14 December 2017
EMA/201755/2018
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/P46/017

## Note

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

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# Table of contents

# 1. Introduction

On 25 September 2017, the MAH submitted a completed paediatric study (Trial NN8022-3967), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This clinical trial report was already submitted and assessed in 2014 under the Victoza®, liraglutide 1.8 mg procedure (EMEA/H/C001026).

The following conclusions were drawn:

- In general, for Victoza® (liraglutide 1.8 mg), trial NN8022-3967, investigating the safety and tolerability of liraglutide administered according to a dose-escalation scheme to a maximum tolerated dose of up to 3.0 mg/day (Saxenda®) for a period of 5−6 weeks in adolescents, did not reveal unexpected safety and tolerability issues apart from the occurrence of hypoglycaemia that needs further elaboration.
- For Saxenda®, the results of this phase 1 trial, can be seen as preliminary data in adolescents.
- In general, the (side) effects of Saxenda® in adolescents are in accordance with adults, with possibly a more pronounced effect on hypoglycaemia.

Above assessment resulted in the use of adult dosing and dose escalation in the ongoing PIP, NN8022-4180: "*Efficacy/ safety in 12-17 year old children with primary obesity, Tanner stage 2-5".*

It is agreed that the results from the above assessment report are largely transferable to Saxenda®.

Trial NN8022-3967 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 NN8022-3967 (hereafter referred to as trial 3967) is the first of the 5 planned paediatric clinical trials to be completed.

Trial NN8022-3967 assesses the safety and tolerability of liraglutide at doses up to 3.0 mg in an obese adolescent population aged 12−17 years and Tanner stage 2-5.

A Marketing Authorisation Application (MAA) for Saxenda® (liraglutide 3.0 mg), indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients was submitted to EMA on 20 December 2013 (EMEA/H/C/003780) and has received a positive opinion at the January 2014 meeting of the Committee for Medicinal Products for Human Use (CHMP).

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that trial NN8022-3967 is part of a paediatric investigating 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. GLP-1 is an incretin hormone secreted predominantly from the L-cells in the lower gut in response to meal ingestion and in turn stimulating the secretion of endogenous insulin in a glucose-dependent manner. GLP-1 also decreases blood glucagon levels and slows down the gastric emptying rate leading to an increased feeling of satiety and a subsequent reduction in food intake.

Liraglutide is a peptide and must be administered by subcutaneous (s.c.) injection to avoid its degradation by the stomach acid. Once daily s.c. injection is the route of administration in both the paediatric, adolescent and adult populations. The formulation of liraglutide used in trial 3967 was the same as that used in clinical trials in adults: liraglutide 6.0 mg/mL, for s.c. injection. The formulation contained liraglutide (6.0 mg/mL), phosphate, propylene glycol and phenol. The placebo solution contained the same excipients and preservatives as the active product, without the active substance. The formulation and the corresponding placebo solutions were clear, colourless or almost colourless solutions, free from turbidity. The products were delivered as solutions in 3 mL cartridges for multiple s.c. injections.

All excipients in the liraglutide formulation are considered suitable for the paediatric/adolescent population. Based on the outcome of the paediatric trials, the optimal administration system for paediatric use will be made available by Novo Nordisk prior to the approval of a paediatric indication.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

NN8022-3967, a randomised, double-blind, placebo-controlled phase 1 trial to asses safety, tolerability and pharmacokinetics of liraglutide in obese adolescent subjects aged 12 to 17 years.

## 2.3.2. Clinical study

### Description

Trial 3967 was a randomised, double-blind, placebo-controlled trial in obese adolescents, 12−17 years of age and Tanner stage 2−5. A total of 21 adolescents were planned to be randomised 2:1 to treatment with either liraglutide or placebo. After a screening visit, the subjects entered a 5-6 week treatment period and 5 to 14 days after the last dose, subjects attended a follow-up visit. The total time from screening to follow-up was, at most, 10 weeks. 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 0.6 mg/day. The dose was then gradually increased with 0.6 mg once weekly until the maximum tolerated dose of up to 3.0 mg/day was reached. If, during dose-escalation, the higher dose was not tolerated, the dose was de-escalated to the previous level and the subject took that dose for the remainder of the treatment period. Alternatively, the subject could take a given dose for two weeks before escalating to the next dose level. Safety and tolerability was assessed during the entire trial. Pharmacokinetic 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 7 (i.e. during week 1-5). In addition, sparse pharmacokinetic blood sampling for population pharmacokinetic analysis (modelling) was performed after the last dose administration at the end of week 5 according to the specific sampling scheme that was assigned at randomisation.

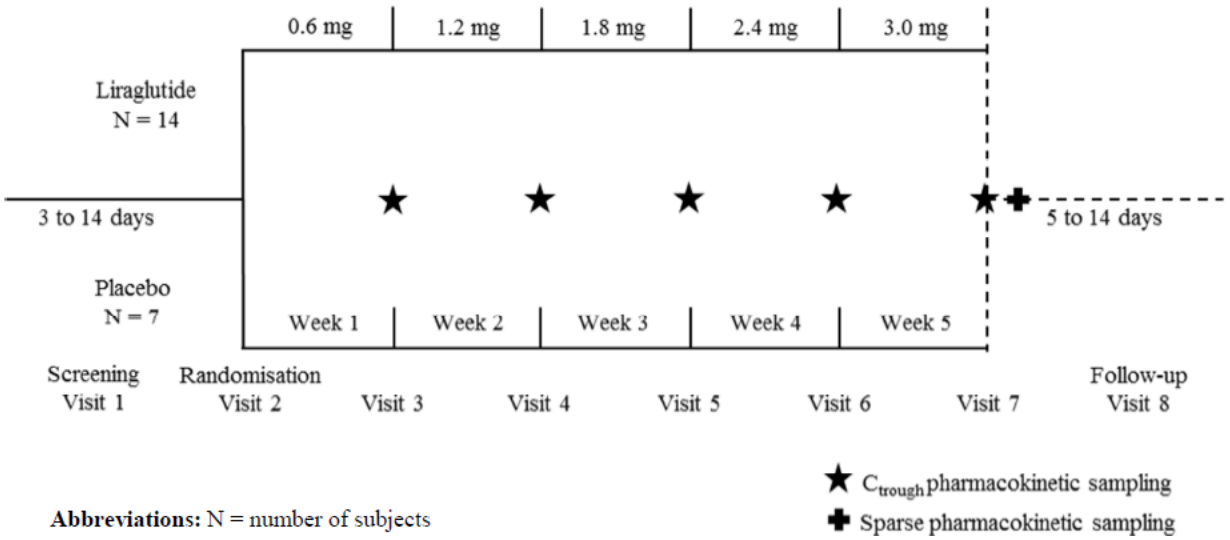
### Methods

- ***Objectives***

The primary objective of the trial was to assess the safety and tolerability of liraglutide at doses up to 3 mg in the adolescents aged 12 to 17 years and Tanner stage 2-5; the secondary objectives were to assess the pharmacokinetics and pharmacodynamics of liraglutide.

- ***Study design***

**Figure 1. Trial design**



- ***Study population /Sample size***

No statistical power calculation was performed. A sample size of 12 subjects randomized to liraglutide and 6 subjects randomized to placebo was considered sufficient to assess the primary and secondary objectives. In order to account for dropouts it was planned to randomize 14 subjects for the liraglutide treatment group and 7 subjects for the placebo group and thus a total of 21 subjects were planned for enrolment into the trial. The key inclusion criteria were:

- Male or female subjects aged 12-17 years (both inclusive) at time of randomization with Tanner stage 2-5 pubertal development.
- BMI corresponding to > 30 kg/$m^2$ for adults by international cut-off points and < 45 kg/$m^2$ and > 95th percentile for age and gender.
- Fasting plasma glucose < 7.0 mmol/L (126 mg/dL).

The key exclusion criteria:

- Subjects with clinically diagnosed secondary causes of childhood obesity such as chromosomal abnormalities (e.g., Turner syndrome), syndromic obesity (e.g., Prader Willi syndrome) or endocrinologic disorders (e.g., Cushing Syndrome).
- Subjects with confirmed diagnosis of bulimia
- Subjects with Tanner stage 1 development (prepubertal).
- Diagnosis of type 1 or type 2 diabetes mellitus as judged by the investigator.
- Previous treatment with GLP-1 receptor agonists (e.g., exenatide or liraglutide or other), DPP-4 inhibitors, orlistat or other weight lowering medication, any antipsychotic medication or systemic corticosteroids within the last 3 months.
- Currently using or have used within 3 months before screening for this trial: any systemic treatment that in the opinion of the investigator interferes with pharmacokinetic, pharmacodynamic and safety endpoints.
- Surgical treatment for obesity.
- Past or current chronic or idiopathic pancreatitis or any of the following: amylase or lipase above 2 times upper normal range; triglycerides above 500 mg/dl; calcium above upper normal range; history of gallstones (not treated by cholecystectomy).
- Uncontrolled treated or untreated hypertension 99th percentile for age and gender in children.
- History of major depressive disorder or history of other severe psychiatric disorders (e.g., schizophrenia or bipolar disorder) that could in the opinion of the investigator interfere with trial compliance or subject safety.
- Subjects with a history of suicide attempts or history of any suicidal behaviour within the past month before entry into the trial.

- ***Treatments***

Treatment with liraglutide (or the corresponding volume of placebo) was initiated at a dose of 0.6 mg/day. The dose was escalated in 0.6 mg weekly steps to a maximum tolerated dose of up to 3.0 mg/day. The dose was not escalated if the subject had had fasting plasma glucose < 3.1 mmol/L (56 mg/dL) or < 3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia in the previous week. Furthermore, the dose was escalated only if the previous dose was tolerated with respect to gastrointestinal AEs, as judged by the investigator. In case of tolerability issues, the dose could be down-titrated and the subject could stay on that lower dose for the rest of the trial or the treatment period could be prolonged for an extra week (i.e., a total period of 6 weeks), allowing subjects to remain at one dose for up to a maximum of two weeks before escalating the dose. After the last dose and sampling for pharmacokinetics, the subjects attended a follow-up visit. The total time from screening to follow-up was, at most, 10 weeks.

- ***Outcomes / endpoints***

The primary endpoint was:
Number of treatment emergent AEs (TEAEs) recorded from the time of first dosing and until completion of the follow-up visit.

The secondary pharmacokinetic endpoints were:

- At steady state at each dose step: $C_{trough}$
- At steady state (last dose day): model derived AUCτ (area under the pharmacokinetic curve at steady state from 0-24 hours), t½ (plasma half-life), CL/F (apparent clearance), V/F (apparent volume of distribution)

The explorative PD secondary 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, HbA1c and serum insulin

- ***Statistical Methods***

Full analysis set (FAS) – all subjects who were randomized and had received at least one dose of the trial product. In exceptional cases, subjects could be excluded from the FAS. In such cases the exclusion was justified and documented. 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.

The change from baseline to end-of-treatment for all PD endpoints was analyzed using an ANCOVA model with treatment as fixed factor and baseline value as covariate.

**CHMP comments:**

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.

## Results

- ***Recruitment / Number analysed***

In total, 24 obese adolescents were screened; 3 subjects were screening failures; 14 subjects were randomized and exposed to liraglutide (3 boys and 11 girls) and 7 were randomized and exposed to placebo (4 boys and 3 girls). One subject withdrew from treatment after 4 days of treatment due to a storage temperature deviation of trial product at site. 20 subjects completed the trial. Mean exposure to treatment was similar between treatment groups and was 33.3 days (median: 35 days) in the liraglutide group and 35.4 days (median: 35 days) in the placebo group. Except for one subject who reached 2.4 mg of liraglutide, subjects reached a maximum of 3.0 mg.

**CHMP comments:**

In the liraglutide group, an imbalance between boys and girls was reported with 78.6% females in this group. As sex was identified as a relevant covariate for exposure (lower exposure in males), this might have influenced the results. 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. As adverse events are the most profound after starting treatment, this period is acceptable for a first evaluation of safety in children.

- ***Baseline data***

The two treatment groups (liraglutide and placebo) had similar distribution with regard to demographic and baseline characteristics. The mean age was 15 years (ranging between 13 and 17 years), the mean body weight was 105.5 kg (78.5 to 164.4 kg), mean BMI was 36.2 kg/m2 (29.3 to 44.9 kg/m2) and mean BMI z-score was 3.20 (2.50 to 4.52). Most of the enrolled subjects were Tanner stage 5 or 4 of pubertal development and few were Tanner stage 3. No subjects were Tanner stage 2. See Table 2.

**Table 2. Summary of demographics and baseline characteristics**

| | Liraglutide 3.0 mg N (%) | Placebo N (%) | Total N (%) |
|---|---|---|---|
| Number of subjects | 14 | 7 | 21 |
| Sex | | | |
| Female | 11 ( 78.6) | 3 ( 42.9) | 14 ( 66.7) |
| Male | 3 ( 21.4) | 4 ( 57.1) | 7 ( 33.3) |
| Ethnicity | | | |
| Not Hispanic or Latino | 14 (100.0) | 7 (100.0) | 21 (100.0) |
| Race | | | |
| White | 13 ( 92.9) | 7 (100.0) | 20 ( 95.2) |
| Other (Turkish) | 1 ( 7.1) | 0 ( 0.0) | 1 ( 4.8) |
| Age (years) | | | |
| Mean (SD) | 15.1 (0.9) | 14.4 (1.8) | 14.9 (1.3) |
| Median | 15.0 | 14.0 | 15.0 |
| Min ; Max | 13.0 ; 16.0 | 13.0 ; 17.0 | 13.0 ; 17.0 |
| Overall tanner staging | | | |
| II | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| III | 2 ( 14.3) | 1 ( 14.3) | 3 ( 14.3) |
| IV | 3 ( 21.4) | 4 ( 57.1) | 7 ( 33.3) |
| V | 9 ( 64.3) | 2 ( 28.6) | 11 ( 52.4) |
| Body Weight (kg) | | | |
| Mean (SD) | 103.5 (12.8) | 109.6 (30.8) | 105.5 (20.0) |
| Median | 104.6 | 107.7 | 105.2 |
| Min ; Max | 79.9 ; 121.6 | 78.5 ; 164.4 | 78.5 ; 164.4 |
| BMI ($kg/m^2$) | | | |
| Mean (SD) | 36.5 (3.7) | 35.7 (5.4) | 36.2 (4.2) |
| Median | 36.3 | 34.4 | 36.1 |
| Min ; Max | 31.6 ; 44.3 | 29.3 ; 44.9 | 29.3 ; 44.9 |
| BMI Z-score (no unit) | | | |
| Mean (SD) | 3.17 (0.49) | 3.26 (0.75) | 3.20 (0.57) |
| Median | 3.12 | 3.00 | 3.10 |
| Min ; Max | 2.50 ; 4.16 | 2.50 ; 4.52 | 2.50 ; 4.52 |
| $HbA_{1c}$ (%) | | | |
| Mean (SD) | 5.4 (0.3) | 5.5 (0.3) | 5.5 (0.3) |
| Median | 5.5 | 5.5 | 5.5 |
| Min ; Max | 4.9 ; 6.0 | 5.1 ; 6.1 | 4.9 ; 6.1 |
| FPG (mmol/L) | | | |
| Mean (SD) | 5.25 (0.45) | 5.47 (0.30) | 5.32 (0.41) |
| Median | 5.10 | 5.43 | 5.30 |
| Min ; Max | 4.64 ; 5.98 | 5.07 ; 5.90 | 4.64 ; 5.98 |

Note that the term 'Liraglutide 3.0 mg' includes dose-escalation.
N: Number of subjects, %: percentage of subjects, BMI: body mass index, Min: minimum, Max: maximum, FPG: fasting plasma glucose

**CHMP comments:**

The subjects investigated in this trial had a relatively high BMI of 36.2 $kg/m^2$.

- ***Safety results***

*TEAE:*

More treatment emergent adverse events (TEAEs) were reported in the liraglutide group compared to the placebo group; 14 subjects (100%) in the liraglutide group reported 86 TEAEs during the trial compared to 4 subjects (57%) in the placebo group reporting 7 TEAEs. The majority of the TEAEs

reported in the liraglutide group were mild in severity (83 mild events corresponding to 97% of all reported TEAEs in the liraglutide group); 3 of the TEAEs (3%) were moderate. In the placebo group, all reported TEAEs were mild. No severe TEAEs were reported in any of the treatment groups.

Approximately half (44 TEAEs corresponding to 51%) of the TEAEs reported in the liraglutide group were considered to have a causal relationship to the treatment whereas none of the reported TEAEs were considered as related to the treatment in the placebo group. The most frequently reported TEAEs in the liraglutide group were from the system organ class (SOC) 'gastrointestinal disorders' with abdominal pain, nausea, vomiting and diarrhea representing the most common preferred terms within this SOC. No clear association between dose, timing and duration of the gastrointestinal TEAEs was observed in the present short-term trial. None of the reported TEAEs led to withdrawal of subjects from the trial. No deaths or other SAEs were reported during the trial.

**Table 3. Summary of treatment emergent adverse events – safety analysis set**

| | Liraglutide 3.0 mg N (%) | E | Placebo N (%) | E | Total N (%) | E |
|---|---|---|---|---|---|---|
| Number of subjects | 14 | | 7 | | 21 | |
| Events | 14 (100.0) | 86 | 4 ( 57.1) | 7 | 18 ( 85.7) | 93 |
| Death | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Serious | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Events leading to withdrawal | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Severity | | | | | | |
| Severe | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Moderate | 3 ( 21.4) | 3 | 0 ( 0.0) | 0 | 3 ( 14.3) | 3 |
| Mild | 14 (100.0) | 83 | 4 ( 57.1) | 7 | 18 ( 85.7) | 90 |
| Relation to trial product | | | | | | |
| Probable | 2 ( 14.3) | 3 | 0 ( 0.0) | 0 | 2 ( 9.5) | 3 |
| Possible | 13 ( 92.9) | 41 | 0 ( 0.0) | 0 | 13 ( 61.9) | 41 |
| Unlikely | 13 ( 92.9) | 42 | 4 ( 57.1) | 7 | 17 ( 81.0) | 49 |
| Outcome | | | | | | |
| Recovered | 14 (100.0) | 83 | 4 ( 57.1) | 7 | 18 ( 85.7) | 90 |
| Recovering | 3 ( 21.4) | 3 | 0 ( 0.0) | 0 | 3 ( 14.3) | 3 |
| Recovered with sequelae | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Not recovered | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |
| Fatal | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 | 0 ( 0.0) | 0 |

Note that the term 'Liraglutide 3.0 mg' includes dose-escalation. N = number of subjects; % = percentage of subjects; E = number of events.

**CHMP comments:**

Treatment with liraglutide was well-tolerated in the present obese adolescent trial population and no unexpected safety and tolerability issues were identified compared to adults. Liraglutide was tolerated up to 3.0 mg, except for one subject who tolerated 2.4 mg due to recurrent hypoglycaemia. Although, liraglutide 3.0 mg was tolerated, all (100%) treated subjects experienced side effects, most frequently mild gastrointestinal disorders, as judged by the investigator. Non-serious hypoglycaemia were not reported as AE, but reported on hypoglycaemic forms.

*Hypoglycaemia:*

- For one subject in the liraglutide group, dose-escalation was postponed due to hypoglycaemic episodes and this subject only reached a maximum dose of 2.4 mg liraglutide.
- More hypoglycaemic episodes occurred in the liraglutide group compared to the placebo group; 12 hypoglycaemic episodes occurred in 8 subjects in the liraglutide group compared to 2 episodes in 1 subject in the placebo group. No severe episodes occurred in any of the treatment groups. Most of the episodes in the liraglutide group occurred at liraglutide doses of 0.6 mg and 1.2 mg.

**Table 4. Summary of treatment emergent hypoglycaemic episodes by classification safety analysis set**

| | Liraglutide 3.0 mg | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | N | (%) E | N | (%) E | N | (%) E |
| Number of subjects | 14 | | 7 | | 21 | |
| Confirmed | 2 | (14.3) 3 | 0 | ( 0.0) 0 | 2 | ( 9.5) 3 |
| ADA | 8 | (57.1) 12 | 1 | (14.3) 2 | 9 | (42.9) 14 |
| Severe | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 |
| Documented Symptomatic | 2 | (14.3) 4 | 0 | ( 0.0) 0 | 2 | ( 9.5) 4 |
| Asymptomatic | 4 | (28.6) 4 | 1 | (14.3) 2 | 5 | (23.8) 6 |
| Probable Symptomatic | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 |
| Relative | 3 | (21.4) 4 | 0 | ( 0.0) 0 | 3 | (14.3) 4 |
| ADA Unclassifiable | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 | 0 | ( 0.0) 0 |

**Note:** Confirmed corresponds to severe events or to the 'minor' hypoglycaemia as defined by Novo Nordisk, i.e. subjects with an episode with symptoms consistent with hypoglycaemia with confirmation by plasma glucose <3.1 mmol/L (56 mg/dL) or full blood glucose <2.8 mmol/L (<50mg/dL) and which is self-handled by the subject or any asymptomatic plasma glucose <3.1 mmol/L (<56 mg/dL) or full blood glucose <2.8mmol/L (<50 mg/dL). A hypoglycaemic episode is defined as treatment emergent if the onset of the episode is on or after the first day of exposure to randomised treatment and no later than the follow-up visit. Note that the term 'Liraglutide 3.0 mg' includes dose-escalation.
**Abbreviations:** N = number of subjects, % = percentage of subjects with the event, E = number of events.

**CHMP comments:**

At visit 1 and 7, plasma glucose concentration was measured. 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. The data on hypoglycaemia should be interpreted with caution.

The subject who tolerated 2.4 mg only, experienced nausea throughout the trial, as well as recurrent hypoglycaemia. Future trials with liraglutide 3.0 mg in adolescents have to make clear if hypoglycaemia is a recurrent problem in this specific treatment group. In this trial, 57% of the subjects with liraglutide experienced hypoglycaemia versus 14 % in the placebo group. The majority of hypoglycaemia occurred at the lower liraglutide doses and no severe hypoglycaemia was observed. The glucoses measured with glucometer defined as hypoglycaemia are common values in adolescents and may be a variant of normal.

*Laboratory results:*

- One CLAE (clinical laboratory adverse event) (elevated transaminase ) was reported. An increase in serum ALAT of 20.5 U/l at baseline to 36.2 U/l at end of treatment (normal range 8-29 U/l) was reported.
- Otherwise no clinically significant changes in laboratory parameters, physical examination and ECG were observed.
- Few subjects in the liraglutide group had elevated levels of LDH (4 subjects), lipase (2 subjects) and amylase (1 subject) at some points during the trial. The maximum amylase level was 147.1 U/l end of treatment (normal range 28.0-100.0 U/l).
- No anti-liraglutide antibodies were detected during the trial.
-

**CHMP comments:**

One subject with number experienced an increase in lipase and amylase without signs of pancreatitis. This phenomenon is also observed in the adult trials. The development of anti-liraglutide antibodies after long-term treatment can not be excluded due to the short duration of the trial. The subject with elevated transaminase, experienced elevated SGOT, LDH and potassium 6.9 mmol/l as well, without an elevation in creatinine, which might be explained by hemolysis in the tube.

- ***Pharmacokinetic and pharmacodynamics results***

Pharmacokinetic

Dose proportionality of liraglutide was investigated based on $C_{trough}$ values by estimation of the slope β in a linear normal regression model. For the analysis, $C_{trough}$ values were logarithmically transformed and analysed via population PK modelling. The estimate reported from the analysis was the quantity 2β and the resulting p-value represents the test of 2β = 2 (i.e., if 2β = 2, this means that doubling the dose of liraglutide results in a doubling of the exposure).

Blood samples were drawn at specific time points during the trial for liraglutide concentration analysis in order to investigate PK parameters of the treatment.
One blood sample was drawn prior to subjects taking their daily dose of IMP at visit 3 to 7 (i.e., during week 1-5, see Figure 9–1) in order to obtain trough values ($C_{trough}$) at steady state at each dose-escalation step in order to assess dose-proportionality.
In addition, subjects were randomised to one of six different PK blood sampling schemes (A–F, see Table below) at the randomisation visit (visit 2). Within 24 hours of the last dose administration at visit 7 at the end of week 5, 4 samples were drawn per subject and, in addition, one sample was drawn at 48 or 72 hours for population PK analysis (sparse PK blood sampling). The actual time of blood sampling was not to deviate by more than: ± 10 minutes for the 2- and 4-hour samples, ±30 minutes for the 6-, 8- and 10-hour samples, ± 1 hour for the 12- and 14-hour samples and +12 hours (up to 12 hours after the specified time) for the 24-, 48- and 72-hour samples.

| Hours after last dose | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 24 | 48 | 72 |
|---|---|---|---|---|---|---|---|---|---|---|
| A | x | | x | | x | | x | | x | |
| B | | x | | x | x | | x | | | x |
| C | x | | | x | | | x | x | | x |
| D | | x | | | x | x | | x | x | |
| E | | x | x | | | x | | x | x | |
| F | x | | x | x | | x | | | | x |

*Population Pharmacokinetic analysis:*

The objective of the population PK analysis was to investigate the PK properties of liraglutide 3.0 mg in obese adolescents and compare it with steady state PK data from a previous trial with liraglutide 3.0 mg in obese adults (NN8022-3630). The possible relationship between drug exposure and selected markers of pharmacodynamic (PD) effect after 5 weeks of treatment (including escalation) was explored.

A summary of the data and trial characteristics for subjects included in the population PK analysis is shown in Table 5 below.

**Table 5. Summary of the data and trial characteristics for subjects in trials NN8022-3967 and NN8022-3630 included in the population PK analysis.**

| | NN8022-3967 | NN8022-3630 |
|---|---|---|
| Population | Obese adolescents | Obese adults |
| N* | 13 | 29 |
| Female (N (%)) | 10 (77 %) | 11 (38 %) |
| Male (N (%)) | 3 (23 %) | 18 (62 %) |
| Age (median (range)) | 15 (13 – 16) years | 47 (20 – 72) years |
| Body weight (median (range)) | 104 (80 - 119) kg | 98 (70 - 130) kg |
| Doses (mg) | 3.0 | 3.0 |
| PK sampling | 0-72 hours | 0-60 hours |
| Number of PK samples pr. subject | 10 (incl. 5 $C_{trough}$ samples) | 13 |

*Only subjects on active treatment with liraglutide were included in the analysis.

Study **NN8022-3630** was according the modelling report a randomised, placebo-controlled, double-blind, incomplete cross-over design trial to evaluate the effects of liraglutide on gastric emptying,

energy expenditure and appetite, and to evaluate liraglutide PK in obese adults.
Twenty nine subjects were randomised and exposed to liraglutide 3.0 mg. In brief, the subjects included in the trial were adult (age 18 to 75) males and females with a BMI ≥30.0 kg/$m^2$ and < 40.0 kg/$m^2$ and a FPG < 7.0 mmol/L (126 mg/dL). Subjects were randomised to treatment sequence A, B, C, D, E or F:

Sequence A: 3.0 mg liraglutide followed by 1.8 mg liraglutide

Sequence B: 1.8 mg liraglutide followed by 3.0 mg liraglutide

Sequence C: 1.8 mg liraglutide followed by placebo (3.0 mg)

Sequence D: Placebo (3.0 mg) followed by 1.8 mg liraglutide

Sequence E: 3.0 mg liraglutide followed by placebo (1.8 mg)

Sequence F: Placebo (1.8 mg) followed by 3.0 mg liraglutide

Subjects went through a 3 or 5 step dose escalation for the 1.8 mg and 3.0 mg liraglutide treatment, respectively. Between the two treatment periods there was a washout period of 6-8 weeks. Subjects were given an initial 0.6 mg daily dose of liraglutide, and this dose was increased once weekly to 1.2 mg, 1.8 mg, 2.4 mg and finally 3.0 mg. Blood samples for measuring the liraglutide plasma concentration were sampled for 60 hours after the last dose, starting at day 37 after start of treatment (35 days of treatment at home plus two additional days of dosing during the in-house stay). Single blood samples for plasma concentrations of liraglutide were drawn at trough on day 36, at trough on day 37 (in the evening, this dose defined as time=0), then at 2, 4, 11, 13, 15, 18, 20, 24, 36, 48 and 60 h after the last dose.

*The following data was explored in the PK model:*

NN8022-3967: All available plasma concentration measurements of liraglutide, exact time and amount of all doses administered throughout the trial, as well as demographic covariates (baseline body weight, sex, age category (adolescent) and PD markers (change from baseline in body weight, BMI Z-score and FPG).

NN8022-3630: Liraglutide plasma concentrations obtained from serial sampling following the last liraglutide (3.0 mg) dose at day 35 (when steady state concentrations are reached), with dose and exact time after dose for each blood sample. Demographic covariates included body weight, sex, age category (adult) and change from baseline in body weight.

Base PK model:

The base model was used for justifying the structural model and as a base for the covariate analysis.

A standard one-compartment model with first-order absorption and elimination was used to describe the liraglutide PK. The structural model was parameterized in terms of the following parameters:

- KA (absorption rate constants for liraglutide),
- CL/F (apparent clearance for liraglutide),
- V/F (apparent volume of distribution for liraglutide).

A proportional error model was used to describe the residual variability of liraglutide concentrations.

Full covariate model for PK:

The full covariate model containing the investigated covariates was used for obtaining point estimates and CI for all investigated covariate effects and for obtaining parameter estimates for quantifying covariate effects.

The covariate analysis included effects on CL/F and V/F. An alternative model including covariate effects on CL/F and the KA was investigated in a sensitivity analysis.

## Results

*Pharmacokinetics Study NN8022-3967*

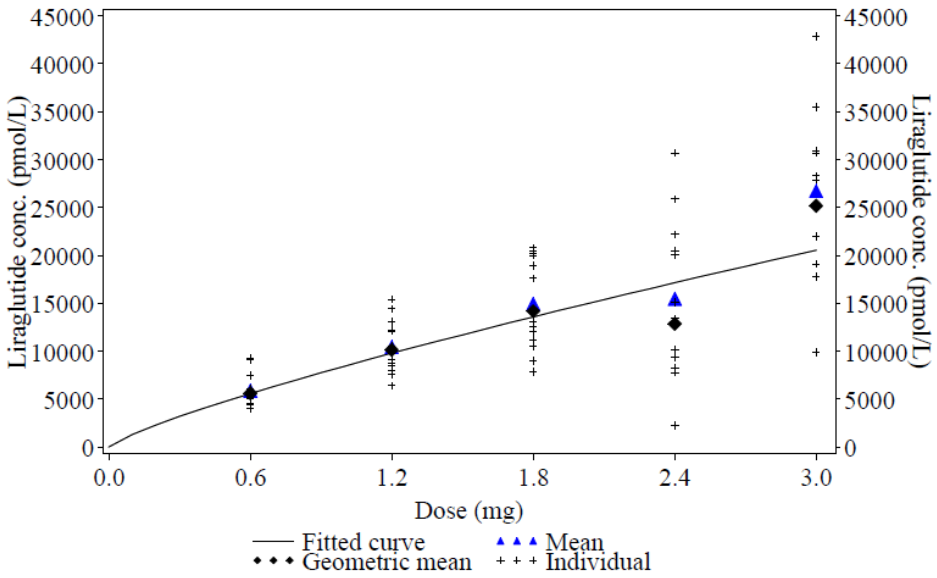
Dose proportionality

In the table below (Table 6) the mean $C_{trough}$ values are listed of the subjects measured on each visiting day (escalating doses) in this study and in **Error! Reference source not found.** the individual date are presented and fitted to estimate the dose proportionality of the pharmacokinetics of liraglutide.

**Table 6. Liraglutide plasma concentration, trough values - descriptive statistics**

| | | Lira 3.0 mg | | | | |
|---|---|---|---|---|---|---|
| | | Visit 3 (day 7) | Visit 4 (day 14) | Visit 5 (day 21) | Visit 6 (day 28) | Visit 7 (day 35) |
| Number of subjects | 13 | | | | | |
| Liraglutide plasma concentration (pmol/L) | | | | | | |
| N | | 13 | 13 | 13 | 13 | 12 |
| Mean (SD) | | 5853 (1899) | 10585 (2717) | 14662 (5091) | 15212 (8161) | 26740 (8727) |
| Geometric mean (CV) | | 5596 (31.31) | 10263 (26.50) | 13800 (38.25) | 12788 (77.31) | 25188 (40.05) |
| Median | | 5150 | 10400 | 13100 | 13400 | 28100 |
| Min ; Max | | 3970 ; 9300 | 6420 ; 15400 | 7840 ; 20800 | 2260 ; 30700 | 9880 ; 42900 |

**Figure 3. Dose proportionality based on $C_{trough}$ values (The fitted curve is based on the estimates from the linear regression model)**




The liraglutide concentration did not appear to increase in a dose-proportional manner, i.e. the estimated 2β with corresponding 95% CI was 1.75 (1.55; 1.98), p = 0.03 indicating that a doubling of the liraglutide dose resulted in a 1.75 times increase in exposure ($C_{trough}$).

Investigating the dose proportionality of liraglutide based on the $C_{trough}$ values in a linear normal regression model indicated that the liraglutide concentration did not increase in a dose-proportional manner mainly due to unexpected low $C_{trough}$ values at the 2.4 mg liraglutide dose. When excluding all $C_{trough}$ values at the dose of 2.4 mg in a post-hoc sensitivity analysis, the increase in liraglutide

concentration with increasing dose was however consistent with dose-proportionality. The reason for the unexpected low $C_{trough}$ values at the 2.4 mg liraglutide dose is not known.

**CHMP comments:**

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

*Population Pharmacokinetic Analysis:*

A total of 964 records from 42 subjects were included in the population PK analysis set. Thirteen subjects were from trial NN8022-3967 (adolescents) and 29 subjects were from trial NN8022-3630 (adults).

Figure 4 shows the individual concentration-time profiles for subjects in the two trials (NN8022-3967 and NN8022-3630) included in the analysis and

Table **7** list the model-derived pharmacokinetic parameters in obese adolescent and adult subjects.

It appeared to be an overlap between the concentration-time profiles from adolescents and adults.

**Figure 2 Individual (left) and geometric mean (95% CI) (right) observed liraglutide 3.0 mg concentration-time profiles for the two trials NN8022-3967 and NN8022-3630.**

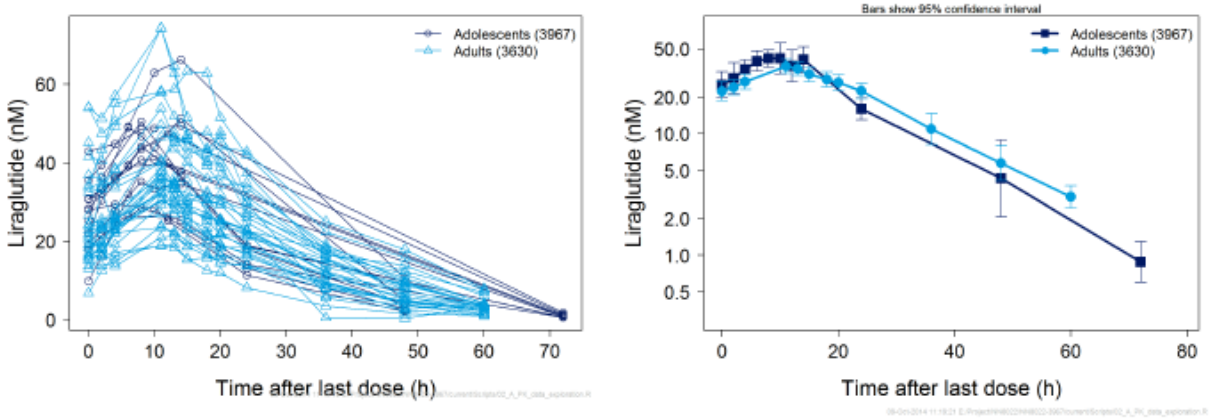


**Table 7. Model derived pharmacokinetic variables of liraglutide in adolescent and adult patients.**

| PK parameter | One-compartment model | | | |
|---|---|---|---|---|
| | Adolescents (trial 3967) (N = 13; 10 females and 3 males) | | Adults (trial 3630) (N = 29; 11 females and 18 males)* | |
| | Mean | [95% CI] | Mean | [95% CI] |
| AUCτ (nM*h) | 836** | [745; 962] | 696 | [640; 832] |
| CL/F (L/h) | 0.96 | [0.85; 1.11] | 1.15 | [1.05; 1.37] |
| $t_{½}$ (h)*** | 8.6 | [8.5; 8.7] | 9.8 | [9.4; 10.4] |
| V/F (L)*** | 10.3 | [9.5; 11.3] | 15.5 | [14.4; 18.2] |

**Note:** * PK estimates were derived by PK modelling on a pooled data set including data from the present adolescent trial and from a previous trial (NN8022-3630) in obese adult subjects and treated with liraglutide 3.0 mg. **AUCτ estimate for Subject 102003 (reached a maximum liraglutide dose of 2.4 mg) was normalised to 3.0 mg. ***V/F and hence t½ could not be estimated separately from the absorption rate (estimated to be 0.08 –h) and the reported values should therefore be interpreted with caution.
**Abbreviations:** CL/F = apparent clearance, V/F = apparent volume of distribution, AUCτ = area under the concentration-time curve at steady state from 0–24 hours, t½ = plasma half-life, N = number of subjects, CI: confidence interval.

The PK of liraglutide could be described by a one-compartment model with first-order absorption and elimination. The structural PK model was parameterized with KA, CL/F and V/F with between-subject variability parameters on CL/F and V/F, including covariance between the random-effect parameters. The residual error was described by a proportional error model.

The estimated parameters for the full covariate model are shown in Table 8.

**Table 8. Parameter estimates of the full model**

| Fixed-effects parameters | Description | Unit | Estimate | Uncertainty Relative Standard Error (%) |
|---|---|---|---|---|
| $K_A$ | Absorption rate constant | L/h | 0.0809 | 5 |
| CL/F | Apparent clearance* | L/h | 0.984 | 9 |
| V/F | Apparent volume of distribution* | L | 13.5 | 12 |
| F | Bioavailability | 1 | 1 (fixed) | NA |
| Cov. CL - BW | CL - Body weight exponent | N/A | 0.449 | 107 |
| Cov. CL - SEX | CL - Sex contrast (MALE/FEMALE) | N/A | 0.261 | 52 |
| Cov. CL – AGEgr. | CL - Age category contrast (ADOLESCENT/ADULT) | N/A | -0.0957 | 98 |
| Cov. V - BW | V - Body weight exponent | N/A | 0.0736 | 863 |
| Cov. V - SEX | V - Sex contrast (MALE/FEMALE) | N/A | 0.234 | 70 |
| Cov. V – AGEgr. | V - Age category contrast (ADOLESCENT/ADULT) | N/A | -0.322 | 43 |
| **Random-effects parameters** | **Description** | **Unit** | **Estimate** | **Shrinkage (%)** |
| CL/F | Between-subject variability in CL/F | % CV | 26.0 | 2 |
| V/F | Between-subject variability in V/F | % CV | 28.7 | 11 |
| Corr. | Correlation coefficient between random-effect parameters | | 0.76 | NA |
| **Residual error parameters** | **Description** | **Unit** | **Estimate** | **Shrinkage (%)** |
| Sigma | Residual error (proportional) | % CV | 19.7 | 7 |

*Estimate for reference (adult, female, body weight 100 kg)

The model fit was acceptable and there were no critical trends in the conditional weighted residuals vs. neither liraglutide concentration nor time. The individual CL/F and V/F estimates appeared to approximate normal distributions. (See Figure 5 and Figure 4 below)

**Figure 5 Diagnostic plots for the full covariate model for liraglutide: Population predicted vs. observed concentrations, individual predicted vs. observed concentrations, and conditional weighted residuals vs. predicted concentrations and vs. time.**

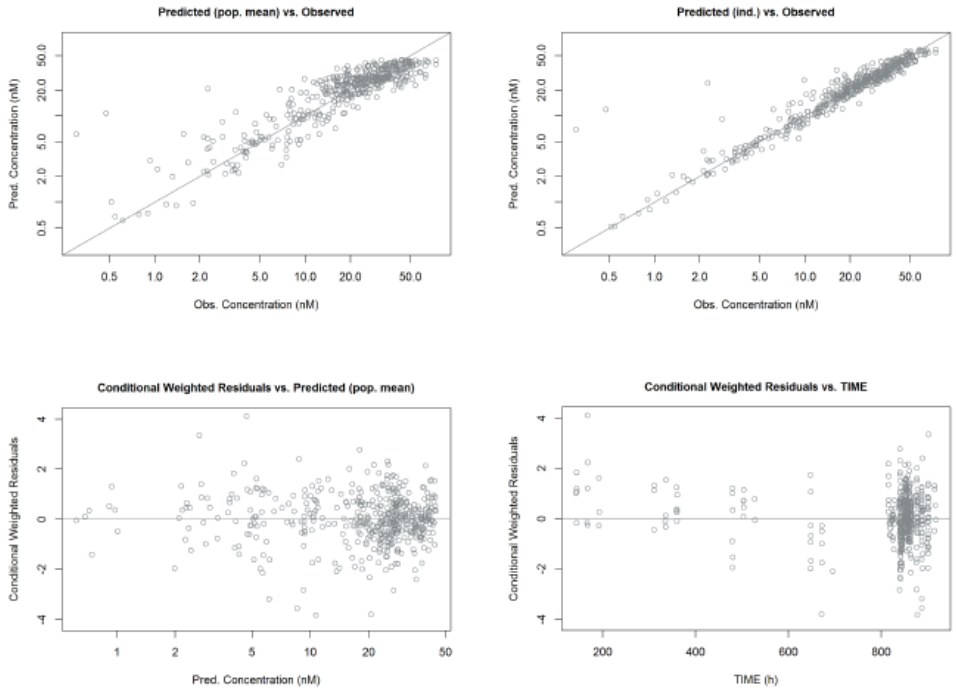
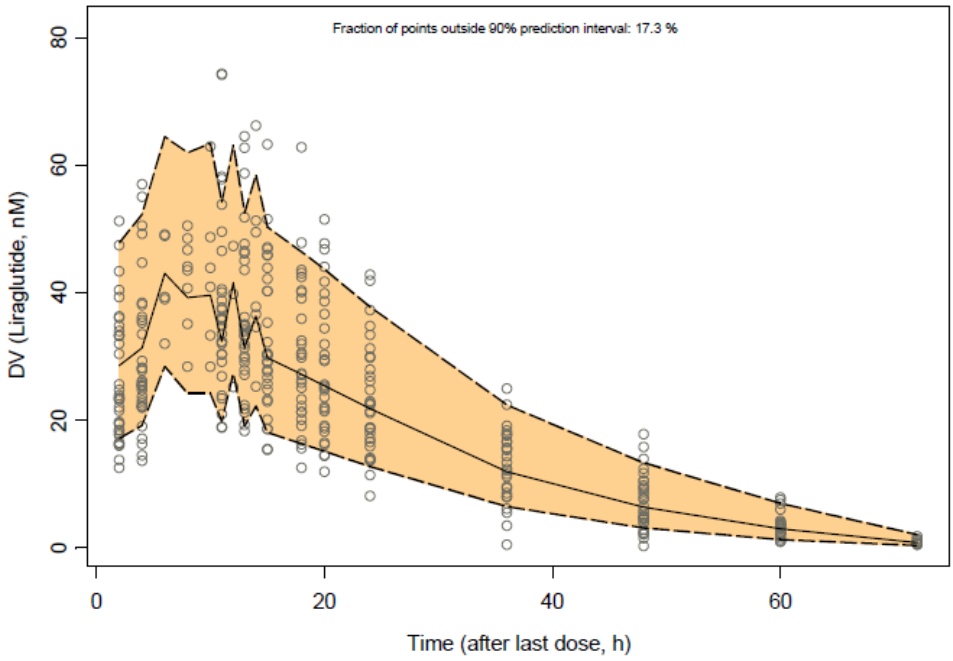


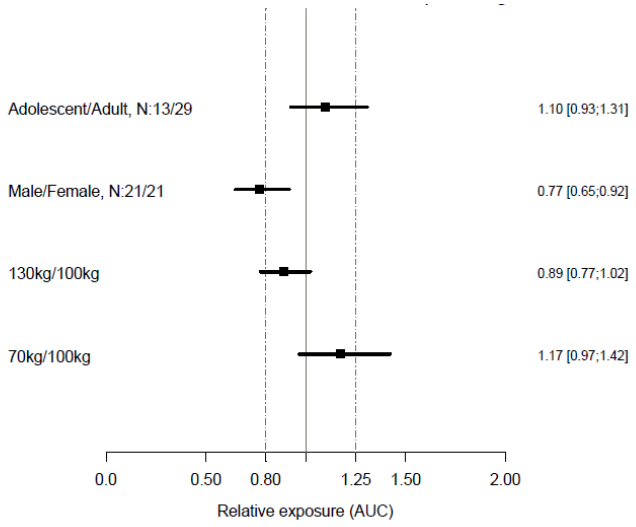

**Figure 3. Visual predictive check of the full population PK model with respect to predicted median profiles and 90% prediction intervals. The observed liraglutide plasma concentrations have not been corrected for covariates or dose. Only data from subjects on 3.0 mg liraglutide in steady state are included in the plot.**




The influence of covariates, besides the possible difference between adolescent and adults, is given in Figure 5. In accordance with this, sex was identified as the only relevant covariate for liraglutide

exposure in the covariate analysis with a 23% (90% CI: 8; 35%) lower exposure in male subjects compared to females (Figure 5). In addition, there was a reduced exposure with increasing body weight (the mean exposure with the highest body weight in the dataset [130 kg] was 11% [90% CI: -23; 2%] lower and the lowest body weight in the dataset [70 kg] was 17% [90% CI: -3; 42%] higher compared to the reference body weight of 100 kg) and a slightly higher exposure in adolescents compared to adults (obese adolescents had a mean difference in exposure of 10% [90% CI: -7; 31%] compared to adults).

**Figure 4. Forrest plot of covariate effects on the pharamcokinetics of liraglutide.**




**Note:** Geometric mean and 90% confidence intervals for effects of covariates relative to a reference subject (adult female weighing 100 kg). The dotted lines represent bioequivalence limits of 0.8 and 1.25.

**CHMP comments:**

The performed pharmacokinetic population analysis on the data of studies in adults and adolescent demonstrates that the exposure to liraglutide in adults and adolescents (12 -17 year) is similar.

Pharmacodynamic

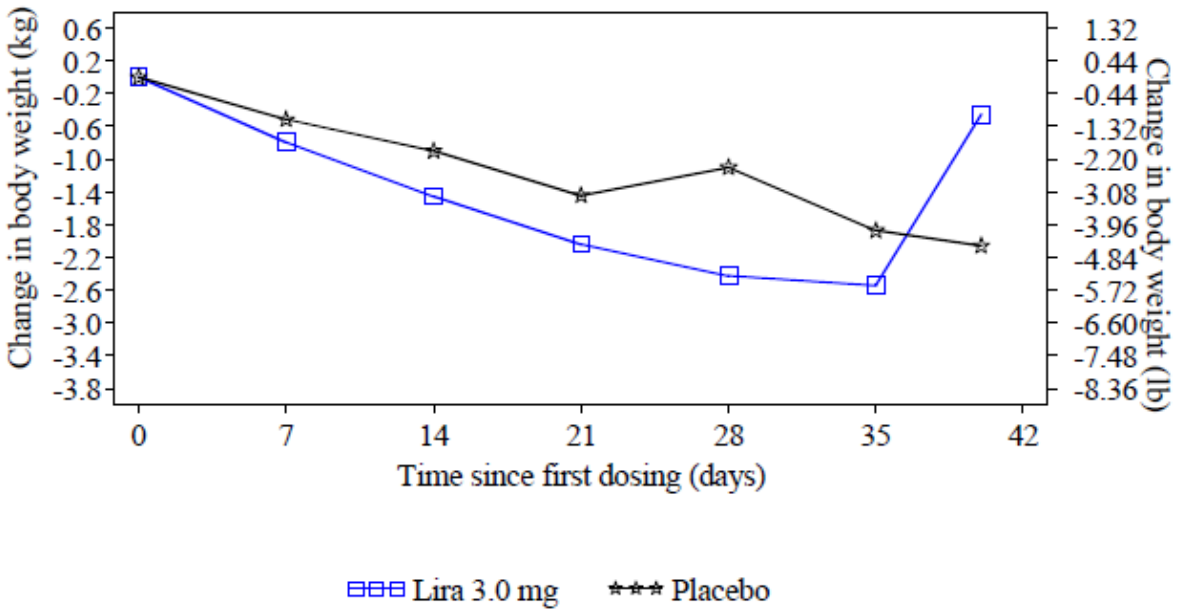
In general, no statistically significant treatment effect of liraglutide was demonstrated for any of the pharmacodynamic endpoints ( BMI z-score, Body weight, Fasting blood glucose, HbA1c, Serum insulin) probably due to the short duration of treatment and low number of subjects. (**Error! Reference source not found.** and

Figure **8**) However, most of the pharmacodynamic endpoints tended to be numerically in favour of liraglutide. None were in favour of placebo.

**Table 9. Statistical analysis of change from baseline to end-of-treatment in different PD parameters-FAS**

| | Fas | N | Estimate | 95% CI | P-value |
|---|---|---|---|---|---|
| Change in Fasting plasma glucose (mmol/l) Least square means | | | | | |
| Liraglutide | 14 | 13 | -0.29 | -0.40;0.01 | 0.1937 |
| Placebo | 7 | 7 | 0.03 | -0.25;0.43 | |
| Change in HbA1c (%) Least square means | | | | | |
| Liraglutide | 14 | 13 | -0.11 | -0.22;0.00 | 0.2037 |
| Placebo | 7 | 7 | 0.01 | -0.15;0.16 | |
| Change in body weight (kg) Least square means | | | | | |
| Liraglutide | 14 | 13 | -2.55 | -4.58;-0.52 | 0.6836 |
| Placebo | 7 | 7 | -1.85 | -4.73;1.03 | |
| Change in Fasting insulin (pmol/l) Least square means | | | | | |
| Liraglutide | 14 | 13 | -10.22 | -44.7;24.26 | 0.4092 |
| Placebo | 7 | 7 | 13.15 | -33.9;60.16 | |

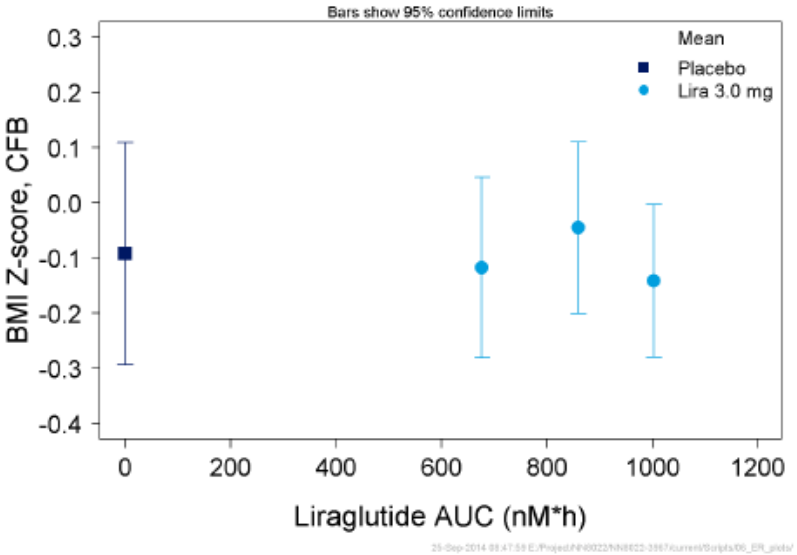
**Figure 5 Mean body weight - change from baseline - mean longitudinal plot - full analysis set**




The relationship between exposure and the pharmacodynamic parameters BMI z-score, body weight and fasting blood glucose after 5 weeks of treatment (including dose-escalation) was explored according to a specific request by the PDCO. No obvious trends of increasing response with increasing exposure were observed for any of these pharmacodynamic parameters in adolescents after 5 weeks of treatment (

**Figure 9**) The same pattern was observed for weight and plasma fasting glucose. The data should be interpreted with caution due to the low number of subjects included in the trial and the short treatment duration leading to low response.

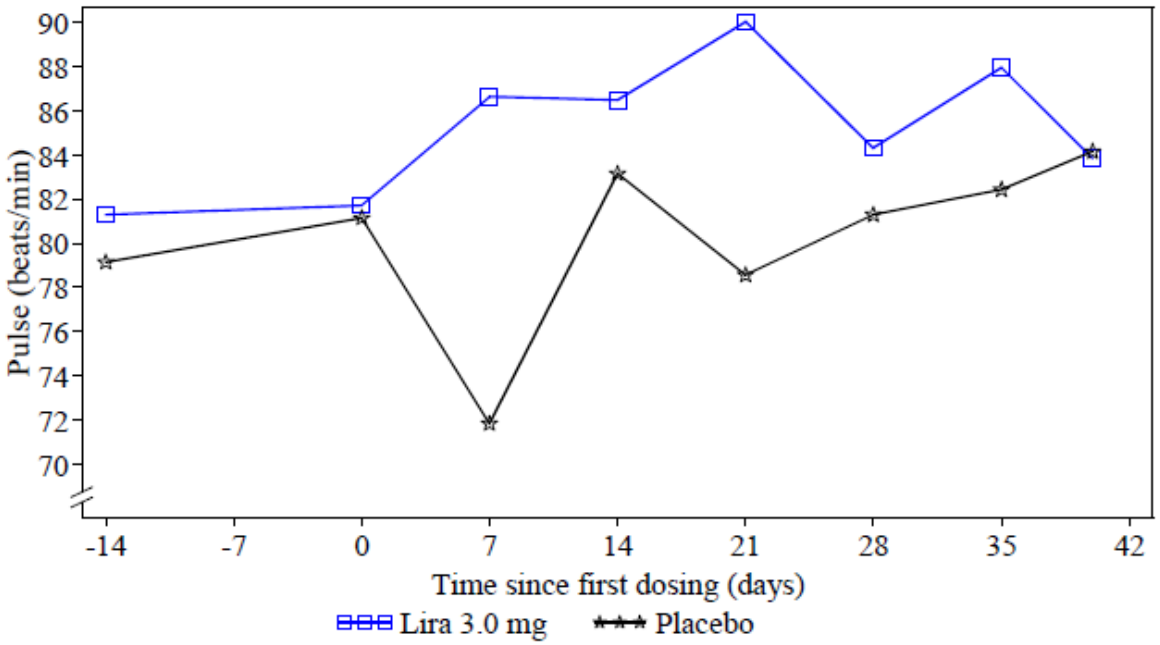
**Figure 6 Change from baseline in BMI z-score versus exposure of liraglutide (AUCτ) after 5 weeks of treatment – FAS**




**Note:** Data are mean values with 95% confidence interval versus exposure expressed as 3 quantiles of AUCτ (steady state, 0-24 hours) (plus placebo AUCτ [steady state, 0-24 hours] of 0 nM*h).
**Abbreviations:** CFB = change from baseline, Lira = liraglutide.

In the liraglutide group, the resting pulse was numerically increased from baseline to end-of treatment (mean change from baseline: 6 beats/minute ranging from -20 to 24 beats/minute) moving towards baseline values at follow-up. In the placebo group, mean change in resting pulse increased by 1 beat/minute (ranging from -10 to 15 beats/minutes.

**Figure 10. Mean resting pulse (beats/ minute) over time – safety analysis set**



**CHMP comments:**

As the MAH stated, a favourable effect was observed for change in weight for liraglutide versus placebo. However, after finishing liraglutide treatment, the weight increased in the liraglutide group. Future research is needed to conclude whether liraglutide can sustain the weight loss.

In accordance with adult data, a mean change of 6 beats/min in heart frequency was observed. The clinical relevance for the paediatric population can not be determined.

# 3. Rapporteur's overall conclusion and recommendation

In this specific trial in adolescents, with a mean age of 15 years, a mean body weight of 105.5 kg (78.5 to 164.4 kg), mean BMI was 36.2 kg/$m^2$ (29.3 to 44.9 kg/m2) and most with Tanner stage 5 or 4, more TEAE were observed in the treatment group. 14 of 14 (100%) subjects experienced 86 events in total, which were most often mild gastro intestinal complaints, compared to 4 of 7 subjects on placebo who experienced 7 events in total. 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 for a first evaluation of safety in the paediatric population.

More hypoglycaemia was present in the liraglutide group. 8 of 14 subjects experienced 12 events, compared to 1 subjects of 7, experiencing 2 hypoglycaemic events in the placebo group. No severe hypoglycaemia was observed and most hypoglycaemia cases were observed at lower doses and were only mild. However, due to recurrent hypoglycaemia, one subject did not reach 3.0 mg liraglutide, but received 2.4 mg maximum. Because glucose measurements were performed with a glucometer during the trial, these data should be interpreted with caution. More research is needed to conclude on the magnitude of this problem in this specific treatment group.

In one subject, combined lipase and amylase increase was observed in the liraglutide group, which is also observed in the adult population. No liraglutide antibodies were observed.

Regarding vital signs, resting pulse was found to be numerically increased and systolic and diastolic blood pressure was numerically lowered in the liraglutide group compared to placebo. The clinical significance of these changes in pulse and blood pressure is not known. However, this phenomenon is also observed in adults. The long-term effects of liraglutide on cardiovascular outcomes and other clinically important events, were examined in 9340 adult patients in the LEADER trial (the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results). The rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in significantly fewer patients in the liraglutide group than in the placebo group ($p<0.001$ for noninferiority; $p=0.01$ for superiority).

Although most of the explorative PD endpoints tended to be numerically in favour of liraglutide no statistically significant treatment effect was demonstrated the BMI Z-score, body weight, fasting plasma glucose, HbA1c and serum insulin after 5 weeks of treatment (including dose-escalation). Remarkably, a rise in weight was observed after finishing liraglutide treatment.

Regarding pharmacokinetics, it is agreed with the applicant that exposure associated with 3.0 mg liraglutide was found to be comparable between the adolescents studied in this clinical trial and what has been demonstrated in adult subjects. There is an overlap between the concentration-time profiles from adolescents and adults, as observed in the compared trials (NN8022-3967 and NN8022-3630).

Additionally, this was confirmed in the pharmacokinetic modelling. After correcting for the difference in sex ratio between trial populations, the exposure determined in adolescents was similar to the exposure in adults.

Further, results of the study demonstrated that the pharmacokinetics of liraglutide can be considered linear, but not fully dose proportional. The deviation from dose proportionality in this patient group is considered not clinical relevant.

**Overall conclusion**

Trial NN8022-3967, investigating the safety and tolerability of liraglutide administered according to a dose-escalation scheme to a maximum tolerated dose of up to 3.0 mg/day (Saxenda) for a period of 5−6 weeks in adolescents, did not reveal unexpected safety and tolerability issues apart from the occurrence of hypoglycaemia that needs further exploration. Exposure associated with 3.0 mg liraglutide was found to be comparable between the adolescents studied and adult subjects.

Trial NN8022-3967 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 NN8022-3967 is the first of the 5 planned paediatric clinical trials to be completed.

Trial NN8022-4181, recently completed, assessed 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 also not reveal unexpected safety and tolerability issues.

The results of the other paediatric clinical trials has to be waited for, to draw definite conclusions, especially in the context of hypoglycaemia. In general, the side effects of Saxenda in the adolescent population aged 12−17 years are in accordance with adults, with possibly a more pronounced effect on hypoglycaemia, which need a further exploration.

### Recommendation

X Fulfilled:

No regulatory action required.

## 4. Additional clarification requested

Not applicable.

# Annex. Line listing of all the 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) | | |