22 May 2025
EMA/CHMP/158256/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Saxenda

International non-proprietary name: Liraglutide

Procedure No. EMEA/H/C/003780/II/0042

Marketing authorisation holder (MAH) Novo Nordisk A/S

Note:

Variation assessment report as adopted by CHMP and removed from any information of commercially confidential nature.

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List of abbreviations

AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	asparate aminotransferase
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
COVID	coronavirus disease
CV	Coefficient of variation in %
ECG	electrocardiogram
EMA	European Medicines Agency
ETD	estimated treatment difference
EU	European Union
FAS	full analysis set
FDA	Food and Drug administration
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GLP 1	glucagon like peptide 1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HDL	high density lipoprotein
HOMA-B	homeostasis model assessment of β-cell function
HOMA-IR	homeostasis model assessment for insulin resistance
ICH	International Council for Harmonisation
IGF	insulin like growth factor
ITT	intent-to-treat
J2R	Jump to Reference
LDL	low density lipoprotein
MI	multiple imputation
PBRER	Periodic Benefit Risk Evaluation Report

PD	pharmacodynamics
PDCO	European Paediatric Committee
PK	pharmacokinetic
PSUR	Periodic Safety Update Report
PP	per-protocol
PT	preferred term
PYE	patient years of exposure
PYO	patient years of observation
s.c	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SDS	Standard deviation score
SOC	System Organ Classification
SUSAR	Suspected unexpected serious adverse reaction
TBL	total bilirubin
T2D	type 2 diabetes
TEAE	treatment-emergent AE
USA	United States of America

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 24 July 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the use of SAXENDA for weight management in children from the age of 6 years to less than 12 years based on results from study NN8022-4392; this is a 56-week, double-blind, randomised, placebo-controlled study investigating safety and efficacy of liraglutide on weight management in children with obesity aged 6 to <12 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 34.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0468/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0468/2023 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-C-000128-PIP02-09-M05.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application was requested to include a critical report addressing the possible similarity with authorised orphan medicinal product: Imcivree.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Thalia Marie Estrup Blicher

Timetable	Actual dates
Submission date	24 July 2024
Start of procedure:	17 August 2024
CHMP Rapporteur Assessment Report	8 October 2024
PRAC Rapporteur Assessment Report	8 October 2024
PRAC members comments	23 October 2024
CHMP Co-Rapporteur Assessment	23 October 2024
Updated PRAC Rapporteur Assessment Report	8 November 2024
PRAC Outcome	31 October 2024
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 November 2024
Request for supplementary information (RSI)	14 November 2024
CHMP Rapporteur Assessment Report	30 January 2025
PRAC Rapporteur Assessment Report	29 January 2025
PRAC Outcome	13 February 2025
CHMP members comments	
Request for supplementary information (RSI)	27 February 2025
CHMP Rapporteur Assessment Report	28 April 2025
CHMP members comments	12 May 2025
Updated CHMP Rapporteur Assessment Report	15 May 2025
Opinion	22 May 2025
The CHMP adopted a report on similarity of Saxenda with Imcivree (setmelanotide) on date	22 May 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Proposed indication (bold italic text to be added)

Adults

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:

- ≥ 30 kg/m² (obesity), or

- ≥ 27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

Adolescents (≥ 12 years)

Saxenda can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:

- obesity (BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-off points)* and
- body weight above 60 kg.

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

*IOTF BMI cut-off points for obesity by sex between 12-18 years (see table 1), ***in accordance with study design of the Trial 4180, see section 5.1.***

Table 1 IOTF BMI cut-off points for obesity by sex between 12–18 years

Age (years)	BMI corresponding to 30 kg/m^2 for adults by international cut-off points.	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

Children (6 to <12 years)

Saxenda is indicated as an adjunct to healthy nutrition and increased physical activity for weight management in children from the age of 6 to <12 years with

- ***obesity (BMI ≥95th percentile)* and***
- ***body weight ≥45 kg***

Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.

****CDC BMI cut-off points for obesity (≥95th percentile) by sex between 6 to <12 years (see table 2), in accordance with study design of the Trial 4392, see section 5.1.***

Table 2 Cut-off points for BMI (Weight in kg/Height in m2) for obesity (≥95th percentile) by sex for children from 6 and < 12 years of age

Age (Years)	*Obesity BMI ≥ 95th percentile*	
	Males	*Females*
6	*18.41*	*18.84*
6.5	*18.76*	*19.23*
7	*19.15*	*19.68*
7.5	*19.59*	*20.17*
8	*20.07*	*20.70*
8.5	*20.57*	*21.25*
9	*21.09*	*21.82*
9.5	*21.62*	*22.40*
10	*22.15*	*22.98*
10.5	*22.69*	*23.57*
11	*23.21*	*24.14*
11.5	*23.73*	*24.71*

Disease or condition

The prevalence of childhood obesity has reached epidemic proportions in many countries around the world and the prevalence is still increasing at an alarming rate. The medical and societal impacts are extensive; childhood obesity is a significant public health challenge worldwide.

Childhood obesity is associated with a number of complications, including hypertension, T2D, early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems, thus predisposing to future comorbid conditions and reduced life expectancy. More than 70% of the children suffering from obesity before entering puberty will also continue living with obesity as adults. Additionally, childhood obesity increases the risk of earlier development of obesity related comorbidities during adulthood. These comorbidities are associated with a wide range of severe health-related and psychosocial consequences, including a higher risk of disability in adulthood and premature death. Hence, prevention of childhood obesity is a high priority in paediatric healthcare. Although lifestyle modification is the recommended first-line treatment, widespread adoption of this treatment method and long-term compliance are problematic and treatment intensification may be needed for the treatment of childhood obesity.

2.1.2. About the product

Liraglutide is a once-daily GLP-1 RA', with 97% homology to human GLP-1. Liraglutide has unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycaemic control in people living with T2D and other weight related comorbidities.

Liraglutide 3.0 mg was approved by the European Medicines Agency (EMA) on 23 March 2015 in adults with obesity and overweight and on 26 March 2021 in adolescents with obesity.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The aim of this variation application is to support the extension of the indication of Saxenda for use in children (6 to <12 years) with obesity (BMI ≥95th percentile for age and gender).

The paediatric development programme for liraglutide 3.0 mg was designed in agreement with the EMA PDCO. Key binding elements for the programme were included in the paediatric investigation plan (PIP) agreed upon with the EMA (EMEA-000128-PIP02-09-M05). There is a Positive Opinion of the Paediatric Committee on compliance with a Paediatric Investigation Plan: EMA/PDCO/236464/2024.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The relevant non-clinical data in relation to this extension indication have already been discussed within Saxenda variation II/26, concerning the extension of indication in adolescents aged from 12 to less than 18 years of age.

An ERA had been submitted. The ERA consists of a justification for not performing any ERA studies. Liraglutide is a peptide consisting of natural amino acids and a natural fatty acid (palmitic acid).

Therefore, in accordance with the guidance (EMEA/CHMP/SWP/4447/00 cor 21), liraglutide is exempted from performing ERA studies, under the expectation that e.g. due to their nature they are unlikely to result in a significant risk to the environment. Any increase in consumption of liraglutide, is considered not to have any impact on the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The paediatric weight management clinical development programme with liraglutide 3.0 mg is based on 5 clinical studies (NN8022-3967, -4181, -4179, -4180 and -4392) in adolescents and children aged 6 to < 18 years. Liraglutide 3.0 mg was investigated in children (6 to <12 years) living with general obesity in two (2) studies:

- NN8022-4181, referred to as Study **4181**: a phase 1 clinical pharmacology study to assess the safety, tolerability, PK and PD of liraglutide 3.0 mg in children aged with obesity aged 7 to 11 years and with Tanner stage 1 pubertal development
- NN8022-4392, referred to as Study **4392**: a phase 3a study to assess the efficacy and safety of liraglutide 3.0 mg in children aged 6 to <12 years with obesity

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC (both of these studies

were designed and conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and FDA 21 CFR 312.120).

Tabular overview of clinical studies.

Study ID	Participants	Brief description
Study 4181 Paediatric population (ages 7 to 11 years)	N=20	Phase 1, 7-13 week, randomised, double-blinded, placebo-controlled study investigating tolerability, safety, pharmacokinetics and pharmacodynamics of liraglutide 3.0 mg once daily in children with obesity.
Study 4392 Paediatric population (ages 6 to <12 years)	N=82	Phase 3a, 56-week, randomised, double-blind, placebo-controlled study investigating efficacy and safety of liraglutide 3.0 mg once daily in children with obesity (BMI corresponding to ⩾95th percentile*)

*on gender and age-specific growth charts (CDC.gov)

2.3.2. Pharmacokinetics

2.3.2.1. *Methods*

Bioanalysis

Bioanalysis of liraglutide in plasma samples in both studies (Studies 4181 and 4392) was performed using a validated enzyme linked immunosorbent assay method, which is identical to the assay used in previous Saxenda applications. The method was developed and validated by Novo Nordisk A/S and afterwards validated by the CROs responsible for bioanalysis of liraglutide in the clinical studies: Syneos Health formerly known as InVentiv Health Clinical Lab, Inc and PharmaNet, US, for both the studies. The lower level of quantification was 30 pmol/L.

Pharmacokinetic endpoints and analysis - Study 4181

Trial 4181:

The trial was a multicentre, randomised, double-blind, placebo-controlled safety and tolerability, PK and PD trial in children with obesity aged 6 to <12 years at Tanner stage 1. 21 subjects were randomised 2:1 to receive either liraglutide or placebo. Treatment duration was at least 7 week (with 6 optional flex weeks). BMI (body mass index) corresponded to ≥30 kg/m^2 for adults by international cut-off points and BMI ≤45 kg/m^2 as well as BMI ≥95th percentile for age and sex at the time of signing informed consent. Treatment was initiated with s.c. liraglutide 0.3 mg OD for one week and increased as tolerated in weekly steps of 0.3 mg until a dose of 1.2 mg was reached, and then 0.6 mg until a dose of maximum 3.0 mg liraglutide was reached. The dose was escalated over 7 weeks with flexibility up to 13 weeks.

Blood samples for PK assessment of liraglutide were drawn at specific time points. The dose proportionality of liraglutide exposures were assessed based on C_{trough}. This was done by estimating the slope β in a linear normal regression model with the logarithm of C_{trough} as dependent variable, a common intercept as fixed factor and log dose as fixed covariate. Furthermore, a subject specific intercept was included as random effect. The estimated quantity 2^{β} with 95% confidence interval (CI) was reported and

the resulting p-value represents the test of $2^{\beta} = 2$ (i.e., if $2^{\beta} = 2$ this means that doubling the dose of liraglutide results in a doubling of the exposure).

Pharmacokinetic endpoints and analysis - Study 4392

Trial 4392:

The trial was a 56 week, double blinded, randomised, placebo controlled, multinational clinical study comparing liraglutide 3.0 mg s.c once daily with placebo in children, aged 6 to <12 years with obesity.

Treatment was once-daily s.c. doses of liraglutide or placebo. Starting at 0.6 mg (0.3 mg in children with body weight < 45 kg), the dose was escalated in weekly 0.6 mg increments (or placebo equivalent) until the 3.0 mg dose of liraglutide/placebo or the individual maximum tolerated dose (MTD).

This study included two phases, a Main phase and an Extension phase. The Main phase was comprised of a 2-week screening, 12 weeks run in and a 56-week treatment period with an off drug follow up period of 26-week. In the Main phase, participants who fulfilled the randomisation criteria were randomised 2:1 to receive liraglutide 3.0 mg or placebo.

Population PK analysis

Two analyses based on the popPK analysis, which included only liraglutide-treated participants, are provided:

- a covariate analysis using data from clinical studies in paediatric participants with obesity (Studies 4392, 4180, 3967, and 4181) and adults with obesity (Study 3630).
- a comparison of liraglutide exposure in the paediatric population (children and adolescents) with obesity (Study 4392 and 4180 respectively) versus exposure in adults with obesity or overweight, with or without T2D in phase 3a studies (Studies 1839, 1922) and a phase 2a study (Study 1807).

These two presentations, as well as details for the studies in adults, are described below.

Covariate analysis in popPK

PopPK analysis was conducted based on the combined data set for the studies including paediatric participants (Study 4392, Study 4180, Study 3967, and Study 4181) and a clinical pharmacology study in adults (Study 3630).

The liraglutide popPK model, which is based on a 1-compartment structure with first-order absorption and elimination kinetics, was originally developed using the data from Studies 3630, 3967, 4180, and 4181. Selected parameters of the model were updated after integrating the data from Study 4392 in the analysis dataset.

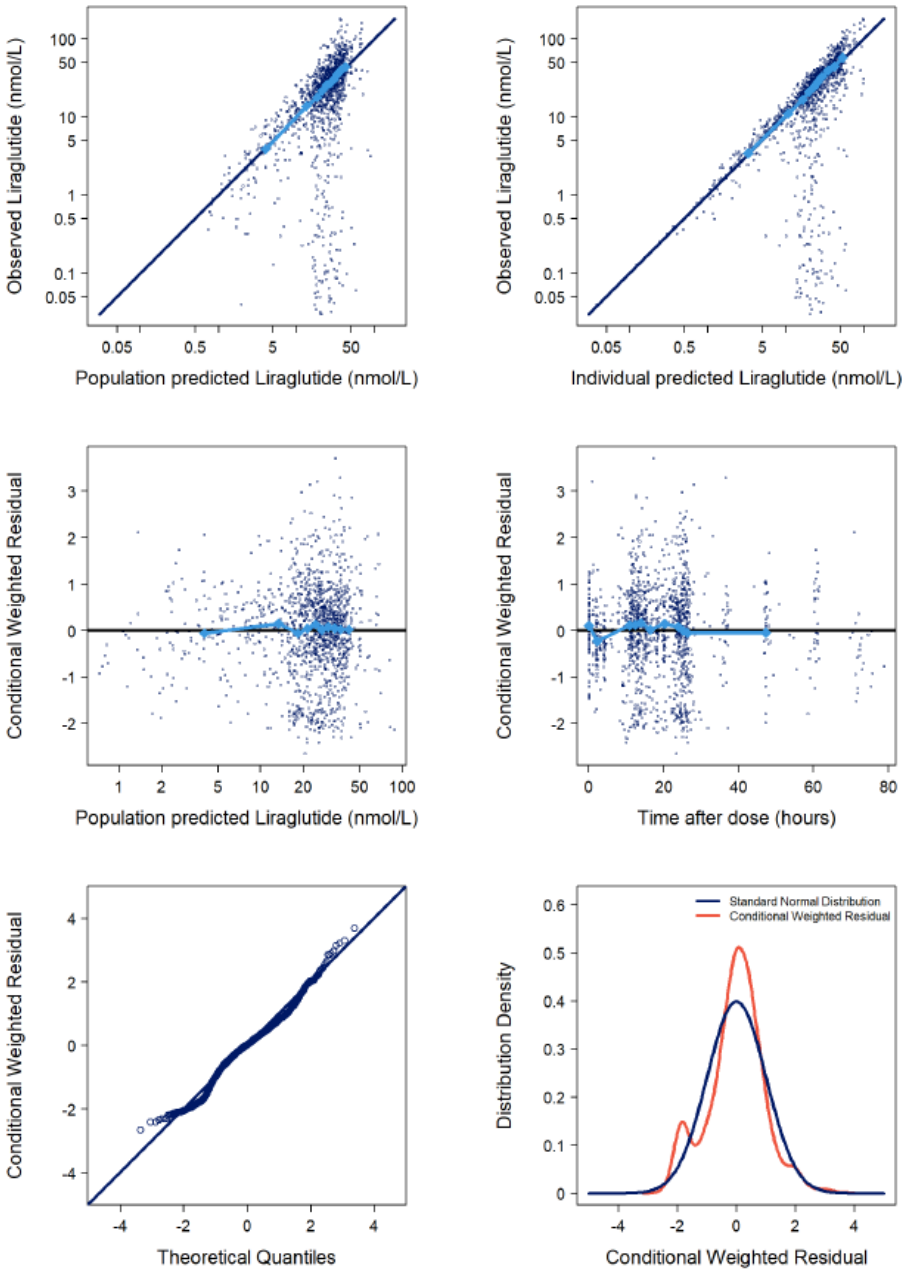
A full model was subsequently utilised to evaluate covariates. The full model included effects of body weight (centred at 100 kg), sex (female, male) and age group (children, adolescents, adults) on CL /F and effects of body weight on V/F (Table 1). The model was validated by a.o., GOF plots (Figure 1) and visual predictive check plots (Figure 2).

Table 1. Parameter estimates from the full PK model (popPK Study 4392)

Parameter	Parameter name [unit]	Estimate	95% CI Lower bound	95% CI Upper bound	RSE (%)	IIV (%CV)	Shrinkage (%)
Absorption rate constant	k_a [1/h]	0.0813	Fixed	Fixed	Fixed	NA	NA
Apparent clearance	CL/F [L/h]	1.00	0.909	1.10	4.75	31.1	14.1
Apparent volume of distribution	V/F [L]	13.8	Fixed	Fixed	Fixed	27.6	21.3
Body weight exponent on CL/F	CL-BW	0.787	0.500	1.07	18.6	NA	NA
Sex contrast (male/female) on CL/F	CL-male	1.12	0.998	1.24	5.56	NA	NA
Age contrast (child/adult) on CL/F	CL-child	0.963	0.773	1.15	10.1	NA	NA
Age contrast (adolescent/adult) on CL/F	CL-adole	1.08	0.939	1.22	6.54	NA	NA
Body weight exponent on V/F	V-BW	0.749	0.377	1.12	25.4	NA	NA
Proportional error	Prop. Error [%CV]	46.0	-	-	9.14	NA	5.96

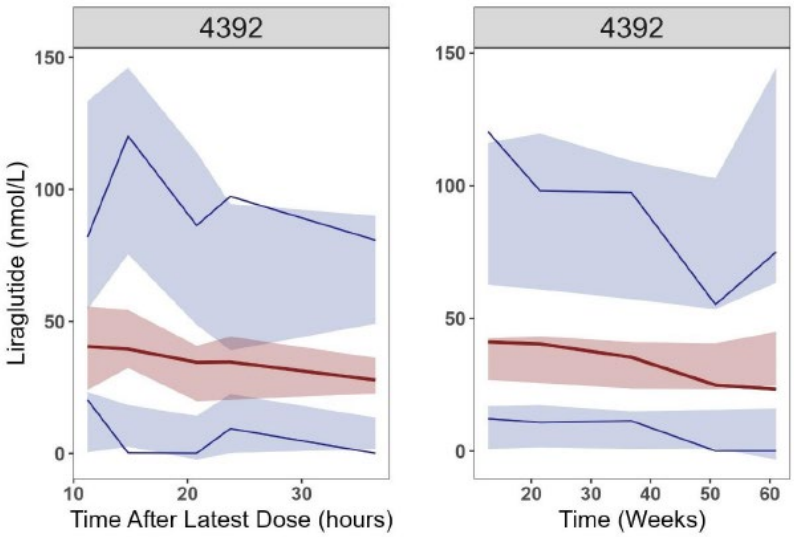
Abbreviations: %CV = percentage of the coefficient of variation; adole = adolescent; BW = body weight; CI = confidence interval; CL = clearance; CL/F = apparent clearance; IIV = interindividual variability; ka = absorption rate constant; NA = not applicable; PK = pharmacokinetic; Prop. = proportional; RSE = relative standard error; V = volume of distribution; V/F = apparent volume of distribution.

Figure 1. Standard GOF plots for the full PK model Study 4392



Note: The data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, a QQ plot of conditional weighted residuals, and a distribution plot of conditional weighted residuals. The data are from trials 4392, 4180, 3967, 3630, and 4181.

Figure 2. Visual predictive check of the full popPK model of liraglutide in children with obesity or overweight children



Note: The data are the observed (lines) and simulated (shaded area; n=2000) medians and 5th and 95th percentiles for concentrations after the first dose (left) and time after first dose (right). The data are from trial 4392.

The popPK model provides a description of the limited liraglutide PK data for children in Study 4392. Of note, a double peak is observed in the CWRES plot. The same phenomenon was observed during the previous type II variation for liraglutide for extension to include adolescents. The same reason as discussed during that variation, in which an analogous popPK model and PK data were used, i.e., the occurrence of an unexpected second peak is likely the result of unexpected lower concentration values, linked to possible poor adherence, is considered to be applicable here as well.

For exposure comparison and covariates evaluation, subject-specific C_{avg} at steady state was derived from the subject-specific post hoc CL/F based on a model excluding data below LLOQ, at the planned maintenance dose (3.0 mg) and a dose interval (24 hours). Key demographics for participants in the studies whose data were included in the covariate analysis are presented in Table 2.

Table 2. Key baseline demographics for participants in the popPK analysis - Studies 4392, 4180, 3967, 4181 and Study 3630 (popPK Study 4392)

Study		**4392**	**4180**	**3967**	**4181**	**3630**
Population (N)	Paediatric participants aged 7-11 years	46	-	-	13	-
	Adolescent participants aged 12−17 years	-	121	13	-	
	Adults	-	-	-	-	29
Sex	Female	21 (45.7)	67 (55.4%)	10 (76.9%)	7 (53.8%)	11 (37.9%)
	Male	25 (54.3)	54 (44.6%)	3 (23.1%)	6 (46.2%)	18 (62.1%)
Body weight (kg)	Mean	69.0	99.4	102.1	69.1	102.3
	Range	34.5-114	62.1-178.2	79.9-119.2	53.9-86.8	74.2-131.6
Age (years)	Mean	9.61	14.6	15.1	9.8	47.8
	Range	7-12	1217	13-16	8-11	20-72

Cross-reference: Modified from Study 4392 popPK report, Table 5-1

Exposure evaluation for children and adolescents versus adults in popPK

The exposure from Studies 4392 and 4180 in children and adolescents, respectively, was compared to exposure in the combined data set data from phase 2 and 3 in adults with obesity or overweight, with or without type 2 diabetes (Studies 1807, 1839, and 1922). Key demographics for participants in the studies whose data were included in the exposure evaluation and exposure-response analysis are presented in Table 3.

Table 3. Key baseline demographics for exposure-response analysis participants in Study 4392, Studies 4180, 1807, 1839 and 1922

Study		4392[a]	4180	1807	1839	1922
Population[a] (N)	Children with obesity	72				
	Adolescent participants with obesity		247[b]	-	-	-
	Adults with obesity		-	415	3250	707
No of participants on liraglutide treatment	-	56	121	331	2339	584
No of participants on placebo treatment	-	26	126	84	911	123
Sex	Female	33 (45.8)	145 (58.7%)	313 (75.4%)	2535 (78.0%)	352 (49.8%)
	Male	39 (54.2)	102 (41.3%)	102 (24.6%)	715 (22.0%)	355 (50.2%)
Body weight (kg)	Mean	72.3	100.8	97.7	106.7	106.0
	Range	33.5-128	62.1-178.2	69.2-141.2	63.0-244.0	60.1-193.3

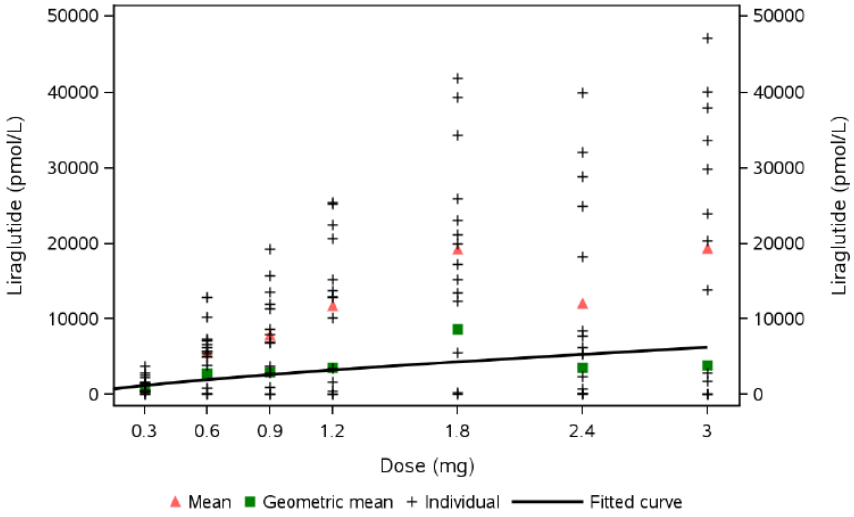
[a]A total of 7 participants from study 4392 did not have any analysable PK samples and were excluded from the E-R analysis. Three participants were excluded due to time after dose greater than 6-half-lives of liraglutide.
[b]Four participants from the final analysis set from study 4180 were excluded from the exposure-response dataset because of missing exposure observations.
Cross-reference: modified from Study 4392 popPK report, Table 4-2 and Table 5-3

2.3.2.2. *Results*

Results steady-state pharmacokinetic properties - Study 4181

In Study 4181, dose proportionality (0.3 mg to 3.0 mg) was assessed for C_{trough} as illustrated graphically in Figure 3. The liraglutide concentration appeared to be consistent with dose proportionality. The estimate (95% CI) of 2^{β} was 1.66 (1.26; 2.19), p-value = 0.1898, indicating that a doubling of the liraglutide dose resulted in 1.66 times increase in exposure (C_{trough}). A post-hoc sensitivity analysis was performed excluding participants with unexpectedly low concentrations at all time points, and there was an increase in C_{trough} concentration with increasing dose was consistent with dose-proportionality (estimated (95% CI) 2^{β} was 1.94 (1.53; 2.45), p-value = 0 .7854).

Figure 3. C_{trough} of liraglutide at steady state – dose proportionality - Full analysis set Study 4181

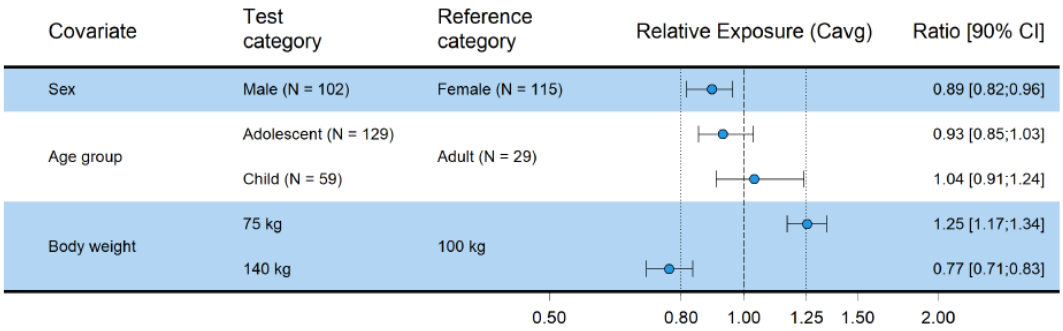


Pop pharmacokinetic analysis – Study 4392

Covariate analysis in popPK

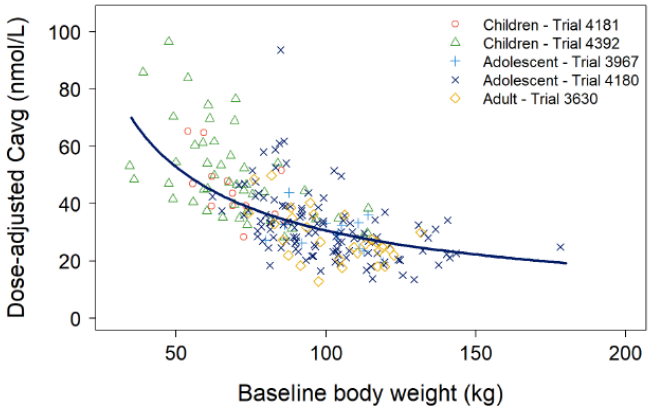
Effects of intrinsic covariates on liraglutide exposure are shown in Figure 4. In accordance with previous findings in adults, body weight was the main intrinsic covariate for liraglutide exposure, with lower exposure at higher body weight. Age group and sex were of no or little importance. The inverse relationship between body weight and exposure appeared across studies and age groups and was captured by the covariate model included in the popPK model (Figure 5).

Figure 4. Forest plot of covariate analysis for liraglutide exposure in participants with obesity (PopPK part Study 4392)



Note: The data are individual values of C_{avg} versus baseline body weight. The line represents the mean covariate-adjusted, model-derived concentrations versus body weight for 3.0 mg dose across all age groups. The data are from trials 4392, 4180, 3967, 3630, and 4181.

Figure 5. Liraglutide exposure (C_{avg}) versus body weight by age group (popPK Study 4392)

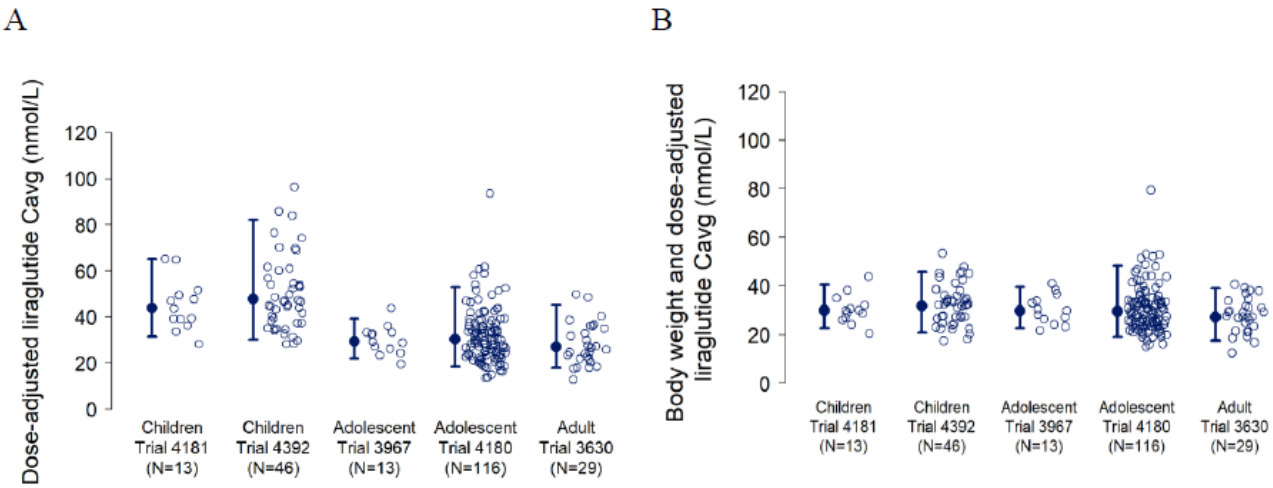


Exposure comparison for paediatric and adult population in popPK

The outcome of the popPK analysis showed that individual and mean liraglutide C_{avg} values appeared to be similar in adolescents and adults when adjusted to the 3.0 mg dose, whereas children had slightly higher concentrations (Figure 6). When adjusting for differences in body weight, exposures were similar across studies and age groups, including children (Figure 6).

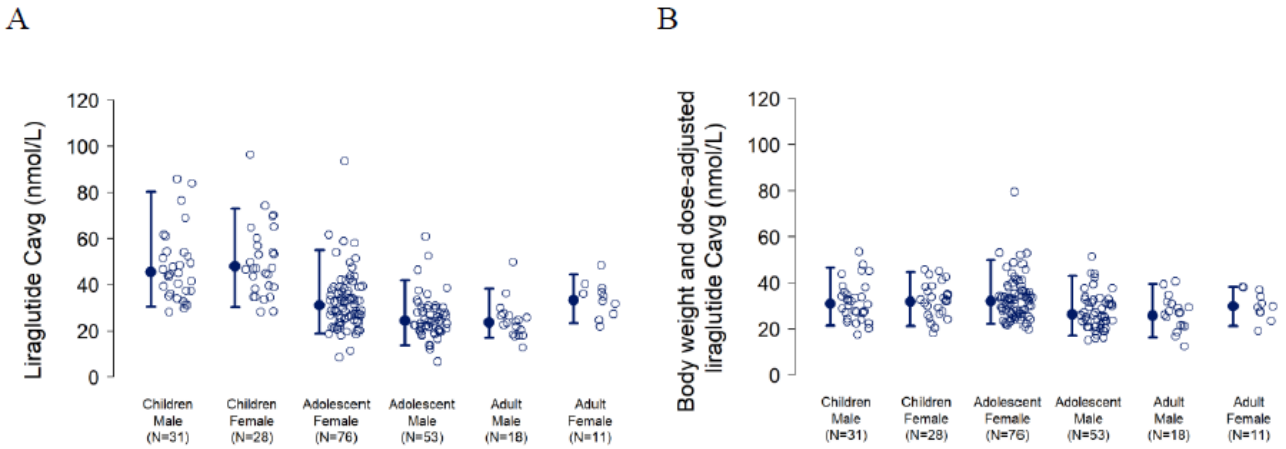
Similarly, upon further stratifying the exposure by sex, no meaningful difference between the sexes was observed. After adjusting for variations in body weight, exposures were found to be consistent across studies, sex, and age groups (Figure 7).

Figure 6. Liraglutide steady-state exposure across studies in participants with obesity, without (A) and with (B) adjustment for body weight (popPK part Study 4392)



Note: The data are individual (open symbols) and geometric mean Cavg estimates adjusted by dose (Panel A; $Cavg,adj = Cavg * (3/Dose)$) and body weight (Panel B; $Cavg,adj = Cavg * (3/Dose) * (BW/100)$) with 95% CIs (closed symbols with error bars) from the final PK model for each trial. The data are from trials 4392, 4180, 3967, 3630, and 4181.

Figure 7. Liraglutide exposure versus sex by age group, without (A) and with (B) adjustment for body weight (popPK part Study 4392)



Note: The data are individual (open symbols) and geometric mean Cavg estimates adjusted to the 3.0 mg dose (Panel A) and body weight (Panel B) with 95% CIs (closed symbols with error bars) from the full PK model for each trial. The data are from trials 4392, 4180, 3967, 3630, and 4181.

Clearance and exposure estimates in paediatric participants

A summary of model-derived baseline body weight, CL/F values, and C_{avg} across studies is provided in Table 4.

Table 4. Summary of liraglutide clearance and exposure estimates across studies included in the PK analysis (popPK part Study 4392)

Study	Baseline body weight (kg)	CL/F (L/h)	C_{avg} (nmol/L)
4392 - children	66.6 [61.3, 72.2]	0.70 [0.64, 0.76]	47.7 [43.6, 52. 2]
4181 - children	68.3 [62.2, 75]	0.76 [0.66, 0.88]	43.8 [37.9, 50.7]
4180 - adolescents	97.5 [94.1, 101.1]	1.1 [1.03, 1.17]	30.3 [28.5, 32.2]
3967 - adolescents	101.4 [94.1, 109.2]	1.13 [1.0, 1.28]	29.5 [26.0, 33.4]
3630 - adults	101.1 [95.3, 107.3]	1.24 [1.10, 1.40]	26.9 [23.80, 30.4]

Note: Numbers and intervals in brackets show geometric means and 95% CIs, respectively. C_{avg} was estimated for the 3.0 mg dose of liraglutide.

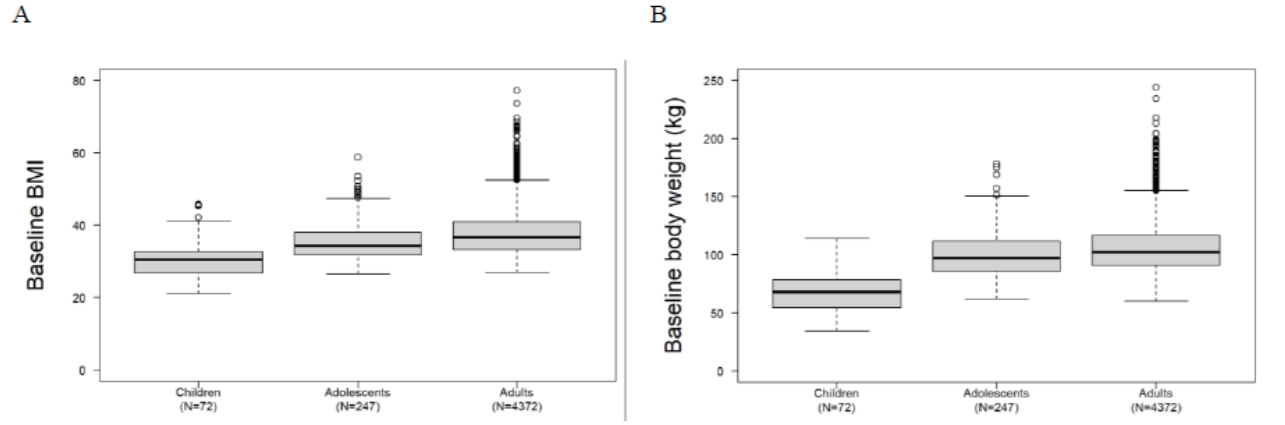
Both the individual clearance and exposure estimates (CL/F and Cavg) were comparable between adolescents and adult participants except for children who had slightly lower clearance and higher exposure. This difference can be mainly explained by differences in body weight (Table 3).

Exposure evaluation for children compared to adolescents and adults included in exposure response evaluation

The exposure in Study 4392 (children) and Study 4180 (adolescents) was compared to exposure in the combined data set from Studies 1839 and 1922, phase 3a studies and Study 1807, a phase 2 study conducted in adults with obesity. The data showed a higher proportion of females compared to males for both adolescents and adults. Conversely, the opposite trend was observed for children. The mean baseline body weights were comparable between adolescents and adults, with children showing lower values.

As shown in Figure 8, there were large overlaps in BMI (Figure 8A) and body weight (Figure 8B) values between adolescents and adults. The demographic characteristics of adolescents and adults included in the E-R analyses are similar apart from the age distribution.

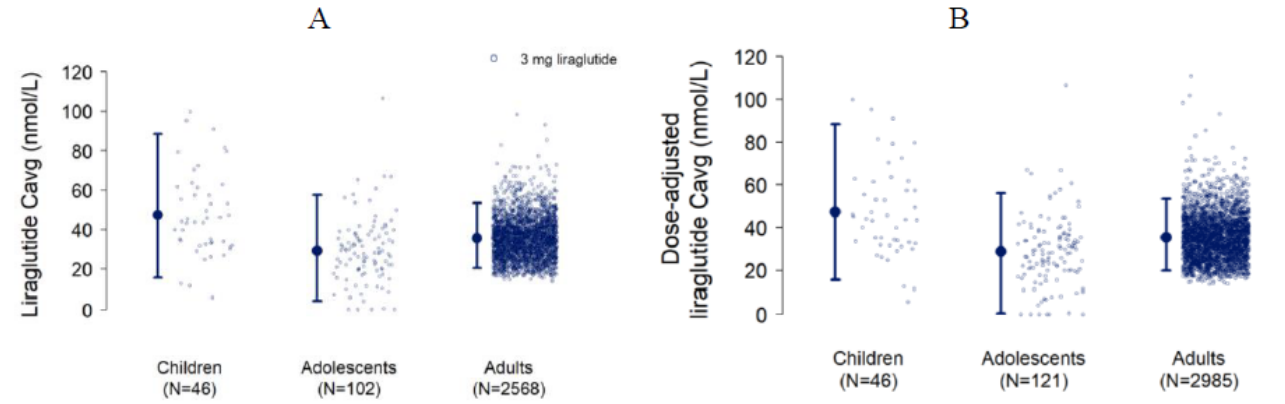
Figure 8. Boxplots of distribution of body weight (A) and BMI values (B) for children compared to adolescents and adults (popPK part of Stud 4392)



Note: The boxes represent the 25th, 50th, and 75th percentiles. The whiskers represent the 5th and the 95th percentiles. The circles are outliers. The data are from studies 4392, 4180, 1807, 1839, and 1922.

With the comparable demographic characteristics of adults and adolescents included in the analysis, the liraglutide exposures were found to be similar in these 2 groups. In contrast, children exhibited overlapping but slightly higher levels of liraglutide exposure (Figure 9).

Figure 9. Liraglutide exposure (C_{avg}) across studies in participants treated with 3.0 mg liraglutide (A) and in all participants with doses adjusted to 3.0 mg liraglutide (B)



Note: The data are individual and geometric mean Cavg estimates with 95% CIs from the full PK model for each trial. The data are from studies 4392, 4180, 1807, 1839, and 1922. In study 4180, BLQ data were included, and data cleaning was less strict compared to studies 1807, 1839, and 1922. No BLQ measurements were observed in study 4392. Average concentration for adults is based on previous predictions.

2.3.3. PK/PD modelling

Exposure-response – Study 4392

Methods

In Study 4392, exposure-response analyses were performed for relative change in BMI, relative change in body weight and proportion of participants reaching ≥5% reduction in BMI from baseline. The exposure-response meta-analyses included the data from Studies 4392 and 4180 in children and adolescents, respectively, as well as the data from phase 2 and 3 studies in adults with obesity or overweight (Studies 1807, 1839, and 1922).

The E-R dataset comprised placebo and treatment data from a total of 4691 participants: 4372 adults from Studies 1807, 1839, and 1922; 247 adolescents from Study 4180; and 72 children from Study 4392 (Table 3). The E-R analysis related the model-derived C_{avg} exposures at steady state to the relative change in body weight and relative change in BMI, as well as the proportion of participants with >5% reduction in BMI.

The E-R relationship at end of study for relative change in BMI, relative change in body weight, BMI response (defined as ≥5% reduction in BMI at the study endpoint compared to baseline) were successfully described by a sigmoidal E_{max} model with sex and age group (adults versus children and adolescents) as covariates on Emax and age group (adults versus adolescent and children) as covariates on the placebo response.

Exposure-response results

The E-R analysis showed increasing reduction in BMI with increasing exposure of liraglutide (Figure 10). Differences between age groups was primarily driven by differences in the placebo effect, indicating similar effect of liraglutide across age groups at the same exposure level.

The E-R analysis of the proportion of participants achieving at least 5% weight loss showed similar results, with increasing proportion of participants achieving at least 5% weight loss with increasing exposure and a similar benefit of treatment across age groups (Figure 11).

Figure 10. Relative change in BMI versus liraglutide exposure for children compared to adolescents and adults (popPK part Study 4392)

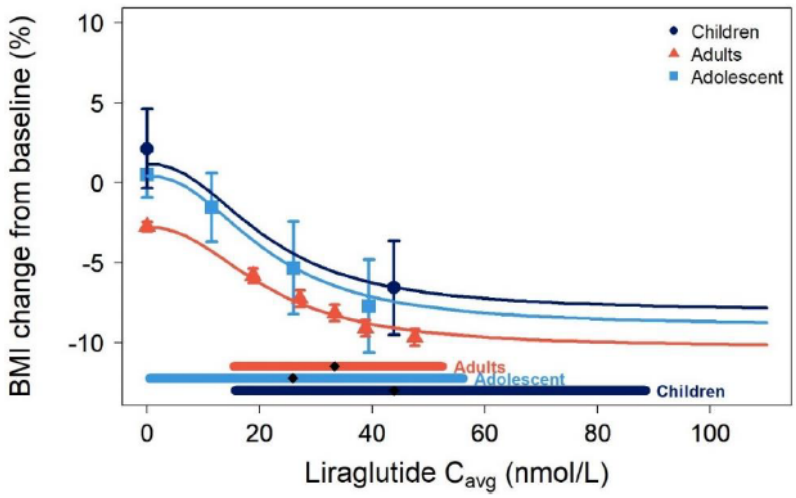
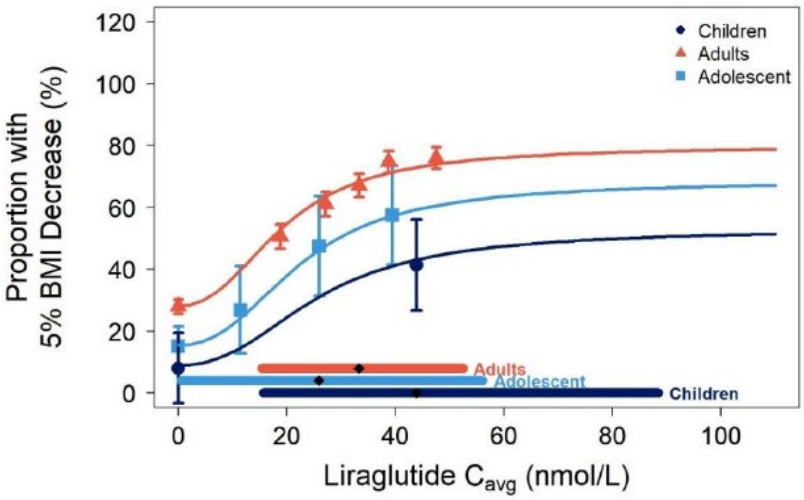
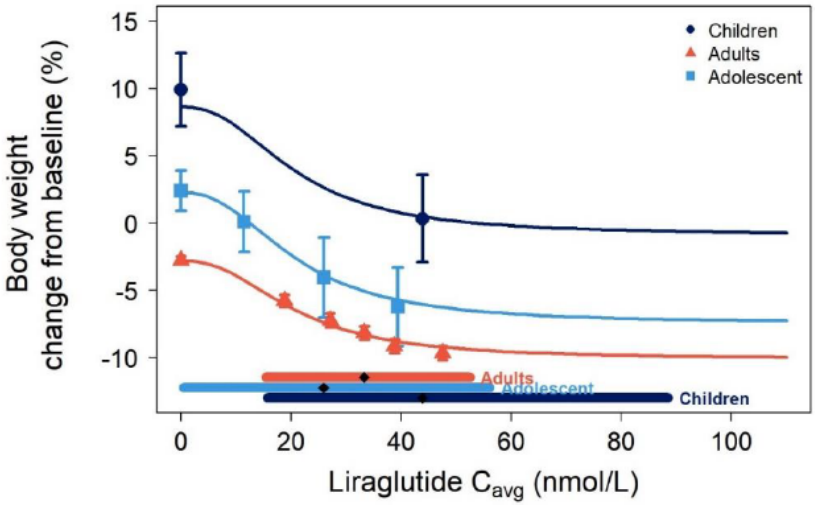


Figure 11. Exposure-response relationships for the proportion of participants reaching≥5% reduction in BMI for children compared to adults (popPK part Study 4392)



Similar to BMI, an increase in exposure of liraglutide correlates with a greater relative reduction in body weight at week 56 with a meaningful separation between age groups (Figure 12). The variation observed in placebo response among the populations may be from a combination of factors, such as ongoing growth in children and adolescents.

Figure 12. Relative change in body weight versus liraglutide exposure for children compared to adolescents and adults (popPK part Study 4392)



2.3.4. Discussion on clinical pharmacology

The main objectives of the clinical pharmacology programme for the use of liraglutide in children aged 6 to <12 years with obesity were to assess the safety, tolerability and pharmacokinetic properties in this population and compare the liraglutide exposure to the exposure in the corresponding adolescent and adult populations.

The bioanalytical method was the same as used for the original submission in 2013. Both clinical studies in children (NN8022-4181 and NN8022-4392) showed acceptable reproducibility of data (incurred sample reproducibility).

The bioanalysis for NN8022-4181 was performed in 2017. The bioanalysis performed for this study appears robust with good precision, accuracy and 100% reproducibility for the incurred sample analysis.

An interim bioanalytical report was submitted with study 4392. It appears that only 327 out of 488 samples were analysed and several samples are still pending reanalysis as only 285 data points were reported (Table 2). In the second round of assessment, a new interim report was provided, with 312 final results now available. The applicant has committed to submit the final bioanalytical report for Study 4392 along with the extension phase CSR in the second half of 2027 as a Post Authorisation Measure.

Analysis for immunogenicity was also using already established and validated methods. E.g. the modified RIP method for the semiquantitative determination of anti-liraglutide antibodies was validated in 2011 at Celerion. Hence, ADA results are anticipated to be comparable with previous studies in adults and adolescents. In response to the request, a validation report for the nAb assay was provided. Furthermore, in the second round of assessment, an interim ADA analysis report from Celerion was also provided. The applicant has committed to the final ADA report for Study 4392 along with the extension phase CSR in the second half of 2027 as a Post Authorisation Measure.

The clinical pharmacology study (Study 4181) provided evidence that PK properties of liraglutide 3.0 mg in children aged 7 to 11 years with obesity were reasonably comparable with PK in adolescents. Further, in Study 4181, the liraglutide C_{trough} concentration appeared to be consistent with dose proportionality. This conclusion remained after excluding participants with unexpectedly low liraglutide C_{trough} concentration levels in a post-hoc sensitivity analysis. Based on the safety/tolerability results and the PK data from Study 4181, the adult/adolescent dosing regimen (dose escalated to 3.0 mg of liraglutide or a maximum tolerated dose) was chosen for children in Study 4392.

The phase 3a efficacy/safety Study 4392 was designed to test the same dose regimen in children as used in adults and adolescents: a starting dose of 0.6 mg OD (0.3 mg in children with body weight < 45 kg) during the first week and increased weekly steps of 0.6 mg until the 3.0 mg dose of liraglutide or a maximum tolerated dose was reached.

Pharmacokinetics of liraglutide in children aged 6 to <12 years was said to be investigated in clinical phase 3a study 4392. However, Novo Nordisk confirmed that all the participants in the Study 4392 were 6 to <12 years as per the inclusion criteria, at the time of screening. In Study 4180, participants were 12 to <18 years at the time of screening, as per the inclusion criteria. The historical clinical phase 1 study 4181 included children aged 7 to <12 years. The pharmacokinetic results were compared to historical clinical studies performed in adolescents (phase 1 study 3967 and phase 3 study 4180) and adults (phase 1 study 3630). Children treated with 3.0 mg liraglutide exhibited higher exposure (Cavg) than adolescents and adult treated with the same dose. When adjusting for body weight, the liraglutide exposure became similar indicating that the clearance per kg is comparable across the different age groups. Gender did not impact the pharmacokinetics of liraglutide. In the span of approximately 24 hours, the individual observed liraglutide concentrations across trials presents a highly variable Ctrough data of the phase 3 studies 4392 and 4180 ranging from less than 0.1 nmol/L to above 100 nmol/L. This large difference in Ctrough is due to different level of compliance among the study participants. This variability is occurring in phase 3 studies of all age groups.

PopPK and Exposure-response

PopPK analysis was conducted based on the combined data set for the studies including paediatric participants (Study 4392, Study 4180, Study 3967 and Study 4181) and a clinical pharmacology study in adults (Study 3630).

A previous 1-compartment model for liraglutide was updated with data from a Phase 3 trial (4392) conducted in obese children aged 6-<12 years. Of note, no 6-year old were enrolled on active treatment and 5 treated children were 12 years old. The final PK dataset from Study 4392 included 165 observations from 46 subjects. About 17.5% of samples were excluded. The excluded samples had sampling times >6 half-lives or were observations after EOT. The maintenance dose was 3 mg QD which was stepped up gradually during the first weeks of treatment. If tolerability issues occurred during dose escalation, the process could take as long as 8 to 10 weeks dependent of the body weight. The first PK samples were scheduled at Visit 13 (week 8). End-of-treatment PK sampling was scheduled at Visit 23 (week 56). Six children received lower doses than 3 mg OD, while 17 had dose reduction.

Body weight, age and sex were significant covariates of liraglutide exposure. The effect of body weight on disposition parameters was incorporated in the model structure by allometric scaling with estimated exponents. Use of fixed "theoretical" exponents for weight-effect had no relevant impact on predicted Cavg.

The Applicant was asked to provide the baseline characteristics of children who reached a maximum tolerated dose (MTD) in Study 4392. A list of participants who reached liraglutide 3.0 mg was presented and indicated that 6, 6, 10, 6 and 17 children of 7, 8, 9, 10 and 11 years of age, respectively, achieved a 3 mg dose. The Applicant provided two tables showing treatment completion/discontinuation in relation to exposure (high/low) or body weight. No trends were observed. In Study 4392, there is very sparse PK data collected in children <9 years of age. There were no 6-year old children enrolled. Several children of 7 or 8 years of age had usual low concentrations, no detectable concentration or status "pending". The exposure in the children with lowest body weight tended to have the highest exposure which is in line with BW being the covariate with most influence on PK. Several children with body weights ≤50 kg experienced liraglutide concentrations above 100 nM which is more than 3-fold above the adult geometric mean Cavg and well above the highest adult exposure in Study 3630. Body weight is the main intrinsic covariate for liraglutide exposure, with higher exposure at lower BW. The concentration data in the

youngest children is limited and characterised by great variation in exposure, probably caused by incompliance to treatment. In the limited data, individual concentrations >100 nM were observed in 7 children from Study 4392, with body weights ranging from 39.0 to 69.8 kgs. Reassuringly, liraglutide concentrations >100 nM were also observed in adolescents (Study 4180; body weights from 79.1 to 102.7 kgs) and adults (Phase 3 trials, 1922 and 1839; body weights from 67.7 to 93.1 kgs). Model-derived Cavg plots with or without dose-adjustment indicated a similar trend, with higher geometric mean Cavg for children as compared to adolescents and adults, and overlapping exposure range between children and adults. Treatment cut-off was set to ≤45 kg. With the limited data in young children and limited safety concerns for liraglutide, the issue will not be further pursued.

Exposure-response analyses of change in body weight or BMI were described using model-derived Cavg and effect described by Emax models. The parameters of the Emax models were estimated with adequately precision except for the covariate effect of age in children on the placebo response in the BMI model. Diagnostic plots indicated the models could well describe initial changes in BW or BMI but were more imprecise at larger changes. Upon request, the diagnostic plots for the E-R models were presented with OBS vs PRED using similar scales on axis.

Exposure-response indicated a larger response upon increasing liraglutide exposure for three efficacy markers, i.e., relative change in BMI, relative change in body weight, and for the proportion of participants with at least 5% BMI reduction.

Overall, the absolute PD response was smaller for children than for adolescents and smaller for children and adolescents compared to adults. This is however not a problem as children are still growing and a smaller absolute weight loss is needed to achieve a healthy weight.

No E-R analyses of safety was included.

Whereas the absolute weight loss was less in children compared to adolescents and adults, the benefits of increasing exposures of liraglutide, i.e., larger efficacy, were similar in children as compared to adolescents with obesity and adult participants with obesity or who are overweight. The ER analysis indicates similarity in the relative change in BMI between children and adolescents with obesity, further supporting the efficacy of the 3.0 mg treatment dose.

Following the finding of a somewhat higher exposure in children as compared to adolescents/adults, the Applicant provided a discussion on the occurrence of gastrointestinal (GI) events such as vomiting, nausea and diarrhea in relation to the increased exposure in children as compared to adults and adolescents. No difference was observed in the reporting of nausea and diarrhea between children vs adolescents and adults. Although the proportion of children experiencing vomiting appeared higher as compared to adolescents and adults in both the placebo and liraglutide 3.0 mg groups, it is agreed that the proportion of children experiencing GI events did not increase with increasing exposure, suggesting that the higher percentage of GI events seen in children is not driven by the higher exposure. The increased exposure in the children population is indicated in the SmPC section 5.2. Despite the absence of a clear exposure-response for the occurrence of vomiting, the 2-fold increase in children as compared to adolescents is notable, and is therefore indicated in the SmPC section 4.8.

In conclusion, the pharmacokinetic data supports the same liraglutide dose regimen for children aged 6 to < 12 years with obesity, as used by adolescent with obesity and adult patients with obesity or who are overweight.

2.3.5. Conclusions on clinical pharmacology

The bioanalytical methods used in the two clinical studies in children appeared to be the same as in the original submission for the obesity indication in adults. However, no final bioanalytical and ADA reports

were yet submitted with this application. The Applicant has committed to provide these final reports along with the extension phase CSR by the second half of 2027 as Post Authorisation Measures.

Regarding pharmacokinetics, overall, it can be agreed that the study results and popPK analysis demonstrate that the liraglutide exposure is reasonably comparable. Exposure tends to be somewhat higher in children as compared to the adolescent/adult study population. The higher exposure in children can be explained by the lower weight of the children, and the effect on most GI AEs appears limited.

The following measures are considered necessary to address issues related to pharmacology:

- Bioanalytical report for Study 4392 along with the extension phase CSR will be submitted in the second half of 2027 as a Post Authorisation Measure
- Final ADA report for Study 4392 along with the extension phase CSR will be submitted in the second half of 2027 as a Post Authorisation Measure.

These measures are included in a letter of recommendation which is appended to this CHMP assessment report.

2.4. Clinical efficacy

2.4.1. Main study

There was one Phase 3a efficacy and safety trial of liraglutide 3.0mg in children with obesity aged 6 to <12 years (Trial 4392).

Study 4392

Study title

Effect and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6 to <12 years: 56-week, double-blind, randomised, placebo-controlled trial.

Methods

Trial design

The main phase of the Study 4392 was a 56 week, double blinded, randomised, placebo-controlled, multi-national clinical study comparing liraglutide 3.0 mg s.c. once daily with placebo in children aged 6 to <12 years with obesity. The main phase of the study included a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-week (see Figure 13).

In the Main phase, subjects who had fulfilled the randomisation criteria were randomised 2:1 to receive liraglutide 3.0 mg s.c. or placebo s.c. once daily. Randomisation was stratified by gender and Tanner stage (1 [premature adrenarche included] vs 2-3 vs 4-5).

All subjects (and parent(s)/LAR) received counselling in healthy nutrition and physical activity from run-in (week 12) until end of the 2-week off-drug, follow-up period (week 142), for a total of 154 weeks.

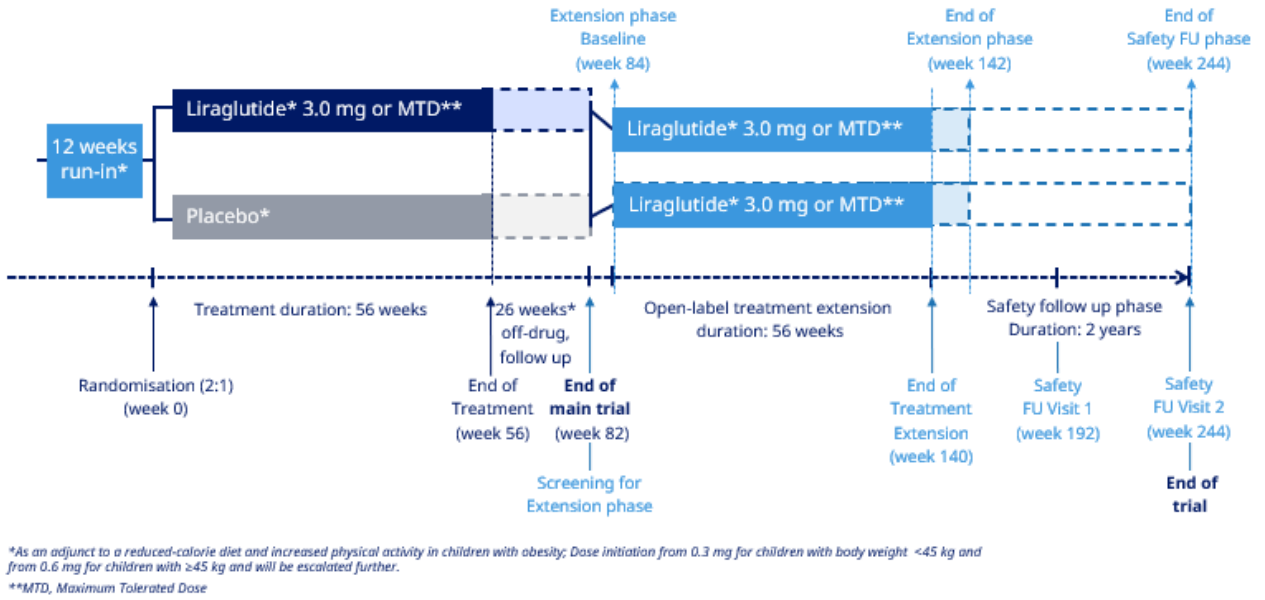


Figure 13 Study design Study 4392

Study participants

The population included children (males and females) aged 6 to < 12 years with obesity and Tanner stage 1-5 pubertal development with a BMI ≥95th percentile on a gender and age-specific growth chart (CDC.gov). Table 5 provides detail on the internal cut-off points for body mass index by sex between 6.0 years and <12 years.

Table 5 Cut-off points for BMI (Weight in kg/Height in m2) obesity (≥95th percentile) by gender for children from 6 and < 14 years of age

z

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
06:00	17.01	17.10	18.41	18.84
06:01	17.04	17.14	18.47	18.90
06:02	17.07	17.17	18.52	18.96
06:03	17.09	17.21	18.58	19.03
06:04	17.12	17.25	18.64	19.09
06:05	17.15	17.29	18.70	19.16
06:06	17.18	17.34	18.76	19.23
06:07	17.22	17.38	18.82	19.30
06:08	17.25	17.43	18.88	19.37
06:09	17.29	17.48	18.95	19.45
06:10	17.32	17.52	19.01	19.52
06:11	17.36	17.57	19.08	19.60
07:00	17.40	17.63	19.15	19.68
07:01	17.44	17.68	19.22	19.76
07:02	17.48	17.73	19.29	19.84
07:03	17.53	17.79	19.37	19.92
07:04	17.57	17.84	19.44	20.00
07:05	17.61	17.90	19.52	20.08
07:06	17.66	17.95	19.59	20.17
07:07	17.71	18.01	19.67	20.25
07:08	17.76	18.07	19.75	20.34
07:09	17.80	18.13	19.83	20.43
07:10	17.85	18.19	19.91	20.52

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
07:11	17.90	18.25	19.99	20.61
08:00	17.96	18.32	20.07	20.70
08:01	18.01	18.38	20.15	20.79
08:02	18.06	18.44	20.23	20.88
08:03	18.12	18.51	20.32	20.97
08:04	18.17	18.57	20.40	21.06
08:05	18.23	18.64	20.48	21.15
08:06	18.28	18.71	20.57	21.25
08:07	18.34	18.77	20.65	21.34
08:08	18.40	18.84	20.74	21.44
08:09	18.45	18.91	20.83	21.53
08:10	18.51	18.98	20.91	21.63
08:11	18.57	19.05	21.00	21.72
09:00	18.63	19.12	21.09	21.82
09:01	18.69	19.19	21.18	21.91
09:02	18.75	19.26	21.26	22.01
09:03	18.82	19.33	21.35	22.11
09:04	18.88	19.40	21.44	22.20
09:05	18.94	19.47	21.53	22.30
09:06	19,00	19.55	21.62	22.40
09:07	19.07	19.62	21.71	22.50
09:08	19.13	19.69	21.80	22.59
09:09	19.20	19.76	21.89	22.69
09:10	19.26	19.84	21.98	22.79
09:11	19.32	19.91	22.06	22.89
10:00	19.39	19.98	22.15	22.98
10:01	19.46	20.06	22.24	23.08
10:02	19.52	20.13	22.33	23.18
10:03	19.59	20.20	22.42	23.27
10:04	19.66	20.28	22.51	23.37
10:05	19.72	20.35	22.60	23.47
10:06	19.79	20.43	22.69	23.57
10:07	19.86	20.50	22.78	23.66
10:08	19.92	20.57	22.86	23.76
10:09	19.99	20.65	22.95	23.85
10:10	20.06	20.72	23.04	23.95
10:11	20.13	20.80	23.13	24.05
11:00	20.20	20.87	23.21	24.14
11:01	20.27	20.94	23.30	24.24
11:02	20.33	21.02	23.39	24.33
11:03	20.40	21.09	23.47	24.43
11:04	20.47	21.16	23.56	24.52

Age	Overweight BMI ≥ 85th percentile		Obesity BMI ≥ 95th percentile	
Year : Month	Males	Females	Males	Females
11:05	20.54	21.24	23.64	24.61
11:06	20.61	21.31	23.73	24.71
11:07	20.68	21.38	23.81	24.80
11:08	20.75	21.45	23.90	24.89
11:09	20.82	21.53	23.98	24.98
11:10	20.89	21.60	24.06	25.07
11:11	20.95	21.67	24.15	25.17

The study was conducted at 25 sites in 9 countries (Belgium, India, Israel, Malaysia, Mexico, Portugal, Russia, Switzerland and the US) which allowed for the inclusion of participants with different racial and ethnic backgrounds. In accordance with the regulatory commitment in the Paediatric Investigational Plan, at least 30% of the randomised participants were from countries with a lifestyle and nutrition comparable to those in the European Union.

Randomisation criteria

- BMI corresponding to ≥95th percentile
- Ability to comply with protocol requirements assessed by the investigator based on compliance with procedures and visit schedules in the 12-week run-in period
- Have been included in accordance with the inclusion and exclusion criteria
- Have not participated in another clinical study during the run-in period
- No history or presence of pancreatitis (acute or chronic)
- No safety concerns as judged by the investigator
- Participants not fulfilling the randomisation criteria for the Main phase were considered run-in failures.
- Participants not randomised in the Main phase of the study will not be able to participate in the Extension phase.

Key inclusion criteria

- Informed consent of parent(s) or LAR of participant and child assent, obtained before any study-related activities for the Main phase as well as for the Extension phase of the study. Study-related activities were any procedures that were carried out as part of the study, including activities to determine suitability for the study.
- Male or female, aged 6 to <12 years at the time of signing informed consent for the Main phase
- Tanner stage 1-5 pubertal development at the time of signing informed consent
- BMI ≥95th percentile
- History of failing to lose sufficient weight with lifestyle modification prior to entering the Main phase as judged by the investigator
- For participants with T2D at screening the following inclusion criteria applied in addition to above criteria:
- Participant with T2D treated with either diet and exercise alone or stable treatment with metformin for at least 90 days prior to screening
- HbA1c ≤10.0% (86 mmol/mol) as measured by central laboratory at screening

Key exclusion criteria

- A self-reported (or by parent(s)/LAR where applicable) change in body weight >5 kg (11 lbs) within 90 days before screening visit (week 12) for the Main phase, irrespective of medical records
- Participants with secondary causes of obesity (for example hypothalamic, monogenic or endocrine causes)
- Type 1 diabetes

Treatments

For children with a body weight ≥45 kg at randomisation, dosing was initiated with liraglutide/placebo 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo or the individual maximum tolerated dose (MTD) is reached.

For children with a body weight <45 kg at randomisation, dosing was initiated with liraglutide/placebo 0.3 mg daily for one week and increased to 0.6 mg after the first week, thereafter the dose was increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo or the individual MTD was reached.

All subjects should aim at reaching the recommended target dose of 3.0 mg liraglutide once daily or the corresponding volume of placebo. The trial product dose was escalated only if the current dose was tolerated.

Justification for starting dose

Body weight is an important covariate for exposure, which was confirmed in children aged 7 to <12 years with obesity in the NN8022-4181 pharmacokinetic (PK) trial, where children with a baseline body weight ≥ 45 kg had exposure within, but at the higher end of the previously-observed range of liraglutide exposure in adults and adolescents. In the NN8022-3967 PK trial in adolescents aged 12 to <18 years with obesity, it was demonstrated that liraglutide could be initiated at a daily dose of 0.6 mg with subsequent weekly dose escalation of 0.6 mg in accordance with the Saxenda® prescribing information to mitigate GI side effects. At present, no data exist on exposure with liraglutide in subjects with a body weight <45 kg. Due to exposure being inversely related to body weight, children with a body weight <45 kg are expected to have a higher exposure compared to children with higher weight. Therefore, a differentiated starting dose was applied with 0.3 mg and 0.6 mg for children weighing <45 kg and ≥45 kg, respectively, to improve GI tolerability.

Objectives

The primary objective of the study was to compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo on weight management in children aged 6 to <12 years with obesity.

The secondary objective was to compare the effect of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity on cardiovascular risk factors and glucose metabolism, and to evaluate the safety and tolerability of liraglutide 3.0 mg s.c. once daily versus placebo in children aged 6 to <12 years with obesity.

Outcomes/endpoints

Primary endpoint

- Relative change in BMI from baseline (week 0) to week 56

Secondary endpoints

- Relative change in body weight from baseline (week 0) to week 56
- Subjects achieving ≥5% reduction of BMI from baseline (week 0) to week 56

Supportive secondary endpoints

Efficacy

- Change in body weight from baseline (week 0) to week 56
- Change in BMI standard deviation score from baseline (week 0) to week 56
- Subjects achieving ≥10% reduction of BMI from baseline (week 0) to week 56
- BMI percentage of the 95th percentile on gender and age-specific growth charts from baseline (week 0) to week 56
- Change in waist circumference from baseline (week 0) to week 56
- Change in systolic blood pressure from baseline (week 0) to week 56
- Change in diastolic blood pressure from baseline (week 0) to week 56
- Change in HbA1c from baseline (week 0) to week 56

Safety

- Treatment emergent adverse events (TEAEs) from baseline (week 0) to week 82
- Treatment emergent serious adverse events (SAEs) from baseline (week 0) to week 82

Exploratory endpoints

Effect endpoints

- Change in homeostasis model assessment (HOMA-B) from baseline (week 0) to week 56
- Change in HOMA-IR from baseline (week 0) to week 56
- Body weight reduction ≥5% from baseline from baseline (week 0) to week 56
- Low density lipoprotein (LDL) cholesterol from baseline (week 0) to week 56
- High density lipoprotein (HDL) cholesterol from baseline (week 0) to week 56
- Triglycerides from baseline (week 0) to week 56
- Relative change in BMI from baseline (week 0) to week 140 and to week 244
- Relative change in body weight from baseline (week 0) to week 140 and to week 244
- Change in waist circumference from baseline (week 0) to week 140 From baseline (week 0) and to week 244
- BMI percentage of the 95th percentile on gender and age-specific growth charts \ from baseline (week 0) to week 140 and to week 244

Safety endpoints

- Treatment emergent adverse events (TEAEs) from baseline (week 0) to week 142 From baseline (week 0) and to week 244
- Treatment emergent serious adverse events (SAEs) from baseline (week 0) to week 142 From baseline (week 0) and to week 244

Safety endpoints (for children with T2D only)

- Number of treatment emergent hypoglycaemic episodes (Appendix 9) from baseline (week 0) to week 142 From baseline (week 0) to week 244

Primary estimand

The primary estimand quantified the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised participants regardless of adherence to treatment or initiation of rescue interventions (such as weight management drugs or bariatric surgery) ("effectiveness"/"treatment policy" estimand). The estimand covered all effect-related objectives.

Secondary estimand

The secondary estimand quantified the average treatment difference of liraglutide 3.0 mg relative to placebo after 56 weeks, in all randomised participants had they remained on their randomised treatment for the entire planned duration of the study and not started any rescue intervention (such as weight management drugs or bariatric surgery) ("efficacy"/"hypothetical" estimand). The estimand covered the primary objective.

Sample size

In agreement with EMA, the minimum number of randomised participants for Study 4392 was 78. In a fixed sample size design with a total of 78 participants, the power calculation was performed using the following scenarios with SD of 4%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0% and 7.5%.

The effect of withdrawals on the analysis was accounted for as a reduction of the anticipated treatment difference and an increase of the SD. Missing values were handled by assuming that withdrawn participants respond as if treated with placebo for the entire study. The assumed withdrawal percentage for this paediatric study was 20%.

The study was designed with an effective power of at least 80% and a treatment difference of -5.0% with a randomisation ratio of 2:1 for a fixed sample size of 78 participants.

Power calculation for different investigated scenarios of treatment difference and SD is shown in Table 11-2.

Table 11-2 Summary of power calculation for fixed sample size

Sample Size	Power (%)	SD						
	Treatment difference	4	5	**5.5**	6	6.5	7	7.5
78	-4.5	94.10%	81.80%	74.60%	67.50%	60.80%	54.80%	49.40%
	-5	97.20%	88.60%	**82.50%**	76.00%	69.60%	63.40%	57.70%

(Total sample size of 78 subjects and withdrawal rate of 20% and a=0.05; two-sided)

Randomisation

In the Main phase, subjects who had fulfilled the randomisation criteria were randomised 2:1 to receive liraglutide 3.0 mg s.c. or placebo s.c. once daily. Randomisation was stratified by gender and Tanner stage (1 [premature adrenarche included] vs 2-3 vs 4-5). The interactive web response system (IWRS) was used for blind-breaking. Placebo treatment was used as a comparator. The Main phase of the trial was double-blind, the active drug and placebo drug were visually identical.

Blinding

Main Phase
The Main phase of the study was double-blinded. The active drug and placebo drug were visually identical for the following study products:
-Liraglutide 6.0 mg/mL, 3.0 mL, for s.c. injection with FlexPen®.
-Liraglutide placebo, 3.0 mL, for s.c. injection with FlexPen®.

The IWRS was used for blind-breaking. The blind was permitted to be broken in a medical emergency if knowing the actual treatment would influence the treatment of the participant. In that case, Novo Nordisk was to be notified immediately after breaking the blind. The date when and reason why the blind was broken had to be recorded in the source documentation. In the event the blind was broken, the person breaking the blind had to print the "code break confirmation" notification generated by the IWRS, record the reason and sign and date the document.

Database lock (DBL) occurred after the last participant had completed the Main phase of the study. When the blind was broken at DBL of the Main phase (V28, week 82), the treatment allocation was accessible to the investigator and the Novo Nordisk Global Safety department.
According to standard pharmacovigilance procedures, specific members of the Novo Nordisk A/S Global Safety department were not blinded to SUSARs (for reporting purposes), whereas the clinical study group and the investigator remained blinded throughout the study.

Extension Phase
The open-label treatment period was un-blinded. All participants eligible for treatment with liraglutide 3.0 mg received liraglutide 6.0 mg/mL, 3.0 mL, s.c. injection with FlexPen®.

Analytical sets: Two analysis sets were defined in accordance with the ICH E9.

The **full analysis set (FAS)** included all randomised participants according to the intention-to-treat principle, i.e., participants were included according to planned treatment.

The **safety analysis set (SAS)** included all randomised participants exposed to at least one dose of randomised treatment and participants were included according to actual treatment.

Effect endpoints were analysed using the FAS; safety endpoints were analysed using the SAS.

Two observation periods were defined for each participant:

- In-trial: The in-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with study site.
- On-treatment (with study product): A time-point was considered as ‘on-treatment’ if defined as events with onset date between the first day of study product administration and whatever came first: a) 14 days after the last day on study product, b) first follow-up visit (V24 for participants with study product discontinued), or c) last study visit (participants withdrawn without follow-up visit).

The in-trial and on-treatment periods defined the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

Efficacy analyses

The primary endpoint changed from baseline to week 56 in BMI (%) was analysed as a linear regression (ANCOVA) assuming unequal variances between the treatment arms of % change in BMI on randomised

treatment and stratification group (gender *Tanner stage group) as factors and baseline BMI (kg/m2) as covariate. The estimated treatment difference between liraglutide 3.0 mg once-daily and placebo was reported together with the associated two-sided 95% CI and corresponding p-value. Superiority was claimed if the upper limit of the estimated two-sided 95% CI is below 0.

Considering no randomized participants had T2D, the planned analysis of hypoglycaemic episodes in T2D participants was not completed in Study 4392.

The primary endpoint followed by the two confirmatory secondary endpoints was evaluated using a hierarchical testing procedure starting with the treatment difference between the relative change in BMI. In the case of a significant treatment difference the test procedure proceeds to test the treatment difference between the relative change in body weight followed by the treatment difference between the subjects achieving ≥5% reduction of BMI. This test procedure would protect the family-wise type 1 error in the strong sense on a 5% level of significance.

Primary imputation approach for handling missing values addressing the primary estimand
Multiple imputation approach using retrieved subjects (RD-MI): The primary imputation approach for the primary estimand was a multiple imputation similar to the one described by McEvoy1.
In this method missing BMI measurement at week 56 for non-retrieved dropouts (MD) were imputed by sampling from values obtained from retrieved dropouts (AD) in each randomised treatment arm. This was done according to the timing (monthly) of last available observation (of BMI measurement) on randomised treatment (LAO-OT). Missing BMI measurements at week 56 for subjects on drug treatment (MT) were imputed by sampling from subjects on randomised treatment (AT) in the relevant randomised treatment arm. The multiple imputation approach was done in three steps:

1. Imputation: Defined an imputation model using retrieved subjects (AD) from FAS and done within groups defined by randomized treatment. The model would be a linear regression of BMI (kg/m2) at week 56 on stratification group (gender and Tanner stage group and their interaction) as factors and baseline BMI (kg/m2), timing of LAO-OT of BMI (kg/m2) and LAO-OT of BMI (kg/m2) as covariates. If the imputation model could not be fit, then the model would be reduced until the model could be fit. Reduction would be done in a fixed order by first removing Tanner stage, then removing gender and finally removing baseline BMI. If the model still could not be fit, the imputation would be done regardless of the randomised treatment arm. If no LAO-OT existed post- measurements at week 56 for MT subjects would also be defined using AT subjects in a similar way. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models were then used to impute missing week 56 BMI values for each randomised treatment arm. This would be done 1000 times and result in 1000 complete data sets.
2. Analysis: Analysis of each of the 1000 complete data sets, using the analysis model (ANCOVA), resulting in 1000 estimations.
3. Pooling: Pooling the 1000 estimation results into a final result using Rubin’s formula

Sensitivity Analysis

To investigate the sensitivity of the results of the main analysis of the primary endpoint with regards to the handling of missing data, the following sensitivity analyses were performed:
Jump to reference multiple imputation approach (J2R-MI): The approach for multiple imputations of missing values of BMI (kg/m2) at week 56 (type MT+MD for both the liraglutide 3.0 mg and placebo group was by sampling all available assessments at respective landmark visits in the placebo group (type AT+AD). This approach was also known as jump to reference and made the assumptions that subjects instantly after discontinuation lose any effect of randomised treatment beyond what could be expected from placebo treatment as adjunct to reduced-calorie diet and increased physical activity. The multiple imputation approach was done as above with the first step replaced by:

1. Imputation: Defined an imputation model using placebo subjects from FAS with a week 56 measurement (AT and AD). The model would be a linear regression of BMI (kg/m2) at week 56 on stratification group (gender and Tanner stage group and their interaction) as a factors and baseline BMI (kg/m2) as covariate. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models were then used to impute missing week 56 BMI values for each randomised treatment arms. This would be done 1000 times and result in 1000 complete data sets.

Wash-out multiple imputation approach (WO-MI): In this method missing BMI measurement at week 56 would be imputed using same framework (Imputation, Analysis, Pooling) as described above in primary imputation method with the first step replaced by:

1. Imputation: Defined an imputation step procedure utilizing different imputation models depending on randomised treatment group and end of treatment status (on-drug/off-drug) as described in the following steps:
   i. For on-drug subjects in the liraglutide 3.0 mg arm, missing BMI (kg/m2) at week 56 were imputed based on observed data from the on-drug subjects in the liraglutide 3.0 mg arm and according to the RD-MI procedure described above. This would result in 1,000 complete data sets for on-drug subjects in the liraglutide 3.0 mg arm.
   ii. For the subjects in placebo arm, missing BMI (kg/m2) at week 56 were imputed based on all observed data at all time points in the placebo arm, and using an MMRM model with stratification group (gender and Tanner stage group and their interaction) as a factor and baseline BMI (kg/m2) as covariate – all nested within visit. An unstructured covariance matrix for measurements within the same subject would be employed, assuming that measurements for different subjects were independent. Each missing value of BMI (kg/m2) at week 56 is imputed 1,000 times by random sampling from normal distribution with the MMRM-predicted value at week 56 as mean and variance as a sum of prediction variance and residual variance.
   iii. For off-drug subjects in the liraglutide 3.0 mg arm, missing BMI (kg/m2) at week 56 were imputed from the placebo arm assuming that all drug effect will be washed out and gone before the landmark visit. The imputation procedure would be similar to jump to reference multiple imputation as defined above. An imputation model would be fitted to each of 1,000 complete data sets resulting from MMRM imputation for the placebo arm in the previous step. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation model from each of 1,000 fits was then used to impute missing week 56 BMI (kg/m2), ultimately resulting in 1,000 complete data sets for off-drug subjects in liraglutide 3.0 mg arm.
   iv. Data sets obtained in steps i-iii were combined resulting in 1,000 complete data sets for all randomised participants.

ANCOVA for equal variance: An alternative analysis model similar to the primary analysis model (ANCOVA), following the primary imputation approach (RD-MI), but assuming equal variances instead of unequal variances. The analysis model would be fitted with stratification group (gender and Tanner stage group and their interaction) as a factors and baseline BMI (kg/m2) as covariate. The estimated treatment difference between liraglutide 3.0 mg and placebo would be reported together with the associated two-sided 95% confidence interval (CI) and corresponding p-value.

Results

Participant flow

See also Table 6. A total of 92 participants were screened, of which 3 were screen failures. The main reason for screen failure was violation of the exclusion criteria. Seven participants withdrew prior to randomisation. A total of 82 participants were randomised 2:1, all were exposed to study products.

Treatment completers: A total of 66 (80.5%) participants were on treatment at end of study visit.

A total of 66 (80.5%) participants completed the study end visit (visit 28) without permanent discontinuation of study product.

Discontinuation (with or without withdrawing from the study): A total of 16 (19.5%) participants permanently discontinued treatment and 8 (9.8%) participants withdrew from the study. The main reasons for discontinuation of study product were adverse events.

Table 6 Participants disposition - summary - all participants

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Screened			92
Screening failures			3
Withdrawn before randomisation			7
Run-in failures			0
Randomised	56 (100)	26 (100)	82 (100)
Exposed	56 (100)	26 (100)	82 (100)
Analysis sets			
Full analysis set	56 (100)	26 (100)	82 (100)
Safety analysis set	56 (100)	26 (100)	82 (100)
Treatment completion			
On-treatment at week 56 (treatment completers)	44 (78.6)	22 (84.6)	66 (80.5)
Trial product permanently discontinued	12 (21.4)	4 (15.4)	16 (19.5)
Primary reason for permanent discontinuation of trial product			
Adverse event	6 (10.7)	0	6 (7.3)
Protocol violation	0	0	0
Included in the study in violation of the inclusion and/or exclusion criteria	0	0	0
Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study	0	0	0
Calcitonin >=20 ng/L	0	0	0
Diagnosis of type 1 diabetes	0	0	0
Other	0	0	0
Suspicion of acute pancreatitis	0	0	0
Lack of efficacy	1 (1.8)	1 (3.8)	2 (2.4)
Lost to follow-up	1 (1.8)	1 (3.8)	2 (2.4)
Pregnancy	0	0	0
Technical problems	1 (1.8)	0	1 (1.2)
At the discretion of the investigator	0	0	0
Site closure	0	0	0
Epi/Pandemic	0	0	0
Other	3 (5.4)	2 (7.7)	5 (6.1)
Withdrawal of consent	1 (1.8)	1 (3.8)	2 (2.4)
Other	2 (3.6)	1 (3.8)	3 (3.7)
Attended end-of-treatment visit after permanent discontinuation of trial product	9 (16.1)	2 (7.7)	11 (13.4)

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Study completion			
Attended end-of-main-phase visit (study completers)	51 (91.1)	23 (88.5)	74 (90.2)
Attended end-of-main-phase visit and end-of-treatment visit without permanent discontinuation of trial product	44 (78.6)	22 (84.6)	66 (80.5)
Withdrawn from study	5 (8.9)	3 (11.5)	8 (9.8)
Primary reason for study withdrawal			
Withdrawal by subject	1 (1.8)	0	1 (1.2)
Lost to follow-up	2 (3.6)	1 (3.8)	3 (3.7)
Withdrawal by parent/guardian	2 (3.6)	2 (7.7)	4 (4.9)
Investigator decision	0	0	0
Site closure	0	0	0
Epi/Pandemic	0	0	0
Death	0	0	0
Withdrawn from study before week 56	4 (7.1)	3 (11.5)	7 (8.5)
Withdrawn from study without prior permanent discontinuation of trial product	0	0	0

N: Number of participants, %: Percentages are based on randomised participants.
On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product. Permanent discontinuation is when a participant stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 56).
End-of-treatment refers to main phase end of treatment visit 23 (week 56).

Recruitment

Subjects were enrolled at 25 sites in Belgium, India, Israel, Malaysia, Mexico, Portugal, Russia, Switzerland and the United States.

Conduct of the study

Protocol amendments

There were 3 amendments to the protocol, one for MMST updates (version 2.0), one to update the EudraCT number to an EU-CT number (version 3.0) and on substantial amendment, which described below.

The final amendment of the Protocol to version 4.0 (19 May 2022) was considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union for the countries participating in the Extension phase of the study. The overall rationale for amending the protocol was to include an Extension phase consisting of a one year open-label treatment period, followed by yearly safety follow-up visits for 2 years to be reported in the Extension phase CSR. In addition, this amendment included details regarding the additional collection of biosamples at visit 28 (week 82), along with updates to the injection instructions and minor changes to the text to improve readability.

Protocol deviations

In total, 116 important PDs were reported before DBL:

- 17 were site-level deviations

- 99 were participant-level deviations

These protocol deviations were not likely to have affected the statistical inferences, analyses, participant safety, or conclusions presented in this report.

Site-level and participant level PDs are summarised by category and subcategory in Table 4-2 below.

Dosing

At the end of treatment, 50 (89.3%) of participants who were exposed to liraglutide 3.0 mg received the intended target dose, 25 (96.2%) of participants who were exposed to treatment with placebo received the intended target dose.

Table 7 Exposure - summary - full analysis set

	Lira 3.0mg		Placebo	
Dose	n (%)	Median (%)	n (%)	Median (%)
Number of subjects	56		26	
0.3mg	0		0	
0.6mg	0		0	
1.2mg	3 (5.4)	75.0	0	
1.8mg	1 (1.8)	48.0	1 (3.8)	15.6
2.4mg	2 (3.6)	75.2	0	
3.0mg	50 (89.3)	88.8	25 (96.2)	92.2

n: Number of participants; %: Percentage of participants, Median (%): Median percentage of time on each dose.

Baseline data

Overall, the demographic and baseline characteristics were well-balanced between the liraglutide 3.0 mg and placebo groups as shown in Table 8 and

Table 9. Most participants had baseline BMI from 25 to <35 kg/m2 in the liraglutide 3.0 mg group while participants were evenly distributed among baseline BMI categories (<25, 25 to <30, 30 to <35, and ≥35 kg/m2) in the placebo group. Overall, 34 participants (liraglutide 3.0 mg: 6 females and 18 males; placebo: 3 females and 7 males) with Tanner stage 1 were included in the Study 4392.

Table 8 Demographics and baseline characteristics for categorical data - summary - full analysis set

	Lira 3.0 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	56		26		82	
Age (years)						
N	56	(100.0)	26	(100.0)	82	(100.0)
6-<9	24	(42.9)	13	(50.0)	37	(45.1)
10-<12	32	(57.1)	13	(50.0)	45	(54.9)
Sex						
N	56	(100.0)	26	(100.0)	82	(100.0)
Female	26	(46.4)	12	(46.2)	38	(46.3)
Male	30	(53.6)	14	(53.8)	44	(53.7)
Country						
N	56	(100.0)	26	(100.0)	82	(100.0)
Belgium	7	(12.5)	5	(19.2)	12	(14.6)
Switzerland	4	(7.1)	1	(3.8)	5	(6.1)
India	3	(5.4)	2	(7.7)	5	(6.1)
Israel	4	(7.1)	3	(11.5)	7	(8.5)
Mexico	7	(12.5)	0	(0.0)	7	(8.5)
Malaysia	2	(3.6)	0	(0.0)	2	(2.4)
Portugal	5	(8.9)	4	(15.4)	9	(11.0)
Russian Federation	7	(12.5)	5	(19.2)	12	(14.6)
United States	17	(30.4)	6	(23.1)	23	(28.0)
Ethnicity						
N	56	(100.0)	26	(100.0)	82	(100.0)
Hispanic or Latino	10	(17.9)	1	(3.8)	11	(13.4)
Not Hispanic or Latino	46	(82.1)	25	(96.2)	71	(86.6)
Race						
N	56	(100.0)	26	(100.0)	82	(100.0)
White	37	(66.1)	22	(84.6)	59	(72.0)
Black or African American	4	(7.1)	2	(7.7)	6	(7.3)
Asian	6	(10.7)	2	(7.7)	8	(9.8)
Native Hawaiian or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
American Indian or Alaska Native	1	(1.8)	0	(0.0)	1	(1.2)
Other	8	(14.3)	0	(0.0)	8	(9.8)
BMI (kg/m^2)						
N	56	(100.0)	26	(100.0)	82	(100.0)
<25.0	5	(8.9)	5	(19.2)	10	(12.2)
25.0-<30.0	17	(30.4)	8	(30.8)	25	(30.5)
30.0-<35.0	26	(46.4)	6	(23.1)	32	(39.0)
>=35.0	8	(14.3)	7	(26.9)	15	(18.3)

Demographics and baseline characteristics for categorical data - summary - full analysis set

	Lira 3.0 mg	Placebo	Total
	N (%)	N (%)	N (%)
Weight category CDC			
N	56 (100.0)	26 (100.0)	82 (100.0)
Overweight	0 (0.0)	0 (0.0)	0 (0.0)
Obesity class I	10 (17.9)	10 (38.5)	20 (24.4)
Obesity class II	26 (46.4)	4 (15.4)	30 (36.6)
Obesity class III	20 (35.7)	12 (46.2)	32 (39.0)
Stratification on Tanner Stage and sex			
N	56 (100.0)	26 (100.0)	82 (100.0)
Female With Tanner Stage 1	6 (10.7)	3 (11.5)	9 (11.0)
Female with Tanner Stage 2-3	12 (21.4)	6 (23.1)	18 (22.0)
Female with Tanner Stage 4-5	8 (14.3)	3 (11.5)	11 (13.4)
Male With Tanner Stage 1	18 (32.1)	7 (26.9)	25 (30.5)
Male with Tanner Stage 2-3	10 (17.9)	7 (26.9)	17 (20.7)
Male with Tanner Stage 4-5	2 (3.6)	0 (0.0)	2 (2.4)
Overall tanner stage			
N	56 (100.0)	26 (100.0)	82 (100.0)
Stage 1	24 (42.9)	10 (38.5)	34 (41.5)
Stage 2-3	22 (39.3)	13 (50.0)	35 (42.7)
Stage 4-5	10 (17.9)	3 (11.5)	13 (15.9)

N: Number of participants, %: Percentages are based on number of participants. Overall Tanner Stage for each participant is calculated as maximum Tanner Stage combining all the categorical questions per visit. CDC: Centers for Disease Control and Prevention. The last available and eligible observation at or prior to the randomisation visit was selected for summary except for age where date of informed consent was used.
Weight categories as per CDC are based on BMI growth charts: Normal weight: BMI <85th percentile; Overweight: BMI >=85th - <95th percentile; Obesity class I: BMI >=95th - <120% of the 95th percentile; Obesity class II: BMI >=120% of the 95th percentile - <140% of the 95th percentile; Obesity class III: BMI >=140% of the 95th percentile

Table 9 Baseline characteristics (for continuous data) - full analysis set

	Lira 3.0 mg	Placebo	Total
Number of subjects	56	26	82
Mean age (years)	10	10	10
Mean BMI SDS	3.65	3.87	3.72
Mean BMI (kg/m^2)	30.9	31.3	31.0
Mean body weight (kg)	69.8	71.0	70.2
Mean HbA_{1c} (%)	5.4	5.4	5.4
Mean FPG (mmol/L)	5.0	4.9	5.0
Mean LDL (mmol/L)	2.5	2.4	2.4
Mean triglyceride (mmol/L)	1.16	1.22	1.18

Numbers analysed

The overall participant disposition is provided in Table 6 and summarised below.

A total of 92 participants were screened, of which 3 were screen failures. The main reason for screen failure was violation of the exclusion criteria.

A total of 82 participants were randomised 2:1 and 7 participants withdrew prior to randomisation.

A total of 82 participants were exposed to study products and 0 randomised participants were withdrawn prior to study product exposure.

Outcomes and estimation

Primary efficacy endpoint – primary estimand

Relative change in BMI From baseline (week 0) to week 56 was the primary endpoint.

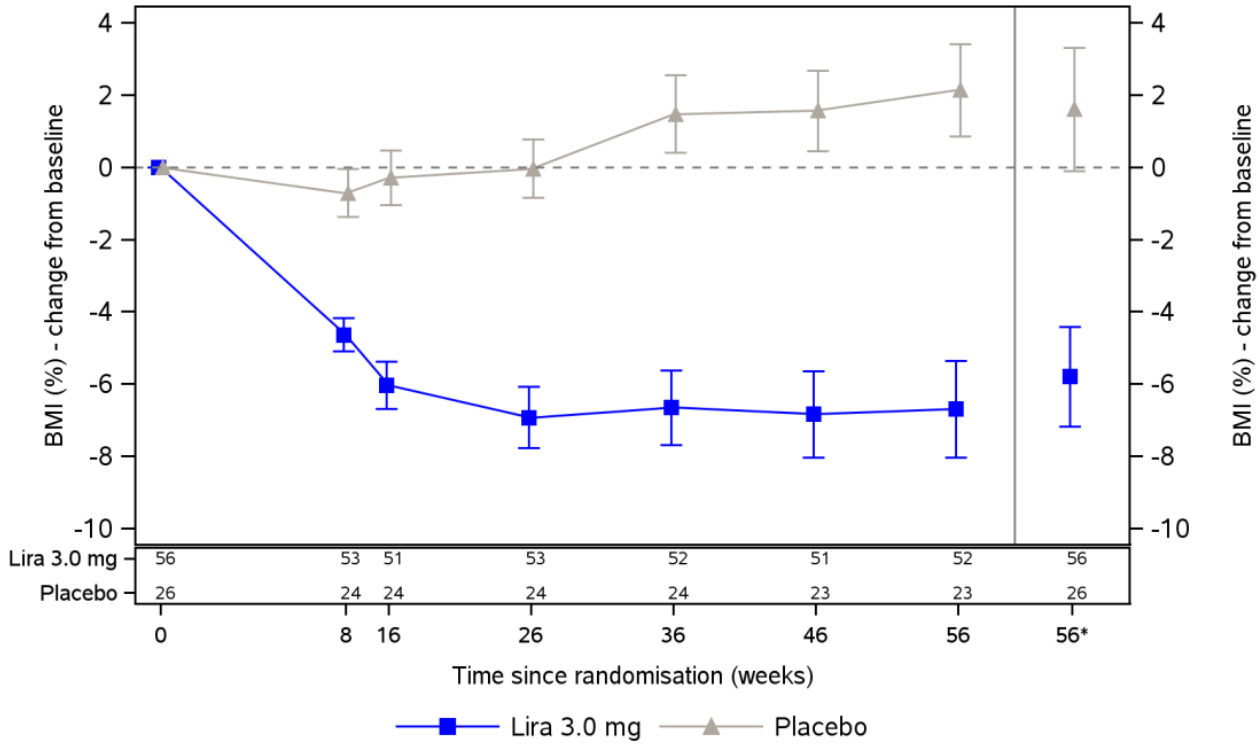
At week 0, the observed mean (SD) BMI was 30.9 (4.7) kg/m2 for participants in the liraglutide 3.0 mg treatment group and 31.3 (7.0) kg/m2 for participants in the placebo treatment group.

At week 56, the estimated mean change in BMI for the treatment policy estimand was (Figure 14):

- -5.8 % for participants in the liraglutide 3.0 mg treatment group
- 1.6 % for participants in the placebo treatment group.

For the treatment policy estimand, the change for BMI from week 0 to week 56 was statistically significantly different in favour of liraglutide 3.0 mg; ETD (liraglutide 3.0 mg vs placebo): Estimate -7.40 [-11.56; -3.24] 95% CI; p-value = 0.0005.

For the endpoint, multiple imputation sensitivity analyses were performed evaluating the robustness of the assumptions about the missing data. The sensitivity analyses supported the robustness of the conclusions for the endpoint.



BMI: Body mass index. Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the primary analysis. Numbers shown in the lower panel are participants contributing to the mean.

nn8022/nn8022-4392-main/csr_20240321_er
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Figure 14 BMI (%) change from baseline by week - mean plot - treatment policy estimand - full analysis set

Persistence of efficacy week 56 to 82 (off-study-drug follow up period)

During the off-drug follow-up period of 26-weeks (from week 56 to week 82) in the Main phase of Study 4392, the BMI % increased in both the liraglutide 3.0 mg and the placebo groups (change from baseline to week 82 was -0.8 and 6.7%).

Confirmatory secondary endpoints

- *Relative change in body weight From baseline (week 0) to week 56*

At week 0, the observed mean (SD) body weight was 69.8 (17.7) kg for participants in the liraglutide 3.0 mg treatment group and 71.0 (23.2) kg for participants in the placebo treatment group.

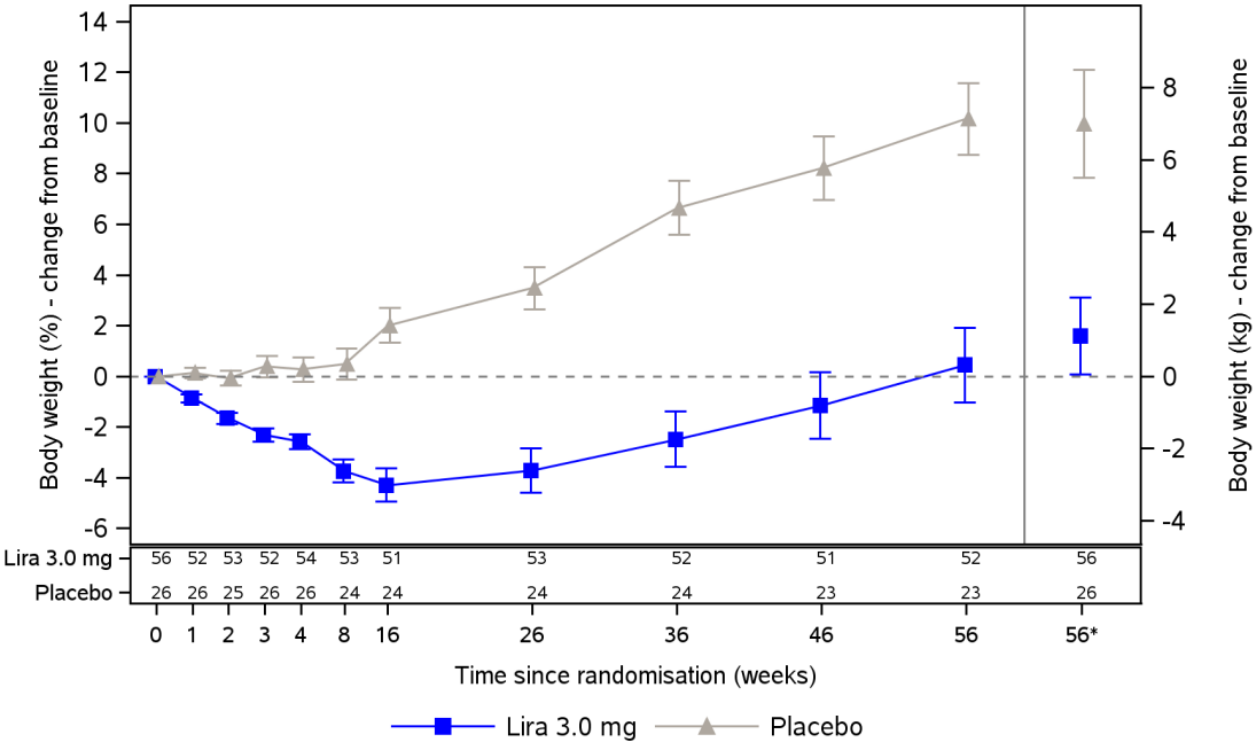
At week 56, the estimated mean change in body weight for the treatment policy estimand (Figure 15):

- 1.59 % for participants in the liraglutide 3.0 mg treatment group
- 9.96 % for participants in the placebo treatment group

For the treatment policy estimand, the change for body weight from week 0 to week 56 was statistically significantly different in favour of Liraglutide 3.0 mg; ETD (liraglutide 3.0 mg vs placebo): Estimate -8.37 [-13.39; -3.34] 95% CI; p-value = 0.0011.

For the endpoint, multiple imputation sensitivity analyses were performed evaluating the robustness of the assumptions about the missing data. The sensitivity analyses supported the robustness of the conclusions for the endpoint.

For the liraglutide 3.0 mg group, the trajectory for percentage body weight change showed reduction from week 0 to week 16 and weight gain was observed from week 16 to week 56, whereas placebo treated participants had stable weight from week 0 to week 8 and weight gain was observed from week 8 to week 56 (Figure 2-4). Although participants had not reduced their weight at the end of treatment compared to baseline in both the treatment groups, participants in the liraglutide 3.0 mg group had gained less weight compared with the placebo group. This may represent a more normalized weight gain that is seen in growing children.



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the confirmatory secondary analysis. Numbers shown in the lower panel are participants contributing to the mean.

nn8022/nn8022-4392-main/csr_20240321_er
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Figure 15 Body weight (%, kg) change from baseline by week - mean plot - treatment policy estimand - full analysis set

- *Subjects achieving ≥5% reduction of BMI From baseline (week 0) to week 56*

At week 56, the observed proportion of participants achieving ≥5% baseline BMI loss was:

- 46.2 % participants in the liraglutide 3.0 mg treatment group
- 8.7 % participants in the placebo treatment group

For the treatment policy estimand, the odds of achieving at least ≥5% baseline BMI loss by week 56 was statistically significantly different in favour of liraglutide 3.0 mg; OR (liraglutide 3.0 mg vs placebo): Estimate 6.27 [1.36; 28.79] 95% CI; p-value = 0.0183.

For the endpoint, multiple imputation sensitivity analyses were performed evaluating the robustness of the assumptions about the missing data. The sensitivity analyses supported the robustness of the conclusions for the endpoint.

Figure 16 shows the range of BMI % change from baseline to week 56 in the liraglutide 3.0 mg group and the placebo group. The majority of participants in the liraglutide 3.0 mg group had a decrease in BMI % as compared to a smaller number of participants who experienced an increase from baseline.

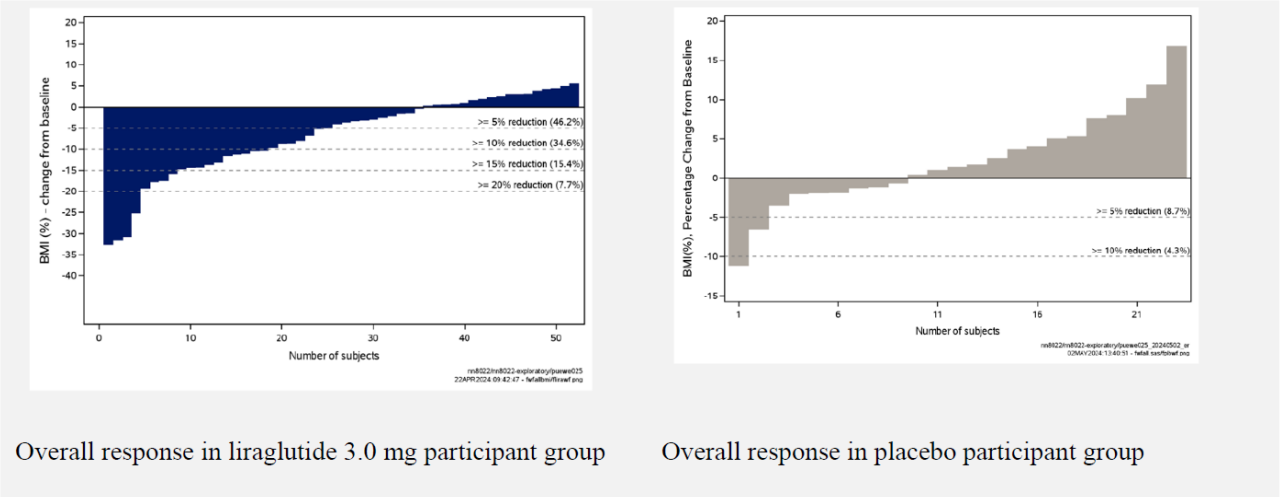


Figure 16 BMI (%) change from baseline - Liraglutide participant response and placebo participant response - waterfall plot - week 56 - full analysis set

Persistence of efficacy week 56 to 82 (off-study-drug follow up period)

During the off-drug follow-up period of 26-weeks (from week 56 to week 82) in the Main phase of Study 4392:

- the body weight (% and in kg) increased from week 56 to week 82 in both the liraglutide 3.0 mg and the placebo group. Change in body weight % was 0.4% (0.1 kg) and 10.2% (7.5 kg) from baseline to week 56 and 10.7% (6.9 kg) and 19% (13.9 kg) from baseline to week 82.
- the number of responders with ≥5% reduction in BMI from week 56 to week 82 decreased in both liraglutide 3.0 mg and placebo group; 46.2% and 29.4 for the liraglutide group and 8.7% and 4.3% for the placebo group.

Although BMI and body weight increase were seen in the liraglutide 3.0 mg group during the off-drug follow-up period of 26-weeks (from week 56 until week 82), the difference between the groups remained comparable at week 56 and week 82.

Overview of the primary and confirmatory secondary endpoints

An overview of the primary and confirmatory secondary endpoints in a statistical test hierarchy in Study 4392 (% BMI change, % body weight change and 5% reduction in BMI responders) is presented in Table 10.

Table 10 Overview of confirmatory analyses (test hierarchy) - treatment policy estimand - full analysis set

Endpoint	Est.	95% CI	p-value	alpha	Hypothesis	Conclusion
Primary endpoint						
BMI (%) change from baseline to week 56						
Lira 3.0 mg - Placebo	-7.4	[-11.56; -3.24]	0.0005	0.05	Superiority	Confirmed
Confirmatory secondary endpoints						
Body weight (%) change from baseline to week 56						
Lira 3.0 mg - Placebo	-8.4	[-13.39; -3.34]	0.0011	0.05	Superiority	Confirmed
Odds of achieving baseline BMI loss >=5% at week 56						
Lira 3.0 mg / Placebo	6.27	[1.36; 28.79]	0.0183	0.05	Superiority	Confirmed

Est: Estimate, alpha: Local significance level, CI: Confidence interval, p-value: Unadjusted two-sided p-value for test of no difference.

Supportive secondary endpoints

The results of the non-confirmatory hypothesis for the supportive secondary endpoints are showed in Table 11.

Table 11 Changes in body weight, BMI SDS, odds of achieving ⩾10% BMI loss, BMI percentage of the 95th percentile, blood pressure, HbA1c and waist circumference

Endpoint	Baseline values		Estimated mean change from baseline on treatment 0		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=56 (52)	Placebo N=26 (23)	Lira 3.0 mg N=56 (52)	Placebo N=26 (23)		
Body weight (kg) at week 56	69.8	71.0	1.10	7.07	-5.97kg [-9.27; -2.67]	0.0004
BMI SDS	3.65	3.87	-0.73	-0.34	-0.40 [-0.60; -0.19]	0.0002
Odds of achieving baseline BMI loss ≥10%			0.78	0.10	8.15 [1.02 ; 65.34]	0.0482
BMI percentage of the 95th percentile:	135.5	138.7	-13.98	-4.01	-9.98 [-15.11; -4.84]	0.0001
Diastolic blood pressure (mmHg):	67	71	-1.19	3.03	-4.22 [-8.43; -0.01]	0.0497
HbA1c (%):	5.4	5.4	-0.17	-0.06	-0.12 [-0.23; -0.00]	0.0433
Change in waist circumference (cm)	94.36	91.39	-2.03	1.34	-3.37 [-9.38; 2.65]	0.2727
Change in systolic blood pressure (mmHg)	113	115	-1.73	1.72	-3.44 [-8.93; 2.04]	0.2184

Exploratory endpoints

The change in HOMA-B, HOMA-IR, LDL, HDL and triglycerides were not statistically significant different between the two groups; the respective estimated treatment ratio (ETR) were 1.01, 0.93, 0.98, 1.05 and 0.93.

Ancillary analyses

The consistency in the treatment effect for the primary endpoint (relative change in BMI) and the two confirmatory secondary endpoints (relative change in body weight and participants achieving ≥5% reduction of BMI) was explored by subgroups based on baseline information for participants in Study 4392. In all subpopulations, the numbers of participants included were low and insufficient to conduct statistical analyses. Therefore, only descriptive statistics are presented, and the results should be interpreted with consideration of these limitations.

Upon review of the data across subpopulations based on age, sex, ethnicity, race, baseline Tanner stage, BMI category, and region (US vs non-US), small variations were noted. Definitive conclusions could not be made as the sample size is limited for the subgroups.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial 4193

Title: Effect and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6 to <12 years: 56-week, double-blind, randomised, placebo-controlled trial.			
Study identifier	NN8022-4392		
Design	A double-blind, randomised, parallel group, placebo-controlled, multi-national clinical study in children, aged 6 to <12 years, with obesity with or without comorbidities.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		56 weeks 12 weeks 26 weeks
Hypothesis	Superiority		
Treatments groups	Liraglutide 3.0 mg		Initial dose: - For children with a body weight ⩾45 kg: 0.6 mg daily for one week - For children with a body weight <45 kg: 0.3 mg daily for one week and increased to 0.6 mg after the first week. Dose escalation for both body weight groups: Increased in weekly steps of 0.6 mg until a dose of 3.0 mg liraglutide/placebo or the individual maximum tolerated dose (MTD) is reached 56 subjects randomised.
	Placebo		Equal to Liraglutide 3.0 mg group 26 subjects randomised.
Endpoints and definitions	Primary endpoint: Relative change in BMI	%	From baseline (week 0) to week 56
	Confirmatory secondary endpoint: Relative change in body weight	%	From baseline (week 0) to week 56
	Confirmatory secondary endpoint: Subjects achieving ⩾ 5% reduction of BMI	Yes/ no	From baseline (week 0) to week 56
Database lock	06 March 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Liraglutide 3.0 mg	Placebo
	Number of subject	56	26
	Change in BMI	-5.80	1.60
		ETD: -7.40 % [-11.56; -3.24], p-value = 0.0005	
	Change in body weight	1.59	9.96
		ETD: -8.37 % [-13.39; -3.34], p-value = 0.0011	
	⩾5% reduction of BMI	46.2	8.7
		OR: 6.27 [1.36; 28.79], p-value = 0.0183	

Analysis performed across trials (pooled analyses and meta-analysis)

An overview of the results of analyses of relative change in BMI in comparison to Study 4180 (adolescents, 12- <18 years) is shown below Table 12.

Change in BMI

The relative change in BMI from baseline to week 56 was the primary endpoint in Study 4392, while it was an exploratory endpoint in Study 4180. Liraglutide 3.0 mg once daily was superior to placebo in relative change in BMI from baseline (week 0) to week 56 in Study 4392 and Study 4180.

Table 12 Comparison of relative change in BMI (%) across Study 4392 and Study 4180

	Study 4392	**Study 4180**
Treatment duration	56 weeks	56 weeks
Age	6 -<12 years	12 -<18 years
No. of participants	82	251
Baseline BMI	31 kg/m^2	35.6 kg/m^2
ETD (95% CI)[a]	-7.40 (-11.56; -3.24)	-4.64 (-7.14; -2.14)
Change in BMI (%) from baseline at week 56	Liraglutide s.c. 3.0 mg: -5.80 Placebo: -1.60	Liraglutide s.c. 3.0 mg: -4.29 Placebo: 0.34

[a]statistically significant vs placebo. Notes: Treatment policy estimand in study 4392: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue medication. J2R MI in study 4180.

Change in body weight

An overview of the results of analyses of relative change in body weight across studies is shown below (

Table 13). Percent change in body weight from baseline (week 0) to week 56 was a confirmatory secondary endpoint in Study 4392 and a supportive secondary endpoint in Study 4180. Percentage change in fasting body weight from baseline (week 0) to week 56 was a primary endpoint in the adult Study 1839.

When comparing body weight %-change between Study 4392 (children) and Study 4180 (adolescents) and Study 1839 (adults), Study 4392 results reported slight weight gain in both liraglutide 3.0 mg group and the placebo group. This could possibly be due to normal growth seen with this age group (6 to <12 years). For this reason, change in body weight (kg) over time was not considered to be the most appropriate measure for improvement in weight management studies. Improvement in BMI% was considered as the primary endpoint to evaluate efficacy of treatment in paediatric population.

Table 13 Comparison of change in body weight (%) across Study 4392, Study 4180, and Study 1839

	Study 4392	**Study 4180**	**Study 1839**
Treatment duration	56 weeks	56 weeks	56 weeks
Age	6 -<12 years	12 -<18 years	>= 18 years

	Study 4392	Study 4180	Study 1839
No. of participants	82	251	3731
Baseline body weight	70.2 kg	100.8 kg	106.0 kg
ETD (95% CI)[a]	-8.37 (-13.39; -3.34)	-5.01 (-7.63; -2.39)	-5.39 (-5.82; -4.95)
Change in body weight (%) from baseline at week 56	Liraglutide s.c. 3.0 mg: 1.6 Placebo: 10.0	Liraglutide s.c. 3.0 mg: -2.65 Placebo: 2.37	Liraglutide s.c. 3.0 mg: -7.98 Placebo: -2.62

[a] Statistically significant vs placebo

Abbreviations: ETD: estimated treatment difference; CI: confidence interval; BW, body weight. treatment policy estimand in study 4392: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue medication. LOCF in study 1839. J2R MI in study 4180.

Achieving ≥5% reduction of BMI

An overview of the results of analyses of participants achieving ≥5% reduction of BMI across studies are shown below

Table 14). Percentage of participants achieving ≥5% reduction in baseline BMI from baseline (week 0) to week 56 was a supportive secondary endpoint in study 4180 and a confirmatory secondary endpoint in study 4392.

Table 14 Comparison of participants achieving ≥5% reduction of BMI across Study 4392 and Study 4180

	Study 4392	Study 4180
Treatment duration	56 weeks	56 weeks
Age	6 -<12 years	12 -<18 years
No. of participants	82	251
Baseline BMI	31 kg/m^2	35.6 kg/m^2
OR (95% CI)[a]	6.27 (1.36; 28.79)	3.31 (1.78; 6.16)
Proportion of participants (%) achieving ≥5% reduction of BMI from baseline at week 56	Liraglutide s.c. 3.0 mg: 46.2 Placebo: 8.7	Liraglutide s.c. 3.0 mg: 43.25 Placebo: 18.73

[a] Statistically significant vs placebo

Abbreviations: CI: confidence interval; BMI: body mass index.

Treatment policy estimand in Study 4392: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue medication. J2R MI in Study 4180.

Clinical studies in special populations

In this trial no subgroup analyses in special populations were performed.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Trial 4392 was a 56 week, double blinded, randomised, placebo-controlled, multi-national clinical study comparing liraglutide 3.0 mg s.c. once daily with placebo in children aged 6 to <12 years with obesity. The main phase of the study included a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-week. The primary endpoint was change in BMI. Although following the EMA guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev. 1) addendum on weight control in children, change in BMI SDS is preferred, BMI is also considered acceptable and in line with the PIP. A randomized treatment period of 56 weeks is considered relatively short, for a drug to be used on a long-term basis. It is acknowledged that there is an open-label extension period of 56 weeks with a safety follow-up phase, however, this is not part of this variation application, but this will be submitted for assessment once it has been completed (second half of 2027).

The BMI inclusion criteria in study 4392 was based on the US gender and age-specific growth charts (CDC.gov). This was agreed in the PIP. However, the adolescent indication refers to IOTF BMI cut-off points for obesity by sex. This results in a large jump in BMI cut-off to meet the indication requirement as a patient transitions from childhood to adolescence (for males from 23.7 to 26.0 and for females from 24.7 to 26.7 kg/m2).

The MAH's rationale for keeping the CDC BMI cut-offs in children (6 to <12 years) is based on the expectation that clinicians working with paediatric patients are familiar with differences in BMI references, and the fact that the study population in the study 4392 exhibited BMIs substantially exceeding the

obesity thresholds, thus, implying that this will also be the case in the patient population to be treated in clinical practice.

It is not ideal to have two different sets of BMI cut-offs in indication statements in the paediatric patient populations, but a solution to replace the CDC BMI cut-offs that was used in the pivotal study 4393 in children 6 to <12 years with IOTF BMI cut-offs in the same age-group may also have some challenges. At this stage it is not clear, what the impact would be on the study results if these were re-analysed based on the IOTF BMI cut-offs.

During the assessment, the MAH provided arguments on expectations towards paediatric clinicians' familiarity with different BMI references and the expectation that the BMIs of the patient population in clinical practice substantially exceeding the obesity thresholds, i.e., regardless of whether the IOTF or CDC BMI reference are used. This was acknowledged and are at least partly agreed. The MAH's proposal may therefore be considered a pragmatic approach to solve the problem of the different sets of BMI cut-offs in indication statements in the paediatric population.

In general, the statistical analyses are acceptable. The statistical analyses in the trial design are based on an intention to treat analysis and 21.4% of the patients in the liraglutide group did not complete treatment.

It is accepted that the starting dose for children <45 kg was reduced to 0.3 mg. It seems that only a total of 5 patients were below 45 kg at baseline and following the proposed SmPC, the indication states a minimum body weight of 45 kg, which is supported. The majority of the subjects could be escalated to liraglutide 3.0mg (89.3%), which is a higher percentage than in the adult and adolescent population. The inclusion criterion on age is 6 to <12 years.

Efficacy data and additional analyses

A total of 92 subjects were screened, of which 82 were randomized (2:1), 56 in the liraglutide group and 26 in the placebo group, this number is quite limited but in agreement with the PIP. Slightly less subjects completed treatment in the liraglutide group (78.6%) compared to the placebo group (84.6%). This is in line with the adolescent study (80.1%).

Not all baseline characteristics were well-balanced between the treatment groups. The mean age at baseline was 10 years. The percentage Hispano or Latino ethnicity was higher in the liraglutide group and white race was higher in the placebo group. BMI class <25 kg/m2 and >=35 kg/m2 was higher in the placebo group compared to the liraglutide group. In the liraglutide group, almost half of the patients had a BMI 30-<35 kg/m2. About 40% of the study population had Tanner stage 1, an additional 40% stage 2-3 and only a minor percentage had stage 4-5, which is logical due to the age group studied. Tanner stage 5 was covered in trial 4180 among adolescents.

Overall, the mean BMI SDS was 3.72, the mean BMI was 31.0 kg/m2 and the mean body weight 70.2 kg, with no significant difference among the two groups. The mean HbA1c was 5.4%, there were no patients with diabetes at baseline.

Primary and confirmatory secondary outcomes – change in BMI, body weight and >5% reduction in BMI

The reduction in BMI was -5.8% for the liraglutide group and +1.6% for the placebo group, the estimated treatment difference (ETD) is -7.8% (95% CI: -11.56; - 3.24). Compared to baseline, subjects in the liraglutide group gained 1.59% weight, placebo group patients gained 9.96%. A total of 46.2% of the

participants reached the endpoint of >5% reduction in BMI in the liraglutide group, compared to 8.7% in the placebo group. This reduction was not maintained during the off-drug period of 26 weeks, this has also been seen in adults and adolescents.

There was a net weight gain, this can be explained by the fact that these children are growing. The gain in weight in the placebo group was significantly higher compared to the liraglutide group. After a period of weight loss (until week 16 of treatment), subjects gained weight up to week 56, to just above baseline. Also in BMI change, there seems to be a time effect, after a steep reduction up to week 16, BMI remained stable. It is clear that not all children responded to treatment with liraglutide. The MAH was therefore requested to include a stopping rule for children in SmPC section 4.1, in line with the agreed stopping rule already in place for the adolescent population i.e.: *Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.*

There is a high incidence of nausea and a significant number of non-completers (21.4%). Weight loss in participants without GI AEs compared to participants with GI AEs was slightly lower (6.1 vs 8.3%), but this was not statistically significant. The effects of liraglutide on weight loss were considered to be largely independent of the GI adverse events.

It was observed that children have higher exposures compared to adults and adolescents (see PK section). The higher plasma exposure seen in children compared to adolescents and adults is not associated with higher frequency of GI events.

Other endpoints
Concerning the non-confirmatory secondary endpoints, all were statistically significant except for waist circumference and systolic blood pressure. BMI SDS change (liraglutide – placebo) was -0.4, body weight increased with 1.1 kg in the liraglutide group, and increased with 7.07 kg in the placebo group, resulting in a net body weight change of -5.97 kg. Although not statistically significant, there was a reduction of -2.03 cm in waist circumference in the liraglutide group, compared to +1.34 cm in the placebo group.

All exploratory endpoints (HOMA-B, HOMA_R, LDL, HDL, triglycerides) were not different between the two groups.

Ancillary analyses were performed for the primary and confirmatory secondary endpoints. There seems to be some difference in the effect for the primary endpoint concerning Tanner stage, however there is not a clear trend.

2.4.3. Conclusions on the clinical efficacy

Taking into account the prevalence of the disease, a total number of 78 subjects is limited, but this is in line with the agreed PIP by PDCO. The primary and confirmatory secondary endpoints showed superiority of liraglutide compared to placebo. Most of the weight-related parameters, BMI, BMI SDS, body weight and waist circumference, showed improvement, although the last one was not statistically significant. Efficacy in children is comparable to that in adults and adolescents. A major limitation of the study results is observed in the responder analysis, where Liraglutide was superior to placebo, with a statistically significant odds ratio of 6.7 in favour of Liraglutide to achieve ≥5% baseline BMI loss, but also reflected that 53% of the Liraglutide treated patients did not achieve ≥5% baseline BMI loss. In the SmPC, it was requested to add a stopping rule in this patient group in line with the stopping rule agreed for the

adolescent population which is already in place in the Product Information. This stopping was included in the Product Information for children.

2.5. Clinical safety

Patient exposure

In total, 92 participants were screened, out of which a total of 82 were randomised 2:1 to treatment, all were exposed to trial product: 56 participants in the liraglutide 3.0 mg group (54.4 patient-years of exposure (PYE), 84.5 patient-years of observation (PYO)) and 26 participants in the placebo group (26.8 PYE, 38.9 PYO).

The mean duration of exposure was comparable between the treatment groups (49.1 weeks in the liraglutide 3.0 mg group and 51.8 weeks in the placebo group, respectively). The total duration of exposure was 2749.0 weeks and 1345.7 weeks respectively for liraglutide 3.0 mg and placebo, respectively.

The majority of participants in the liraglutide 3.0 mg group (50[89.3%]) were escalated to a 3.0 mg dose and remained on the same dose for 88.8% of median time through the 56-weeks treatment period, suggesting that liraglutide 3.0 mg was overall well-tolerated.

In total, 66 (80.5%) participants completed the study treatment (week 56) without permanent discontinuation (treatment completers) of trial product and 74 (90.2%) participants attended the end-of-study visit (study completers). Comparable proportions of participants in both treatment groups completed the treatment (44[78.6%] and 22 [84.6%]) for liraglutide 3.0 mg and placebo, respectively) and the study (55[91.1%] in liraglutide 3.0 mg group; 23[88.5%] in placebo group).

The proportion of participants who permanently discontinued trial product was slightly higher in the liraglutide 3.0 mg group (12 [21.4%]) as compared to the placebo group (4 [15.4%]).

Adverse events

In Study 4392, AEs were summarised by three different periods, that were classified as follows:

- Run-in period (12 weeks): Events with onset date between visit 2 (included) and the first day of trial product administration (not included).
- **'In-trial' period** (82 weeks): Events with onset date between the first day of trial product administration and the last study visit.
- **'On-treatment'** period (56 weeks): Events with onset date between the first day of trial product administration and any of the following date, whichever came first:

a) 14 days after the last day on trial product, or
b) follow-up visit (visit 24) for participants with trial product discontinued, or
c) last study visit (participants withdrawn without follow-up visit)

During 'on-treatment' period, the proportion of participants with AEs was comparable between both the groups (89.3% in liraglutide 3.0 mg group vs 88.5% in placebo group) (Table 15). The reporting rate of AEs was higher in liraglutide 3.0 mg group (801.1 events per 100 PYE) than with placebo group (582.7 events per 100 PYE), driven primarily by a higher reporting of Gastrointestinal adverse events (GI AEs). Most of the AEs reported in the liraglutide 3.0 mg group and placebo group were non-serious and mild or

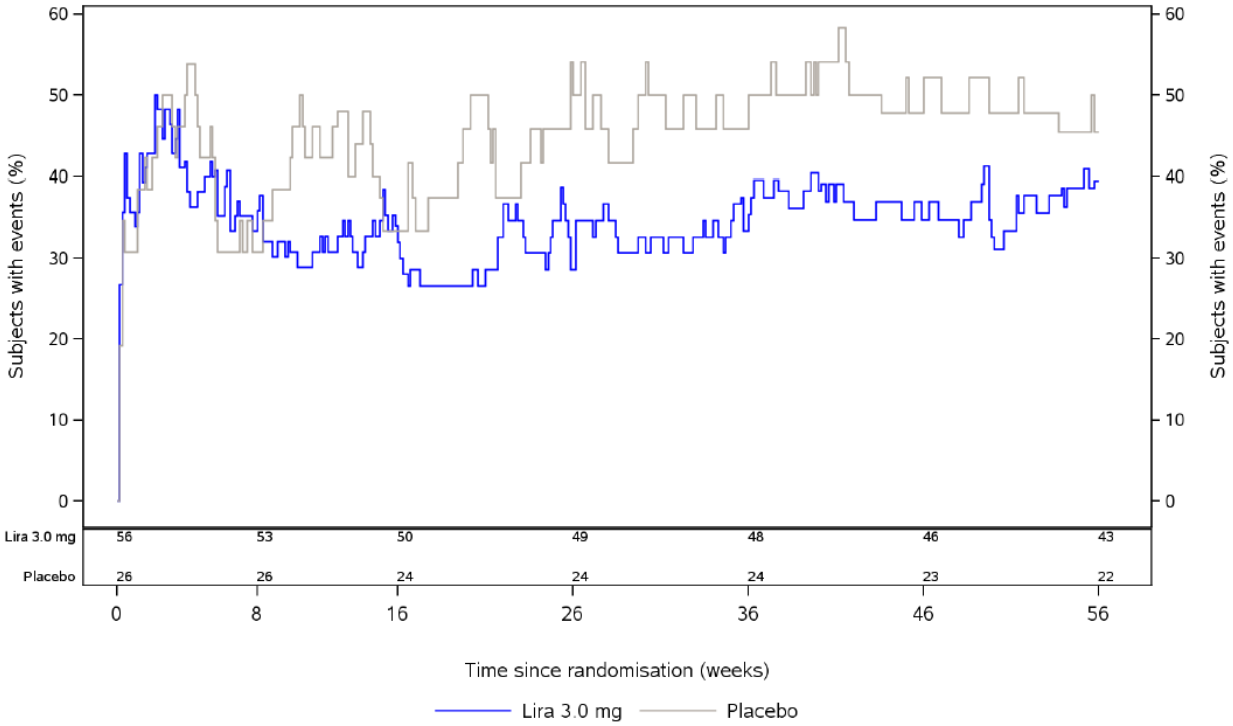
moderate in severity and ‘unlikely’ related to trial products as judged by the investigator. Most participants had recovered by the end-of-Main phase.

Table 15 Adverse events - overview - safety analysis set

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	56				26			
Patient years of exposure (PYE)	54.4				26.8			
Patient years of observation (PYO)	84.5				38.9			
Adverse Events (OT)	50	(89.3)	436	801.1	23	(88.5)	156	582.7
Adverse Events (IT)	51	(91.1)	517	612.1	24	(92.3)	185	475.1
Serious								
Yes (OT)	7	(12.5)	12	22.0	2	(7.7)	2	7.5
Yes (IT)	7	(12.5)	16	18.9	2	(7.7)	2	5.1
No (OT)	49	(87.5)	424	779.0	23	(88.5)	154	575.2
No (IT)	51	(91.1)	501	593.2	24	(92.3)	183	470.0
Severity								
Severe (OT)	1	(1.8)	1	1.8	2	(7.7)	2	7.5
Severe (IT)	1	(1.8)	1	1.2	2	(7.7)	2	5.1
Moderate (OT)	24	(42.9)	90	165.4	12	(46.2)	31	115.8
Moderate (IT)	26	(46.4)	119	140.9	17	(65.4)	43	110.4
Mild (OT)	49	(87.5)	345	633.9	22	(84.6)	123	459.4
Mild (IT)	51	(91.1)	397	470.0	22	(84.6)	140	359.5
Relationship to trial product								
Probable (OT)	30	(53.6)	121	222.3	7	(26.9)	15	56.0
Probable (IT)	30	(53.6)	121	143.3	7	(26.9)	15	38.5
Possible (OT)	34	(60.7)	131	240.7	13	(50.0)	38	141.9
Possible (IT)	34	(60.7)	134	158.7	13	(50.0)	38	97.6
Unlikely (OT)	38	(67.9)	180	330.7	22	(84.6)	102	381.0
Unlikely (IT)	41	(73.2)	256	303.1	23	(88.5)	130	333.9
Missing (OT)	3	(5.4)	4	7.3	1	(3.8)	1	3.7
Missing (IT)	5	(8.9)	6	7.1	2	(7.7)	2	5.1
Outcome								
Fatal (OT)	0				0			
Fatal (IT)	0				0			
Recovered (OT)	48	(85.7)	415	762.5	22	(84.6)	144	537.8
Recovered (IT)	49	(87.5)	477	564.8	23	(88.5)	168	431.5
Recovering (OT)	0				1	(3.8)	1	3.7
Recovering (IT)	1	(1.8)	1	1.2	1	(3.8)	1	2.6
Recovered With Sequelae (OT)	0				0			
Recovered With Sequelae (IT)	0				0			
Not Recovered (OT)	12	(21.4)	21	38.6	8	(30.8)	11	41.1
Not Recovered (IT)	17	(30.4)	39	46.2	11	(42.3)	16	41.1
Unknown (OT)	0				0			
Unknown (IT)	0				0			
Leading to								
Permanent treatment discontinuation (OT)	7	(12.5)	7	12.9	0			
Permanent treatment discontinuation (IT)	7	(12.5)	7	8.3	0			
Temporary interruption of trial product (OT)	5	(8.9)	12	22.0	2	(7.7)	5	18.7
Temporary interruption of trial product (IT)	5	(8.9)	12	14.2	2	(7.7)	5	12.8
Dose reduction of trial product (OT)	17	(30.4)	35	64.3	0			
Dose reduction of trial product (IT)	17	(30.4)	35	41.4	0			

N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years PYO: The duration of the in-trial period in years. PYE: The duration of the on-treatment period in years OT: On-treatment IT: In-trial
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
MedDRA version 26.1

In liraglutide 3.0 mg group, the proportion of participants reporting AEs was highest during week 0 to 8 (dose escalation period) and remained relatively steady between 25% and 40% over the remaining course of the study. For the placebo group, the proportion of participants reporting AEs appeared to fluctuate between 30% and 60% throughout the course of the study (Figure 18).

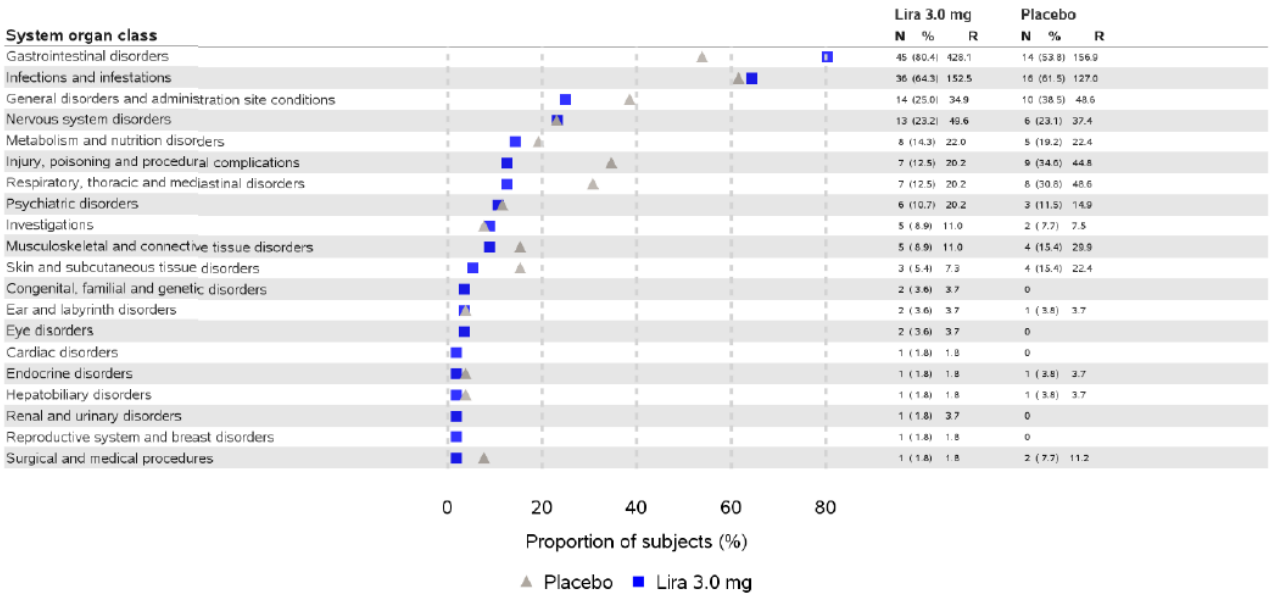


Lower panel: Number of participants at risk.
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
MedDRA version 26.1

Figure 17 Adverse events - prevalence plot - on-treatment - safety analysis set

Common adverse events

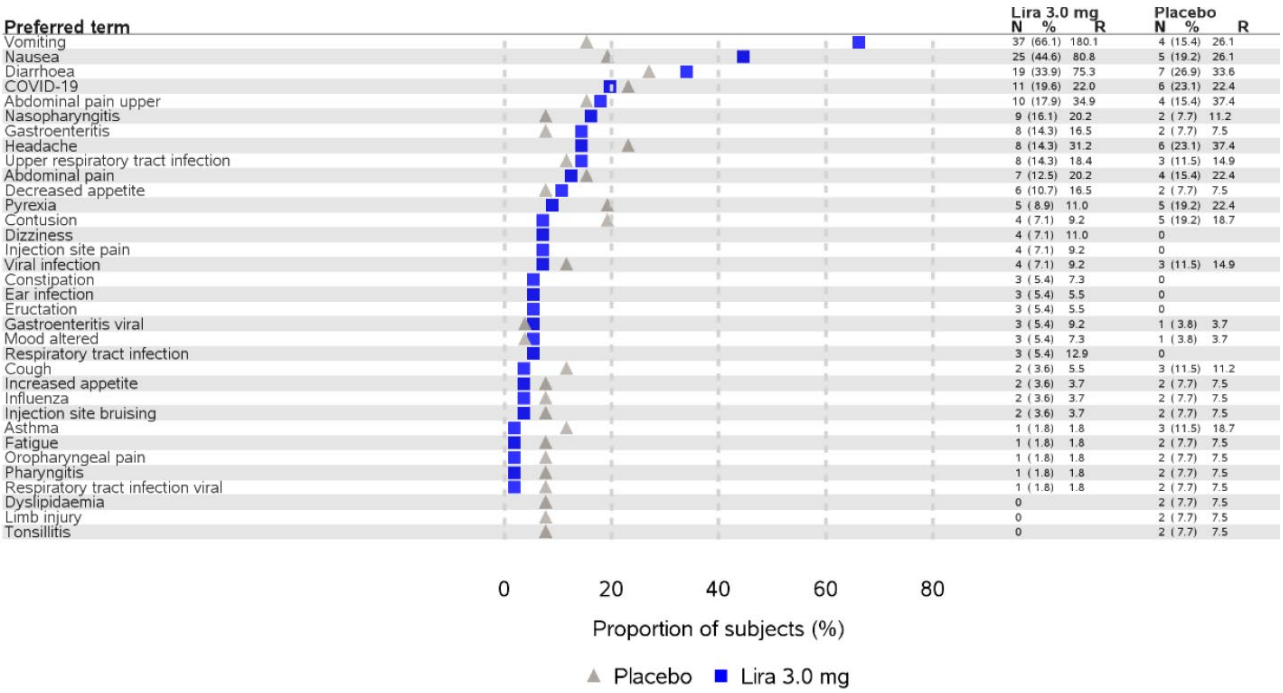
The most frequently reported AEs (reported by ≥5% of participants) during the 'on-treatment' period in the liraglutide 3.0 mg group were from the SOCs 'Gastrointestinal disorders' followed by 'Infections and infestations' (Figure 19). GI disorders were reported by a higher proportion of participants, and at a higher rate, in the liraglutide 3.0 mg group compared to placebo group (80.4%, 428.1 events per 100 PYE vs 53.8%, 156.9 events per 100 PYE, respectively)



N: Number of participants experiencing at least one event. %: Percentage of participants experiencing at least one event. R: Event rate per 100 years
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
Sorted in descending order by system organ class based on the percentage of participants in the Lira 3.0 mg arm experiencing at least one event.
MedDRA version 26.1

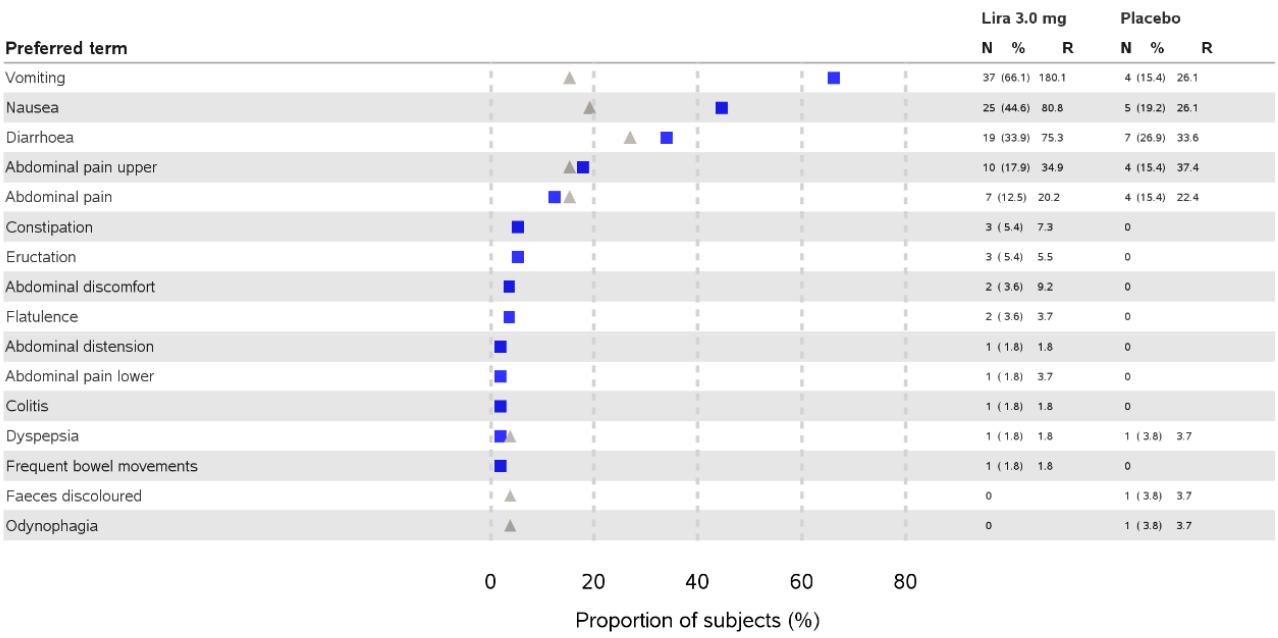
Figure 18 Adverse events by system organ class - summary plot - on-treatment - safety analysis set

Greater proportions of participants reported events of 'vomiting' (66.1%), 'nausea' (44.6%) and 'diarrhoea' (33.9%) in the liraglutide 3.0 mg group than in the placebo group ('vomiting' 15.4%, 'nausea' 19.2%, 'diarrhoea 26.9%) (Figure 20 and Figure 21). Most of the frequently reported AEs (reported by >5% of participants) were non-serious, of mild or moderate severity, 'unlikely' related to trial products as judged by the investigator and most of the events were reported as recovered.



N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, R: Event rate per 100 years
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
Adverse events with preferred terms reported for at least 5% of participants in any arm.
Sorted in descending order by preferred term based on the percentage of participants in the Lira 3.0 mg arm experiencing at least one event.
MedDRA version 26.1

Figure 19 Adverse events by preferred term - most frequent (>=5%) - summary plot - on-treatment - safety analysis set

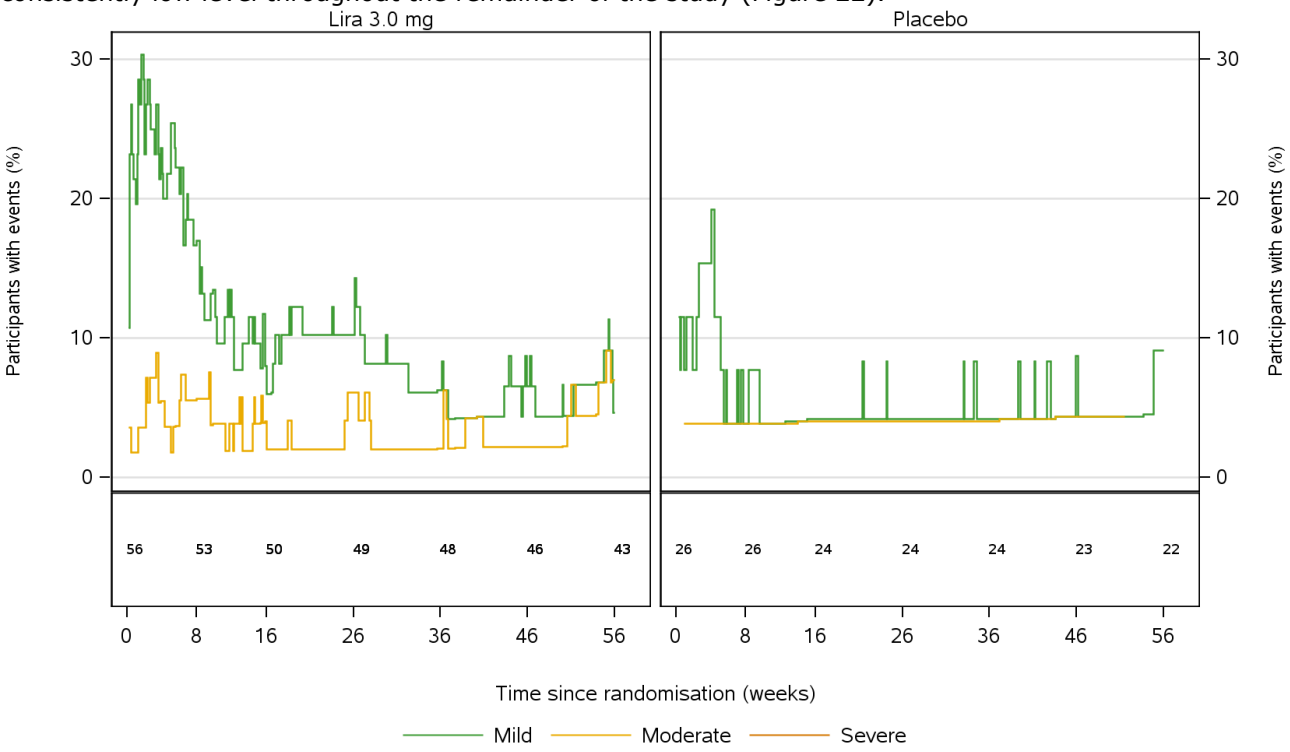


N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, R: Event rate per 100 years
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
Sorted in descending order by preferred term based on the percentage of participants in the Lira 3.0 mg arm experiencing at least one event.
MedDRA version 26.1

Figure 20 Gastrointestinal adverse events by preferred term - summary plot - on-treatment - safety analysis set

Gastrointestinal AEs over time

In the liraglutide 3.0 mg group, most GI AEs were mild in severity and reported during the first 8 weeks of the study (dose escalation), with the prevalence tapering down until week 16 and increasing slightly until week 26. After week 26, the prevalence remained at a consistent low level through the remainder of the study.
In the placebo group, most GI AEs were mild in severity and reported during the first 8 weeks of the trial. This was followed by a steep decrease after week 8 after which the prevalence rate remained at a consistently low level throughout the remainder of the study (Figure 22).



Lower panel: Number of participants at risk.
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
MedDRA version 26.1

nn8022/nn8022-4392-main/csr_20240321_er
02MAY2024:13:28:01 - faeprevalence.sas/faegiprevalot.png

Figure 21 Gastrointestinal adverse events by severity - pre-defined MedDRA search - prevalence plot - on-treatment - safety analysis set

Gastrointestinal events compared to adults and adolescents

The prevalence of vomiting was higher in both the liraglutide 3.0 mg group and placebo group in Study 4392 in comparison with studies in adults (Study 1839) and adolescents (Study 4180) population. However, the ratios of participants reporting AEs of vomiting between the liraglutide 3.0 mg group, and the placebo group were similar (4:1) for the studies 4392 (66.1% and 15.4%) and 1839 (16.3% and 4.1%) and was higher (8:1) in Study 4180 (34.4% and 4.0%). The proportion of participants reporting AEs of diarrhoea was higher in both the liraglutide 3.0 mg group and the placebo group in Study 4392 compared to Study 4180 and Study 1839. The proportion of participants reporting AEs of nausea was similar across the three studies. Overall, a larger proportion of children in both the liraglutide 3.0 mg group and the placebo group reported gastrointestinal (GI) events compared to the liraglutide 3.0 mg and placebo group in Study 4180 and Study 1839. (Table 16)

Table 16 Proportions of participants with reported GI disorders in Study 4392 in comparison with Study 4180 and Study 1839

GI events	Study 4392		Study 4180		Study 1839	
	Liraglutide 3.0 mg	Placebo	Liraglutide 3.0 mg	Placebo	Liraglutide 3.0 mg	Placebo
Vomiting	66.1%	15.4%	34.4%	4.0%	16.3%	4.1%
Diarrhoea	33.9%	26.9%	22.4%	14.3%	20.9%	9.3%
Nausea	44.6%	19.2%	42.4%	14.3%	40.2%	14.7%

Adverse events of special interest

Hepatic events

The proportion and reporting rate of AEs were comparable in the liraglutide 3.0 mg group and the placebo group (3.6%, 3.7 events per 100 PYE vs 3.8%, 3.7 events per 100 PYE). A total of two (2) hepatic events were reported in the liraglutide 3.0 mg group ('hepatomegaly', 'blood bilirubin increased') and one (1) hepatic event ('hepatic steatosis') was reported in the placebo group. All the events were non-serious, mild in severity and were judged as 'unlikely' related to the trial product.

Acute gallbladder disease

One (1) event was reported in the liraglutide 3.0 mg group ('blood bilirubin increased') (1.8%, 1.8 events per 100 PYE) and none was reported in the placebo group. The event of "blood bilirubin increased" was non-serious, mild in severity and was judged as 'unlikely' related to the trial product and was reported as recovered.

Allergic reactions

The proportion of participants reporting allergic reactions was comparable between the liraglutide 3.0 mg group and the placebo group (7.1% and 7.7% respectively). A total of 4 allergic reactions were reported in the liraglutide 3.0 mg group (2 events of 'rash', 'dermatitis allergic', and 'swelling of eyelids') and 2 allergic reactions ('rash' and 'rhinitis allergic') were reported in the placebo group.

Abuse and misuse, suicide and self-injury

One (1) AE of suicide attempt, assessed by investigator as 'unlikely' related to trial product, was reported in the placebo group (3.8%, 3.7 events per 100 PYE) and none was reported in the liraglutide 3.0 mg group.

Serious adverse event/deaths/other significant events

No fatal events were reported in Study 4392.

Serious adverse events

The proportion of participants with SAEs was higher in liraglutide 3.0 mg group (12.5%) than the placebo group (7.7%) and the reporting rates of SAEs were higher in the liraglutide 3.0 mg group (22.0 events per 100 PYE) compared to the placebo group (7.5 events per 100 PYE).

During the 'on-treatment' period, a total of 12 SAEs were reported in seven (7) participants in liraglutide 3.0 mg group:

- five (5) SAEs reported in one (1) participant
- two (2) SAEs reported in one (1) participant
- remaining five (5) SAEs reported in five (5) participants

A total of two (2) SAEs were reported in two (2) participants in the placebo group.

Most of the SAEs reported in the liraglutide 3.0 mg group were mild or moderate in severity. Three (3) SAEs from the SOC 'Gastrointestinal disorders' (two vomiting events and one colitis) were 'probable' and 'possible' related to trial products as judged by the investigator and the remaining SAEs were 'unlikely' related to trial products as judged by the investigator. All of the SAEs in the placebo group were mild in severity and 'unlikely' related to trial product as judged by the investigator. All participants had recovered by the end-of-Main phase in both the groups.

Majority of the SAEs were reported from the SOC 'Gastrointestinal disorders', followed by the events from the SOC 'Nervous system disorders'. The SAEs in both groups were distributed, in low numbers, across several PTs, with no evident clustering except for the SOC 'Gastrointestinal disorders'. Two (2) SAEs ('vomiting', 'epilepsy') were reported in liraglutide 3.0 mg group led to permanent discontinuation of the trial product. One (1) SAE in the liraglutide 3.0 mg group ('vomiting') led to dose reduction of trial product. No SAEs resulted in temporary discontinuation of trial product.

Three (3) of the 14 SAEs were categorised as SUSARs, see Table 17.

Table 17 Reported SUSARs

Participant ID/Case no	Preferred Term	Study date of onset	Onset latency	Severity	Causality	Action	Outcome
Liraglutide 3.0 mg							
307002/869595	Vomiting	05-Nov-2021	9 Study Day	Moderate	Possible	Drug withdrawn	Recovered
450003/922123	Colitis	12-May-2022	44 Study Day	Mild	Probable	Dose not changed	Recovered
453001/1050654	Vomiting	31-Jan-2023	314 Study Day	Mild	Probable	Dose reduced	Recovered

There were two (2) SAEs reported in the run-in period. The two (2) events were classified as severe in severity and the outcome as recovered.

Laboratory findings

No apparent clinically relevant safety findings were identified in relation to haematology, biochemistry, hormones, lipids, or calcitonin.

Anti-liraglutide antibodies

The highest portion of samples testing positive for anti-liraglutide antibodies occurred at week 16, when 5 participants out of 47 (10.6%) analysed were positive for anti-liraglutide antibodies. A total of 7 participants (12.5% of liraglutide treated participants) developed anti-liraglutide antibodies at any time during the study.

The antibody response appeared to decline over time as only one (1) participant was positive for anti-liraglutide antibodies both at week 56 and at week 58. None of the anti-liraglutide antibody positive samples cross reacted with endogenous GLP-1.

The levels of anti-liraglutide antibodies in terms of %B/T were low (range 0.8 - 2.24) in participants who had anti-liraglutide antibodies detected at week 8 to week 58. Both the small number of participants and the low antibody levels preclude drawing a conclusion regarding the effect of the observed immune response.

The lack of anti-liraglutide antibody positive samples at week 82 after 6 months without liraglutide treatment shows that endogenous GLP-1 cannot sustain the antibody response to liraglutide.

Pancreatic enzymes (amylase and lipase)

No participant in both groups had amylase above 3 x ULN. At week 56, the mean amylase levels in the liraglutide 3.0 mg group increased by 10% (to 70 (SD: 32) U/L) whereas the mean levels increased by 1% in the placebo group (to 55 (SD: 32) U/L). The mean level remained below the upper limit for the reference range. No events of acute pancreatitis were reported in this study.

One (1) participant in the placebo group had a lipase level reported as above 3 x ULN at baseline and week 56. During the 'on-treatment' period, at week 56, the mean lipase levels in the liraglutide 3.0 mg group increased by 22% (to 24.0 (SD: 9.6) U/L) whereas the mean levels increased by 3% in the placebo group (to 26.3 (SD: 26.8) U/L). No events of acute pancreatitis were reported from this study.

Vital signs and other observations related to safety

ECG

There were no clinically relevant treatment differences between liraglutide 3.0 mg group and placebo group in shifts in ECG categories and pulse. The majority of participants had normal ECG at baseline which remained normal throughout the study.

Pubertal progression

On review of pubertal progression in children treated with liraglutide 3.0 mg, four female participants aged 8 to 10 years, and a male participant, 10 years of age appeared to have an acceleration in pubertal development during the 56 weeks of on treatment

In the five (5) cases, the bone age was advanced with respect to chronological age by a range of approximately two (2) to four (4) years at baseline. These participants advanced more than one (1) Tanner stage during the 'On-treatment' period (from baseline to week 56). An advancement in bone age is not unexpected in a population of children, especially in females with obesity. Early puberty is also associated with obesity, more commonly in females than in males.

No adverse events related to pubertal development were reported for these participants. None of the four (4) female participants, nor the male participants exhibited 'precocious puberty' while participating in the study. In each case, bone age was accelerated beyond chronological age at baseline and at week 56, consistent with pubertal development

Growth and development

In addition to body measurement, growth and development were evaluated by assessing height SDS, chronological age, bone age, bone metabolism biomarkers, and insulin like growth factor 1. Additionally, hormones including thyroid stimulating hormone (TSH), free thyroxine (free T4), dehydroepiandrosterone sulfate (DHEAS), luteinising hormone (LH), follicle stimulating hormone (FSH), estradiol (females),

testosterone (males), sex hormone binding globulin (SHBG) (males), prolactin, adrenocorticotropic hormones (ACTH), and cortisol were measured in the Study 4392. No apparent clinically relevant findings were observed for these hormones.

No clinically relevant treatment differences were noted in any of the growth and development parameters.

Mental health

At baseline, in liraglutide 3.0 mg group, one (1) participant had changes in the mood and none was reported in the placebo group. One (1) participant was referred to mental health professional.

In the maintenance period, one (1) participant had changes in the mood in both the treatment groups. Three (3) participants had changes in behaviour or school performance in the liraglutide 3.0 mg group and one (1) participant had changes in behaviour or school performance in the placebo group. Two (2) participants from liraglutide 3.0 mg group and one (1) participant from placebo group was referred to a mental health professional.

At week 56, none of the participants reported changes in the mood and none was referred to any mental health professionals in either of the treatment groups.

No apparent clinically relevant findings were observed between groups in mental health evaluations.

Safety in special populations

No new information is available.

Safety related to drug-drug interactions and other interactions

No new information is available.

Discontinuation due to adverse events

Adverse events leading to withdrawal from the study

One (1) participant from placebo group withdrew consent from the study citing the AE (Alopecia) as the reason for withdrawal.

Adverse events leading to permanent trial product discontinuation

A total of six (6) AEs led to permanent discontinuation of trial product in the liraglutide 3.0 mg group (10.7%) and none in the placebo group, see also Table 15. One participant in the liraglutide 3.0 mg treatment group had 'Drug withdrawn' marked as an action for an AE in the associated eCRF. This participant resumed treatment prior to week 56 and completed treatment, however the participant was captured as having permanently discontinued trial product in Trial 4392. Events leading to permanent discontinuation of trial product were mainly due to GI AEs ('nausea', 'diarrhoea', 'vomiting'). The majority of the events were non-serious and mild in severity. Most of the events were assessed as 'possibly' or 'probably' related to the trial product and all had an outcome as recovered.

Out of six (6) AEs that led to permanent discontinuation of trial product, two (2) participants experienced SAEs of 'epilepsy', 'vomiting', which were evaluated by the investigator to be 'unlikely' and 'possibly' related to trial products, respectively.

Table 18 Adverse events leading to permanent trial product discontinuation by system organ class and preferred term - summary - on-treatment - safety analysis set

System organ class Preferred term	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	56				26			
Patient years of exposure (PYE)	54.4				26.8			
Events	7	(12.5)	7	12.9	0			
Gastrointestinal disorders	4	(7.1)	4	7.3	0			
Nausea	2	(3.6)	2	3.7	0			
Diarrhoea	1	(1.8)	1	1.8	0			
Vomiting	1	(1.8)	1	1.8	0			
General disorders and administration site conditions	2	(3.6)	2	3.7	0			
Influenza like illness	1	(1.8)	1	1.8	0			
Injection site pain	1	(1.8)	1	1.8	0			
Nervous system disorders	1	(1.8)	1	1.8	0			
Epilepsy	1	(1.8)	1	1.8	0			

N: Number of participants experiencing at least one event, %: Percentage of participants experiencing at least one event, E: Number of events, R: Event rate per 100 years, PYE: The duration of the on-treatment period in years
Adverse events with onset date during on-treatment period On-treatment period represents the time period in which participants are considered treated with trial product, lasting until 14 days after the last day on the trial product.
Sorted in descending order by system organ class and preferred term based, respectively, on the percentage of participants in the Lira 3.0 mg arm experiencing at least one event.
MedDRA version 26.1

Adverse events leading to temporary discontinuation of trial product

A comparable proportion of participants in the liraglutide 3.0 mg group (12 events in 5 patients (8.9%)) temporarily interrupted treatment with trial product due to AEs compared to the placebo group (5 events in 2 patients (7.7%)). Most of the events in both treatment groups occurred in the SOC 'GI disorders', including 'diarrhoea', and 'vomiting'.

Adverse events leading to dose reduction of trial product

The adverse events leading to dose reduction of trial product were reported in the liraglutide 3.0 mg group (35 events in 17 patients (30.4%)) and none was reported in the placebo group. Most of the events occurred in the SOC 'GI disorders', led by 'vomiting', 'nausea', 'diarrhoea'.

Post marketing experience

The post-marketing safety data for liraglutide received by Novo Nordisk A/S are made available in the PSURs according to the regulatory requirements. More detailed information can be found in the latest submitted PSUR (FDA and EMA: reporting interval 01 January 2021 to 31 December 2023).

2.5.1. Discussion on clinical safety

In this 56-week study, 56 paediatric patients were exposed to liraglutide for a mean duration of 49.1 weeks. The majority of participants in the liraglutide 3.0 mg group (50 out of 56 participants, 89.3%)

were escalated to a 3.0 mg dose and remained on the same dose for 88.8% of median time through the 56 weeks treatment period. In general, the results of study 4392 demonstrated that the safety profile of liraglutide in children was comparable to the safety profile of liraglutide shown in adults and adolescents. However, a period of 56 weeks is relatively short for a drug intended to be used on a long-term basis, mainly in developing children. It is acknowledged that an open-label study of 1 year, followed by 2 years of safety follow-up is currently ongoing. This is mainly important for the unknown clinical relevance of the increase in amylase (please see below).

Adverse events

The proportions of subjects who experienced AEs was comparable between the liraglutide group versus the placebo group (89.3% versus 88.5%, respectively), the reporting rate of AEs in the liraglutide group was although higher (801.1 versus 582.7 events per 1000 PYE), mainly due to gastrointestinal events (nausea, vomiting, diarrhoea).

Adverse events leading to treatment discontinuation of the trial product, during the 'on-treatment' period, were reported in 7 subjects in the liraglutide 3.0 mg group (12.5%) versus 0 subjects in the placebo group. An additional 5 subjects (8.9%) interrupted treatment, and 17 subjects (30.4%) had a dose reduction. The most common AEs that led to trial product discontinuation in the liraglutide 3.0 mg group were GI AE (2 nausea, 1 diarrhoea and 1 vomiting. There were no hypoglycaemic adverse events reported in this study.

Serious adverse events

There was no fatal event during the trial. The proportion of subjects with SAEs, as well as the event rate was higher in the liraglutide group than in the placebo group during, a total of 12 SAE in 7 patients (12.5%) in the liraglutide group compared to 2 SAE in 2 subjects (7.7%) in the placebo group. Concerning the liraglutide group, 3 SAE (all in the SOC GI disorders) were probable or possible related to the trial product.

Gastrointestinal adverse events

The proportion of subjects with AEs within the SOC gastrointestinal disorders, as well as the AE rate, were higher in the liraglutide group compared to the placebo group; 80.4%, 428.1 events per 100 PYE and 53.8%, 156.9 events per 100 PYE, respectively. The incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment, however, also after this period, it was slightly higher compared to placebo until the end of the entire treatment period.

The frequency of vomiting in subjects treated with liraglutide seems very high, also compared to adults and adolescents. However, the proportion of patients on placebo reporting vomiting was also high compared to the other age groups. After correction, the ratio is comparable to adults, therefore, SmPC section 4.8 has been updated to describe that "*Children reported more GI events in both liraglutide and placebo groups compared to adolescents and adults, with a 2-fold increase in vomiting observed in children compared to adolescents".*

Other adverse events

There were no clinically relevant changes from baseline or differences between groups in safety laboratory parameters (haematology, hormones, lipids or calcitonin). However, there was an increase in mean pancreatic enzyme levels, mainly amylase, in the liraglutide group. Although this remained below the upper limits of the reference range and there were no events of acute pancreatitis, the MAH provided upon request, an overview of all the evidence that is currently available from non-clinical toxicology data, clinical and post marketing experience. The data provided was assessed and it does not suggest any adverse or negative effects on the pancreas in children. However, negative effects in the long term cannot be excluded. Therefore, pancreatic safety will be monitored continuously through routine

pharmacovigilance activities, and ADRs within the paediatric population from post-marketing sources will be presented in future PSURs.

A total of 7 subjects developed anti-liraglutide antibodies at some point during the clinical trial. There were no differences in the ranges of change in BMI from baseline between ADA positive and ADA negative participants. Hence, there was no apparent impact of the ADAs on BMI. With respect to safety, only allergic reactions were investigated in relation to antibody status. This is considered acceptable. Allergic reactions were not reported in any of the ADA positive participants.

2.5.2. Conclusions on clinical safety

In general, the results of study 4392 demonstrate that the safety profile of liraglutide in children is comparable to the safety profile of liraglutide shown in adults and adolescents. However, a randomised treatment period of 56 weeks is relatively short for a drug that is intended to be used on a long-term basis. Long term effects in children may be different due to the fact that organs are still in a developmental state.

The incidence of all GI AEs was higher in the liraglutide group than in the placebo group, mainly during the initial 8 weeks of treatment (where the dose is increased). Although the ratio GI AE liraglutide vs placebo is comparable to adults (4:1), the proportion of subjects with GI AE was high.

The MAH will also monitor pancreatic safety in children and report on this safety concern in the upcoming PSURs for the active substance.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

2.6. Risk management plan

The MAH submitted an updated RMP version 34.0 with DLP 31 March 2024 with the initial application, and subsequently an updated RMP version 34.1 during the assessment of the application once a final wording for the indication in children was finally agreed.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 34.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 34.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit−risk)				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities (by the FDA)				
NN2211-3965 MTC registry (MTC-22341) Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Protocol submission	28 May 2010
			Final report	01 Dec 2026

Abbreviations: FDA = U.S. Food and Drug Administration; MTC = medullary thyroid cancer; PRAC = Pharmacovigilance Risk Assessment Committee.

Risk minimisation measures

Safety concern	**Risk minimisation measures**
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None ***Additional risk minimisation measures*** None
Important potential risk	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3.

Safety concern	Risk minimisation measures
Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information *Patients with a history of major depression or other severe psychiatric disorders*	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Concomitant use of other weight lowering products	***Routine risk communication:*** • The lack of data supporting co-administration with other products for weight management is included in Section 4.4 of the SmPC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None

Abbreviations: MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Since the indication, posology and relevant other information is very similar to the information regarding

adults, which passed user testing successfully during the original marketing authorisation application procedure, this is found to be acceptable that no additional user testing was performed. Of note within previous variation II/26 (extension of indication in adolescents aged 12 to 18 years), no additional user testing was performed and this was found to be acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Childhood obesity continues to be a major health problem worldwide with the consequent associated comorbidities that can become apparent at an early age and can increase throughout life. The complications associated with childhood obesity include but are not limited to hypertension, type 2 diabetes mellitus (T2D), early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders, psychological problems, demonstrating a wide range of potentially severe health-related and psychosocial consequences, including a higher risk of disability in adulthood and premature death.

In the past 30 years, childhood obesity has more than doubled in children and tripled in adolescents worldwide. It is a chronic, refractory, and relapsing disease, affecting, approximately 159 million children and adolescents aged between 5 to 19 years. By 2035, the prevalence of childhood and adolescent obesity is predicted to double when an estimated 383 million 5- to 19-year-old children would be living with obesity worldwide. Childhood obesity requires long-term management. With the dramatic rise in the number of children affected by obesity, there is an unmet need of effective methods for the prevention and treatment of childhood obesity.

3.1.2. Available therapies and unmet medical need

Current international treatment guidelines for childhood obesity suggest community/environment-based prevention, behaviour-oriented, and family-centred lifestyle modification as first line treatment and standard of care, with the aim of helping patients adopt healthier eating habits, increase physical activity, and decrease sedentary time. In studies conducted in children and adolescents with obesity, weight loss has been associated with improvements in cardiovascular and metabolic risk factors. As in adults, most children and adolescents with obesity, especially those with severe obesity, struggle to achieve, and maintain, weight loss.

A staggered approach of increasing treatment intensity is often recommended. The stages range from prevention to structured lifestyle changes (diet and exercise counselling) and can progress to tertiary care intervention with multidisciplinary teams, potentially including pharmacotherapy and surgery. Use of bariatric surgery has been primarily restricted to adolescents with unsuccessful weight loss and comorbidities after implementation of lifestyle modifications and/or pharmacotherapy.

Weight loss surgery is however safe and effective for paediatric patients in comprehensive metabolic and bariatric surgery settings that have experience working with youth and their families. However, data on surgical interventions in younger patients are limited. To date, there remains a treatment gap for children and adolescents who have failed lifestyle modifications but do not meet criteria for bariatric surgery.

Pharmacotherapy may serve as a valuable adjunct to lifestyle modification for children and adolescents with obesity or who are overweight. Pharmacotherapy has the potential to help this population to achieve and to sustain clinically relevant weight loss, as well as to improve or prevent comorbid conditions and facilitate a healthier lifestyle.

Currently, the GLP-1 RA semaglutide 2.4 mg (Wegovy) and liraglutide 3.0 mg (Saxenda) are available for the management of obesity in the paediatric population aged ≥12 years. Setmelanotide is approved by the EMA for the treatment of monogenetic obesity for patients aged 2 and older. However, there are no pharmacotherapies approved for weight management in young children with general obesity below the age of 12 in either the EU or the USA.

3.1.3. Main clinical studies

Trial 4392 was a 56 week, double-blind, randomised, placebo-controlled, multi-national clinical study comparing liraglutide 3.0 mg s.c. once daily with placebo in children aged 6 to <12 years with obesity (defined as BMI ≥95th percentile on gender and age-specific CDC growth charts). The main phase of the study included a 2-week screening, 12-week run-in and a 56-week treatment period with an off-drug follow-up period of 26-weeks. The primary endpoint was relative change in BMI from baseline (week 0) to week 56.

A total of 92 subjects were screened, of which 82 were randomized (2:1), 56 in the liraglutide group and 26 in the placebo group. A total of 78.6% completed treatment in the liraglutide group (78.6%) compared to the placebo group (84.6%).

The starting dose and dose escalation were similar to those in adults and adolescents (0.6 mg), except for children with a body weight at baseline <45 kg. The majority of the subjects could be escalated to liraglutide 3.0mg (89.3%), which is a higher percentage than in the adult and adolescent population.

The mean age at baseline was 10 years. There were slightly more male subjects (53.7%) than female subjects (46.3%), with a comparable distribution in both treatment groups. At baseline, the mean body weight was 70.2 kg and the mean BMI was 31 kg/m2. The mean waist circumference was 95.32 cm. The mean BMI SDS at baseline was 3.72. Overall, the mean HbA1c was 5.4%.

3.2. Favourable effects

BMI

Treatment with liraglutide led to a reduction BMI from baseline to week 56 of -5.8%. This reduction did not sustain during the 26-week follow-up period. In the placebo group, BMI increased with 1.6% after 56-weeks. The treatment difference between the active treatment and placebo group was -7.8% (95% CI: -11.56; -3.24).

Other endpoints

Compared to baseline, subjects in the liraglutide group gained 1.59% weight, placebo group patients gained 9.96%, the estimated treatment difference for relative change in body weight was -8.37% (95% CI: [-13.39; -3.34]. A total of 46.2% of the participants reached the endpoint of ≥5% reduction in BMI in the liraglutide group, compared to 8.7% in the placebo group.
Concerning the non-confirmatory secondary endpoints, all were statistically significant except for waist circumference and systolic blood pressure. BMI SDS change (liraglutide – placebo) was -0.4, body weight increased with 1.1 kg in the liraglutide group, and increased with 7.07 kg in the placebo group, resulting in a net body weight change of -5.97 kg.

All exploratory endpoints (HOMA-B, HOMA-R, LDL, HDL, triglycerides) were not different between the two groups.

3.3. Uncertainties and limitations about favourable effects

Not all children responded to treatment with liraglutide (i.e. 53% of the Liraglutide treated patients did not achieve ≥5% baseline BMI loss). Therefore, the data suggest that introducing a stopping rule (i.e. 12 weeks and at least 4% loss of BMI/ BMI SDS) is necessary in order to select patients that benefit most from the treatment and protect others from unnecessary long-term treatment. The MAH was requested during the assessment of this procedure to include a stopping rule which stipulates that the treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose. This stopping rule was added to the Product Information and is aligned with the stopping rule for the adolescents which is already in place in the Product Information.

The reduction in BMI stabilised after 16 weeks of treatment and there was a small weight gain during the trial period of 56 weeks with liraglutide. This can be explained since these children are still growing. Since the randomized treatment period was only 56 weeks, it is not known if this effect of slower weight gain remains during several years of treatment. In order to assess the maintenance of this observed effect, it is of utmost relevance that the MAH submits the (interim) data of the open-label study, after the open-label part has ended (i.e. an interim analysis before the two-year safety follow-up has ended).

The pharmacokinetics data show that children have higher exposure compared to adults and adolescents, mainly as a result of a lower weight. For adolescents, a minimum body weight of 60 kg is included in the indication, the current proposed indication for children is a body weight ≥45 kg.

3.4. Unfavourable effects

Adverse events were common, both in the liraglutide group and the placebo group (89.3% versus 88.5%, respectively). As it was expected, the SOC mostly affected was gastrointestinal disorders. The proportion of subjects with AEs within the SOC gastrointestinal disorders was 80.4% (428.1 events per 100 PYE) and 53.8% (156.9 events per 100 PYE) for the liraglutide and the placebo group, respectively. Of the GI events, the frequency of vomiting was highest, being 66.1% in the liraglutide group, compared to 15.4% in the placebo group. SmPC section 4.8 has been updated to specify that children reported more GI events in both liraglutide, and placebo groups compared to adolescents and adults, with a 2-fold increase in vomiting observed in children compared to adolescents.

The proportion of subjects with serious adverse events was slightly higher in the liraglutide group (12.5%) compared to the placebo group (7.7%). There was no fatal event during the trial.

A total of 7 patients discontinued treatment in the liraglutide group. An additional 5 subjects (8.9%) interrupted treatment, and 17 subjects (30.4%) had a dose reduction. The most common AEs that led to trial product discontinuation in the liraglutide group were GI AEs.

There was an increase in mean pancreatic enzyme levels. Amylase increased by 10% in the liraglutide group, whereas the mean levels increased by 1% in the placebo group. No events of acute pancreatitis were however reported in this study.

A total of 7 subjects developed anti-liraglutide antibodies at some point during the clinical trial.

There were no hypoglycaemic adverse events reported in this study

3.5. Uncertainties and limitations about unfavourable effects

A randomised treatment period of 56 weeks is relatively short for a medicine that is intended to be used on a long-term basis. Long term effects in children may be different due to the fact that organs are still in a developmental state.

Taking this into account, the clinical relevance of pancreatic (amylase) enzyme elevations with liraglutide is considered unknown at this stage, but long-term negative effects on the pancreas may be serious, especially when liraglutide is started in paediatric subjects with a developing pancreas. With respect to pancreatic safety, the MAH was requested to provide during the assessment of this procedure, an overview of all available evidence from non-clinical toxicology data, clinical and post marketing experience on pancreatic safety of liraglutide in children. The data provided and assessed does not suggest any adverse or negative effects on the pancreas in children. However, negative effects in the long term cannot be excluded, therefore, the MAH will monitor pancreatic safety in children via routine pharmacovigilance activities and continuously report on this safety topic in the upcoming PSURs for the active substance.

There were no differences in the ranges of change in BMI from baseline between ADA positive and ADA negative participants. Hence, there was no apparent impact of the ADAs on BMI. With respect to safety, only allergic reactions were investigated in relation to antibody status, which is considered acceptable. Allergic reactions were not reported in any of the ADA positive participants.

3.6. Effects Table

Table 19 Effects Table for Saxenda for weight management in childeren (data cut-off: March 2024)

Short description	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects			
BMI Change from baseline at week 56 [%]	-5.80	1.6	ETD -7.40% [-11.56; -3.24], p-value = 0.0005
Body weight Change from baseline at week 56 [%]	1.59	9.96	ETD: -8.37% [-13.39; -3.34], p-value = 0.0011
[%] subjects achieving ≥ 5% BMI reduction	46.2	8.7	OR: 6.27 [1.36; 28.79], p-value = 0.0183
Unfavourable Effects			
AE On treatment period, % (R)	89.3 (801.1)	88.5 (582.7)	Difference in event rate primarily driven by GI AEs
GI AE On treatment period, % (R)	80.4 (428.1)	53.8 (156.9)	Difference in event rate primarily driven by vomiting
SAE On treatment period, % (R)	12.5 (22.0)	7.7 (7.5)	Except for vomiting (N=3), no clustering in preferred term within SOC (all N=1)
Death On treatment period, n	0	0	

Abbreviations: AE, adverse event; BMI, body mass index; ETD, estimated treatment difference; GI, gastrointestinal; N, number of subjects; OR, odds ratio; R, events per 100 patient years of exposure; SAE, serious adverse event; SOC, system organ class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH proposes an extension of indication of liraglutide in children from 6 to less than 12 years of age, with obesity (defined as BMI ≥95th percentile for age and sex), in adjunct to diet and exercise. Currently, there is no pharmacotherapeutic option for children with obesity available for those who fail on lifestyle interventions.

The primary as well as the confirmatory secondary endpoints (change in BMI (%), change in body weight (%) and ≥5% BMI reduction) showed superiority of liraglutide compared to placebo. Estimated treatment difference for change in BMI was -7.4%, change in body weight was -8.37% and the odds ratio for ≥5% BMI reduction was 6.27 (46.2% achieved this endpoint in the liraglutide group). During the 26-week follow-up period, a small net increase in body weight was seen in the liraglutide group, which could be explained by the fact that children are still growing, which is supported by a larger increase in body weight in children on placebo. It is not known if this effect of slower weight gain remains during several years of treatment.

The maximum effects were reached after 12-16 weeks of treatment. Not all children responded to treatment with liraglutide (i.e. 53% of the Liraglutide treated patients did not achieve ≥5% baseline BMI loss). Therefore, the data suggests that introducing a stopping rule (i.e. 12 weeks and at least 4% loss of BMI/ BMI SDS) is considered necessary in order to select patients that benefit most from treatment and protect others from unnecessary long-term treatment. This stopping rule takes into account possible effects of growth, and it is in line with the stopping rule already in place for liraglutide in the adolescent population. The SmPC has been updated in section 4.1 to introduce this stopping rule for children as such: *Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose.*

The exposure in children is slightly higher compared to adults. Nevertheless, a great majority (89.3%) could be escalated to the intended dose of 3.0 mg liraglutide. The most common adverse events observed during the trial were, as expected, gastrointestinal events. The 2-fold increase in vomiting as compared to adolescents in Study 4392 has been introduced in the SmPC section 4.8 as such: *Children reported more GI events in both liraglutide and placebo groups compared to adolescents and adults, with a 2-fold increase in vomiting observed in children compared to adolescents.*

A double-blind, randomised treatment period of 56 weeks is relatively short for a medicine that is intended to be used long-term. Long term effects in children may be different from adults due to the fact that their organs are still in a developmental state. Despite an increase in mean pancreatic enzyme levels observed in the trial, all available evidence provided by the MAH on pancreatic safety in children and assess during the procedure does not suggest any adverse or negative effects on the pancreas in children. However, negative effects in the long term cannot be excluded. Therefore, the MAH will monitor pancreatic safety in children via routine pharmacovigilance activities and continuously report on this safety topic in the upcoming PSURs for the active substance.

Appropriate use of pharmacotherapy requires specific expertise in the use of these drugs, ongoing intensive lifestyle treatment and close follow-up. It is considered of utmost important that treatment with liraglutide in children should be initiated by a physician experienced in the management of overweight/obesity in children. This requirement has been clearly added in SmPC section 4.2: *Liraglutide in children should be initiated by a physician experienced in the management of obesity in children.*

3.7.2. Balance of benefits and risks

Based on the assessment of the final results of Study 4392, and with the introduced updates to the SmPC including the requirement for a stopping rule in children, that liraglutide in children should be initiated by a physician experienced in the management of obesity in children, and the requirement to monitor pancreatic safety in children in the upcoming PSURs, the B/R balance of liraglutide in children from 6 to less than 12 years of age is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of liraglutide is positive.

The following measures are considered necessary to address issues related to pharmacology:

- Bioanalytical report for Study 4392 along with the extension phase CSR will be submitted in the second half of 2027 as a Post Authorisation Measure
- Final ADA report for Study 4392 along with the extension phase CSR will be submitted in the second half of 2027 as a Post Authorisation Measure.

In addition, the MAH will monitor pancreatic safety in children via routine pharmacovigilance activities and report of this safety concern in the upcoming PSURs for the active substance.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the use of SAXENDA for weight management in children from the age of 6 years to less than 12 years based on results from study NN8022-4392; this is a 56-week, double-blind, randomised, placebo-controlled study investigating safety and efficacy of liraglutide on weight management in children with obesity aged 6 to <12 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the text of the previously agreed indication in adolescents (12-18 years) has been updated in section 4.1 to add a link between the BMI cut-off points used and the related study. Versions 34.0, 34.1 of the RMP have also been submitted and version 34.1 of the RMP was approved.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0468/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Saxenda is not similar to Imcivree within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion.