


ORIGINAL RESEARCH

A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity

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Summary

Background: Pharmacological treatment options for adolescents with obesity are very limited. Glucagon-like-peptide-1 (GLP-1) receptor agonist could be a treatment option for adolescent obesity.

Objective: To investigate the effect of exenatide extended release on body mass index (BMI)-SDS as primary outcome, and glucose metabolism, cardiometabolic risk

Abbreviations: ADR, adverse drug reaction; AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; BMI-SDS, body mass index-SD score; GLP-1, glucagon-like peptide-1; IMP, investigational medicinal product; ITT, intention-to-treat; LFC, liver fat content; LOCF, last observation carried forward; MEN-2, multiple endocrine neoplasia syndrome type 2; MRI, magnetic resonance imaging; MTC, medullary thyroid carcinoma; NAFLD, non-alcoholic fatty liver disease; OGTT, oral glucose tolerance test; RCT, randomized controlled trial; SAP, statistical analysis plan; SAT, subcutaneous adipose tissue; SUSAR, suspected unexpected serious adverse reaction; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue; WHO, World Health Organization.

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factors, liver steatosis, and other BMI metrics as secondary outcomes, and its safety and tolerability in adolescents with obesity.

Methods: Six-month, randomized, double-blinded, parallel, placebo-controlled clinical trial in patients ($n = 44$, 10-18 years, females $n = 22$) with BMI-SDS > 2.0 or age-adapted-BMI $> 30 \text{ kg/m}^2$ according to WHO were included. Patients received lifestyle intervention and were randomized to exenatide extended release 2 mg ($n = 22$) or placebo ($n = 22$) subcutaneous injections given once weekly. Oral glucose tolerance tests (OGTT) were conducted at the beginning and end of the intervention.

Results: Exenatide reduced ($P < .05$) BMI-SDS (-0.09 ; -0.18 , 0.00), % BMI 95th percentile (-2.9% ; -5.4 , -0.3), weight (-3 kg ; -5.8 , -0.1), waist circumference (-3.2 cm ; -5.8 , -0.7), subcutaneous adipose tissue (-552 cm^3 ; -989 , -114), 2-hour-glucose during OGTT (-15.3 mg/dL ; -27.5 , -3.1), total cholesterol (11.6 mg/dL ; -21.7 , -1.5), and BMI (-0.83 kg/m^2 ; -1.68 , 0.01) without significant change in liver fat content (-1.36 ; -3.12 , 0.4 ; $P = .06$) in comparison to placebo. Safety and tolerability profiles were comparable to placebo with the exception of mild adverse events being more frequent in exenatide-treated patients.

Conclusions: Treatment of adolescents with severe obesity with extended-release exenatide is generally well tolerated and leads to a modest reduction in BMI metrics and improvement in glucose tolerance and cholesterol. The study indicates that the treatment provides additional beneficial effects beyond BMI reduction for the patient group.

KEYWORDS

Body mass index, exenatide, GLP-1 receptor agonist, glucose metabolism, liver steatosis, metabolic syndrome, pediatric obesity

1 | INTRODUCTION

More than 40 million children globally under the age of 5 years suffer from obesity, and the number shows no sign of retrenchment.¹ Lifestyle modification interventions are the cornerstones of treatment of pediatric obesity, but in general the efficacy in reducing weight and body mass index (BMI) is low.^{2,3} As a result, there is considerable interest in combining lifestyle modification with additional strategies to ameliorate pediatric obesity, such as pharmacological treatment. The pharmacological treatment options in pediatric obesity are few, and the BMI lowering effects of existing agents, such as Metformin and Orlistat, are modest.⁴ Thus, effective pharmacotherapy that reverses excessive adiposity and improves obesity-related comorbid conditions in pediatric patients remains largely elusive.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) including exenatide and liraglutide were first developed and consequently approved for the treatment of Type 2 diabetes (T2DM) in adults and have also been shown to reduce weight in adults with obesity.⁵ Beyond weight loss, GLP-1 RA have been shown to improve glucose control by the glucose-dependent increase in postprandial insulin secretion, and inhibition of glucagon secretion⁶ and further metabolic comorbidities including non-alcoholic fatty liver disease (NAFLD).⁷ Pleiotropic mechanisms of action influencing appetite and satiety are

thought to be related to central as well as peripheral pathways.⁸ Safety, tolerability, and efficacy of exenatide administered twice daily in children and adolescents with obesity have been assessed in a pilot study⁹ followed by a 3-month randomized controlled trial (RCT), where the drug reduced weight.¹⁰ Extended-release formulation with administration of exenatide once weekly is available for T2DM treatment in adults. However, so far, there are no data on the efficacy, safety, and tolerability of extended-release GLP-1 analogue in the pediatric age group, neither for T2DM nor obesity.

To respond to this need, the RCT Combat-JUDO (Combating Juvenile Diabetes and Obesity) was conducted. Combat-JUDO investigated the effects of exenatide administered once weekly on BMI, glucose metabolism, liver steatosis, and associated cardiometabolic risk parameters as well as safety and tolerability in adolescents with obesity.

2 | PATIENTS AND METHODS

2.1 | Study design and eligibility criteria

The study was a 6-month parallel, double-blinded, randomized, placebo controlled two-arm study with lifestyle intervention plus either exenatide 2 mg or placebo subcutaneous (s.c.) injections once weekly

conducted at two study sites in 10 to 18 years old children and adolescents (referred to as “adolescents” hereafter) with obesity (Figure 1). Eligible patients were randomized 1:1 (exenatide:placebo) after a screening visit (up to 3 weeks prior to randomization) at each center and received the randomization number at baseline visit by a computer-generated randomization scheme with no stratification provided. The treatment with lifestyle and exenatide or placebo for 6 months (24 weeks) contained seven visits at the study site and six telephone contacts in between visits, and a follow-up visit 2 weeks after the last dose of study medication. The study was conducted from September 2015 to September 2016.

Inclusion criteria were signed informed consent, males or females of age 10 to 18 years and 5 months with obesity, sexually inactive or usage of adequate contraception, negative pregnancy tests in females, and ability to understand and comply with the requirements of the study. Obesity was defined as BMI-SD score (SDS) > 2.0 or age-adapted BMI $> 30 \text{ kg/m}^2$. BMI-SDS and BMI percentile were calculated using WHO growth reference charts.¹¹ Severe obesity was defined as BMI $\geq 120\%$ of the 95th percentile for age and sex,¹² calculated using Centers of Disease Control and Prevention 2000 Growth Charts (CDC).¹³ CDC growth charts were also used to calculate percent BMI above the 95th (%BMI_{p95}).

Exclusion criteria were syndromal obesity, pregnancy or lactation, indigestion-causing disease, severe gastrointestinal disease, total or partial gastric or small intestine resection, diabetes mellitus, kidney disease, hypo-/hyperthyroidism (unless under stable treatment), severe vitamin D insufficiency (defined as $<10 \text{ ng/mL}$; 13 subjects [seven in the exenatide arm and six in the placebo group] had levels

$<20 \text{ ng/mL}$ and received supplementation), abnormal QT interval, clinically significant abnormal laboratory values, psychiatric disorder referred to or undergoing special treatment, severe sleep apnea, metformin treatment within 3 months prior to screening or concomitant medication influencing blood glucose or other parameters of the metabolic syndrome, steroid treatment, concomitant medication addressing attention disorders, antidepressants that can lead to weight gain, hypersensitivity to exenatide, pacemaker or metal implant that may interfere with magnetic resonance imaging (MRI), claustrophobia or abdominal diameter exceeding an MR gantry diameter of 70 cm, current or within 3 months participation in another clinical study involving an IMP, personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2). Pregnancy, diabetes mellitus, kidney disease, hypo-/hyperthyroidism, vitamin D insufficiency (laboratory), and QT interval assessed by electrocardiogram (ECG) were based on tests, all other exclusion criteria on history.

Lifestyle intervention was applied in both study arms, consisting of nutritional, psychological, and physical treatment according to harmonized standard operating procedures at both study sites. In brief, the nutritional intervention (four individual sessions) was based on current recommendations for healthy diets¹⁴ with participants being advised to follow a traffic light system, dividing foods and drinks into red (alert), orange (consider amount) and green (ok, when hungry or thirsty). Four individual psychological sessions were conducted aiming to optimize issues related to disturbed eating behavior,¹⁵ sleep pattern, media consumption, and sedentary behavior in general, as well as to increase structured (at least one session per week in addition to physical

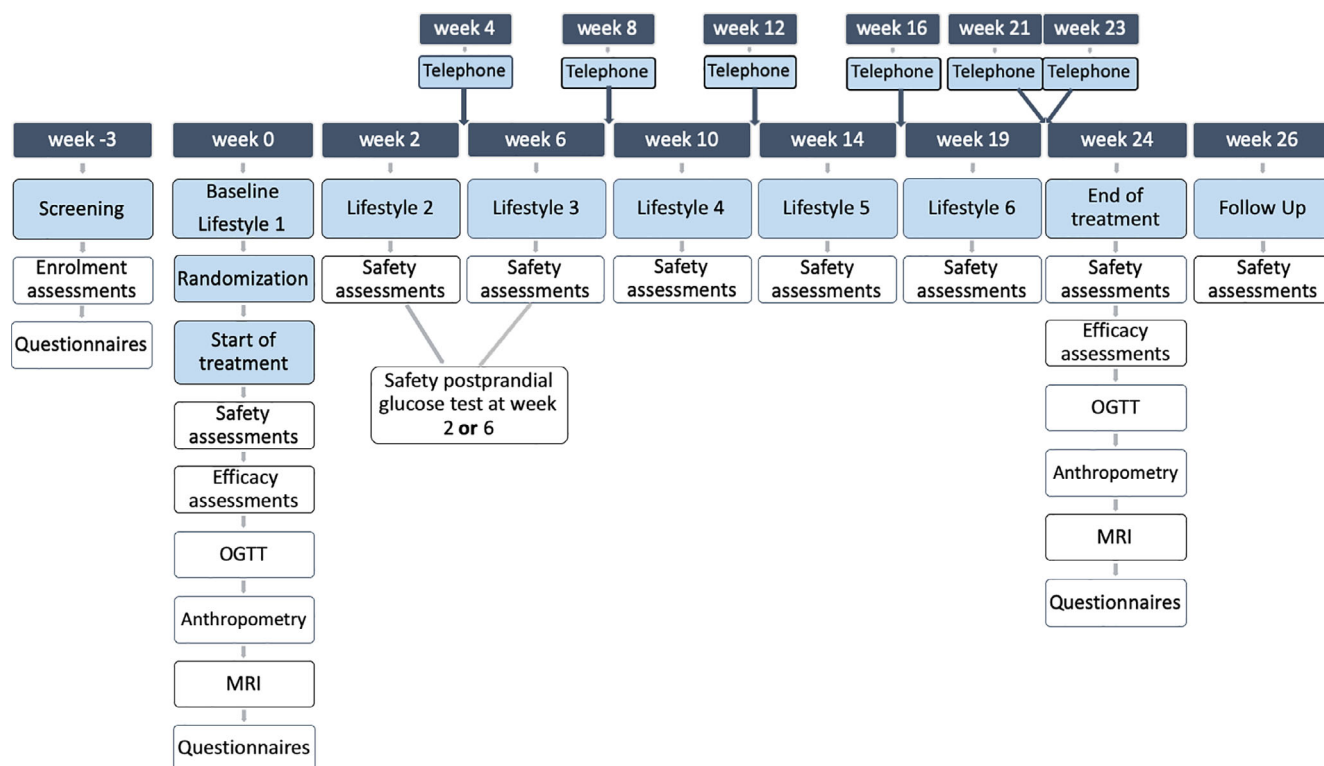


FIGURE 1 Study flow chart

education at school) and nonstructured physical activity. Ultimately, these measures targeted the participants' "health competence" including self-efficacy, the ability to act, communication, and motivation skills.¹⁶

Efficacy was assessed after 24 weeks, while safety was assessed after 2, 6, 10, 14, 19, and 24 weeks of the study and 2 weeks after last study dose.

2.2 | Pharmacological treatment

Each patient received weekly subcutaneous injections of the GLP-1 analogue Bydureon (exenatide) 2 mg, the investigational medicinal product (IMP), or placebo for a total of 24 weeks. Treatments were self-administered by the patient following individual training or administered by trained adult or personnel at the study site. The active product and the placebo were identical in appearance and labeled blinded. Treatment compliance and concomitant medication were checked at each study visit and at telephone contacts by a study nurse.

2.3 | Ethical and regulatory procedure

The study was accepted for Voluntary Harmonisation Procedure (VHP673, VHP2015061) and approved by Ethics Committees and Regulatory Authorities in Sweden and Austria (EudraCT No: 2015-001628-45; EC Sweden: Dnr 2015/279; EC Austria: 415-E/1544/20-2014). Informed consent and assent were obtained from parents and patients, respectively. The trial was conducted according to the Declaration of Helsinki (World Medical Association; Version 2013) and the E6 Guideline for Good Clinical Practice (International Conference on Harmonisation).

2.4 | Methods for assessing, recording, and analyzing efficacy variables

Anthropometry: All measurements were performed according to standard operating procedures harmonized between centers as reported previously.¹⁷ Weight (kg) was assessed with the patient wearing light clothing, by using a standardized, calibrated scale (Uppsala: SECA model 704; Salzburg: SECA model 801, Hamburg, Germany), height (cm) measured twice using a stadiometer, and the mean result was recorded (Uppsala: Ulmer stadiometer, Busse, Elchingen, Germany; Salzburg: SECA, model 222 stadiometer, Hamburg, Germany). Waist circumference (cm) was measured with a flexible tape midway between the superior border of the iliac crest and the lowest rib on the standing patient. BMI was calculated as weight in kilograms divided by the square of height in meters. The BMI-SDS was calculated with Microsoft Excel add-in LMS Growth using WHO growth report (Version 2.76). BMI percentile and BMI as percent of the 95th percentile (%BMI_{p95}, CDC)¹³ were also calculated.

Blood pressure, pulse, and temperature: Systolic and diastolic blood pressure (mmHg) was assessed by the mean of two measurements with

a standardized clinical aneroid sphygmomanometer with appropriate cuffs (Uppsala: CAS 740, CAS Medical Systems, Inc, Branford, CT, USA; Salzburg: Carescape V100, Dinamap Technology/GE, Vienna, Austria) in sitting position, right arm after 5 minutes of quiet rest. Pulse was assessed by palpation at the radial artery. Thereafter, tympanic body temperature was assessed (Uppsala: ThermoScan PRO 4000, BRAUN, WelchAllyn, NY, USA; Salzburg: Covidien, model Genius 2, Paris, France).

Magnetic resonance imaging (MRI) examinations were performed to determine visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and liver fat content (LFC) as described before.¹⁸ All examinations were performed using 1.5 Tesla clinical MRI systems from Philips Medical System (Best, The Netherlands; Uppsala: Philips Achieva system, Salzburg: Philips Ingenia system). The water-fat image reconstruction was performed using a multiresolution version that employs a whole-image optimization approach.¹⁹ The reconstruction used the same triglyceride spectrum model,²⁰ a common R2* parameter, and a regularization parameter $\mu = 10$. The liver volumes were delineated manually by one operator from the water images (axial slices) using the software ImageJ (version 1.42q, <http://rsbweb.nih.gov/ij/>). The median fat fraction value in the segmented liver was used as estimated liver fat. Uppsala developed and standardized the imaging protocol at both sites and performed all image analyses.

Blood sampling and analyses: Blood was sampled at fasting and analyzed locally at the respective hospital in Uppsala and Salzburg. Validation of analyses was performed between the laboratories in Uppsala and Salzburg using reference blood samples. Plasma was used for central analyses of insulin, proinsulin, and C-peptide using single-plex enzyme-linked immunosorbent assay kits for each analyte (Mercodia AB, Uppsala, Sweden). Total cholesterol, HDL- and LDL-cholesterol, and triglycerides were analyzed by enzymatic photometric analysis. Oral glucose tolerance tests (OGTT) were conducted as previously described.¹⁷ Plasma glucose was analyzed by enzymatic chromatic test. ASAT, ALAT, and GGT were analyzed by enzymatic photometric test. Apolipoprotein A + B was analyzed by immunologic turbidometric test. Hs-CRP was analyzed using Abbot Architect Instrument with Modular (P-Module) by Roche and Roche reagents in Salzburg and Abbot reagents in Uppsala.

Safety and tolerability outcomes: Safety and tolerability outcomes included the number of treatment-emergent adverse events (AEs), vital signs (blood pressure and heart rate), body temperature, number of hypoglycemic episodes as defined by the American Diabetes Association,²¹ the change in physical examination from baseline to follow-up, ECG, and clinical laboratory evaluations (TSH, T3, T4, FSH, LH, SHBG, testosterone, oestradiol, cortisol, prolactin, calcitonin, cobalamin, GH, IGF-1, vitamin D, lipase, amylase, ALAT, ASAT, GGT, LDH, bilirubin, creatinine, GFR, urea, uric acid, Na⁺, K⁺, Ca²⁺, Cl⁻, Mg²⁺, phosphate, albumin, CRP, cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein A1 and B, NT-proBNP, HbA1c, hematology including differential count and urinary alpha-1microglobulin). In addition, at visit 3 (week 2) or at visit 4 (week 6), a safety glucose measurement after a standardized meal (NutriniDrink Smoothie, Nutricia, Erlangen, Germany) of 600 kcal was performed to assess for postprandial hypoglycemia, whereas blood glucose was measured at given time points (0 to 60 min).

2.5 | Statistical analyses

The analysis of the primary efficacy variable in BMI-SDS (according to WHO) was done using analysis of covariance (ANCOVA) model with treatment group adjusting for baseline BMI-SDS. The secondary variables were analyzed and presented descriptively. The number of subjects who experienced adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), or suspected unexpected serious adverse reaction (SUSARs) were summarized as counts and percentages. Missing data were replaced using last observation carried forward (LOCF) according to the statistical analysis plan (SAP). The primary analysis was performed on the intention-to-treat (ITT) population. The ITT population consisted of all patients who were randomized and had received at least one dose of study medication or placebo and provided at least one efficacy baseline assessment and at least one corresponding postbaseline efficacy assessment. Sensitivity analysis was performed using observed cases.

2.6 | Power calculations

A mean treatment difference in BMI-SDS change from baseline to 6 months of -0.3 was considered as clinically relevant improvement difference. Assuming a conservative SD of 0.3 , a sample of 17 patients in each arm would provide 80% power to detect the assumed difference at a 5% significance level. Anticipating a dropout rate of 20% , 22 patients per arm (44 patients in total) were needed. The outcome data with variance of 0.0279 are substantially smaller than initially assumed. Taking into account the estimated correlation between the baseline BMI-SDS and the outcome (0.425), applying the standard ANCOVA sample size calculation formula with a small-sample size correction²² yields $n = 5$ per group. Thus, although the initially assumed difference of -0.3 was too large, the study was nevertheless adequately powered.

3 | RESULTS

3.1 | Study population

The study population included 44 patients, 22 to receive exenatide and 22 to receive placebo, which required that 52 patients were screened (Figure 2). The mean age of the exenatide and placebo groups were 14.5 ± 2.3 and 13.5 ± 2.3 with Tanner stage of 4.1 ± 1.2 and 3.6 ± 1.4 , respectively (no significant differences; not shown in tables or figures). Whereas there were nine (41%) males in the exenatide group, there

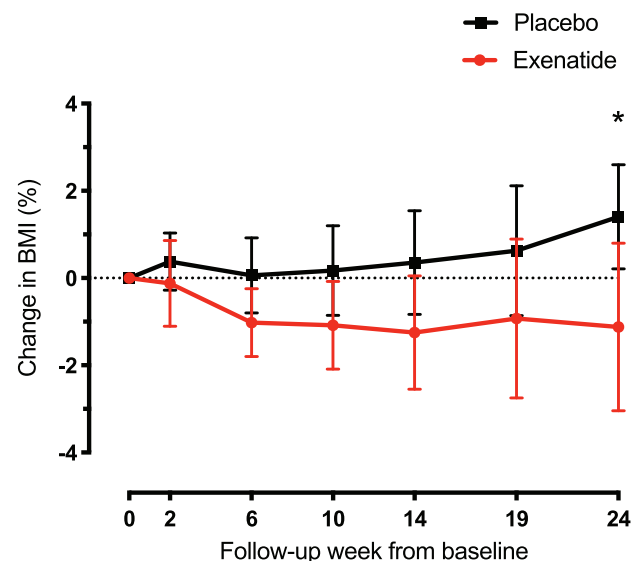


FIGURE 3 Group changes in BMI in % of baseline over the 24-week study period in exenatide- (red) and placebo- (black) treated groups with 10 to 18 years old subjects, $n = 22$ in each group. Mean and 95% CI. * $P < .05$ comparison between treated and placebo groups

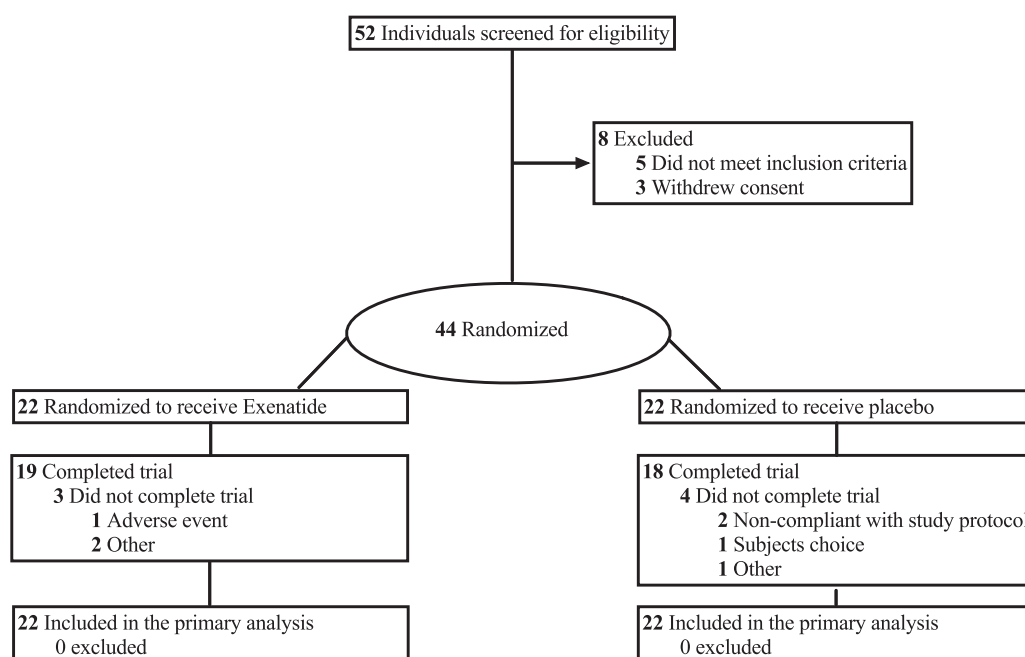


FIGURE 2 Combat-JUDO patient flow diagram

were 13 males (69%) in the placebo group. In the exenatide group, 22 were white, whereas there were 19 white, one black, one Asian, and one other in the placebo group. The number of severely obese subjects were 14 and 17 subjects in the exenatide and placebo groups at baseline, respectively (not shown in tables or figures).

Seven patients (16%), three in the treatment group and four in the placebo group, discontinued early (9.7 ± 2.5 vs 4.3 ± 3.9 weeks in exenatide and placebo group, respectively) due to inappropriate

handling of study medication ($n = 3$; other), family reasons ($n = 1$; adverse event), voluntary reasons ($n = 1$; subject choice), and protocol noncompliance ($n = 2$) (Figure 2). All patients, 22 exenatide-treated and 22 placebo-treated patients, were included in the safety population and constituted the ITT population and thus included in analyses as described and decided in the SAP. Treatment compliance was regarded as satisfactory (92 vs 89% of study drug doses administered in exenatide vs placebo group, respectively (no significant differences;

TABLE 1 Study population characteristics before and after treatment given as means with SD given in parenthesis, if not otherwise indicated. %BMI_{p95} = % BMI at the 95th percentile. All BMI metrics were based on WHO apart from %BMI_{p95} where CDC was used. ^a Three subjects in the exenatide group did not conclude the study, ^b four subjects in the placebo group did not conclude the study. * $P < .05$

	Exenatide Pre (n = 22)	Post (n = 22 ^a)	Placebo Pre (n = 22)	Post (n = 22 ^b)	Exenatide Effect (95%, CI)
Primary outcome variable					
BMI-SDS	3.1 (0.5)	3.0 (0.6)	3.3 (0.4)	3.3 (0.4)	-0.09 (-0.18, -0.00)*
Secondary outcome variables					
Other BMI metrics and anthropometric measures					
Weight, kg	106.2 (19.7)	105.7 (21.7)	102.5 (24.5)	105.0 (24.0)	-3.0 (-5.8, -0.1)*
Height, cm	171.3 (7.5)	171.7 (7.3)	167.2 (11.6)	168.2 (10.8)	
Waist circumference, cm	115.1 (9.6)	113.2 (12.8)	112.6 (12.5)	113.6 (13.3)	-3.2 (-5.8, -0.7)*
BMI	36.0 (4.8)	35.7 (5.7)	36.2 (5.0)	36.7 (5.2)	-0.83 (-1.68, 0.01)*
BMI percentile	99.8 (0.4)	99.6 (0.8)	99.9 (0.2)	99.9 (0.2)	-0.2 (-0.4, -0.0)
%BMI _{p95}	131.8 (17.9)	128.9 (20.8)	136.6 (15.8)	136.6 (15.9)	-2.9 (-5.4, -0.3)*
Cardiometabolic variables					
Systolic blood pressure, mmHg	126 (11)	121 (12)	122 (13)	119 (15)	-0.2 (-6.5, 6.1)
Diastolic blood pressure, mmHg	70 (9)	69 (9)	68 (9)	69 (10)	-2.9 (-6.9, 1.1)
HDL-cholesterol, mg/dL	43.0 (8.3)	42.8 (7.3)	42.3 (8.1)	49.6 (22.4)	-7.1 (-17.2, 3.0)
LDL-cholesterol, mg/dL	93.3 (23.2)	85.0 (17.6)	95.2 (37.4)	92.1 (25.1)	-7.3 (-14.2, -0.4)*
Triglycerides, mg/dL	98.3 (45.5)	102.5 (42.7)	115.4 (65.7)	109.2 (65.1)	8.0 (-8.2, 24.2)
Total cholesterol, mg/dL	154.1 (27.9)	141.3 (24.7)	159.3 (44.5)	155.7 (29.4)	-11.6 (-21.7, -1.5)*
Apolipoprotein A, mg/dL	125.6 (13.8)	121.1 (15.4)	125.9 (16.8)	125.7 (15.9)	-3.0 (-10.3, 4.4)
Apolipoprotein B, mg/dL	73.7 (14.0)	69.8 (11.9)	76.4 (28.5)	72.1 (16.7)	-2.9 (-7.6, 1.7)
CRP, mg/L	4.0 (3.6)	4.0 (4.5)	4.8 (6.3)	6.2 (8.1)	-0.8 (-3.1, 1.5)
Glucose, mg/dL					
0 min	95.1 (8.6)	91.7 (10.3)	95.4 (5.9)	93.1 (11.4)	-2.0 (-6.2, 2.1)
120 min	115.5 (19.1)	102.4 (18.7)	117.5 (19.6)	121.7 (27.2)	-15.3 (-27.5, -3.1)*
Insulin, μ U/mL					
0 min	14.6 (7.4)	13.4 (5.6)	16.8 (11.0)	14.4 (9.5)	-1.0 (-2.6, 0.7)
120 min	66.4 (37.6)	58.5 (39.8)	85.9 (54.4)	79.0 (91.4)	-1.2 (-33.3, 30.9)
Glucagon, pg/mL					
0 min	56.9 (28.6)	61.5 (36.4)	55.2 (40.8)	(52.1)	-2.9 (-14.4, 8.6)
120 min	23.3 (17.4)	38.3 (64.9)	16.7 (13.3)	28.6 (28.0)	-2.1 (-27.3, 23.2)
ASAT (U/L)	25.4 (8.0)	22.7 (9.9)	26.8 (10.9)	26.6 (11.3)	-2.6 (-7.7, 2.6)
ALAT (U/L)	26.1 (11.7)	22.2 (10.2)	33.2 (21.9)	32.8 (19.9)	-3.5 (-9.4, 2.3)
GGT (U/L)	21.7 (11.8)	18.6 (8.3)	19.9 (17.1)	19.8 (16.1)	-3.0 (-7.5, 1.5)
Imaging variables					
VAT, cm ³	1739 (558)	1680 (684)	1612 (431)	1618 (438)	-93 (-243, 57)
SAT, cm ³	8514 (1468)	8361 (1951)	8136 (2122)	8475 (2181)	-552 (-989, -114)*
Liver fat content, %	6.2 (6.3)	5.1 (4.7)	6.5 (4.6)	6.8 (4.8)	-1.4 (-3.1, 0.4)

not shown in tables or figures). Compliance to lifestyle intervention was similar in both groups and satisfactory.

3.2 | Study progress and efficacy

3.2.1 | Anthropometric and body composition characteristics

BMI-SDS was significantly decreased in the exenatide compared with the placebo group over the 24-week study period (Figure 3). After 24 weeks, exenatide reduced BMI-SDS by 0.09 ($-0.18, 0.00$; $P < .05$), corresponding to 3.0 kg ($-5.8, -0.1$; $P < .05$) weight reduction, BMI by 0.83 kg/m^2 ($-1.68, 0.01$; $P < .05$) and BMI as % of the 95th percentile by 2.9% ($-5.4, -0.3$; $P < .05$) (Table 1). In addition, exenatide reduced waist circumference by 3.2 cm ($-5.8, 0.7$; $P < .05$) and SAT by 552 cm^3 ($-989, -114$; $P < .05$). VAT was not reduced significantly. BMI reduction in absolute numbers and as percentage was also studied at the individual level (Figure 4A,B). Considerable heterogeneity was observed. The number of severely obese subjects in the exenatide and placebo groups did not change during the intervention.

3.2.2 | Fasting and OGTT plasma analytes

Exenatide reduced 2-hour glucose concentration by 15.3 mg/dL ($-27.5, -3.1$; $P < .05$) after the 24-week study period (Table 1). Appropriately, the drug had no effect on fasting glucose concentration. The 2-hour glucose concentrations were also studied individually, which showed considerable variability (Figure 4C). The main glucose regulatory hormones insulin and glucagon were neither altered at start or end of the OGTT (Table 1). Whereas exenatide reduced LDL-cholesterol by 7.3 mg/dL ($-14.2, -0.4$; $P < .05$) and total cholesterol by 11.6 mg/dL ($-21.7, -1.5$; $P < .05$), the drug did not affect concentrations of triglycerides and HDL-cholesterol (Table 1).

3.2.3 | Liver fat content and liver enzymes

Exenatide lowered LFC by 1.4%, meaning that approximately one fifth of the LFC prior to the treatment had disappeared during the 24-week study period (Table 1). This lowering was not significant ($P = 0.06$), however. Variation in the reduction became evident when LFC was displayed at the individual level (Figure 4D). There was no

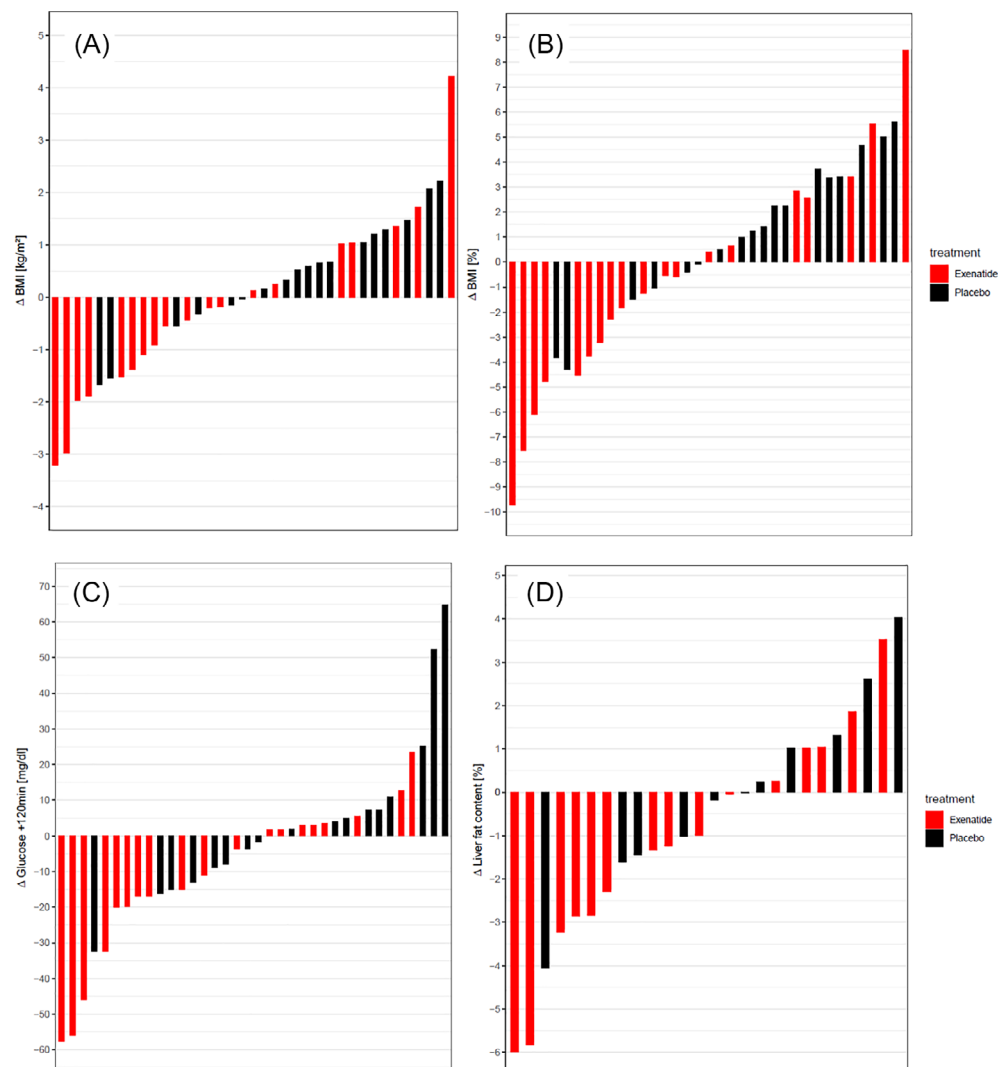


FIGURE 4 Individual changes in absolute BMI (Panel A), in BMI % of baseline (Panel B), 2-h glucose (Panel C) and liver fat % of baseline (Panel D) over the 24-week study period for each exenatide- (red) and placebo- (black) treated subject. Results from subjects for whom start and end results were available

effect of the treatment on concentrations of circulating enzymes connected with liver function. At baseline, 8/22 subjects (36%) in the exenatide group and 10/22 (46%) in the placebo group had steatosis (no significant differences; not shown in tables or figures) as defined by a hepatic fat content $>5.5\%$.²³ At the end of the study, 6/22 subjects (27%) in the exenatide group and 9/22 (41%) in the placebo group had steatosis, which was not significant (no significant differences; not shown in tables or figures).

3.3 | Safety

The number of AEs was similar between the two groups (Table 2). When classifying the AEs according to System Organ Class, the most common AEs were gastrointestinal (flatulence, nausea, diarrhea, constipation, abdominal pain, burping, vomiting, and mouth pain), infections (respiratory, gastrointestinal, and urinary), and nervous system disorders (headache, dizziness, syncope, tremor of hands, and paresthesia). Whereas the gastrointestinal AEs were more common in the

exenatide group (18 vs 10), the infection AEs (18 vs 20) and the central nervous system disorder AEs (16 vs 13) were similar between exenatide-treated and placebo-treated groups. Syncope was overrepresented in the exenatide-treated subjects (3 vs 0). One event was experienced prior to intervention start and thus not related to study drug or placebo. No common denominator for the AEs was identified. Further, no difference in or tendency to hypoglycemia in the exenatide group was observed. In addition, AEs were classified according to type of AEs and treatment groups (exenatide vs placebo): not related (0 vs 4), possibly related (18 vs 15), and likely related (3 vs 3). No serious AEs occurred that were deemed related to the study drug.

4 | DISCUSSION

In the present study, we report for the first time that extended-release exenatide improves glycemic control, total cholesterol, and LDL cholesterol while simultaneously modestly reducing BMI in adolescents with obesity. Delivery forms of exenatide twice a day and once weekly have both been shown to reduce BMI in adults with T2DM.²⁴ The BMI reduction achieved with exenatide is similar to treatment with orlistat or metformin hydrochloride.²⁵ So far, only two studies have assessed the weight loss effects of GLP-1 RA treatment among nondiabetic adolescents with obesity. Initially, Kelly et al conducted a small randomized, controlled, crossover trial in 12 adolescents with similar BMI and age as patients enrolled in our study, who received either exenatide twice a day or the lifestyle modification therapy for 3 months, and were then crossed over to the other condition.⁹ The authors reported a reduction of BMI by approximately 5% in the exenatide vs control groups. In contrast to the present study, the authors observed lowered fasting insulin levels and only a trend to improved glucose tolerance.

The same authors then performed a double-blind, randomized, placebo-controlled trial with 26 adolescents with severe obesity (mean BMI 42 kg/m², mean age 15 years) to either exenatide twice daily or placebo for 3 months, followed by an open label extension during which all participants received exenatide treatment.¹⁰ The placebo-subtracted BMI reduction with exenatide was approximately 3% after 3 months and 4% among patients who received exenatide treatment for the entire 6 months of the trial. This compares to a modest treatment effect of exenatide once weekly of approximately 2.3% in our study. Whether the difference between these results can be attributed to the once weekly vs twice daily injections remains unclear. When looking at change in BMI of the study participants at the individual level, a heterogeneous response was evident. This emphasizes the importance to study individual outcomes in order to effectively treat adolescents with obesity.²⁶

Improved glycemic control with decreased 2-hour glucose value during OGTT was recorded in subjects taking the GLP-1 analogue. Exenatide has previously shown indication of improving blood glycemia in adolescents with obesity although not confirmed in a study using exenatide twice daily.^{9,10} In adults with T2DM, exenatide once

TABLE 2 Adverse events experienced by exenatide-treated and placebo-treated patients. Events coded according to MedDRA System Organ Class. Number (and %) of participants in exenatide and placebo groups experiencing the different events are indicated

Adverse Events According to System Organ Class	Exenatide (n = 22)	Placebo (n = 22)
Blood and lymphatic system disorders	0	2 (9.1)
Ear and labyrinth disorders	2 (9.1)	0
Endocrine disorders	1 (4.6)	0
Eye disorders	1 (4.6)	1 (4.6)
Gastrointestinal disorders	18 (81.8)	10 (45.5)
General disorders and administration site conditions	11 (50.0)	9 (40.9)
Immune system disorders	1 (4.6)	0
Infections and infestations	18 (81.8)	20 (90.9)
Injury, poisoning, and procedural complications	5 (22.7)	3 (13.6)
Investigations	5 (22.7)	5 (22.7)
Metabolism and nutrition disorders	2 (9.1)	2 (9.1)
Musculoskeletal and connective tissue disorders	5 (22.7)	6 (27.3)
Nervous system disorders	16 (72.7)	13 (59.1)
Psychiatric disorders	1 (4.6)	2 (9.1)
Renal and urinary disorders	2 (9.1)	0
Reproductive system and breast disorders	5 (22.7)	1 (4.6)
Respiratory, thoracic, and mediastinal disorders	8 (36.4)	8 (36.4)
Skin and subcutaneous tissue disorders	5 (22.7)	1 (4.6)
Social circumstances	1 (4.6)	0
Not coded	1 (4.6)	0

weekly produced similar glycemic control compared with exenatide twice daily.²⁷ The GLP-1 analogue also reduced total and LDL cholesterol. The extended release may be of importance for this effect since no effect on cholesterol was observed when delivering exenatide twice daily.^{9,10} The reducing effect of the GLP-1 analogue may be of considerable importance given the increased risk of adolescents with obesity to develop cardiovascular disease, glucose intolerance, and T2DM.²⁸ However, we did not see any effect on systolic and diastolic blood pressure, CRP, and Apolipoprotein A and B in our study. Although these data are in line with the previously mentioned pediatric studies testing exenatide by Kelly et al,^{9,10} they need to be interpreted with caution given the relatively low number of participants.

To the best of our knowledge, our study is the first to assess the effect of a GLP-1 RA on liver fat content of subjects with obesity in the pediatric age group. The prevalence of pediatric NAFLD has swiftly increased, paralleling the obesity epidemic and is now estimated to be the most common liver disease in children and adolescents. NAFLD, as diagnosed by either liver enzymes or ultrasonography, significantly increases the risk of T2DM over a median 5-year follow-up in adults.⁷ The lack of change in liver enzymes in our study is not surprising, as serum liver enzyme concentrations are considered to have a relatively poor sensitivity and specificity in the diagnosis of NAFLD.²⁹ Although exenatide lowered LFC in absolute numbers (from ~6% to 5%, equivalent to a reduction of ~15%), this difference was not statistically significant. Given the borderline significance ($P = .06$) and keeping in mind that LFC was a secondary outcome parameter, this might possibly be due to lack of study power. A previous study indicated that exenatide is an effective treatment to reduce LFC in patients with obesity and T2DM, whereby these effects were mainly weight loss.³⁰ However, our study is in line with a recent study, which reported a lack of change in LFC in adults with obesity and T2DM treated with the GLP-1 RA liraglutide as compared with placebo.³¹ Notably, similar to the latter study, there was no treatment effect on VAT in our study, while SAT was reduced by a significantly greater extent with exenatide than with placebo. In any case, our data call for future trials specifically testing the effect of GLP-1 RA on NAFLD in the pediatric age group.

The extended-release exenatide was tolerable and safe for the 10 to 18-year-old subjects with obesity similar to what has been reported for the adult population.³² Adherence to study medication in our study was good to excellent. Transient and predominantly mild to moderate nausea was the most frequent adverse event and was less common with exenatide once weekly than with exenatide twice daily.²⁴ No episodes of hypoglycemia were reported, and symptoms that might have been related to hypoglycemia (syncope, dizziness) were rare and comparable in both groups. It seems plausible that the less frequent dosing as compared with exenatide twice-daily or liraglutide once daily might be more attractive to adolescents.

The strengths of the present study include the so far largest number of subjects and the longest duration of a pediatric GLP-1 receptor agonist RCT. Additional strengths of the study include the detailed description and execution of the lifestyle intervention in both the treatment and placebo groups and its academic independence.

The study was powered to detect differences in the primary outcome variable BMI-SDS. However, limitations of the study include that the secondary outcomes may potentially be underpowered. In addition, we acknowledge that potential other factors such as socioeconomic variables could have influenced the study. Our data cannot be generalized in terms of race/ethnicity. Also, the long-term efficacy, safety, and drug adherence remain to be demonstrated. In this context, it is noteworthy that reduction in BMI-SDS and BMI was increasing throughout the study period and may be even more pronounced if the treatment duration was extended beyond the 6-month period in the current study. Of note, this is in line with a recent study, in which adolescents with obesity and T2DM were randomly assigned to receive the GLP-1 RA liraglutide or placebo for a 26-week double-blind period, followed by a 26-week open-label extension period, and showed that a reduction in BMI was not significant after 6, but 12 months.³³

5 | CONCLUSION

The present RCT Combat-JUDO provides the first evidence that extended-release exenatide treatment is feasible, generally well tolerated, and leads to reduction, albeit modest, in BMI-SDS in adolescents with obesity. Also, significant improvement in glucose tolerance was observed in the adolescents. Given the burden of childhood obesity and the risk of developing complications including T2DM, the present study gives support for GLP-1 RA as attractive treatment alternatives for this patient group, where pharmacological alternatives are very limited.²⁵ Future trials testing other GLP-1 RA in adolescents, which have shown clinically promising effects on reduction in BMI-SDS and other associated BMI metrics and measures of comorbidities,³⁴ are warranted.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Associate Prof. Forslund, Prof. Weghuber, and Prof. Bergsten conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. Mrs Dahlbom, Ms Bergström, and Dr Lagler developed

study protocol, coordinated and supervised data collection, and critically reviewed the manuscript. Drs Kristinsson and Manell carried out biochemical data collection and statistical analyses, contributed to drafting the initial manuscript, and reviewed and revised the manuscript. Prof Ahlström, Associate Prof. Kullberg, and Mrs Ladinger designed MRI data collection, collected and analyzed the data, and critically reviewed the manuscript. Ms Jansson Blixt carried out statistical analyses and reviewed and revised the manuscript. Ms Brunner, Dr Cadamuro, Dr Ciba, Ms Heu, Dr Hoffman, Mr Lidström, Ms Meirik, Dr Mörwald, Dr Roomp, Prof. Schneider, Dr Staaf, Mrs Vilén, Prof. Widhalm, and Dr Zsoldos contributed to planning of the study and acquisition of data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CLINICAL TRIAL REGISTRATION

Study title: A parallel, double-blinded, randomized, 6-month, two-arm study with lifestyle intervention and exenatide 2 mg once weekly or lifestyle intervention and placebo in adolescents with obesity to explore differences between groups with regard to change in BMI SDS. Acronym: Combat-JUDO (Combating JUvenile Diabetes and Obesity). Registration number: 2015-001628-45. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-001628-45/SE>.

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