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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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}]).