6	4	1	14.3	2
Probable symptomatic	0	0	0	0	0	0
Relative	3	21.4	4	0	0	0

ADA, American Diabetes Association.
*TEAEs/hypoglycemic episodes are reported during dose escalation (liraglutide 0.6-3.0 mg).
†There were no severe TEAEs in either treatment group.
‡Severe events or minor events (Novo Nordisk definition: PG <56 mg/dL [3.1 mmol/L] or full blood glucose <50 mg/dL [2.8 mmol/L] without symptoms or with symptoms and self-handled).
§ADA definitions,[14] briefly: severe, requiring assistance of another person; asymptomatic, no typical symptoms but PG concentration ≤70 mg/dL (3.9 mmol/L); documented symptomatic, typical symptoms, and PG concentration ≤70 mg/dL (3.9 mmol/L); relative, typical symptoms but PG concentration >70 mg/dL (3.9 mmol/L); probable symptomatic, symptoms without PG determination. There were no unclassifiable hypoglycemic episodes in either treatment group.

pre-escalation to 1.2 mg (61 mg/dL [3.4 mmol/L]) and again 2 days postescalation (44 mg/dL [2.4 mmol/L]).

Vital Signs, ECG, and Physical Examination

From baseline to end of treatment, resting pulse rate increased by a mean of 6 beats/minute (range −20 to 24 beats/minute) with liraglutide and 1 beat/minute (range −10 to 15 beats/minute) with placebo. Over the same period, systolic blood pressure decreased in both groups, with a numerically greater decline with liraglutide (mean -7 mm Hg compared with -2 mm Hg with placebo). Similar, but less pronounced findings, were made for diastolic blood pressure (mean -4 mm Hg with liraglutide and -1 mm Hg with placebo). Baseline and end-of-study data for pulse and blood pressure are included in **Table IV** (available at www.jpeds.com). No clinically significant findings were reported for ECGs. For physical examination, there were no changes in clinically significant abnormal findings.

Clinical Laboratory Evaluations

Overall, no clinically significant changes in hematologic, biochemical (including calcitonin levels), hormonal, lipid, or urinary measurements were observed in either group at the end of treatment. In the liraglutide group, 1 participant had postbaseline elevations (above the upper limit of normal [ULN]) in both amylase (103.0-147.1 U/L, ULN = 100 U/L) and lipase (76.0-123.0 U/L, ULN = 67 U/L), and 1 participant had elevations in lipase (85.8 U/L) during treatment. Four participants had elevations in lactate dehydrogenase (LDH) at the end of treatment (one of whom also had treatment-associated elevated transaminase levels). None of these observations were considered to be clinically significant. All participants who developed elevated levels of amylase, lipase, and LDH during the study had normal baseline levels of these enzymes. Either during the trial, or at follow-up after trial completion, elevated lipase or LDH levels had returned to within the normal range (1 participant with elevated lipase),

Table III. Treatment emergent adverse events possibly or probably related to investigational product

	Liraglutide* n = 14			Placebo n = 7		
	Participants		Events	Participants		Events
	n	%	N	n	%	n
GI disorders	11	78.6	34	0	0.0	0
Nausea	7	50.0	11	0	0.0	0
Abdominal pain	4	28.6	12	0	0.0	0
Vomiting	4	28.6	4	0	0.0	0
Diarrhea	3	21.4	3	0	0.0	0
Abdominal pain upper	2	14.3	2	0	0.0	0
Abdominal distension	1	7.1	1	0	0.0	0
Abdominal wall hematoma	1	7.1	1	0	0.0	0
General disorders and administration site conditions	4	28.6	6	0	0.0	0
Injection site pain	3	21.4	5	0	0.0	0
Injection site pruritus	1	7.1	1	0	0.0	0
Investigations	1	7.1	1	0	0.0	0
Transaminases increased	1	7.1	1	0	0.0	0
Skin and subcutaneous tissue disorders	1	7.1	1	0	0.0	0
Alopecia	1	7.1	1	0	0.0	0
Vascular disorders	1	7.1	2	0	0.0	0
Hematoma	1	7.1	2	0	0.0	0

n, number of participants; %, percentages of patients.
*TEAEs/hypoglycemic episodes are reported during dose escalation (liraglutide 0.6-3.0 mg).

or were declining (participants with elevated LDH); the 1 participant with elevated amylase and lipase at the end of treatment was lost to follow-up after completion of the trial, and no further levels are available. No antiliraglutide antibodies were detected.

Pharmacokinetics

C_{trough} values increased with increasing doses of liraglutide, although the plasma liraglutide concentration associated with the dose of 2.4 mg was lower than expected (**Figure 6**, A). Liraglutide dose-proportionality was not observed in the full dataset analysis (estimated 2^{β} 1.75 [95% CI 1.55, 1.98]; $P = .03$) but was indicated in a post-hoc sensitivity analysis that excluded the liraglutide 2.4 mg C_{trough} values (estimated 2^{β} 1.89 [95% CI 1.75, 2.04], $P = .14$).

The liraglutide concentration-time profile in the adolescent trial was similar to that observed previously with liraglutide 3.0 mg in adults with obesity (**Figure 6**, B).

To compare the liraglutide exposure between adolescents and adults, a joint analysis that included data from both of these populations was performed. In the joint pharmacokinetic analysis (**Figure 6**, C), liraglutide exposure (model-derived AUC_{24}) was slightly elevated in adolescents compared with adults, with an estimated ratio of 1.10 (90% CI 0.93; 1.31). In addition, liraglutide exposure was 23% lower in male participants than in female participants (**Figures 6,** C and **7**; **Figure 7** available at www.jpeds.com) and was reduced with increasing body weight.

Exploratory Pharmacodynamic Endpoints

From baseline to end of treatment, mean BMI z score and body weight decreased in both treatment groups (liraglutide: BMI z score -0.12, body weight -2.55 kg; placebo: BMI z score -0.10, body weight -1.85 kg), mean FPG and HbA1c levels decreased with liraglutide and remained stable with placebo (liraglutide: FPG -3.51 mg/dL [-0.19 mmol/L], HbA1c -0.11% [-1.22 mmol/mol]; placebo: FPG 0.63 mg/dL [0.03 mmol/L], HbA1c 0.01% [0.08 mmol/mol]), and mean fasting serum insulin levels decreased with liraglutide (-1.43 μIU/mL [-10.22 pmol/L]) and increased with placebo (1.83 μIU/mL [13.15 pmol/L]) (**Table V**; available at www.jpeds.com). Despite numerically favorable effects of liraglutide, there were no statistically significant differences between the 2 groups in any of these variables (all $P > .05$).

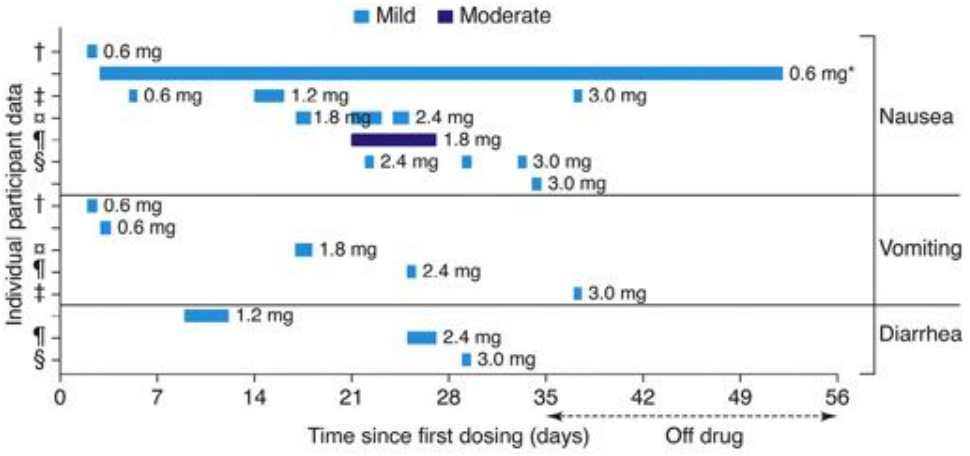

Figure 4. Timing and duration of selected GI events with liraglutide. Doses shown on the plot are those at the start of the event. There were no TEAEs of nausea, vomiting, or diarrhea reported for any participants treated with placebo. The y-axis symbols indicate participants with multiple events. *One participant was treated with liraglutide 1.2 mg for 2 weeks and reached a maximum dose of only 2.4 mg.

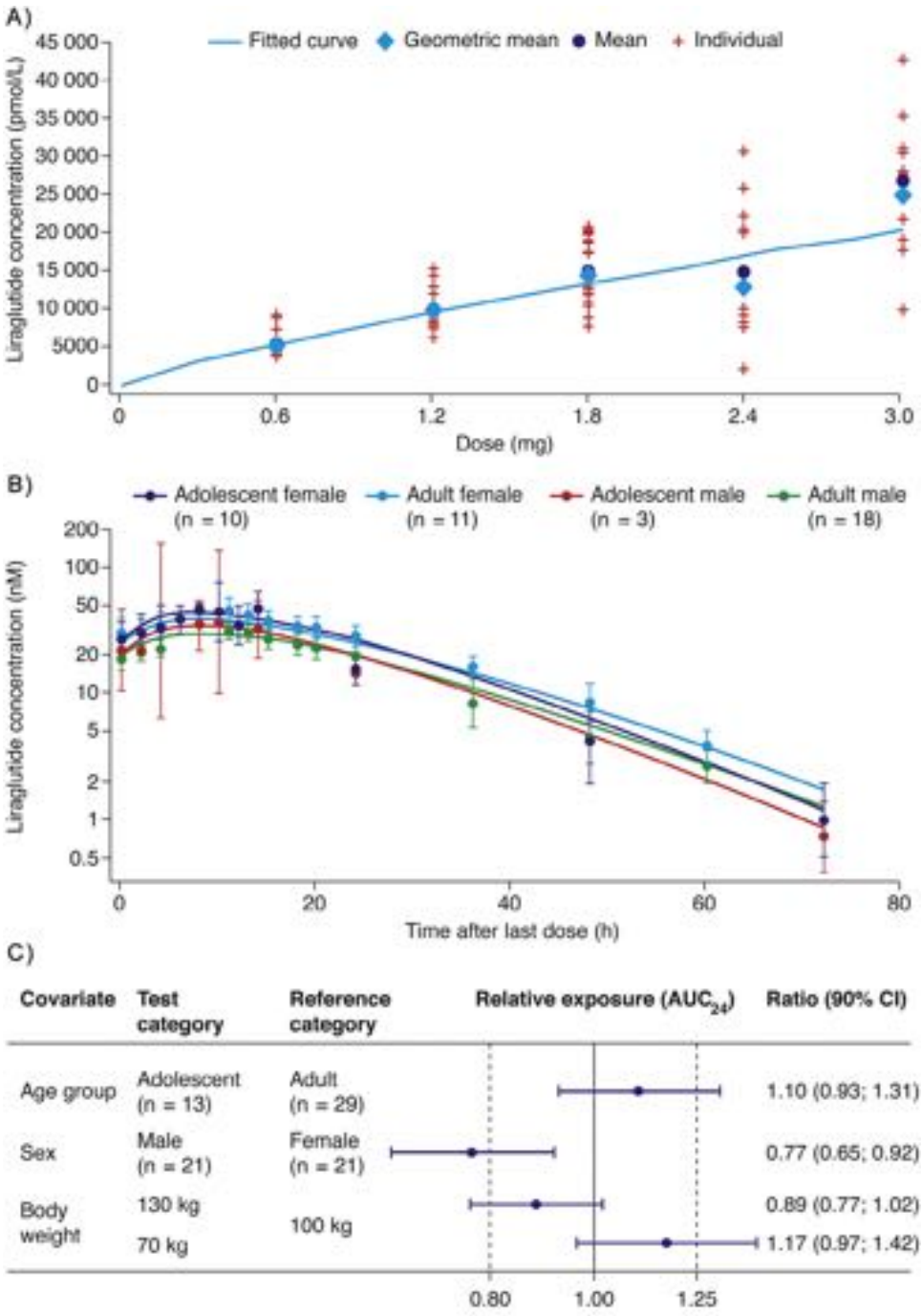

Figure 6. Pharmacokinetic analysis of liraglutide exposure. **A,** Plasma concentration of liraglutide at steady state versus liraglutide dose. Liraglutide C_{trough} are taken at steady state approximately 24 hours after dose administration. The fitted curve is based on the estimates from the linear regression model. **B,** Model-derived and observed mean liraglutide concentrations vs time after last dose in adolescent and adult populations. Liraglutide concentration shown as geometric means with 95% CI vs time. Model-derived concentration-time curve. Data are from the current trial in adolescents and from a previous trial in adults with obesity[17] (NCT00978393) receiving liraglutide 3.0 mg once daily. Concentrations were normalized from 2.4 to 3.0 mg for 1 individual (female adolescent). **C,** Population pharmacokinetic analysis of covariate effects of liraglutide exposure (AUC_{24}). Geometric mean and 90% CI for effects of covariates on liraglutide exposure relative to a reference individual (100-kg female adult). The dotted lines represent bioequivalence limits of 0.8 and 1.25. Data are from the current trial in adolescents and from a previous trial in adults with obesity[17] (NCT00978393) who were receiving liraglutide 3.0 mg once daily.

Discussion

We investigated the use of liraglutide in a population of adolescents with obesity, which is the first time this has been explored. The findings are broadly in line with those reported for adults. The safety and efficacy of liraglutide 3.0 mg for weight management in adults with obesity has been established in the Satiety and Clinical Adiposity-Liraglutide Evidence in individuals with and without diabetes (SCALE) program.[11,12,20,21]

Tolerability and safety are essential in the treatment of any pediatric population. In the present trial, the tolerability profile of liraglutide was generally acceptable. All participants receiving the drug had at least 1 TEAE, but the majority (96.5%) of these were mild. There were no severe or serious TEAEs, and of note, no participants withdrew because of TEAEs. As expected from previous trials,[22] GI disorders were the most common TEAEs and reported by 85.7% of participants receiving liraglutide. The most frequent of the GI events reported with both liraglutide (17 events in 7 participants) and placebo (3 events in 3 participants) was abdominal pain. No clear association between treatment dose and the timing and duration of GI TEAEs, as was observed in adults with obesity[23] and in pediatric/adolescent patients with T2D,[24] was seen in this trial.

There were 12 episodes (in 8 subjects) of hypoglycemia in the liraglutide group, compared with only 2 episodes (in 1 subject) with placebo. Nearly one-half of the hypoglycemic episodes reported with liraglutide occurred 10 hours or more after the previous meal, suggesting that a prolonged fast may have been a contributory factor. Only 3 episodes with liraglutide were confirmed, all of which were designated to be "minor episodes" (PG <56 mg/dL [3.1 mmol/L]). No severe hypoglycemia was reported. The rate of hypoglycemia was higher than that reported for the SCALE Obesity and Prediabetes trial in adults with obesity, although hypoglycemic events in the SCALE Obesity and Prediabetes trial were more common in patients without prediabetes than in those with prediabetes (15.9% vs 9.4%).[14] The difference in rates may be influenced by the fact that, unlike in the SCALE Obesity and Prediabetes trial, the pediatric participants and their parents in this trial were provided with glucose meters and trained in how to use them. Similarly to the present trial, the incidence of hypoglycemic episodes with PG <56 mg/dL (3.1 mmol/L) in the SCALE Obesity and Prediabetes trial was low (around 2%).[14]

The clinical significance of the increase in pulse rate (mean 6 beats/minute) with liraglutide in the present trial is not known, but similar effects have been seen in adults[11,17] and appear to be a class effect of GLP-1 receptor agonists.[25] No TEAEs related to resting pulse were reported during the trial.

Although there were no clinically significant changes in laboratory measurements with liraglutide, a transient elevation of lipase above the ULN was observed in 1 participant and another had levels of both amylase and lipase above the ULN at the end of the study. This is consistent with previous findings from studies in adults with obesity.[11,12,17] The clinical relevance of increases in lipase or amylase <3 × ULN has not been established. Elevated LDH levels in 4 participants were also thought not to be of clinical relevance.

The exposure of liraglutide in this young population with obesity was broadly consistent with findings reported in pediatric (aged 10-17 years) and adult patients with T2D at doses of up to 1.8 mg[13] and in adults with obesity at doses up to 3.0 mg.[17] Sex was found to be a relevant covariate for exposure in the joint population of adolescents and adults, which is in line with findings from a previous investigation of liraglutide in adult patients with obesity.[26] Body weight has also been shown to influence the exposure of liraglutide in adults with obesity.[26] Even though this covariate was not found to be relevant in the joint analysis including adolescents and adults, the trend toward higher liraglutide exposure with lower body weight is in keeping with the previous findings in adults. An explanation for the unexpectedly low C_{trough} values at the 2.4 mg liraglutide dose was not found.

Favorable effects of liraglutide in exploratory pharmacodynamic endpoints such as BMI z score, body weight, FPG, HbA1c, and fasting serum insulin were observed; none was statistically significant. This may be reflective of the short duration of treatment, particularly as liraglutide was administered at the highest dose of 3.0 mg for only 1 week, and the small number of participants.

The limitations of this study are related to its exploratory nature. These include the small sample size and short duration of treatment. Although the results here are promising, given that participants only received the maintenance dose of liraglutide 3.0 mg for 1-2 weeks, it is not possible to determine the longer-term efficacy and safety of liraglutide in this adolescent population. This assessment requires further investigation.

In conclusion, treatment with liraglutide resulted in an acceptable safety and tolerability profile in adolescents with obesity, and no unexpected safety and tolerability issues, compared with adults, were identified. Liraglutide pharmacokinetic properties in this population were consistent with those observed in adults with obesity and indicate that the dose and dose escalation regimen recommended for weight management in adults will result in the same exposure range in adolescents. The results support further investigations of the safety and efficacy of liraglutide in adolescents in a longer-term trial. ■

We thank the patients who participated in the study. Karl Gledhill, PhD (supported by Novo Nordisk A/S; Watermeadow Medical, an Ashfield Company; supported by Novo Nordisk A/S), wrote the first draft of the manuscript under the guidance of the authors.

Submitted for publication May 9, 2016; last revision received Aug 31, 2016; accepted Oct 24, 2016

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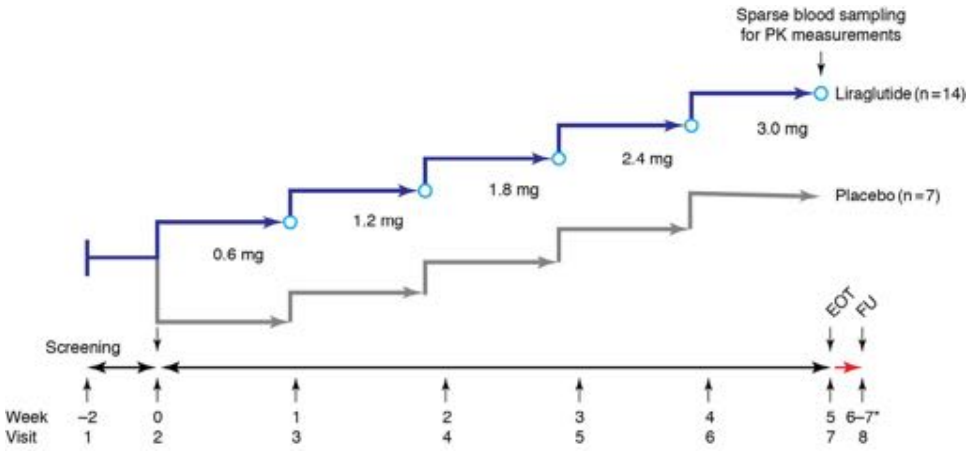

Figure 1. Trial design. *The follow-up (FU) visit (5-14 days after last dose administration) was the last scheduled visit for each participant. *EOT*, end of treatment; *PK*, pharmacokinetic; o, C_{trough}.

Sampling	Time after last dose (hours)									
scheme	2	4	6	8	10	12	14	24	48	72
A	X		X		X		X		X	
B		X		X	X		X			X
C	X			X			X	X		X
D		X			X	X		X	X	
E		X	X			X		X	X	
F	X		X	X		X				X

Figure 2. Sampling scheme for blood sampling for liraglutide plasma bioanalysis after last dose. x, blood sampling. Participants were randomized to 1 of 6 different pharmacokinetic blood sampling schemes (A-F) at randomization. Within 24 hours of the last dose administration at visit 7 at the end of week 5, 4 samples were drawn per participant and another sample was drawn at 48 or 72 hours for population pharmacokinetic analysis (sparse pharmacokinetic blood sampling).

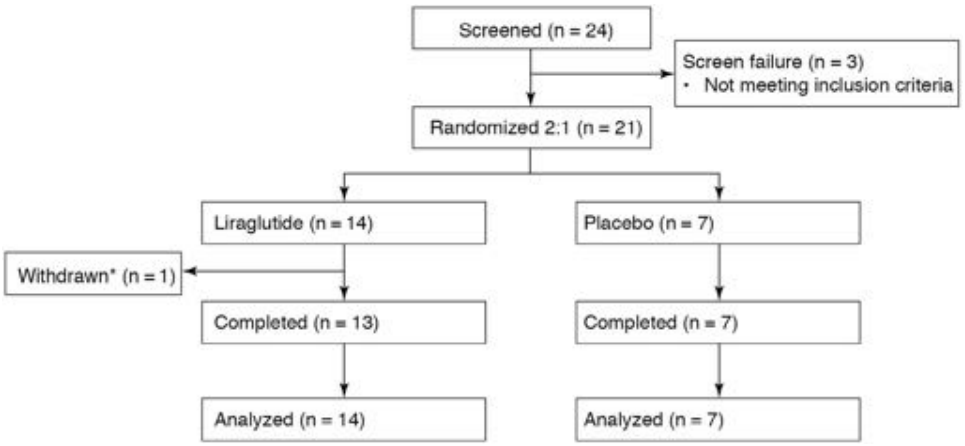

Figure 3. Subject disposition. *Subject was withdrawn after 4 days of treatment because of a storage temperature deviation of trial product at the site.

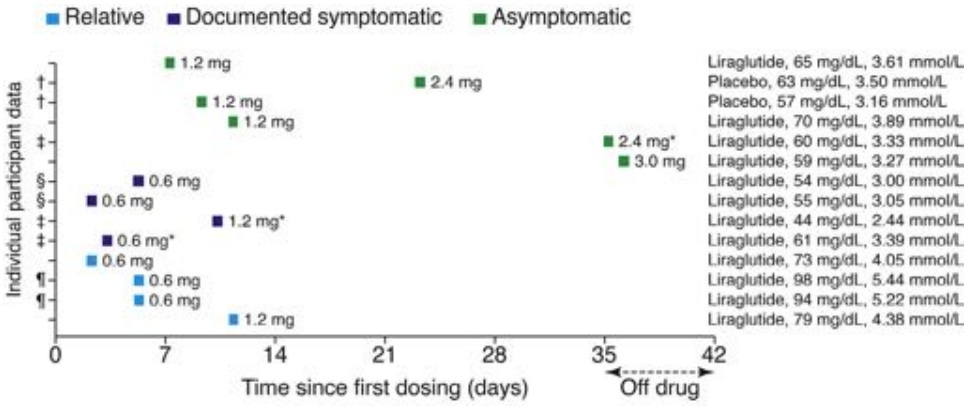

Figure 5. Treatment-emergent hypoglycemic episodes by timing, dose, and PG readings at the time of the event. Data are for participants with treatment-emergent hypoglycemic episodes, showing PG readings at the time of the event. Doses shown on the plot are those at the start of the event. Hypoglycemic episodes shown here are described by American Diabetes Association definitions,[16] briefly: asymptomatic, no typical symptoms but PG concentration ≤70 mg/dL (3.9 mmol/L); documented symptomatic, typical symptoms and PG concentration ≤70 mg/dL (3.9 mmol/L); relative, typical symptoms but PG concentration >70 mg/dL (3.9 mmol/L). The y-axis symbols indicate participants with multiple events. *One participant was treated with liraglutide 1.2 mg for 2 weeks and reached a maximum dose of only 2.4 mg.

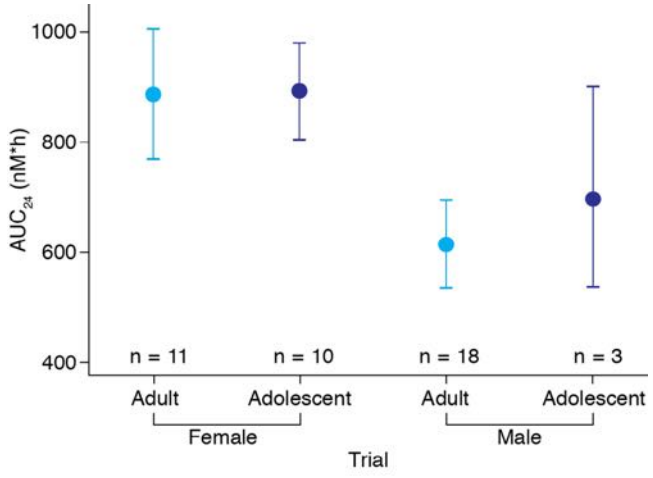

Figure 7. Geometric mean (95% CI) liraglutide exposure (in terms of model-derived AUC_{24}) in adolescents and adults by sex. Data are from the current trial in adolescents and from a previous trial in adults with obesity[17] (NCT00978393) who were receiving liraglutide 3.0 mg once daily.

Table I. Baseline characteristics

	Liraglutide n = 14	Placebo n = 7
Sex, n (%)		
Female	11 (78.6)	3 (42.9)
Male	3 (21.4)	4 (57.1)
Age, y	15.1 (0.9)	14.4 (1.8)
Min; max	13; 16	13; 17
Body weight, kg	103.5 (12.8)	109.6 (30.8)
Min; max	79.9; 121.6	78.5; 164.4
BMI, kg/m^2	36.5 (3.7)	35.7 (5.4)
Min; max	31.6; 44.3	29.3; 44.9
BMI z score*	3.17 (0.49)	3.26 (0.75)
Min; max	2.50; 4.16	2.50; 4.52
HbA1c, %	5.4 (0.3)	5.5 (0.3)
Min; max	4.9; 6.0	5.1; 6.1
HbA1c, mmol/mol	36.0 (3.6)	36.3 (3.6)
Min; max	30.1; 42.1	32.2; 43.2

Min, minimum; *max*, maximum.
Data are mean (SD), unless otherwise stated.
*BMI z score represents the number of SDs from a reference standard population mean BMI.[16]

Table IV. Heart rate and blood pressure changes from baseline

	Liraglutide (n = 14)			Placebo (n = 7)		
	Baseline (mean ± SD)	End of treatment (mean ± SD)	Change from baseline (mean ± SD)	Baseline (mean ± SD)	End of treatment (mean ± SD)	Change from baseline (mean ± SD)
Heart rate (beats/min)	82 ± 10	88 ± 10	6 ± 13	81 ± 14	82 ± 12	1 ± 10
Systolic blood pressure (mm Hg)	124 ± 14	117 ± 11	–7 ± 13	126 ± 7	124 ± 21	–2 ± 25
Diastyolic blood pressure (mm Hg)	61 ± 9	57 ± 10	–4 ± 8	60 ± 6	59 ± 15	–1 ± 13

Table V. Summary of pharmacodynamic endpoints: change from baseline to end of treatment

	Estimated mean change from baseline*	Treatment difference† (95% CI)	*P* value
BMI z score			
Liraglutide (n = 14)	–0.12	–0.02 (–0.17, 0.13)	.75
Placebo (n = 7)	–0.10		
Body weight, kg			
Liraglutide (n = 14)	–2.55	–0.70 (–4.24, 2.84)	.68
Placebo (n = 7)	–1.85		
FPG, mg/dL			
Liraglutide (n = 13‡)	–3.51	–4.14 (–10.6, 2.31)	.19
Placebo (n = 7)	0.63		
FPG, mmol/L			
Liraglutide (n = 13‡)	–0.19	–0.23 (–0.59, 0.13)	.19
Placebo (n = 7)	0.03		
HbA1c, %			
Liraglutide (n = 13‡)	–0.11	–0.12 (–0.31, 0.07)	.21
Placebo (n = 7)	0.01		
HbA1c, mmol/mol			
Liraglutide (n = 13‡)	–1.22	–1.30 (–3.38, 0.79)	.21
Placebo (n = 7)	0.08		
Fasting serum insulin, μIU/mL			
Liraglutide (n = 13‡)	–1.43	–3.26 (–11.4, 4.87)	.41
Placebo (n = 7)	1.83		
Fasting serum insulin, pmol/L			
Liraglutide (n = 13‡)	–10.22	–23.37 (–81.70, 34.97)	.41
Placebo (n = 7)	13.15		

P values presented are from a 2-sided test of the null-hypothesis of no difference in the 2 groups.
*Least square means.
†Liraglutide– placebo.
‡One participant included in the full analysis set/safety analysis set was withdrawn after 4 days and did not provide blood samples for pharmacokinetic analysis and pharmacodynamic endpoints.