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ORIGINAL RESEARCH

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Liraglutide effects in a paediatric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics

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Summary

Background: Childhood obesity is a major public health concern with limited treatment options.

Objective: The aim of this study was to assess safety, tolerability, pharmacokinetics, and pharmacodynamics during short-term treatment with liraglutide in children (7-11 y) with obesity.

Methods: In this randomized, double-blind, placebo-controlled trial, 24 children received at least one dose of once-daily subcutaneous liraglutide (n = 16) or placebo (n = 8) starting at 0.3 mg with weekly dose escalations up to 3.0 mg or maximum tolerated dose, and 20 children completed the trial (14 in the liraglutide group and six in the placebo group). The primary endpoint was the number of adverse events.

Results: Baseline characteristics (mean ± standard deviation) included the following: age 9.9 ± 1.1 years, weight 71.5 ± 15.4 kg, and 62.5% male. Thirty-seven adverse events were reported in nine liraglutide-treated participants (56.3%) versus 12 events in five placebo-treated participants (62.5%). Most adverse events were mild in severity, three were of moderate severity, and none were severe. Gastrointestinal disorders were the most frequently reported events occurring in 37.5% of liraglutide-treated participants compared with placebo (12.5%). Six asymptomatic hypoglycaemic episodes occurred in five participants of whom four were liraglutide treated. Liraglutide exposure was consistent with dose proportionality. Body weight was the only covariate to significantly impact exposure. A significant reduction in body mass index (BMI) *Z* score from baseline to end of treatment (estimated treatment difference: −0.28; $P = 0.0062$) was observed.

Conclusion: Short-term treatment with liraglutide in children with obesity revealed a safety and tolerability profile similar to trials in adults and adolescents with obesity, with no new safety issues.

KEYWORDS

Clinical trial, GLP-1, liraglutide, paediatric

1 | INTRODUCTION

Childhood obesity has emerged as a global public health concern over the past three decades, with prevalence having doubled in more than 70 countries.[1] In the United States, the prevalence of obesity nearly tripled in school-age children (6-11 y) from 6.5% to 18.0% between 1976-1980 and 2009-2010.[2] Childhood obesity is associated with a number of health complications including type 2 diabetes mellitus, hypertension, polycystic ovary syndrome, sleep apnoea, asthma, orthopaedic problems, and psychosocial problems.[3-5] Furthermore, childhood overweight is associated with risk factors for cardiovascular disease.[6,7] Childhood overweight and obesity are independent risk factors for developing obesity in adulthood,[8] and the relative risk of adult obesity increases with age and body mass index (BMI).[9] Taken together, these findings underscore the need to implement safe and efficacious interventions to treat and prevent obesity in children.

Interventions for treating obesity in children have shown limited effectiveness, with the foundation of current treatment strategies focusing on family-based behavioural programmes.[3] If lifestyle modifications to diet and physical activity levels fail, an escalation in medical therapy may be required, including pharmacological treatment.[3] Orlistat and phentermine are the only medications approved in the United States to treat obesity in adolescents (age $\geq$ 12 and $\geq$16 y, respectively). Studies of medications to treat obesity in children had small sample sizes or revealed only modest effects on weight loss.[10-12] Currently, there are no pharmacotherapies approved for weight management in young children below the age of 12 in either the United States or European Union (EU). As such, there exists an unmet medical need in this population for the treatment of obesity.

Liraglutide is an analogue of the gut incretin hormone GLP-1.[13] In response to food intake, GLP-1 is secreted by intestinal L cells and lowers blood glucose by inhibiting glucagon secretion and promoting insulin secretion in a glucose-dependent manner.[13,14] GLP-1 is also a physiological regulator of appetite. Liraglutide belongs to the class of GLP-1 receptor agonists[13] that stimulates weight loss via reductions in appetite and energy intake.[15] Liraglutide 3.0 mg, as an adjunct to a reduced-calorie diet and increased physical activity, is approved for chronic weight management in adults based on the phase 3a Satiety and Clinical Adiposity-Liraglutide Evidence (SCALE) clinical development programme.[16-20] In a previous trial of adolescents with obesity, treatment with liraglutide 3.0 mg revealed no safety or tolerability concerns, and the pharmacokinetic (PK) properties were consistent with previous observations in adults with obesity.[21,22]

The aim of the present trial was to investigate safety, tolerability, PK, and PD during short-term treatment with once-daily liraglutide doses up to 3.0 mg in children with obesity aged 7 to 11 years and Tanner stage 1 pubertal development.

2 | METHODS

2.1 | Trial design and population

This randomized, double-blind, placebo-controlled trial was conducted at seven sites in the United States of which three sites randomized participants (two, eight, and 14 per site; ClinicalTrials.gov Identifier: NCT02696148). All sites received approval by an institutional review board and/or local health authority. This trial was conducted in accordance with the Declaration of Helsinki[23] and International Council for Harmonisation Good Clinical Practice.[24] All participants and their parents or legally acceptable representatives provided assent and informed consent, respectively, prior to any trial-related activities. The key inclusion criteria were male or female children (7-11 y); Tanner stage 1 (children with premature adrenarche were included); BMI corresponding to $\geq$30 kg m^{-2} for adults by international cut-off points[25] (Table S1); and BMI $\leq$ 45 kg m^{-2}, as well as BMI $\geq$ 95th percentile for age and sex. Tanner stage was assessed by genital development stages for boys and breast development stages for girls,[26] as determined by the investigator. Key exclusion criteria included secondary causes of childhood obesity; confirmed bulimia nervosa disorder; diagnosis of type 1 or 2 diabetes mellitus as defined by glycated haemoglobin (HbA1c) $\geq$ 6.5%; pubertal development—Tanner stages 2 to 5 (participants with premature adrenarche were included) at the time of screening; history of pancreatitis (acute or chronic); presence of severe comorbidities as judged by the investigator; family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; and history of major depressive disorder within 2 years before randomization. The complete list of inclusion and exclusion criteria is included in Table S2.

2.2 | Randomization and treatment

Each trial site was supplied with trial products via an interactive voice/web responsive service. Following screening, participants were randomized 2:1 to once-daily subcutaneous injections of liraglutide or placebo, respectively, in accordance with a dispensing unit number allocated by the sponsor. The sponsor, participants, and investigators remained blinded to treatment allocation. Participants and their parents or legally acceptable representatives were instructed in administering injections, and participants performed a self-injection with a prefilled placebo pen injector (FlexPen; Novo Nordisk, Denmark) at the screening visit to ensure they were capable and willing to self-inject. Liraglutide or equal volume of placebo was administered using a prefilled syringe at 9 AM ± 2 hours starting at 0.3 mg once daily. Liraglutide and placebo are visually identical, and therefore, it was not possible to distinguish between the two treatment arms. Daily doses were administered at home or on site during the weekly visits under investigator surveillance. The liraglutide dose was escalated from 0.3 to 1.2 mg in weekly increments of 0.3 mg and then followed with 0.6-mg weekly increments to a maximum dose of 3.0 mg or maximum tolerated dose (Figure S1). The treatment was at least 7 weeks with the allowance of up to six optional treatment weeks, up to a maximum of 13 weeks. Optional treatment weeks aimed to optimize tolerability during dose escalation in this paediatric population by allowing participants to remain on an unchanged or lowered dose if dose escalation criteria were not met at any of the treatment weeks and to escalate the dose at a later time. The dose remained unchanged if fasting plasma glucose (FPG) was <3.1 mmol L^{-1} (56 mg dL^{-1}) or <3.9 mmol L^{-1} (70 mg dL^{-1}) in the presence of hypoglycaemia

symptoms during the previous week, or if the dose was not tolerated with respect to adverse events (AEs), as judged by the investigator. Participants attended a final follow-up visit approximately 10 to 17 days after the last dose.

Treatment compliance was assessed by measuring liraglutide concentrations once at each dose step as part of the PK assessment (C_{trough}), as mentioned below. Additionally, at each dosing visit, the investigator reminded the participants to follow protocol procedures, and the participants returned all used, partly used, and unused trial products. In case of discrepancies, the investigator was to question the child and parent(s)/legally acceptable representative. Moreover, the diaries, in which the time of dosing was to be noted, were checked at each visit.

2.3 | Outcomes

The primary outcome was the number of AEs from the time of first dosing until completion of the follow-up visit in all children who received at least one dose of trial product. Supportive secondary endpoints included the number of hypoglycaemic episodes in the same time period as well as changes from baseline to end of treatment in physical examination parameters, vital signs, clinical laboratory evaluations, electrocardiogram (ECG), and incidence of antiliraglutide antibodies at follow-up. In addition to the American Diabetes Association (ADA) classification for hypoglycaemia,[27] Novo Nordisk used the following classification: severe hypoglycaemia according to ADA classification[27] and symptomatic blood glucose confirmed hypoglycaemia (an episode that is blood glucose confirmed by plasma glucose [PG] value < 3.1 mmol L^{-1} (56 mg dL^{-1}) with symptoms consistent with hypoglycaemia).

Safety and tolerability were assessed throughout the entire trial. Participants were provided with blood glucose meters (Medisense Precision Xtra, Abbott Laboratories, IL) and recorded self-measured PG levels prior to weekly visits following an overnight fast (in the morning before coming to the trial site for the visit) or, in the case of a suspected hypoglycaemic episode, at any time of day while at home, in assigned diaries. All PG values $\leq$ 3.9 mmol L^{-1} (70 mg dL^{-1}), irrespective of symptoms of hypoglycaemia, were reported in diaries.

Secondary PK endpoints included steady-state liraglutide plasma C_{trough} during dose escalation and apparent clearance (CL/F) and $AUC_{0\text{-}24h}$ at steady state following the last dose of liraglutide. Blood sampling to assess steady-state liraglutide C_{trough} concentrations was performed at the end of each dosing week interval. Sparse sampling for population PK modelling was performed following the last dose (1, 2, 3, 24, and 72 h after dose); the timing and number of PK samples were chosen by an optimal design methodology[28] with the aim of optimizing the population estimate of CL/F. The population PK modelling approach (see Section 2.4) allowed for a reduced number of PK samples per participant.

Secondary PD exploratory endpoints included changes from baseline to end of treatment for BMI *Z* score, body weight, FPG, serum insulin, and serum HbA1c. The algorithm used to calculate the BMI *Z* score was previously published by the World Health Organization.[29]

2.4 | Statistical analyses

With 18 participants completing the trial, a sample size of 11 participants on liraglutide and four on placebo was ensured, which was considered sufficient to evaluate safety and tolerability as well as to make appropriate assessments of the PK endpoints. Randomization of up to 25 participants was allowed (with planned inclusion of 21) to account for withdrawn participants. Safety and PD analyses were performed on the same population of 24 participants. PK evaluations were performed on participants treated with liraglutide only. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). For the population PK analysis, R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD) were used.

The AEs and assessments for physical examination, ECG, vital signs, and laboratory tests were summarized descriptively. The hypoglycaemic episodes were summarized by severity.

Liraglutide dose proportionality was based on C_{trough} values. A linear mixed model was used to estimate the slope (β) and the dose-proportionality parameter (2^{β}). In a post hoc sensitivity analysis for dose proportionality, four participants with unexplained low plasma liraglutide concentrations were identified prior to unblinding of treatment allocation and omitted from the analysis.

Estimates of CL/F and $AUC_{0\text{-}24h}$ were obtained from the population PK analysis based on the sparse sampling (after the last dose) and C_{trough} values (obtained during dose escalation period). A standard one-compartment model with first-order absorption and elimination parameters (k_a, CL/F, and apparent volume of distribution [Vd/F]) was used to describe the liraglutide PK in children with obesity as was done previously.[21,22,30,31] Random effects (ie, between-participant variability estimates) were included for both CL/F and Vd/F. A proportional error model assessed residual variability of liraglutide concentrations. A correction factor was estimated for the C_{trough} values to account for the unexpectedly low plasma liraglutide concentrations in order to avoid that these low measurements influenced the parameter estimates in a way that could lead to high estimates of CL/F and thus too high dose recommendations. The impact of covariates for CL/F (age, body weight, sex) and Vd/F (body weight) was investigated in full and reduced models; the full model tested effects of all covariates simultaneously, whereas the reduced model removed the least significant covariates sequentially. This model was fitted to data from the current trial and previous trials in adolescents[21] and adults,[22] and the estimated PK parameters were compared.

Changes in BMI *Z* score and body weight were analysed using a linear model with treatment as a fixed factor with two levels (liraglutide and placebo) and baseline values as covariate. Assessments of FPG, serum insulin, and serum HbA1c were summarized using descriptive statistics.

3 | RESULTS

A total of 33 participants were screened for eligibility between 14 March 2016 and 13 April 2017, of which nine were screen failures (one was an eligible participant who could not self-inject and was

not randomized) (Figure S2). The remaining 24 participants were randomized and exposed to treatment: 16 to liraglutide and eight to placebo. A total of four participants were withdrawn after randomization (two from each treatment group). Of the two participant withdrawals in the liraglutide group, one was reported as lost to follow-up, and the other was a voluntary participant withdrawal. Both withdrawals in the placebo group were reported as withdrawn by parent/guardian. Of the 20 participants (83%) who completed the trial, 19 reached the maximum dose of 3.0 mg (13 liraglutide-treated participants and all six placebo participants). Three completed participants in the liraglutide group used one optional treatment week each during escalation: Two participants experienced vomiting and were treated with 0.9 mg liraglutide for 2 weeks prior to further dose escalation, and one participant experienced episodes of vomiting and reached a maximum tolerated dose of 2.4 mg liraglutide (refer to Figure 1). No participants were treated beyond 8 weeks.

Baseline characteristics are shown in Table 1. The mean age was 9.9 years (age range 7-11 y). A total of three participants (one liraglutide-treated and two placebo-treated participants) were reported to have premature adrenarche at the time of screening. The frequency of male participants was higher in the placebo group than the liraglutide treatment group. The mean height and weight of the liraglutide treatment group were less than the placebo group. Baseline BMI *Z* score and glycaemic parameters (serum HbA1c and FPG) were similar between treatment groups.

TABLE 1 Baseline characteristics[a]

	Liraglutide n = 16	Placebo n = 8	Total n = 24
Sex, n (%)			
Female	8 (50.0)	1 (12.5)	9 (37.5)
Male	8 (50.0)	7 (87.5)	15 (62.5)
Ethnicity, n (%)			
Hispanic or Latino	6 (37.5)	3 (37.5)	9 (37.5)
Not Hispanic or Latino	10 (62.5)	5 (62.5)	15 (62.5)
Race, n (%)			
White	9 (56.3)	5 (62.5)	14 (58.3)
Black or African American	7 (43.8)	3 (37.5)	10 (41.7)
Age, y	9.7 (1.1)	10.4 (1.1)	9.9 (1.1)
Min; max	7; 11	8; 11	7; 11
Height, m	1.45 (0.11)	1.54 (0.08)	1.48 (0.11)
Min; max	1.27; 1.62	1.43; 1.68	1.27; 1.68
Body weight, kg	66.6 (12.6)	81.4 (16.6)	71.5 (15.4)
Min; max	45.0; 86.8	68.1; 115.4	45.0; 115.4
BMI *Z* score[b]	3.8 (0.9)	4.1 (1.0)	3.9 (0.9)
Min; max	2.6; 5.7	2.8; 6.0	2.6; 6.0
FPG (mmol L^{-1})	5.25 (0.27)	5.19 (0.32)	5.23 (0.28)
Min; max	4.79; 5.68	4.65; 5.71	4.65; 5.71
FPG (mg dL^{-1})	95 (5)	94 (6)	94 (5)
Min; max	86; 102	84; 103	84; 103
HbA1c (mmol mol^{-1})	36.8 (4.1)	35.5 (3.9)	36.4 (4.0)
Min; max	27.9; 42.1	30.1; 42.1	27.9; 42.1
HbA1c, %	5.5 (0.4)	5.4 (0.4)	5.5 (0.4)
Min; max	4.7; 6.0	4.9; 6.0	4.7; 6.0

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; Max, maximum; Min, minimum; n, number of randomized participants.

[a]Data are observed means (standard deviation [SD]), unless otherwise stated.

[b]BMI *Z* score represents the number of SDs from a reference standard population mean BMI.[21]

3.1 | Adverse events

A total of 9/16 (56.3%) participants treated with liraglutide reported 37 AEs and 5/8 (62.5%) participants treated with placebo reported 12 AEs; the AEs are presented by system organ class in Table 2 and additionally by preferred term in Table S3. All AEs were mild in severity with the exception of three moderate severity AEs (two events [vomiting] in one participant in the liraglutide treatment group and one event [arthropod bite] in the placebo group). No severe or serious

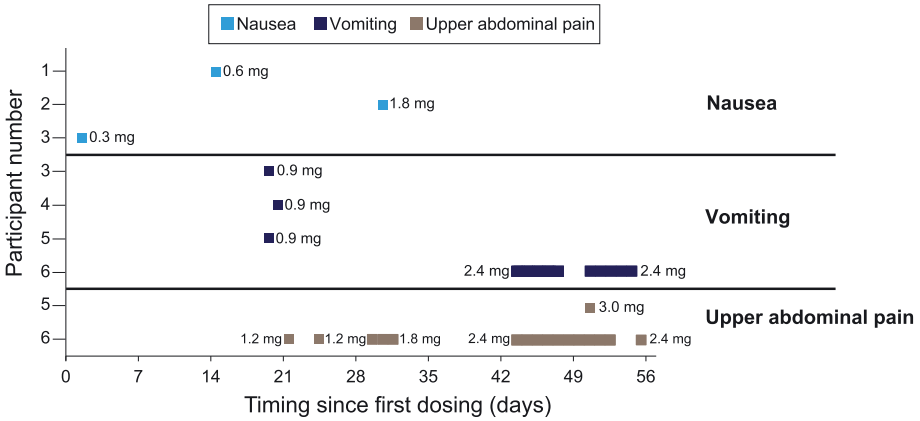

FIGURE 1 Timing and duration of selected gastrointestinal (GI) adverse events (AEs) with liraglutide. The doses shown are those at the start of the event. Individual square boxes indicate the day of AE onset and could have ranged from <1 min to 24 h. There were no AEs of nausea, vomiting, or upper abdominal pain reported in participants treated with placebo. Numbers on the *y* axis designate individual participants. Two participants (participants 3 and 4) each used one optional week and were treated with liraglutide 0.9 mg d^{-1} for 2 wk before further dose escalation. One participant (participant 6) reached a maximum dose of liraglutide 2.4 mg d^{-1} using one optional week and remained at this dose for 3 wk. All GI AEs were mild in severity with the exception of vomiting of moderate severity in participant 6. No participants were treated beyond 8 wk

TABLE 2 Summary of adverse events and hypoglycaemic episodes

	Liraglutide n = 16			Placebo n = 8		
	Participants		Events	Participants		Events
Variables	n	%	n	n	%	n
AEs	9	56.3	37	5	62.5	12
Severity[a]						
Mild	9	56.3	35	5	62.5	11
Moderate	1	6.3	2	1	12.5	1
Relationship to trial product						
Probable/possible	5/3	31.3/18.8	15/6	1/1	12.5/12.5	1/1
Unlikely	5	31.3	16	5	62.5	10
Outcome						
Recovered/recovering	9/1	56.3/6.3	36/1	5/2	62.5/25.0	10/2
AEs by system organ class						
GI disorders	6	37.5	19	1	12.5	1
Nervous system disorders	3	18.8	4	4	50.0	5
General disorders and admin. site conditions	3	18.8	4	1	12.5	1
Infections and infestations	2	12.5	2	1	12.5	1
Musculoskeletal and connective tissue disorders	1	6.3	1	1	12.5	2
Respiratory, thoracic, and mediastinal disorders	2	12.5	4	0	0.0	0
Ear and labyrinth disorders	1	6.3	1	0	0.0	0
Eye disorders	1	6.3	1	0	0.0	0
Injury, poisoning, and procedural complications	0	0.0	0	1	12.5	1
Investigations	0	0.0	0	1	12.5	1
Skin and subcutaneous tissue disorders	1	6.3	1	0	0.0	0
Hypoglycaemic episodes						
ADA[b]	4	25.0	5	1	12.5	1
Asymptomatic	4	25.0	5	1	12.5	1

Abbreviations: ADA, American Diabetes Association; admin, administration; AEs, adverse events; GI, gastrointestinal; n, number of randomized participants or events.

[a]There were no severe AEs in either treatment group.

[b]ADA definitions, briefly: severe, requiring assistance of another person; asymptomatic, no typical symptoms but plasma glucose (PG) concentration $\leq$ 70 mg dL^{-1} (3.9 mmol L^{-1}); probable symptomatic, symptoms without PG determination; relative, typical symptoms but PG concentration > 70 mg dL^{-1} (3.9 mmol L^{-1}).[27] A total of six hypoglycaemic episodes were reported; there were no severe, documented symptomatic, probable symptomatic, or relative hypoglycaemic episodes.

AEs or deaths were reported, and none of the AEs led to participant withdrawal. AEs considered possibly or probably related to treatment, as judged by the investigator, are shown in Table 3; These were more frequent in the liraglutide treatment group (21 AEs, 56.8%) than the placebo group (two AEs, 16.7%) and mostly related to gastrointestinal (GI) disorders (Tables 2 and 3). More participants in the liraglutide treatment group (37.5%), compared with placebo group participants (12.5%), reported GI AEs (Table 2); however, there was no clear association between the treatment dose, timing, duration, or severity of specific GI AEs (nausea, vomiting, and upper abdominal pain) (Figure 1). Two participants treated with liraglutide (12.5%), compared with no participants in the placebo group, reported three AEs (two events of injection site induration and one event of injection site reaction) that were judged by investigators to be possibly or probably related to treatment (Table 3). Apart from two events of headache, which were reported by two participants (12.5%) in the liraglutide group and none in the placebo group, other potentially related AEs were single events in either treatment group. All AEs had outcomes of recovered or recovering at the end of the trial. The AEs with outcomes of recovering concerned one participant in the liraglutide treatment group (rash) and two participants in the placebo group (headache and increased alanine aminotransferase).

3.2 | Hypoglycaemic episodes

A total of six hypoglycaemic episodes were reported during the trial, of which five were reported in four participants in the liraglutide treatment group (Table 2). All episodes were asymptomatic, and four episodes, all in participants treated with liraglutide, occurred following an overnight fast. Glucose measurements reported as hypoglycaemia in participant diaries ranged from 3.4 to 3.9 mmol L^{-1} (62-70 mg dL^{-1}). No treatment was required for these participants.

3.3 | Clinical laboratory evaluations, ECG, physical examination, and vital signs

No clinically relevant safety findings were identified in relation to physical exam, vital signs, ECG, haematology, biochemistry, hormones,

TABLE 3 Adverse events[a] possibly or probably related to investigational product

	Liraglutide n = 16			Placebo n = 8		
	Participants		Events	Participants		Events
	n	%	N	n	%	N
AEs probably or possibly related	7	43.8	21	2	25.0	2
GI disorders	5	31.3	14	1	12.5	1
Vomiting	4	25.0	5	0	0.0	0
Nausea	2	12.5	2	0	0.0	0
Abdominal pain upper	1	6.3	5	0	0.0	0
Diarrhoea	1	6.3	1	0	0.0	0
Dyspepsia	0	0.0	0	1	12.5	1
Salivary hypersecretion	1	6.3	1	0	0.0	0
Nervous system disorders	3	18.8	3	0	0.0	0
Headache	2	12.5	2	0	0.0	0
Dizziness	1	6.3	1	0	0.0	0
General disorders and administration site conditions	2	12.5	3	0	0.0	0
Injection site induration	2	12.5	2	0	0.0	0
Injection site reaction	1	6.3	1	0	0.0	0
Eye disorders	1	6.3	1	0	0.0	0
Orbital oedema	1	6.3	1	0	0.0	0
Investigations	0	0.0	0	1	12.5	1
Increased ALT	0	0.0	0	1	12.5	1

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; GI, gastrointestinal; N, number of events; n, number of randomized participants.

[a]AEs are presented by system organ class and preferred term; causality is assessed by the investigator.

lipids, or calcitonin. Increases in mean serum lipase and amylase were observed in liraglutide-treated participants (Figures S3 and S4); nevertheless, the changes were not considered to be clinically relevant (all elevated levels were below three times the upper limit of the normal range). No participants developed antiliraglutide antibodies.

3.4 | Pharmacokinetics

Liraglutide C_{trough} concentrations were consistent with dose proportionality as a doubling of the liraglutide dose resulted in a 1.66 increase in exposure, estimated 2^{β} = 1.66 (95% confidence interval [CI], 1.26, 2.19), P = 0.19. Exclusion of the four participants with unexpectedly low liraglutide C_{trough} concentrations in a post hoc sensitivity analysis further supported the observation of dose proportionality as a doubling of the liraglutide dose resulted in a 1.94 increase in exposure, estimated 2^{β} = 1.94 (95% CI, 1.53, 2.45), P = 0.79.

The population PK analysis allowed for comparison of liraglutide exposure between children participating in the current trial and previous trials including adolescents[21] and adults.[22] The mean estimate of CL/F in children was lower than that in both adolescents and adults (Table 4). Correspondingly, the model-derived mean estimate of $AUC_{0\text{-}24h}$ at steady state following last dose was higher in children compared with adolescents and adults (Table 4). Estimated C_{avg} was higher in children compared with adults (Figure 2A and Table 4). These differences can be explained by the fact that body weight was the only covariate of importance for liraglutide exposure. When adjusted for body weight, the exposure was similar for children, adolescents, and adults (Figure 2B).

TABLE 4 Summary of apparent clearance and liraglutide exposure values in children compared with adolescents and adults with obesity—geometric mean (95% CI)

Trial population	CL/F (L h^{-1})	$AUC_{0\text{-}24,ss}$ (h·nmol L^{-1})[a]	C_{avg} (nmol L^{-1})[a]
Children (n = 13)	0.69 (0.6, 0.82)	1161 (1002, 1398)	48.4 (41.8, 58.2)
Adolescent (n = 13)	0.99 (0.88, 1.14)	808 (720, 931)	33.7 (30, 38.8)
Adult (n = 29)	1.15 (1.05,1.37)	697 (640, 833)	29.0 (26.7, 34.7)

Abbreviations: $AUC_{0\text{-}24,ss}$, area under the concentration-time curve from 0 to 24 h following last dose; C_{avg}, estimated average plasma liraglutide concentration in a dosing interval; CL/F, apparent clearance following last dose; n, number of participants analysed.

[a]Values are for liraglutide 3.0 mg at steady state. Data are from the current trial in children and previous clinical pharmacology trials in adolescents[21] and adults.[22]

3.5 | Pharmacodynamic evaluations

From baseline to end of treatment (7-8 wk after first dose), a statistically significant reduction in BMI Z score was observed in liraglutide-treated participants (estimated mean − 0.3) compared with the placebo group (−0.01), treatment difference (95% CI): −0.28 (−0.47, −0.09), P = 0.0062. A decrease was observed in body weight at end of treatment for liraglutide-treated participants (estimated mean − 0.52 kg) as compared with an observed increase in participants in the placebo (0.98 kg), treatment difference (95% CI): −1.50 (−3.54; 0.54), although this difference was not statistically significant. Individual changes in body weight are presented in Figure S5. A minor reduction in FPG was observed in liraglutide-treated participants compared with participants treated with placebo from baseline to end of treatment (not statistically tested) (Table S4). There were no differences in levels of serum insulin and HbA1c observed between treatment groups (Table S4).

4 | DISCUSSION

This trial was performed as part of a paediatric clinical development programme for liraglutide in weight management in agreement with regulatory agencies in the United States and EU. This trial follows the earlier trial in adolescents,[21] and, hence, the development plan uses a staggered approach. The safety profile observed in children aged 7 to 11 years was similar to that in liraglutide trials conducted in adults or adolescents with obesity and without diabetes,[16,17,19-21] with no new safety concerns identified.

The frequencies of AEs were similar between liraglutide and placebo treatment groups. More AEs associated with GI disorders, most notably nausea and vomiting, occurred in participants treated with liraglutide compared with placebo, which is consistent with findings

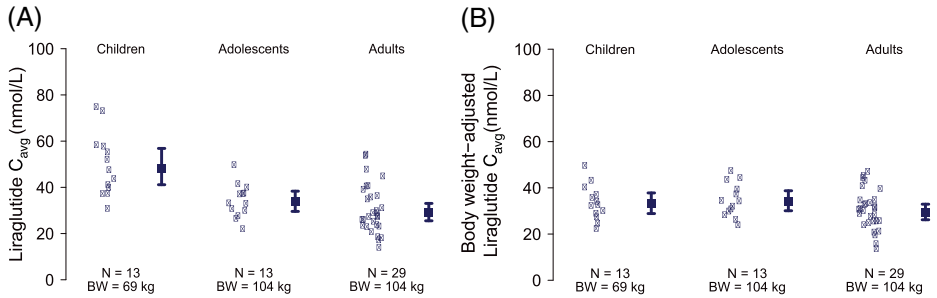

FIGURE 2 Dose-normalized average concentrations in children, adolescents, and adults (A) before and (B) after adjustment for differences in body weight. Individual data points are represented by shaded rectangles. Squares indicate geometric mean model–based estimates of the average concentration in steady state with 95% CI for each trial assuming full compliance to liraglutide 3.0 mg treatment. Data in (B) are adjusted on the basis of individual body weights. Mean body weights are shown. Data are from the current trial in children and previous clinical pharmacology trials in adolescents[21] and adults.[22] BW, body weight; C_{avg}, estimated average plasma liraglutide concentration in a dosing interval at steady state; CI, confidence interval; N, number of participants analysed

from previous trials in adolescents and adults.[15,16,18,21] There was no clear relationship between treatment dose, timing, duration, or severity of specific GI AEs in children, which is consistent with previous findings in adolescents with obesity.[21] Nausea and vomiting occurred primarily within the first 4 to 8 weeks following initiation of liraglutide treatment in previous weight management trials in adults.[16,18] Additionally, more related AEs of injection site induration and injection site reactions (three events in total) were reported in liraglutide-treated participants as compared with no events in placebo, similar to previous findings in adolescents with obesity,[21] although the overall frequency of such events was low.

More hypoglycaemic episodes were reported in the liraglutide group compared with the placebo group in the present trial. All events were asymptomatic and only detected during study-related FPG self-measurements. In a previous trial with adolescents, more hypoglycaemic events were observed in participants treated with liraglutide, and nearly half of the events occurred following an overnight fast of 10 hours or more.[21] These findings indicate that extended fasting in conjunction with liraglutide treatment may have contributed to episodes of hypoglycaemia, as suggested previously.[21]

In general, all other safety parameters indicated no clinically relevant findings. Treatment with liraglutide resulted in increased lipase and amylase levels (all below three times the upper limit of the normal range), consistent with previous observations in adolescents[21] and adults with obesity.[15,16,18] In SCALE trials in adult participants with overweight and obesity, the elevations of amylase and lipase occurring in those treated with liraglutide did not predict acute pancreatitis, and levels returned to baseline levels following discontinuation of therapy.[32] Furthermore, the clinical relevance and mechanisms underlying these increases remain unclear.[32] The potential effects of liraglutide on blood pressure and pulse could not be determined in this short-term trial.

The PK analyses of liraglutide revealed that liraglutide C_{trough} values were consistent with dose proportionality. The joint population PK analysis for liraglutide in children, adolescents, and adults confirmed that body weight was a relevant covariate for exposure, in agreement with previous observations; thus, a lower body weight is associated with a higher liraglutide exposure.[22,33,34] Unlike the previous trial in adults,[22] sex was not a relevant covariate on exposure in children aged 7 to 11 years; however, this may be due to the low number of female children in the current study. A thorough investigation of sample handling, bioanalysis, subject diaries, and drug accountability records did not provide an explanation for the unexpectedly low concentrations of liraglutide in four participants. Hence, the cause of these low concentrations was not determined. Treatments administered subcutaneously require the ability and willingness to self-inject; thus, support and guidance from parents and caregivers are paramount in order to ensure optimal adherence to therapy.

Treatment with liraglutide resulted in a significantly lower BMI *Z* score at end of treatment, indicating a potential benefit of liraglutide treatment over time in children with obesity. The nonsignificant decrease in body weight observed in participants treated with liraglutide may be due to the short duration of the current trial and/or small sample size.

The limitations in the current study include the variability between the treatment groups. The placebo group contained more males, and participants on average tended to be taller and heavier. Fewer female children participated in the study, likely due to the pubertal exclusion criteria. The short duration of the current trial poses limitations in that long-term safety could not be assessed in this trial of approximately 7 weeks' duration. Similarly, although exploratory PK analyses indicated a relationship between exposure and response, the full exposure-response is not expected from this short-term trial.

In summary, treatment with liraglutide in this paediatric population aged 7 to 11 years showed no unexpected safety or tolerability concerns in the present trial, with no new safety issues as compared with previous trials conducted in adolescents or adults with obesity. Participants treated with liraglutide for up to 8 weeks achieved a statistically significant reduction in BMI *Z* score, nonsignificant decrease in body weight, and minor reduction in FPG. However, because of the short-term treatment in this trial, the pharmacodynamic results should be interpreted with caution. Liraglutide exposure at steady state was consistent with dose proportionality. Furthermore, the joint population PK analysis revealed that body weight was the only relevant covariate to predict liraglutide exposure; no differences were detected between age groups or sex. These findings support further

long-term investigations of safety and efficacy in young children with obesity and will guide dose setting in planned phase 3 trials in this age group.

CONFLICT OF INTEREST

This study was sponsored by Novo Nordisk, which was responsible for the overall trial design, conduct, and analysis and provided a formal review of the manuscript, but the authors had final authority, including choice of journal and the decision to submit the work for publication. L.D.M. serves as site principal investigator for clinical trials supported by Novo Nordisk, AstraZeneca, and Sanofi Aventis. She serves on the oversight committee for the Pediatric Diabetes Consortium. L.W., K.C.C.P., P.M.H., and H.K.H. are employees of Novo Nordisk. K.C.C.P., P.M.H., and H.K.H. own stocks in Novo Nordisk. R.A.R. has no disclosures to report.

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AUTHOR CONTRIBUTIONS

H.K.H., K.C.C.P., and P.M.H. conceived the methodology and study design. L.D.M. and R.A.R. were involved in data collection. L.D.M., L.W., P.M.H., and R.A.R. provided trial supervision and oversight. H.K.H., K.C.C.P., L.D.M., L.W., and P.M.H. contributed to a formal analysis of the data. All authors had full access to the data included in this analysis, analysed and interpreted the data, critically reviewed the manuscript, and approved the final version for submission. All authors also agreed to be accountable for all aspects of the work.

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	adverse event
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from 0 to 24 hours following last dose at steady state
BMI *Z* score	number of SDs from a reference standard population mean BMI
BMI	body mass index
C_{avg}	average plasma concentration in a dosing interval at steady state
CI	confidence interval
CL/F	apparent clearance
C_{trough}	trough concentration
ECG	electrocardiogram
EU	European Union
FPG	fasting plasma glucose
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
k_a	absorption rate constant
PD	pharmacodynamic
PG	plasma glucose
PK	pharmacokinetic(s)
Vd/F	apparent volume of distribution

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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