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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Saxenda

liraglutide

Procedure no: EMEA/H/C/003780/P46/016

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations:

ACTH	adrenocorticotropic hormone
AE	adverse event
AUC_{0-24h}	area under the liraglutide concentration curve from 0-24 hours
BG	blood glucose
BMI	body mass index
BW	body weight
CEA	carcinoembryonic antigen
CL/F	apparent clearance
C_{trough}	plasma concentration immediately prior to dosing
CV	coefficient of variation in %
DHEAS	dehydroepiandrosterone sulphate
ECG	electrocardiogram
FDA	US Food and Drug Administration
FAS	full analysis set
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GLP-1	glucagon-like peptide-1
IGF-1	insulin-like growth factor 1
LDL	low density lipoprotein
LH	luteinizing hormone
PD	pharmacodynamics(s)
PDCO	The Paediatric Committee in EU
PK	pharmacokinetic(s)
PIP	paediatric investigation plan
SAS	safety analysis set
SD	standard deviation
TEAEs	treatment emergent adverse events
TSH	thyroid stimulating hormone
T2DM	type 2 diabetes mellitus
T4	thyroxine
US	United States of America

1. Introduction

The MAH submitted a completed paediatric study for Saxenda to assess, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in obese children aged 7 to 11 years, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Trial NN8022-4181 is part of the PIP (EMEA 000128-PIP02-09) for Saxenda®, liraglutide 3 mg for weight management. The PIP comprises 7 studies (one quality study, one nonclinical study and 5 clinical trials) and is scheduled to be completed in 2023. Trial NN8022-4181 (hereafter referred to as trial 4181) is the second of the 5 planned paediatric clinical trials to be completed. This trial investigates the safety, tolerability and PK of liraglutide at doses up to 3.0 mg in children with obesity (7−11 years and Tanner stage 1) over 7 weeks of treatment (with option to prolong treatment to 13 weeks) prior to the initiation of a longer-term trial investigating the efficacy and safety of liraglutide 3.0 mg in young children with obesity.

These data are also submitted as part of the post-authorisation measures. A waiver for the paediatric populations 0-2 years and 2-5 years of age was granted and a deferral for the trials in the age groups of 6-11 years and 12-17 years. The Agency's decision was agreed on 11 May 2012 (EMA/PDCO/266178).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that trial NN8022-4181 is part of a paediatric investigation plan (PIP) for Saxenda® 3 mg. The extension application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by 2023. A line listing of all the concerned studies is annexed. (Table 1)

Table 1. Overview of planned and completed paediatric clinical trials

Study number	Type of study	Timing
Trial 1 (3967; completed)	Tolerability/ pharmacokinetics in 12-17 year old children with primary obesity, Tanner stage 2-5	26-05-2014
Trial 2 (4180; ongoing)	Efficacy/ safety in 12-17 year old children with primary obesity, Tanner stage 2-5	08-2019
Trial 3 (4181; completed)	Tolerability/ pharmacokinetics in 7-11 year old children with primary obesity, Tanner stage below 2 with premature adrenarche	13-04-2017
Trial 4 (4179; ongoing)	Efficacy/ safety in obese children with Prader Willi Syndrome.	08-2020
Trial 5 (planned)	Safety/ tolerability and efficacy in 6-11 year old children with primary obesity. Tanner stage below 2 and children with premature adrenarche.	08-2023

2.2. Information on the pharmaceutical formulation used in the study

Liraglutide is a long-acting analogue of GLP-1. Liraglutide has been shown to stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, thereby improving fasting and

postprandial glycaemia. The weight-reducing effect of liraglutide largely follows from influence on appetite regulation (fullness, satiety, hunger and prospective food consumption), which leads to lowering of caloric intake. Liraglutide has been approved as an adjunct to diet and exercise for adult weight management in the US in December 2014 and has since received marketing authorisation in other countries and regions, including the EU in 2015.

Liraglutide should be administered once-daily by subcutaneous injection. The formulation of liraglutide used in trial 4181 was the same as that used in clinical trials in adults. Liraglutide (6.0 mg/ml) was provided in a prefilled device (Novo Nordisk FlexPen® pen injector) and was self-administered by the subjects or with assistance from subjects parents or representative. The placebo product contained the same excipients as liraglutide 6.0 mg/mL, 3 mL cartridge, but without the active ingredient, liraglutide. Liraglutide and placebo were supplied in similar 3 mL FlexPen® devices and were visually identical.

All excipients in the liraglutide formulation are considered suitable for the paediatric/adolescent population.

2.3. Clinical aspects

The MAH submitted a final report for:

- Trial NN8022-4181, A randomised, double-blind, placebo-controlled trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in obese children aged 7 to 11 years.

2.3.1. Clinical study

Description

This was a multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and tolerability and pharmacokinetic (PK) properties of liraglutide treatment in children with obesity. A total of 24 children, 7-11 years of age and at Tanner stage 1 were randomised 2:1 to treatment with either liraglutide or placebo. After a screening visit, the subjects entered a 7 week treatment period with 6 optional flex weeks (one flex week between each of the 7 treatment weeks). A flex week on an unchanged or lowered dose was included in case the dose escalation criteria were not met at the end of a mandatory treatment week. Subjects attended a follow-up visit 10-17 days after the last dose.

Treatment with liraglutide (or the corresponding volume of placebo) was administered by subcutaneous injections according to a dose-escalation schedule starting at a dose of 0.3 mg/day. The dose was then gradually increased in weekly steps of 0.3 mg to a maximum dose of 3.0 mg/day. If during dose-escalation the higher dose was not tolerated, the dose could be reduced (or kept at the same dose) and the subject could stay on the dose the remainder of the trial (see Figure 1).

Additionally, there were 6 optional flex weeks (one flex week between each of the treatment weeks). Therefore, the treatment period could be prolonged up to 13 weeks in case a flex week was needed between all 7 treatments.

Safety and tolerability was assessed during the entire trial. PK blood sampling for C_{trough} assessments to investigate dose proportionality was performed prior to the subjects taking their daily dose of liraglutide or placebo at visits 3 to 8. In addition, PK blood sampling for population PK analysis (modelling) was performed after the last dose administration according to the specific sampling scheme.

Methods

Objectives

Primary objective:

- To assess the safety and tolerability of multiple once-daily doses of liraglutide at doses up to 3.0 mg in obese children aged 7-11 years and at Tanner stage 1.

Secondary objectives:

- To assess the pharmacokinetics of liraglutide in steady state at doses up to 3.0 mg in obese children aged 7-11 years and at Tanner stage 1
- To assess the pharmacodynamics of liraglutide in steady state at doses up to 3.0 mg in obese children aged 7-11 years and at Tanner stage 1

Study design

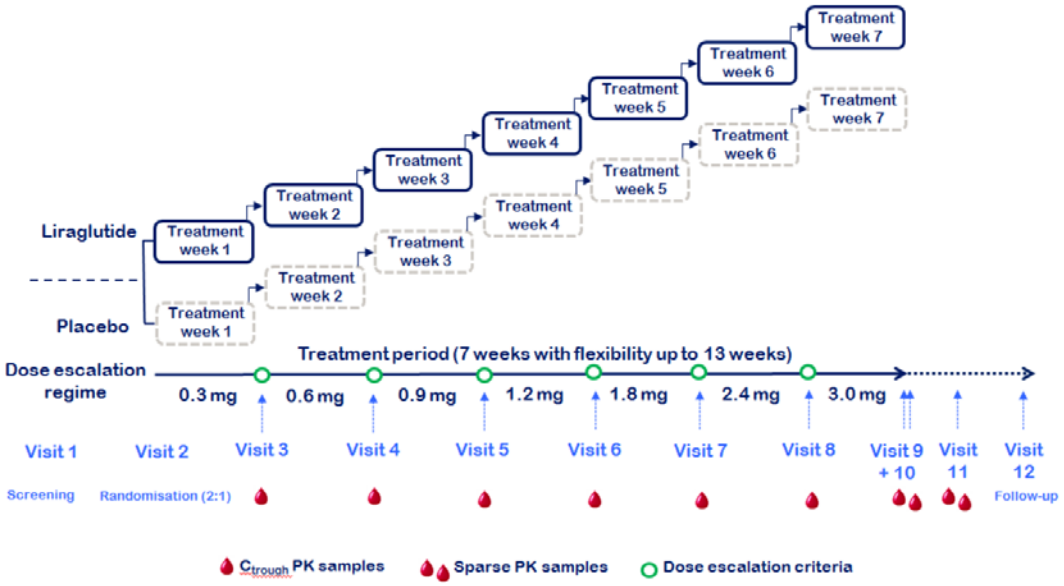


Figure 1. Study design

Study population /Sample size

A sample size of 11 subjects on active treatment (liraglutide) and 4 on placebo was considered sufficient to evaluate safety and tolerability as well as make appropriate assessments of PK endpoints. In order to account for drop-outs, it was planned to randomise 14 subjects to active treatment and 7 subjects to placebo; thus a total of 21 subjects were planned for enrolment into the trial.

Paediatric subjects from the age of 7 to 11 years (both inclusive) and at Tanner stage 1 (pre-pubertal), including children with premature adrenarche (development of pubic hair without the child having entered true puberty), were the target population for this trial. The lower age boundary of 7 years was set in accordance with the requirement from the FDA to the lower age for this paediatric population in clinical trials for weight management. The combination of age and Tanner staging was used in the trial population selection due to the variability in the onset of normal pubertal development and in agreement with the Paediatric Committee in EU (PDCO).

The key inclusion criteria were:

- Male or female subjects 7-11 years of age (both inclusive) at the time of signing informed consent
- Tanner stage 1 (including subjects with premature adrenarche) at the time of signing informed consent
- BMI corresponding 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 gender at the time of signing informed consent

The key exclusion criteria:

- Subjects with secondary causes of childhood obesity (i.e., hypothalamic, genetic or endocrine causes)
- Subjects with confirmed bulimia nervosa disorder
- Diagnosis of DM type 1 or type 2 as defined by HbA1c ≥6.5%
- Subjects with Tanner stage 2-5 (except subjects with premature adrenarche) at the time of screening
- History of pancreatitis (acute or chronic)
- Presence of severe co-morbidities as judged by the investigator
- Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
- History of major depressive disorder within 2 years before randomisation

Treatments

Treatment with liraglutide (or the corresponding volume of placebo) was initiated with 0.3 mg liraglutide daily for one week and increased in weekly steps, with 6 optional flex weeks (one flex week between each of the treatment weeks) until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose. The dose was not escalated if the subject had had fasting plasma glucose below 3.1 mmol/L (56 mg/dL) or below 3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia in the previous week. Additionally, the dose was not escalated if the previous dose was not tolerated with respect to AEs, as judged by investigators. For subjects who could not comply with the dose escalation criteria, the current dose was maintained for another week or the dose was lowered. The treatment period was 7 weeks with option to prolong up to 13 weeks in case a flex week was needed between all 7 treatments.

Outcomes/endpoints

The primary endpoint was:

- Number of treatment emergent adverse events (TEAEs) recorded from the time of first dosing and until completion of follow-up visit

The supportive secondary safety endpoints were:

- Number of treatment-emergent hypoglycaemic events from time of first dosing and until completion of follow-up visit
- Change from baseline to end of treatment in physical examination
- Change from baseline to end of treatment in vital signs (blood pressure and pulse)
- Change from baseline to end of treatment in laboratory tests:
  - Haematology, biochemistry, urinalysis
  - Calcitonin, amylase, lipase
  - Lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides

  - Hormones: IGF-1, TSH, free T4, DHEAS, LH, FSH, CEA, cortisol, ACTH, estradiol (for females only) and testosterone (for males only)
- Change from baseline to end of treatment in ECG
- Incidence of anti-liraglutide antibody at follow up

Pharmacokinetics

The secondary pharmacokinetic endpoints were:

- C_{trough} during dose escalation
- CL/F at steady state following the last dose
- AUC_{0-24h} at steady state following the last dose

Pharmacodynamics

The secondary exploratory PD endpoints were:

- Change from baseline to end of treatment in BMI z-score
- Change from baseline to end of treatment in body weight
- Change from baseline to end of treatment in fasting plasma glucose, serum insulin and HbA1c

CHMP comment:

The secondary exploratory PD endpoints are acceptable. The BMI z-score represents a measure of weight, adjusted for height, sex, and age, relative to a reference distribution.

At the randomisation visit (visit 2), the subjects and their parent(s) or representatives were instructed in the symptoms and treatment of hypoglycaemia and how to measure blood glucose. The subjects and their parent(s) or representatives were instructed to measure the subject's blood glucoseconcentration in case of symptoms of hypoglycaemia and to record the episode in the subject's diary.
However, the glucose measurements during the trial were performed with a glucometer by the subject. From glucometers it is known that they show a wide variability in glucose measurements and most often they measure capillary glucose, which may differ from whole blood or plasma glucose measurements.

Statistical Methods

Full analysis set (FAS) – all subjects who were randomised and who received at least one dose of trial product. In exceptional cases, subjects could have been eliminated from the FAS. In such cases the elimination was to be justified and documented. Subjects contributed to the evaluation 'as treated'. The Safety analysis set (SAS) is identical to the FAS.

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

Changes in BMI z-score and body weight were analysed in a linear model with treatment as a fixed factor with two levels (active or placebo) and baseline values as covariate. Treatment difference was estimated with 95% CI.

CHMP comment:

The proposed analysis sets are considered acceptable for a trial aimed at safety/tolerability, PK and PD. Safety and tolerability will assessed using summary statistics and changes in BMI z-score will be tested using a linear model, which is acceptable. However it is not clear how patients withdrawing from the trial will be handled in the PD analysis. From the results it appears the PD analyses were based on observed cases and thus more using a per protocol analysis set. Nevertheless, since this concerns secondary exploratory endpoints this can be acceptable.

Pharmacokinetic modelling

The objective of the analysis is to study the liraglutide exposure in obese children aged 7 to 11 years and to investigate the effects on liraglutide plasma concentrations of pre-specified covariates for these subjects. A previously developed population PK model for liraglutide will be used. For the PK model, the CL/F will be estimated, while other model parameters may be set to prior pre-defined estimates (based on data from other trials in other populations). AUC_{0-24h} in steady state will be derived from CL/F. The covariates of interest, such as body weight, sex and age group (children/adolescent/adult), will be tested on CL/F. The mean (95% CI) estimate for CL/F and AUC_{0-24h} for each age group will be reported. Data from all 3 trials was included, trial 4181 children with obesity aged 7-11, trial 3967 adolescents with obesity and trial 3630 adults with obesity, see treatment schedules in Table 2 and blood sampling for liraglutide in Table 3. The final compiled data set based on all three trials contained 614 PK observations from 55 subjects.

Table 2: A summary of treatment schedules in the three trials included in the analysis.

	Trial 4181	Trial 3967	Trial 3630
Dose escalation steps (mg)	0.3, 0.6, 0.9, 1.2, 1.8, 2.4, 3.0	0.6, 1.2, 1.8, 2.4, 3.0	0.6, 1.2, 1.8, 2.4, 3.0
Actual maintenance doses (mg)	2.4 (n=1), 3.0 (n=12)	2.4 (n=1), 3.0 (n=12)	1.8, 3.0[3]
Total treatment duration (weeks)[1]	7[2]	5[4]	5

[1]Including dose escalation periods. [2]With flexibility for up to 13 weeks of treatment [3]Only data from 3.0 mg liraglutide was used in the analysis. [4]With flexibility for up to 6 weeks of treatment

Table 3: Summary of pharmacokinetic sampling schedules in trials 4181, 3967 and 3630.

	Trial 4181	Trial 3967	Trial 3630
Number of pre-dose (trough) samples during dose escalation	6	4	0
Number of samples after last dose	6	6	12
Nominal timing of sampling after the last dose	Pre-dose, 1h, 2h, 3h, 24h, 72h	Varying according to treatment sequence	Pre-dose, 2h, 4h, 1h, 13h, 15h, 18h, 20h, 24h, 36h, 48h, 60h

Results

Recruitment / Number analysed

A total of 33 subjects were screened for the trial, 9 subjects failed screening and 24 subjects were eligible, randomised and exposed to treatment. Sixteen (16) subjects were randomised and exposed to liraglutide and 8 were randomised and exposed to placebo. Four (4) subjects withdrew from the trial (2 liraglutide and 2 placebo). See Table 4 for details on subject disposition.

A total of 20 subjects completed the trial (14 liraglutide treated subjects and 6 placebo treated subjects). A total of 19 subjects reached the maximum dose of 3.0 mg (14 liraglutide treated subjects, 5 placebo treated subjects). One subject reached a maximum dose of 2.4 mg liraglutide and remained at this dose for a third week coinciding with the last week in the trial. Two subjects used 1 flex week and were treated with liraglutide 0.9 mg for two weeks before escalating the dose. Both subjects reached the liraglutide 3.0 mg maximum dose. No subjects were treated beyond 8 weeks. Both the full analysis set (FAS) and safety analysis set (SAS) included 16 liraglutide treated subjects and 8 placebo treated subjects (24 subjects total).

Table 4. Subject disposition

	lira N (%)	placebo N (%)	Total N (%)
Screened			33
Screening failures			9
Withdrawn before randomisation			0
Randomised	16 (100.0)	8 (100.0)	24 (100.0)
Exposed	16 (100.0)	8 (100.0)	24 (100.0)
Withdrawn after randomisation	2 (12.5)	2 (25.0)	4 (16.7)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (6.3)	0 (0.0)	1 (4.2)
Technical problems	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	1 (6.3)	0 (0.0)	1 (4.2)
Withdrawal by parent/guardian	0 (0.0)	2 (25.0)	2 (8.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Completed	14 (87.5)	6 (75.0)	20 (83.3)
Full analysis set	16 (100.0)	8 (100.0)	24 (100.0)
Safety analysis set	16 (100.0)	8 (100.0)	24 (100.0)

N: Number of subjects, %: Percentage of randomised subjects

CHMP comment:

24 patients were randomized, 2 out of 16 patients withdrawn in the liraglutide group compared to 2 out of 8 patients in the placebo group, this is acceptable. Except for one subject, the study population reached a maximum dose of 3.0 mg liraglutide. The exposure to the maximum dose of 3.0 mg liraglutide in this trial was only one week.

In the first trial of paediatric clinical trials for Saxenda (trial 3967, EMA/H/C/003780/P46) tolerability/ pharmacokinetics in 12-17 year old children with primary obesity was assessed, the exposure to the maximum dose of 3.0 mg for a period of only one week was identical.

Baseline data

The overall trial population consisted of more males (15) than females (9). Although, there was an even distribution observed in the liraglutide treatment group (i.e., 8 males and 8 females, 16 subjects total), an imbalance was evident in the placebo treatment group where 7 of the subjects were male and 1 subject was female. The mean age was 9.9 years (ranging between 7 and 11 years) in the overall trial population, with no major difference between the treatment groups.

A small difference in height was observed between treatment groups. Mean height of the liraglutide treatment group was shorter than the placebo treatment group.

A difference in mean body weight (kg) between treatment groups was observed. On average, mean weight in the liraglutide treatment group was 66.6 kg, lighter than the mean body weight (81.4 kg) of the placebo group. Body weight ranged from 45.0 to 86.8 kg in the liraglutide treatment group compared to 68.1 to 115.4 kg in the placebo treatment group. For the overall trial population, the

mean BMI z-score was 3.9. The two groups were similar with regard to BMI z-score, which took age and gender into consideration. See Table 3.

Table 5. Demographics and baseline characteristics

	lira N (%)	placebo N (%)	Total N (%)
Number of subjects	16	8	24
Sex			
Female	8 (50.0)	1 (12.5)	9 (37.5)
Male	8 (50.0)	7 (87.5)	15 (62.5)
Ethnicity			
Hispanic or Latino	6 (37.5)	3 (37.5)	9 (37.5)
Not Hispanic or Latino	10 (62.5)	5 (62.5)	15 (62.5)
Race			
Black or African American	7 (43.8)	3 (37.5)	10 (41.7)
White	9 (56.3)	5 (62.5)	14 (58.3)
Age (years)			
Mean (SD)	9.7 (1.1)	10.4 (1.1)	9.9 (1.1)
Median	10.0	11.0	10.0
Min ; Max	7 ; 11	8 ; 11	7 ; 11
Height (m)			
Mean (SD)	1.45 (0.11)	1.54 (0.08)	1.48
Median	1.44	1.53	1.50
Min ; Max	1.27 ; 1.62	1.43 ; 1.68	1.27 ; 1.68
Body weight (kg)			
Mean (SD)	66.6 (12.6)	81.4 (16.6)	71.5 (15.4)
Median	68.0	74.0	69.2
Min ; Max	45.0 ; 86.8	68.1 ; 115.4	45.0 ; 115.4
BMI z-score			
Mean (SD)	3.8 (0.9)	4.1 (1.0)	3.9 (0.9)
Median	3.6	3.8	3.6
Min ; Max	2.6 ; 5.7	2.8 ; 6.0	2.6 ; 6.0
FPG (mmol/L)			
Mean (SD)	5.25 (0.27)	5.19 (0.32)	5.23 (0.28)
Median	5.25	5.19	5.24
Min ; Max	4.79 ; 5.68	4.65 ; 5.71	4.65 ; 5.71
HbA1c (%)			
Mean (SD)	5.5 (0.4)	5.4 (0.4)	5.5 (0.4)
Median	5.6	5.4	5.4
Min ; Max	4.7 ; 6.0	4.9 ; 6.0	4.7 ; 6.0

N: Number of subjects, %: Percentage of subjects, SD: Standard deviation BMIz: Body mass index z-score, min = minimum, max = maximum, FPG = fasting plasma glucose
Tanner stage 1 (including subjects with premature adrenarche) at the time of screening. Baseline information is defined as the measurement at the latest assessment before dosing. BMIz is calculated based on baseline measurements of body weight and height

CHMP comment:

In the placebo group, an imbalance between boys and girls was reported with 87.5% males. This could be associated with the difference in mean body weight (81.4kg in the placebo group at baseline, versus 66.6 kg in the liraglutide group).

In the liraglutide group an even sex distribution was observed.

Compared to trials in adults relative more children with a Hispanic or Latino background were included (37.5% in the liraglutide and placebo group, compared to 9.5% in adult trials with saxenda (MAA for Saxenda)). In the liraglutide group 43.8% of children had a black or African American origin,

compared to 37.5% in the placebo group; in adult trials 10% of subjects was of black of African American. It is unknown of ethnicity and race will influence the results; however, in adults there was no indication that race or ethnicity had an impact on the adverse event pattern.

As BMI z-scores (representing a measure of weight, adjusted for height, sex, and age, relative to a reference distribution) were comparable between liraglutide and placebo group, and the sex distribution was even in the liraglutide group, the assessor agrees with the use of BMI z-score as a secondary outcome measure.

Efficacy results

The primary endpoint in this trial was related to safety and tolerability and the evaluation of the primary endpoint is therefore presented in the safety section.

Safety results

TEAE:

More treatment emergent adverse events (TEAEs) were reported In the liraglutide group compared to the placebo group; 9 subjects (56.3%) in the liraglutide group reported 37 TEAEs during the trial compared to 5 subjects (62.5%) in the placebo group reporting 12 TEAEs. The majority of the TEAEs reported in the liraglutide group were mild in severity (35 of 37 mild events); the remaining 2 of the TEAEs were moderate. In the placebo group, 11 TEAEs were mild in severity and 1 event was of moderate severity. No severe TEAEs were reported during the trial in either treatment group.

Of the TEAEs reported in the liraglutide treatment group, 21 events (corresponding to 57%) were considered to have probable or possible relation to the trial product. In the placebo group, 2 events (corresponding to 17%) were considered to have probable or possible relation to the trial product. For the liraglutide treatment group, the TEAEs were mainly reported within the system organ class (SOC) 'gastrointestinal disorders' with vomiting, nausea, abdominal pain representing the most common preferred terms within this SOC. For the placebo treatment group, the TEAEs were mainly report within the SOC 'nervous system disorders' with headache and dizziness representing the most common preferred terms within this SOC.

Subject IDs and used a flex week at 0.9 mg due to vomiting. Subject ID , used a flex with at 2.4 mg and remained at that dose for a third week coinciding with the last week of the trial and did not receive the maximum dose of 3.0 mg. The two reported TEAEs (vomiting) of moderate severity were reported by subject ID .

No TEAEs led to withdrawal of subjects from the trial.

Table 6. Summary of treatment emergent adverse events – safety analysis set

	lira			placebo		
	N	(%)	E	N	(%)	E
Number of subjects	16			8		
Events	9	(56.3)	37	5	(62.5)	12
Serious						
Yes	0	(0.0)	0	0	(0.0)	0
No	9	(56.3)	37	5	(62.5)	12
Events leading to withdrawal	0	(0.0)	0	0	(0.0)	0
Severity						
Severe	0	(0.0)	0	0	(0.0)	0
Moderate	1	(6.3)	2	1	(12.5)	1
Mild	9	(56.3)	35	5	(62.5)	11
Related to trial product						
Probable	5	(31.3)	15	1	(12.5)	1
Possible	3	(18.8)	6	1	(12.5)	1
Unlikely	5	(31.3)	16	5	(62.5)	10
Action taken to trial product						
Dose not changed	9	(56.3)	37	5	(62.5)	10
Not applicable	0	(0.0)	0	2	(25.0)	2
Related to technical complaint						
Yes	0	(0.0)	0	0	(0.0)	0
No	9	(56.3)	37	5	(62.5)	12
Outcome						
Fatal	0	(0.0)	0	0	(0.0)	0
Not recovered/not resolved	0	(0.0)	0	0	(0.0)	0
Recovered/resolved	9	(56.3)	36	5	(62.5)	10
Recovering/resolving	1	(6.3)	1	2	(25.0)	2
Recovered/resolved with sequelae	0	(0.0)	0	0	(0.0)	0
Unknown	0	(0.0)	0	0	(0.0)	0

N: Number of subjects, %: Percentage of subjects, E: Number of events,
Relationship to trial product is based on investigator(s)'s assessment.

CHMP comment:

9 subjects (56.3%) in the liraglutide group reported 37 TEAEs during the trial. The majority of the TEAEs reported in the liraglutide group were mild in severity (35 of 37 mild events) and included gastrointestinal complaints mainly vomiting, nausea, abdominal pain.

In the adult population the most common reported side effects are gastrointestinal complaints as well (≥1/10), no difference was seen in the children population included in this trial.

Table 7. Treatment emergent adverse events by system organ class

		Liraglutide		Placebo		Total	
		N (%)	E	N (%)	E	N (%)	E
Number of subjects		16		8		24	
Events		9 (56.3%)	37	5 (62.5%)	12	14 (58.3%)	49
Gastrointestinal disorders		6 (37.5%)	19	1 (12.5%)	1	7 (29,2%)	20
	Vomiting	4 (25%)	5	0	0	4 (16.7%)	5
	Nausea	3 (18.8%)	3	0	0	3 (12.5%)	3
	Abdominal pain upper	2 (12.5%)	6	0	0	2 (8.3%	6
	Abdominal discomfort	1 (6.3%)	3	0	0	1 (4.2%)	3
	Diarrhoea	1 (6.3%)	1	0	0	1 (4.2%)	1
	Dyspepsia	0	0	1 (12.5%)	1	1 (4.2%)	1
	Salivary hypersecretion	1 (6.3%)	1	0	0	1 (4.2%)	1
Nervous system disorders		3 (18.8%)	4	4 (50.0%)	5	7 (29.2%)	9
	Headache	2 (12.5%)	3	3 (37.5%)	4	5 (20.8%)	7
	Dizziness	1 (6.3%)	1	1 (12.5%)	1	2 (8.3%)	2
General disorders and administration site conditions		3 (18.8%)	4	1 (12.5%)	1	4 (16.7%)	5
Infections and infestations		2 (12.5%)	2	1 (12.5%)	1	3 (12.5%)	3
Musculoskeletal and connective tissue disorders		1 (6.3%)	1	1 (12.5%)	2	2 (8.3%)	3
Respiratory, thoracic and mediastinal disorders		2 (12.5%)	4	0	0	2 (8.3%)	4
Ear and labyrinth disorders		1 (6.3%)	1	0	0	1 (4.2%)	1
Eye disorders		1 (6.3%)	1	0	0	1 (4.2%)	1
Injury, poisoning and procedural complications		0	0	1 (12.5%)	1	1 (4.2%)	1
Alanine aminotransferase increased		0	0	1 (12.5%)	1	1 (4.2%)	1
Rash		1 (6.3%)	1	0	0	1 (4.2%)	1

Hypoglycaemia:

- No severe or BG-confirmed episodes were reported during the trial (i.e., all subjects were able to treat themselves).

- More subjects in the liraglutide group reported hypoglycaemic episodes compared to the placebo group; 5 hypoglycaemic episodes were reported in 4 subjects in the liraglutide treatment group compared to 1 episode in 1 subject in the placebo group). All of these hypoglycaemic episodes were classified as asymptomatic and the majority occurred after an overnight fast.

Table 8. Hypoglycaemic episodes by classification treatment emergent summary – safety analysis set

	lira N (%)	E	placebo N (%)	E	Total N (%)	E
Number of subjects	16		8		24	
Severe or BG confirmed symptomatic hypoglycaemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
ADA classification	4 (25.0)	5	1 (12.5)	1	5 (20.8)	6
Severe	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Documented symptomatic	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Asymptomatic	4 (25.0)	5	1 (12.5)	1	5 (20.8)	6
Probable symptomatic	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Pseudo-hypoglycaemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

N: Number of subjects, %: Percentage of subjects, E: Number of events
Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia, ADA: American Diabetes Association

CHMP comment:

At the randomisation visit (visit 2), the subjects and their parent(s) or representatives were instructed in the symptoms and treatment of hypoglycaemia and how to measure blood glucose. The glucose measurements were to be performed at home after an overnight fast before coming to the trial site for the following visit (visits 3-8) or in the case of a suspected hypoglycaemic episode.

The glucose measurements during the trial were performed with a glucometer by the subject. From glucometers it is known that they show a wide variability in glucose measurements and most often they measure capillary glucose, which may differ from whole blood or plasma glucose measurements.

However, no severe hypoglycaemic episodes were reported during the trial. In the current registered SmPC a warning regarding hypoglycaemic episodes is already present. Current data do not raise any new safety concerns regarding hypoglycaemia.

Laboratory results:

- There were no clinically relevant changes in hematology, biochemistry, ECG, hormones, lipids and calcitonin observed during the trial.
- Vital signs;
    - Resting pulse; The change in resting pulse from baseline (visit 2) to end of treatment (visit 10) was 7 beats per min for the liraglutide treated subjects compared to placebo (1 beats per min).
    - Blood pressure; Overall there was no clinically relevant change in systolic or diastolic blood pressure in either treatment groups.

- All changes in amylase and lipase were in line with the known safety profile of liraglutide.
    - The mean level of amylase increased during treatment in the liraglutide group compared to placebo. The increase in serum amylase was within normal range for

several subjects; however 4 subjects had elevated amylase above the reference range. These values were not however considered to be of clinical significance.

- A total of 7 subjects in the liraglutide-treated group had lipase values above the reference range. No clinically relevant changes in lipase levels in the placebo group were observed.

- No subjects were positive for positive anti-liraglutide antibodies.

CHMP comment:
The change in resting pulse from baseline (visit 2) to end of treatment (visit 10) was 7 beats per min for the liraglutide treated subjects compared to placebo (1 beats per min). This is also seen in the adult population. The clinical relevance for the paediatric population is unknown.

Pharmacokinetic and pharmacodynamics results

Pharmacokinetics

Dose proportionality

Dose proportionality of liraglutide was investigated based on C_{trough} values, see Figure 1. The liraglutide concentration appeared to be consistent with dose proportionality, (estimate for 2β was 1.66 [1.26; 2.19] 95% CI).

Due to 4 unexpectedly low C_{trough} liraglutide concentrations a post-hoc sensitivity analysis was run excluding the individual subjects with low liraglutide concentrations. When excluding 4 low liraglutide concentration levels, see Figure 2, the increase in liraglutide concentration with increasing dose was consistent with dose proportionality (estimate for 2β was 1.94 [1.53; 2.45] 95% CI), supporting the conclusions in the primary analysis. Subjects 110012, 110013, 113011, 113012 were excluded from the analysis.

Unexpectedly low liraglutide concentration levels were noted in several subjects. Four (4) subjects were identified with low liraglutide C_{trough} concentrations. In addition, 5 subjects did not reach the expected steady-state concentrations when the last dose was administered. An investigation of sample handling, bioanalysis, subject diaries and drug accountability records did not provide an explanation for the low concentrations of liraglutide. Therefore investigators were contacted with regard to potential compliance issues with self-administration of the trial product. No evidence of non-compliance was identified. Hence, the cause of the unexpectedly low concentrations in the individual subjects was not determined.

Figure 2: C_{trough} of liraglutide at steady state – dose proportionality - Full analysis set

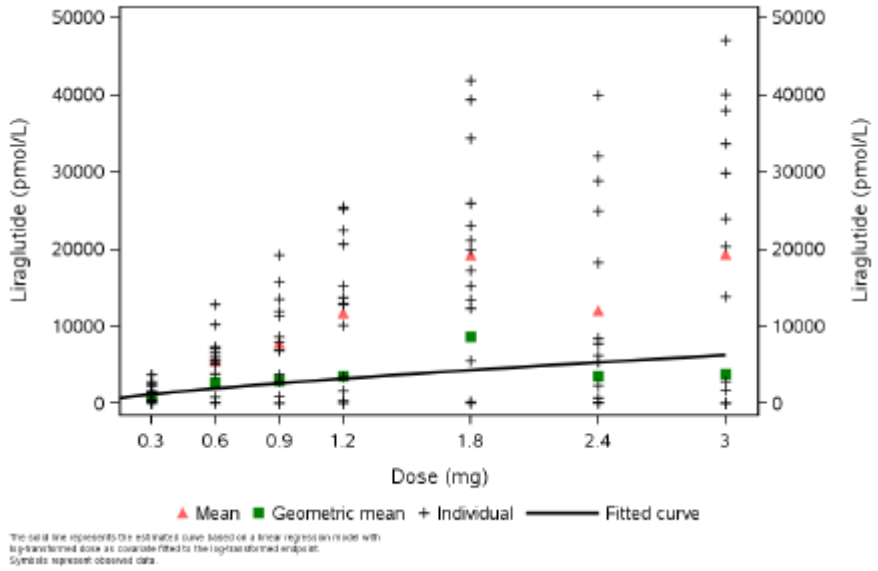
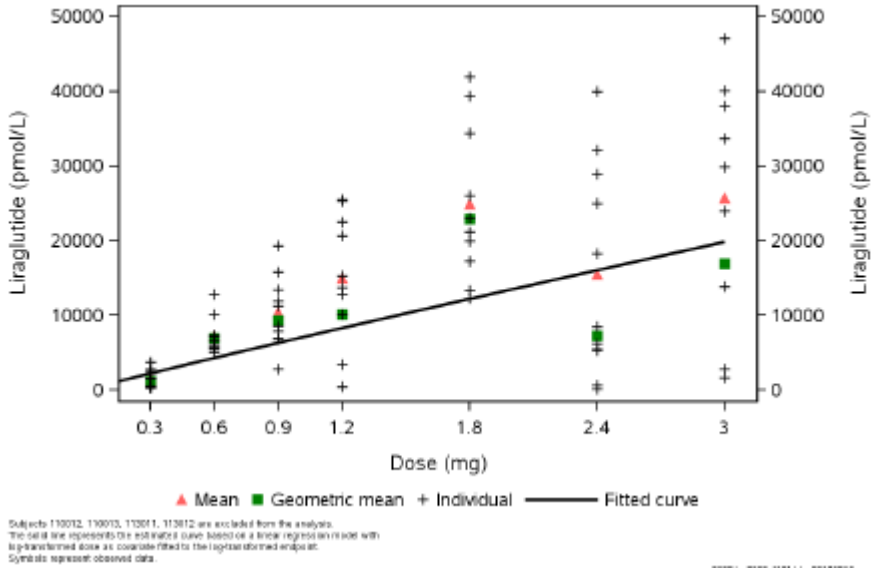


Figure 3: C_{trough} of liraglutide at steady state – dose proportionality after excluding unusual profiles - full analysis set



CHMP comments:

The results of this study demonstrate that the pharmacokinetics of liraglutide can be considered as approximately linear but not fully dose proportional. However, the deviation from dose proportionality is considered not clinical relevant.

The applicant performed a sensitivity analysis by excluding data from 4 subjects demonstrating unexpectedly low profiles. This approach is not necessarily supported. The criteria for exclusion of these profiles is subjective and unclear and these subjects did demonstrate concentration time profiles after the last dose. However, the original analysis of the full analysis set supports the conclusion that the pharmacokinetics of liraglutide can be considered as approximately linear but not fully dose proportional.

The applicant performed an adequate investigation of the cause of the unexpected.

Therefore, these issues are not further pursued.

The population pharmacokinetic modelling was based on a previously developed model; a 1-compartment pharmacokinetic model with first order absorption and elimination parameters (ka, CL/F, V/F). Between-subject variability parameters (random effects) were included for CL/F and V/F. Residual error was described using a proportional error model. The population PK analysis was a meta-analysis, also including PK data from trials in adolescents aged 13–16 years (NN8022-3967) and adults aged 20–72 years (NN8022-3630).

Population pharmacokinetic modeling

The population pharmacokinetic analysis resulted in the following model-derived PK parameters for children (body weight 53.9-86.8 kg) dosed at 0.3 mg liraglutide.

- CL/F: geometric mean: 0.69 l/h [0.6; 0.82] 95% CI
- AUC0-24, ss: geometric mean: 1161 h*nmol/l [1002; 1398] 95% CI

Body weight was found to be the major covariate of importance for liraglutide exposure. Due to unexpectedly low liraglutide concentrations in some subjects, a correction factor was used in the model-based analysis for population PK analysis.

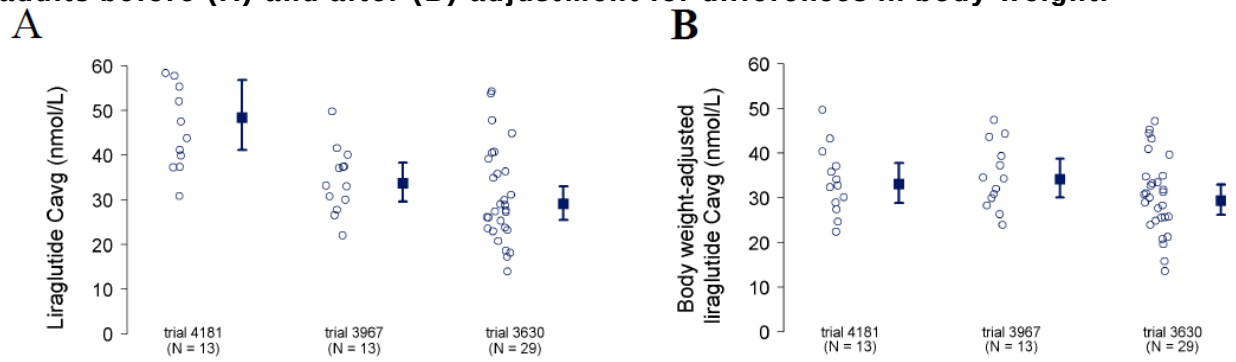
Estimated pharmacokinetic properties for the present child trial population were compared with estimated pharmacokinetic parameters for an adult trial population with obesity (NN8022-3630) and adolescent trial population with obesity (NN8022-3967), see Table 2. The estimated dose-normalised liraglutide concentrations at steady-state were higher in children (body weight 53.9-86.8 kg) compared to adolescents and adults. After adjusting for differences in body weight, mean concentrations were similar in the three age groups see Figure 3.

Table 9. Summary of clearance and exposure values in children compared with Summary of clearance and exposure values in children compared with adolescents and adults with obesity (geometric mean [95% CI])

Trial	CL/F (L/h)	AUC0-244,ss (h*nmol/L)[1]	Cavg (nmol/L)[1]
4181-children	0.69 [0.6, 0.82]	1161 [1002, 1398]	48.4 [41.8, 58.2]
3967-adolescents	0.99 [0.88, 1.14]	808 [720, 931]	33.7 [30, 38.8]
3630-adults	1.15 [1.05, 1.37]	697 [640, 833]	29.0 [26.7, 34.7]

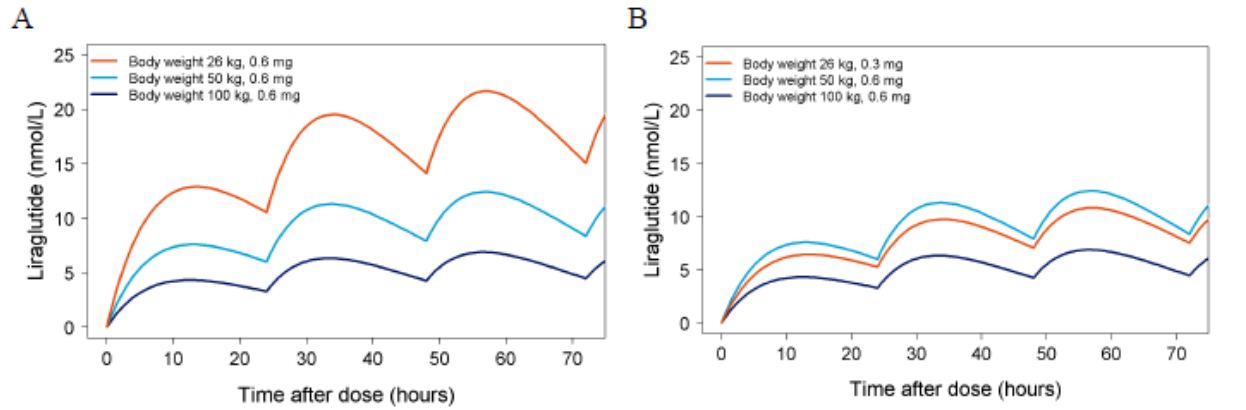
[1]Exposure values are for liraglutide 3.0 mg at steady state

Figure 4: Dose-normalised average concentrations in children, adolescents and adults before (A) and after (B) adjustment for differences in body weight.



In order to evaluate an appropriate starting dose in children with body weights down to 26 kg (relevant for a 6 year old child with obesity), liraglutide concentration profiles were simulated for the first three dosing intervals after treatment initiation, as seen in Figure 4.

Figure 5: Simulated concentration-time profiles in subjects with body weights of 26 kg following liraglutide starting doses of 0.6 mg (A) and 0.3 mg (B), both compared to a starting dose of 0.6 mg in subjects with 50 and 100 kg body weight.



Lines are model-derived mean population profiles versus time after the first dose. The model was the reduced PK model based on data from trials 4181 (children), 3967 (adolescents) and 3630 (adults). Actual body weights in trial 4181 ranged from 53.9 to 86.8 kg.

Concentrations in subjects with low body weights (down to 26 kg) dosed at 0.6 mg were higher than in subjects with high body weights (up to 100 kg) at the same dose level. However, for subjects with body weights down to 26 kg, concentrations using a lower starting dose of 0.3 mg liraglutide were within those seen in subjects with higher body weights (50 to 100 kg) dosed at 0.6 mg.

CHMP comments:

Pharmacokinetic modelling seems to be adequately performed. The model was developed and assessed during other procedures. Modeling for this younger age groups seems to be less reliable, especially since a correction factor was used in the model-based analysis.

However, the conclusion drawn by the applicant is supported that the steady-state exposure for liraglutide 3.0 mg is estimated to be higher in children aged 8-11, compared to adults and adolescents. The differences in exposure between age groups could largely be explained by differences in body weight. After adjusting for differences in body weight, mean concentrations were similar in the three age groups.

Simulations to estimate an appropriate starting dose for younger children (26 kg) with obesity

indicate a starting dose of 0.3 mg liraglutide. This is based on extensive extrapolation as the actual body weight was 54-87kg in this trial, but could indeed be a good starting dose for ongoing or planned trials in the paediatric clinical development.

Pharmacodynamics

The PD results for BMI z-score, body weight, fasting plasma glucose, insulin and HbA1c are presented in Table 10:

Table 10. BMI z-score, body weight, fasting plasma glucose, insulin, HbA1C – statistical analysis

	FAS	N	Estimate	SE	95% CI	p-value
Ch. in BMI z-score						
Mean						
lira	16	14	-0.30	0.05		
placebo	8	6	-0.01	0.08		
Treatment difference						
lira - placebo			-0.28		[-0.47 ; -0.09]	0.0062

	FAS	N	Estimate	SE	95% CI	p-value
Ch BW (kg)						
Mean						
lira	16	14	-0.52	0.47		.
placebo	8	6	0.98	0.77		.
Treatment difference						
lira - placebo			-1.50		[-3.54 ; 0.54]	0.1396
rCh BW (%)						
Mean						
lira	16	14	-1.13	0.68		.
placebo	8	6	0.84	1.11		.
Treatment difference						
lira - placebo			-1.97		[-4.91 ; 0.97]	0.1753

	lira	placebo
Ch FPG (mmol/L)		
Visit 10		
N	14	6
Mean (SD)	-0.51 (0.52)	0.12 (0.55)
Median	-0.52	0.09
Min ; Max	-1.66 ; 0.26	-0.65 ; 1.02
Ch FPG (mg/dL)		
Visit 10		
N	14	6
Mean (SD)	-9 (9)	2 (10)
Median	-9	2
Min ; Max	-30 ; 5	-12 ; 18

	lira	placebo
Number of subjects	16	8
rCh insulin-fast		
Visit 10		
N	14	6
Mean (SD)	0.98 (0.59)	2.35 (2.53)
Geometric mean (CV)	0.82 (74.4)	1.57 (117.0)
Median	0.87	1.11
Min ; Max	0.14 ; 2.47	0.74 ; 7.12

	lira	placebo
Number of subjects	16	8
Ch HbA1c (%)		
Visit 10		
N	14	5
Mean (SD)	-0.1 (0.2)	-0.1 (0.1)
Median	-0.2	-0.1
Min ; Max	-0.6 ; 0.2	-0.2 ; 0.1
Ch HbA1c (mmol/mol)		
Visit 10		
N	14	5
Mean (SD)	-1.2 (2.4)	-0.9 (1.4)
Median	-1.6	-1.1
Min ; Max	-6.6 ; 2.2	-2.2 ; 1.1

The following pharmacodynamics conclusions could be drawn:

BMI z-score; Comparing change from baseline to end of treatment, there was a statistically significant treatment difference for subjects on liraglutide compared to those on placebo. Estimated treatment difference was -0.28 [-0.47; -0.09] 95%CI, p-value=0.0062, favouring liraglutide.

Mean body weight; Decreased (mean relative change -1.7%) from baseline to end of treatment in the liraglutide group compared to an increase (mean relative change 2.2%) in the placebo group. However, no statistically significant treatment difference was shown.

Mean FPG; decreased numerically more from baseline to end of treatment with liraglutide treatment (mean change of -0.51 mmol/L) when compared to placebo (mean change of 0.12 mmol/L).

No clinically relevant differences between the two groups were observed in **fasting serum insulin** or **HbA1c.**

CHMP comments:

As the MAH stated, comparing change from baseline to end of treatment, there was a statistically significant treatment difference in BMI z-score for subjects on liraglutide compared to those on placebo. Mean FPG decreased from baseline to end of treatment. A tendency in decrease in body weight was found, however not significant. This might be associated to the imbalance of boys and girls in the placebo group at baseline, or the imbalance of weight at baseline between the liraglutide and placebo group.

In the currently registered SmPC the following is mentioned in section 4.1:

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.

In this trial no subjects were treated beyond 8 weeks. The exposure to the maximum dose of 3.0 mg liraglutide in this trial was only one week. Long-term future research is needed to draw further conclusions of the efficacy and sustainability of Saxenda for weight and BMI z-score in children.

3. Rapporteur's overall conclusion and recommendation

Regarding pharmacokinetics, the applicant concludes that the extent of the exposure (C_{trough}) at steady-state with respect to liraglutide was consistent with dose proportionality. Further, as resulted from the population pharmacokinetic modelling, after adjusting for differences in body weight, exposure associated with 3.0 mg liraglutide was found to be comparable between the children studied in this clinical trial 7-11 years of age and what has been demonstrated in adolescent and adult subjects. A dose of 0.3 mg liraglutide was estimated to be an appropriate starting dose for younger children (26 kg) with obesity. This is based on extensive weight extrapolation, but could indeed be a good starting dose for ongoing or planned trials in the paediatric clinical development.

In this trial in children aged 7 to 11 years, with a mean age of 9.9 years, a mean BMI z-score of 3.9 at Tanner stage 1, more TEAE were observed in the liraglutide treatment group. Nine subjects (56.3%) in the liraglutide group reported 37 TEAEs during the trial compared to 5 subjects (62.5%) in the placebo group reporting 12 TEAEs. The most common TEAE were mild gastrointestinal disorders mainly vomiting, nausea, abdominal pain.

More subjects in the liraglutide group reported hypoglycaemic episodes compared to the placebo group; 5 hypoglycaemic episodes were reported in 4 subjects in the liraglutide treatment group compared to 1 episode in 1 subject in the placebo group). All of these hypoglycaemic episodes were classified as asymptomatic and the majority occurred after an overnight fast.

The mean level of amylase increased during treatment in the liraglutide group compared to placebo. A total of 7 subjects in the liraglutide-treated group had lipase values above the reference range. No clinically relevant changes in amylase or lipase levels in the placebo group were observed. No liraglutide antibodies were observed.

Regarding vital signs, resting pulse increased 7 beats per min for the liraglutide treated subjects compared to placebo (1 beats per min). This phenomenon is also observed in adults.

At baseline a difference in mean body weight (kg) between treatment groups was observed. On average, mean weight in the liraglutide treatment group was 66.6 kg, lighter than the mean body weight (81.4 kg) of the placebo group. Body weight ranged from 45.0 to 86.8 kg in the liraglutide treatment group compared to 68.1 to 115.4 kg in the placebo treatment group. For the overall trial population, the mean BMI z-score was 3.9. The two groups were similar with regard to BMI z-score.

The secondary exploratory PD endpoints tended to be in favour of liraglutide. A statistically significant treatment difference was shown for the BMI z-score. Mean body weight and mean fasting plasma glucose decreased, but no statistically significant treatment difference was shown. No clinically relevant differences between the two groups were observed in fasting serum insulin or HbA1c. However, the exposure to the maximum dose of 3.0 mg liraglutide in this trial was only one week. As adverse events are the most profound after starting treatment, this period is acceptable to assess adverse events. Long-term future research is needed to draw further conclusions of the efficacy and sustainability of Saxenda for weight and BMI z-score in children.

Overall conclusion

Trial NN8022-4181, assessing the tolerability, pharmacokinetics and pharmacodynamics of liraglutide administered according to a dose-escalation schedule until a maximum dose of 3.0 mg liraglutide or maximum tolerated dose; for a period of 7 weeks (with option to prolong up to 13 weeks in case a flex week was needed) in obese children aged 7 to 11 years, did not reveal unexpected safety and tolerability issues. Exposure associated with 3.0 mg liraglutide was found to be comparable between the children aged 7 to 11 and adolescents and adult subjects, if corrected for body weight.

Trial NN8022-4181 is part of the PIP (EMEA/H/C/003780) for Saxenda®, liraglutide 3 mg for weight management. The PIP comprises 7 studies (one quality study, one nonclinical study and 5 clinical trials) and is scheduled to be completed in 2023. Trial NN8022-4181 is the second of the 5 planned paediatric clinical trials to be completed.

The results of the other paediatric clinical trials has to be waited for, to draw definite conclusions. In general, the side effects of Saxenda in children aged 7 to 11 years are in accordance with adults. No pronounced effect on hypoglycaemia was found. Long-term future research is needed to draw further conclusions of the efficacy and sustainability of Saxenda for weight and BMI z-score in children.

☒ **Fulfilled:**

A type II variation in which the SmPC will be adapted as suggested has to be submitted.

4. Additional clarification requested

Not applicable.

Annex. Line listing of all studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
Tolerability/ pharmacokinetics in 12-17 year old children with primary obesity, Tanner stage 2-5	Trial 1 (3967; completed)	26-05-2014	
Tolerability/ pharmacokinetics in 7-11 year old children with primary obesity, Tanner stage below 2 with premature adrenarche	Trial 3 (4181; completed)	13-04-2017	
Efficacy/ safety in 12-17 year old children with primary obesity, Tanner stage 2-5	Trial 2 (4180; ongoing)		
Efficacy/ safety in obese children with Prader Willi Syndrome.	Trial 4 (4179; ongoing)		
Safety/ tolerability and efficacy in 6-11 year old children with primary obesity. Tanner stage below 2 and children with premature adrenarche.	Trial 5 (planned)		