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Committee for Medicinal Products for Human Use (CHMP)

Victoza

(liraglutide)

Procedure No. EMEA/H/C/001026/P46 029

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

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

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I. RECOMMENDATION

Based on the review of the data on safety and efficacy the Rapporteur considers that results of trial NN2211-1800 do not give rise to changes in the labelling of Victoza®.

II. EXECUTIVE SUMMARY

II.1 Introduction

In accordance with article 46 of Regulation (EC) No 1901/2006 the MAH has submitted the final Clinical Trial Report for Trial NN2211-1800: A Randomised, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10–17 years old) Subjects with Type 2 Diabetes.
The trial is part of the Paediatric Investigation Plan (EMEA 000128-PIP01-07-M03). A waiver for children below the age of 10 years has been granted on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset.
The agreed PIP contains an additional paediatric clinical study in children older than 10 years with Diabetes type 2 : Multicentre, 14-week double-blind, randomised, parallel-group, placebo-controlled clinical trial followed by at least 38-week open-label extension. Completion of this study is expected in 2015.

Liraglutide (Victoza®) is a long-acting human analogue of the naturally occurring incretin hormone GLP-1, suitable for once-daily administration. Liraglutide is approved in the major markets (i.e., EU, Japan, Australia, USA and China) for the treatment of adults with type 2 diabetes mellitus who are not able to achieve adequate glycaemic control on oral antidiabetic drugs (OADs). In adults, liraglutide can be administered in combination with metformin, sulphonylurea (SU), metformin + SU or metformin + thiazolidinedione (TZD). Furthermore, liraglutide is approved to be used in monotherapy as second-line treatment in the USA.

Based on the prevalence of type 2 diabetes in children and adolescents and considering the pharmacology of liraglutide, it is conceivable that liraglutide may prove to be a useful tool in the management of the disease. Based on the general consensus that development of type 2 diabetes is of most concern in older children and adolescents, the clinical programme with liraglutide is performed in children and adolescents aged 10–17 years.

III. SCIENTIFIC DISCUSSION

Trial NN2211-1800 was a randomised, double-blind, placebo-controlled, 5-week trial in which paediatric subjects (10–17 years) with type 2 diabetes were randomised 2:1 either to liraglutide or placebo treatment (administered subcutaneous once daily). The primary objective of the trial was to assess the safety and tolerability of liraglutide in the paediatric population. In addition, the trial was designed to gain valuable information on pharmacokinetics and pharmacodynamics of liraglutide in the paediatric population (secondary objectives).
As safety was the primary objective, the order of the discussion below will be

1. Clinical safety, including methods;
2. Pharmacokinetics;
3. Pharmacodynamics

III.1 Clinical Safety

III.1.1 Methods

Study design

This was a randomised, double-blind, placebo-controlled trial in which paediatric subjects with type 2 diabetes were randomised 2:1 either to liraglutide or placebo treatment (administered s.c,. once daily) for five weeks. Subjects continued their pre-trial treatment (diet and exercise or metformin) unchanged during the trial period. Subjects randomised to liraglutide treatment received 0.3 mg liraglutide daily (starting on Day 1) during the first week, followed by 0.6 mg daily (starting on Day 8) during the second week, 0.9 mg daily (starting on Day 15) during the third week, 1.2 mg daily (starting on Day 22) during the fourth week, and 1.8 mg daily (starting on Day 29) during the fifth and final treatment week. Subjects randomised to placebo were given matched placebo treatments during each of the corresponding five weeks in order to maintain blinding. Safety and tolerability were assessed throughout the five-week treatment period. Serial sampling for the 13-hours liraglutide PK profile was performed for each subject at the end (Day 7) of Weeks 1 (0.3 mg), 2 (0.6 mg), 4 (1.2 mg) and 5 (1.8 mg). Additional single samples for the final dose, 72-hours liraglutide PK profile were obtained for each subject at Week 6 Day 1 (24 hours), Week 6 Day 2 (48 hours) and Week 6 Day 3 (72 hours). Dose escalation was based on safety and tolerability (as an average of 3 measurements of FPG >110 mg/dL [6.1 mmol/L]) at each dose level. If dose escalation was not applicable, subjects continued on the highest reached dose for the remainder of the trial. A follow-up visit occurred 5 days after the last liraglutide dose.

This trial was designed to assess whether paediatric subjects with type 2 diabetes could tolerate treatment with once-daily liraglutide doses, ranging from 0.3 mg/day to 1.8 mg/day. In addition, the PK and exploratory PD information collected in this trial would form a guiding basis for dose selection in the safety and efficacy trial mentioned above. The sample size determination for the current trial was based on clinical judgement, which deemed that the primary endpoint (safety and tolerability) could be adequately assessed in a trial population comprising at least 18 paediatric subjects.

Study population

Main **inclusion criteria** were:

- Male and Female subjects with T2DM
- aged 10-17 years at screening, BMI >85th percentile for age and gender,
- Drug-naïve (diet and exercise) or treated with metformin, stable dose and regimen for at least 4 weeks prior to screening with HbA1c ≥6.5% and ≤11.0% (changed by amendment, originally: ≥7.0% and ≤10.0%)
- At randomisation (Visit 2): FPG ≥110 and ≤240 mg/dL (or, ≥6.1 mmol/L and ≤13.3 mmol/L); changed by amendment, originally FPG 130-220mg/dL (or, ≥7.2 mmol/L and ≤12.2 mmol/L)

Main **exclusion criteria** were:T1DM, Previous treatment within the last three months with any anti-diabetic agent other than metformin; impaired liver function or renal function; Recurrent major hypoglycaemia or hypoglycaemic unawareness as judged by the Investigator; Past or current history of pancreatitis; Calcitonin value >50 ng/L.

Objectives

Primary objective was to assess the safety and tolerability of 0.3, 0.6, 0.9, 1.2 and 1.8 mg doses of liraglutide in the paediatric population (10 – 17 years of age).
Secondary objectives were to estimate the pharmacokinetic (PK) parameters of liraglutide in children and to estimate the pharmacodynamic (PD) parameters of liraglutide in children.

Endpoints
The primary endpoints were: AEs, laboratory tests (including biochemistry, haematology, urinalysis, amylase and lipase fasting lipids and relevant biomarkers and hormones), Vital signs, Physical examination, ECG, Funduscopy, Liraglutide antibodies, and Hypoglycaemic episodes.
Secondary endpoints were PK and PD parameters. These are described below in the relevant paragraphs.

Statistical analysis
The two analysis sets used in this trial, the full analysis set and the safety analysis set.
Full analysis set included all randomised subjects. Safety analysis set included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety analysis set contributed to the evaluation 'as treated.'
The analysis of the primary endpoint (safety and tolerability) was based on the safety analysis set.
Analyses of the secondary PK and PD endpoints were based on the full analysis set.

No statistical power calculation was performed for this trial. Based on the primary and secondary objectives, it was considered clinically sufficient to obtain the data needed pertaining to the safety, pharmacokinetic and pharmacodynamic endpoints by randomly allocating a minimum of 12 subjects to receive liraglutide and 6 subjects to receive placebo.

No 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.

PK endpoints were summarised by liraglutide dose using descriptive statistics. PD endpoints were presented as changes from baseline by treatment.

Assessor's comments
The design of the study only allows for a first inventory of safety and PK and PD parameters. A limited number of patients were to be included. No statistical power calculation was performed.
Inclusion criteria were amended to include a wider range of subjects based on HbA1c and FPG values. Patients were included with baseline HbA1c of 6.5, which is considered rather low for diabetic patients.

III.1.2 Results

Disposition of subjects
A total of 57 subjects were screened, of which 21 were randomised and exposed to treatment (Table 1). Thirty-six (36) subjects failed screening, 33 out of 36 due to one or more inclusion and/or exclusion criteria. The screen failure reasons for the 3 remaining subjects were 'withdrawal of consent', 'lost to follow-up' and 'investigator wanted root canal work done before randomisation'. The most common

single reason for failing screening was the HbA1c inclusion criterion (19 out of 36 subjects), with the majority of subjects not meeting the lower limit of HbA1c inclusion.
Of the 21 (100%) randomised subjects, 2 subjects withdrew during the trial: a liraglutide-treated subject during Visit 3 due to a blood draw issue and a placebo-treated subject after Visit 2 due to not wanting to undergo trial procedures.
A total of 19 subjects (90.5%) completed the trial. All 21 randomised subjects were included in the safety analysis set (i.e. all subjects exposed to treatment) and the full analysis set (i.e. all randomised subjects).

Some data from 7 subjects were relevantly excluded form PK analyses

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Table 1: Subject disposition

	Liraglutide N (%)	Placebo N (%)	Total N (%)
Screened			57
Screening failures			36
Non-randomized			0
Randomised	14 (100)	7 (100)	21 (100)
Exposed to Trial Product	14 (100)	7 (100)	21 (100)
Withdrawals	1 (7.1)	1 (14.3)	2 (9.5)
Withdrawal criteria	1 (7.1)	0 (0.0)	1 (4.8)
Other	0 (0.0)	1 (14.3)	1 (4.8)
Completers	13 (92.9)	6 (85.7)	19 (90.5)
Full analysis set	14 (100)	7 (100)	21 (100)
Safety analysis set	14 (100)	7 (100)	21 (100)

Demographics and baseline characteristics
A summary of demographics and baseline characteristics for all randomised subjects is presented in Table 2. Twenty-one (21) paediatric subjects with type 2 diabetes were enrolled in this trial, 14 in the liraglutide and seven in the placebo group. In total, subjects were between 10-17 years in age, 57.3-214.4 kg in weight and 29.2-71.6 kg/m2 in BMI. Mean age, weight and BMI were comparable between liraglutide and placebo groups. Three (3) subjects were under 12 years of age: 2 in the liraglutide group and 1 in the placebo group. The majority of subjects were female (66.7%). Subjects were predominantly White 14 (66.7%); 7 (33.3%) were Black or African American. All subjects in the placebo group were post-pubertal. In the liraglutide group, 1 subject was at Tanner stage I and 1 subject at Tanner stage II, while the remaining subjects were post-pubertal.
Duration of diabetes ranged from 0.1 to 5.5 years and mean duration (1.7 years) was identical for subjects randomised to either liraglutide or placebo. Three (3) liraglutide subjects and 2 placebo subjects were previously treated with diet and exercise only, while the 16 remaining subjects were previously treated with metformin, with daily doses ranging from 500 to 3000 mg. It should be noted that 1 placebo subject was incorrectly categorised to ‘metformin’ when he should have been assigned

to the 'diet and exercise' category (see footnote in Table 2). Screening HbA1c ranged from 6.5 to 11.0% (limits of inclusion) and mean HbA1c was higher for the liraglutide group (8.3%) than the placebo group (7.8%).

Table 2: Summary of demographic and baseline characteristics – full analysis set

	Liraglutide	Placebo	Total
Full Analysis Set	14	7	21
Age (years)			
N	14	7	21
Mean (SD)	14.4 (2.2)	15.6 (2.1)	14.8 (2.2)
Median	15.0	16.0	15.0
Min ; Max	10.0 ; 17.0	11.0 ; 17.0	10.0 ; 17.0
Sex, N (%)			
N	14 (100)	7 (100)	21 (100)
Male	5 (35.7)	2 (28.6)	7 (33.3)
Female	9 (64.3)	5 (71.4)	14 (66.7)
Race, N (%)			
N	14 (100)	7 (100)	21 (100)
White	10 (71.4)	4 (57.1)	14 (66.7)
Black or African American	4 (28.6)	3 (42.9)	7 (33.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, N (%)			
N	14 (100)	7 (100)	21 (100)
Hispanic or Latino	3 (21.4)	0 (0.0)	3 (14.3)
Not Hispanic or Latino	10 (71.4)	6 (85.7)	16 (76.2)
NA	1 (7.1)	1 (14.3)	2 (9.5)
Height (m)			
N	14	7	21
Mean (SD)	1.67 (0.14)	1.68 (0.13)	1.67 (0.14)
Median	1.62	1.65	1.63
Min ; Max	1.40 ; 1.92	1.55 ; 1.94	1.40 ; 1.94
Weight (kg)			
N	14	7	21
Mean (SD)	112.7 (37.3)	114.2 (34.7)	113.2 (35.6)
Median	105.7	98.3	105.5
Min ; Max	57.3 ; 214.4	86.8 ; 186.0	57.3 ; 214.4
BMI (kg/m^2)			
N	14	7	21
Mean (SD)	40.0 (10.3)	39.9 (6.8)	40.0 (9.1)
Median	37.4	36.1	36.4
Min ; Max	29.2 ; 71.6	33.9 ; 49.4	29.2 ; 71.6
HbA1c (%)			
N	14	7	21
Mean (SD)	8.3 (1.4)	7.8 (0.9)	8.1 (1.2)
Median	8.1	7.6	7.7
Min ; Max	6.5 ; 11.0	7.2 ; 9.8	6.5 ; 11.0
Previous anti-diabetic treatment, N (%)			
N	14 (100)	7 (100)	21 (100)
Metformin	11 (78.6)	6 (85.7)+	17 (81.0)
Diet and Exercise Only	3 (21.4)	1 (14.3)	4 (19.0)
Puberty, N (%)			
N	14 (100)	7 (100)	21 (100)
I	1 (7.1)	0 (0.0)	1 (4.8)
II	1 (7.1)	0 (0.0)	1 (4.8)
III	0 (0.0)	0 (0.0)	0 (0.0)
IV	4 (28.6)	0 (0.0)	4 (19.0)
V	8 (57.1)	7 (100)	15 (71.4)

N: Number of subjects, %: Percentage of exposed subjects, BMI: body mass index, SD: standard deviation ; NA: Not Available

+ One subject 201002 (in placebo group) was incorrectly classified in "metformin". In fact, he stopped Metformin before the trial, hence he should be in "diet/exerise" instead.

Assessor's comments

There were no significant differences in demographic data and baseline characteristics between treatment groups, apart from a higher HbA1c for the liraglutide group (8.3% vs 7.8% for liraglutide vs placebo). Compared to studies in adults, paediatric subjects had a high mean BMI (40 kg/m^2). The majority of subjects were post-pubertal. Only three subjects (2 liraglutide, 1 placebo) were below 12 years of age. Therefore, the experience in children below 12 years and pubertal stage I-III is very limited.

Exposure

The formulation of liraglutide used in this trial was the same as the formulation and pens used in clinical trials including adults: liraglutide 6.0 mg/mL, 3 mL FlexPen® for subcutaneous injection. The formulation contains liraglutide (6.0 mg/mL), phosphate to stabilise pH, propylene glycol as isotonic agent and phenol added as a preservative.

As a safety precaution, dose escalation took place only if the mean fasting plasma glucose (FPG) taken on 3 consecutive days before the dose escalation visits was above 6.1 mmol/L. Nine (9) liraglutide subjects escalated to the maximum dose of 1.8 mg liraglutide, while 3 subjects remained on 0.6 mg liraglutide. One (1) subject, who was diet and exercise treated, remained on 0.3 mg liraglutide. This subject had an HbA1c at screening of 6.9%. All subjects who did not escalate the liraglutide dose to the maximum dose of 1.8 mg did so based on FPG measurements, and not due to lack of tolerability or due to adverse events. All subjects randomised to placebo were escalated to a dose volume corresponding to 1.8 mg liraglutide.

The 14 subjects randomised to liraglutide treatment were exposed for a mean duration of 34 days. One (1) liraglutide-treated subject withdrew after 7 days of treatment due to a blood draw issue (morbidly obese subject was unwilling to undergo repeated unsuccessful attempts at blood sampling). The 7 subjects randomised to placebo were exposed for a mean duration of 31 days. One (1) placebo-treated subject withdrew after 5 days due to not wanting to undergo the trial procedures (home self-measured plasma glucose [SMPG] assessments).

Adverse events, Deaths, other serious adverse events and withdrawals due to AEs.

There were 10 subjects with 38 TEAEs in the liraglutide group and 3 subjects with 18 TEAEs in the placebo group (Table 3). None of these TEAEs were serious and no deaths were reported in this trial. There were no TEAEs that led to subject withdrawal in this trial.

For subjects receiving liraglutide, the TEAEs were primarily reported in the SOC of 'gastrointestinal disorders' (17 events in 8 subjects), followed by the SOCs 'injury, poisoning and procedural complications' (7 events in 3 subjects) and 'nervous system disorders' (5 events in 3 subjects) (Table 4). The most frequently reported GI TEAEs with liraglutide were diarrhoea, nausea and vomiting. 'Headache' was the most commonly reported nervous systems disorder, whereas 'joint sprain' was the most frequently reported preferred term for 'injury, poisoning and procedural complications'.

All GI TEAEs were mild in severity for liraglutide subjects.

Examination of TEAEs by liraglutide dose showed that the majority of events occurred at liraglutide 0.3 mg and 0.6 mg doses during the 2 initial treatment weeks (Table 5). The majority of GI TEAEs were reported at the liraglutide 0.3 mg dose and occurred within 0-5 days of treatment initiation.

For subjects receiving placebo, most frequently reported TEAEs were also in the SOC of 'gastrointestinal disorders' (7 events in 2 subjects); see Table 3. Both, mild (5) and moderate (2) GI TEAEs were reported by placebo-treated subjects.

Sixteen (16) TEAEs possibly or probably related to treatment were reported by 6 liraglutide-treated subjects (Table 3). All events reported by the placebo subjects were classified as unlikely to be related to treatment.

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

	Liraglutide N	(%)	E	Placebo N	(%)	E	Total N	(%)	E
Safety Analysis Set	14			7			21		
All Adverse Events	10	(71.4)	38	3	(42.9)	18	13	(61.9)	56
Serious Adverse Events	0	(00.0)	0	0	(00.0)	0	0	(00.0)	0
Relation to Treatment Regimen									
Probable	2	(14.3)	3	0	(00.0)	0	2	(9.5)	3
Possible	5	(35.7)	13	0	(00.0)	0	5	(23.8)	13
Unlikely	5	(35.7)	21	3	(42.9)	18	8	(38.1)	39
Missing	1	(7.1)	1	0	(00.0)	0	1	(4.8)	1
Severity									
Severe	0	(00.0)	0	0	(00.0)	0	0	(00.0)	0
Moderate	0	(00.0)	0	1	(14.3)	4	1	(4.8)	4
Mild	10	(71.4)	38	3	(42.9)	14	13	(61.9)	52

N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Hypoglycaemia

Three (3) liraglutide-treated subjects experienced 11 hypoglycaemic episodes of which 4 episodes fulfilled the definition of a “minor hypoglycaemia” (confirmed plasma glucose <3.1 mmol/L with or without symptoms). Of the 3 subjects, each subject had 1 minor hypoglycaemia episode occurring approximately 1–2.5 weeks after dose escalation to 0.6 mg, approximately 2–3 hours after a meal and could be potentially attributable to post-prandial hyperinsulinemia. None of the 3 subjects had their liraglutide dose escalated past 0.6 mg, had a screening HbA1c ranging from 7.0 to 11.0% and their body weight was >105 kg. Two (2) of the 3 subjects were co-treated with metformin (1000 mg). One (1) placebo-treated subject on 2000 mg metformin experienced one hypoglycaemic episode. No severe or nocturnal hypoglycaemic episodes were reported and all episodes were self-treated.

Laboratory values and vital signs

No clinically significant findings for haematology, biochemistry or urinalysis occurred in this trial.
Calcitonin levels remained below the upper normal limits in female and male liraglutide subjects.
Of the 14 liraglutide-treated subjects, 4 had elevated lipase levels at Follow-up (end of trial), with 1 subject already exhibiting elevated levels at Screening. No lipase levels >3 times the upper limit of normal were observed. Amylase levels remained within the normal range at Screening and Follow-up for subjects treated with liraglutide. Of the 7 placebo-treated subjects, 1 subject exhibited elevated lipase levels at Screening and Follow-up, while amylase levels remained below normal limits in all subjects.
No clinically significant findings for physical examinations, electrocardiogram (ECG), and funduscopy, occurred during the trial and samples from all subjects were negative for liraglutide antibodies at baseline and at the end of the trial.
Per Novo Nordisk’s agreement with the European Medicines Agency’s Paediatric Committee (PDCO), an external hormonal safety board reviewed the paediatric hormonal data for any evidence of hormonal disruption due to trial product treatment. There was no evidence of hormonal disruption based on evaluation of the following hormones and biomarkers measured pre-dose and post-dose: estradiol (female subjects), testosterone (male subjects), carcinoembryonic antigen (CEA), insulin-like growth

factor 1 (IGF-I), dehydroepiandrosterone sulfate (DHEAS), thyroid stimulating hormone (TSH), lutinising hormone (LH), follicle stimulating hormone (FSH), prolactin, C-peptide and fructosamine.

Table 4: Treatment emergent adverse events by system organ class and preferred term – safety analysis set

	Liraglutide			Placebo			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	14			7			21		
Adverse Events	10	(71.4)	38	3	(42.9)	18	13	(61.9)	56
Gastrointestinal disorders	8	(57.1)	17	2	(28.6)	7	10	(47.6)	24
Diarrhoea	6	(42.9)	7	1	(14.3)	1	7	(33.3)	8
Nausea	3	(21.4)	4	1	(14.3)	1	4	(19.0)	5
Vomiting	2	(14.3)	2	2	(28.6)	3	4	(19.0)	5
Abdominal Discomfort	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Abdominal Pain	1	(7.1)	1	1	(14.3)	2	2	(9.5)	3
Abdominal Pain Upper	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Dry Mouth	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Injury, poisoning and procedural complications	3	(21.4)	7	1	(14.3)	1	4	(19.0)	8
Joint Sprain	2	(14.3)	2	0	(0.0)	0	2	(9.5)	2
Arthropod Bite	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Contusion	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Incorrect Dose Administered	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Muscle Strain	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Sunburn	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Ligament Rupture	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Nervous system disorders	3	(21.4)	5	1	(14.3)	2	4	(19.0)	7
Headache	3	(21.4)	4	1	(14.3)	2	4	(19.0)	6
Dizziness	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Infections and infestations	2	(14.3)	3	1	(14.3)	1	3	(14.3)	4
Gastroenteritis Viral	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Nasopharyngitis	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Tonsillitis	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Upper Respiratory Tract Infection	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Ear and labyrinth disorders	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Ear Pain	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Eye disorders	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Conjunctivitis	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
General disorders and administration site conditions	1	(7.1)	1	1	(14.3)	1	2	(9.5)	2
Chest Pain	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Injection Site Pain	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Metabolism and nutrition disorders	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Decreased Appetite	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Respiratory, thoracic and mediastinal disorders	1	(7.1)	2	0	(0.0)	0	1	(4.8)	2
Oropharyngeal Pain	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Rhinorrhoea	1	(7.1)	1	0	(0.0)	0	1	(4.8)	1
Musculoskeletal and connective tissue disorders	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Back Pain	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Psychiatric disorders	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Nervousness	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1

N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

	Liraglutide N	(%)	E	Placebo N	(%)	E	Total N	(%)	E
Skin and subcutaneous tissue disorders	0	(0.0)	0	2	(28.6)	2	2	(9.5)	2
Hyperhidrosis	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Rash	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Vascular disorders	0	(0.0)	0	1	(14.3)	2	1	(4.8)	2
Flushing	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1
Hot Flush	0	(0.0)	0	1	(14.3)	1	1	(4.8)	1

N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Table 5: Treatment emergent adverse events by system organ class and preferred term by liraglutide dose

	Dose 0.3mg N	(%)	E	Dose 0.6mg N	(%)	E	Dose 0.9mg N	(%)	E	Dose 1.2mg N	(%)	E	Dose 1.8mg N	(%)	E	After Dosing N	(%)	E
Safety Analysis Set	14			12			9			9			9			13		
Adverse Events	6	(42.9)	12	6	(50.0)	15	1	(11.1)	2	3	(33.3)	3	3	(33.3)	5	1	(7.7)	1
Gastrointestinal disorders	5	(35.7)	9	3	(25.0)	4	1	(11.1)	1	1	(11.1)	1	2	(22.2)	2	0	(0.0)	0
Diarrhoea	3	(21.4)	3	3	(25.0)	3	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0
Nausea	3	(21.4)	3	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0
Abdominal Discomfort	1	(7.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Abdominal Pain	1	(7.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dry Mouth	1	(7.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Abdominal Pain Upper	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0
Vomiting	0	(0.0)	0	1	(8.3)	1	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Nervous system disorders	2	(14.3)	2	2	(16.7)	3	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Headache	2	(14.3)	2	2	(16.7)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Dizziness	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Infections and infestations	1	(7.1)	1	1	(8.3)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Gastroenteritis Viral	1	(7.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Nasopharyngitis	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Tonsillitis	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ear and labyrinth disorders	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Ear Pain	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Eye disorders	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Conjunctivitis	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
General disorders and administration site conditions	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Chest Pain	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Injury, poisoning and procedural complications	0	(0.0)	0	1	(8.3)	2	1	(11.1)	1	2	(22.2)	2	1	(11.1)	1	1	(7.7)	1
Arthropod Bite	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Contusion	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0
Incorrect Dose Administered	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0
Joint Sprain	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0	1	(7.7)	1
Muscle Strain	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0
Sunburn	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Metabolism and nutrition disorders	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Decreased Appetite	0	(0.0)	0	1	(8.3)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Respiratory, thoracic and mediastinal disorders	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	2	0	(0.0)	0
Oropharyngeal Pain	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0
Rhinorrhoea	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0

N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Assessor's comments

Overall liraglutide was well tolerated. There were no serious adverse events, and no unexpected safety issues were noted. GI disorders were the most commonly reported TEAEs.
Three subjects did not escalate beyond 0.6 mg liraglutide and 1 subject did not escalate beyond 0.3 mg liraglutide. According to the MAH this was not due to safety concerns or adverse events, but because average FPG was ≤110 mg/dL [6.1 mmol/L]. However, non-escalation was a safety precaution, which is acceptable, but which also argues for a prudent dose escalation with a low starting dose.
The MAH has examined the relationship between TEAEs and liraglutide dose and concluded that the majority of events occurred at the liraglutide 0.3 mg and 0.6 mg doses during the initial treatment weeks. However, it is known that GI disorders especially occur at the initiation of liraglutide treatment and decrease later on. As all patients started on 0.3 mg, making a correlation between dose and adverse events is not right.

III.2 Pharmacokinetics

Serial sampling for the 13-hours liraglutide PK profile was performed for each subject at the end (Day 7) of Weeks 1 (0.3 mg), 2 (0.6 mg), 4 (1.2 mg) and 5 (1.8 mg). Additional single samples for the final dose, 72-hours liraglutide PK profile were obtained for each subject at Week 6 Day 1 (24 hours), Week 6 Day 2 (48 hours) and Week 6 Day 3 (72 hours).
The PK endpoints were derived from the individual liraglutide concentration-time curves. In general, PK endpoints were summarised by liraglutide dose using descriptive statistics. In addition, PK endpoints were also summarised by gender and age group; dose-normalised (excluding t_{max} and $t_{½}$); body weight-adjusted (excluding t_{max} and $t_{½}$).
Dose proportionality was assessed using a 95% confidence interval (CI) for the slope for C_{SSmax}, C_{SSmin}, $C_{SStrough}$ (assessed from the 0-13 hours liraglutide concentration profile at all dose levels).
The 95% confidence interval was derived from a random coefficient model i.e., a linear normal regression model, with log C_{SSmax}, C_{SSmin}, or log $C_{SStrough}$ as the dependent variable, a common intercept as fixed factor and log dose as fixed covariate. A subject-specific intercept and slope (i.e. log dose) were included as random effects, assuming an unstructured covariance between the two.
Population PK analyses were applied to assess dose proportionality ($AUC_{SS\ 0\text{-}24}$), identify covariates and to compare exposure with historic PK data in adult subjects with type 2 diabetes.

III.2.1 Pharmacokinetic results

In Table PK 1 and Figure PK 1 the mean pharmacokinetic variables are listed from this study of the subjects in which the plasma concentrations could be measure over a period of 13 hours.

Table PK 1: Summary of the pharmacokinetic endpoints of liraglutide doses.

	Lira 0.3mg	Lira 0.6mg	Lira 1.2mg	Lira 1.8mg
Number of subjects				
N	9	10	6	9
AUC 0-13(h*pmol/L)				
N	9	10	6	9
Mean (SD)	31548 (16191.1)	60675 (29047.4)	106582(80602.6)	177157(109768)
Median	29123.5	55545.0	86188.7	162127
Geometric mean (CV)	27212 (51.3)	54637 (47.9)	87444 (75.6)	146868(62.0)
Min ; Max	6231.16;63654	19300.9;128324	32471.7;263814	36888.3;417059
Cmax(pmol/L)				
N	9	10	6	9
Mean (SD)	3036 (1403)	5972 (2458)	11308 (6379)	20040 (13070)
Median	3006	6196	9409	16350
Geometric mean (CV)	2647 (46.2)	5446 (41.2)	9881 (56.4)	16288 (65.2)
Min ; Max	619 ;5326	1872 ;11080	4253 ;21790	4307 ;40890
Cmin(pmol/L)				
N	9	10	6	9
Mean (SD)	1430 (901)	3230 (2121)	6272 (6309)	9794 (7504)
Median	1270	2604	4550	10770
Geometric mean (CV)	1220 (63.0)	2739 (65.7)	2418 (100.6)	4847 (76.6)
Min ; Max	389 ;3546	1134 ;8230	30 ;17690	30 ;24630
Cmin/Cmax				
N	9	10	6	9
Mean (SD)	0.48 (0.1)	0.52 (0.1)	0.47 (0.3)	0.45 (0.2)
Median	0.47	0.49	0.47	0.43
Geometric mean (CV)	0.46 (29.1)	0.50 (27.6)	0.24 (71.8)	0.30 (54.0)
Min ; Max	0.23 ;0.67	0.35 ;0.76	0.01 ;0.83	0.01 ;0.75
Tmax(h)				
N	9	10	6	9
Mean (SD)	9.47 (1.9)	9.83 (1.8)	7.69 (2.3)	7.41 (5.1)
Median	8.18	10.00	8.08	8.00
Geometric mean (CV)	9.31 (20.3)	9.69 (18.3)	7.39 (29.3)	6.78 (69.3)
Min ; Max	7.93 ;13.00	7.98 ;12.32	5.00 ;10.00	-0.25 ;13.00

AUC=Area under the curve, Cmax=maximum concentration,tmax=time to Cmax, Cmin=minimum concentration

*The PK endpoints above are based on the 13-hours liraglutide concentration over time profile

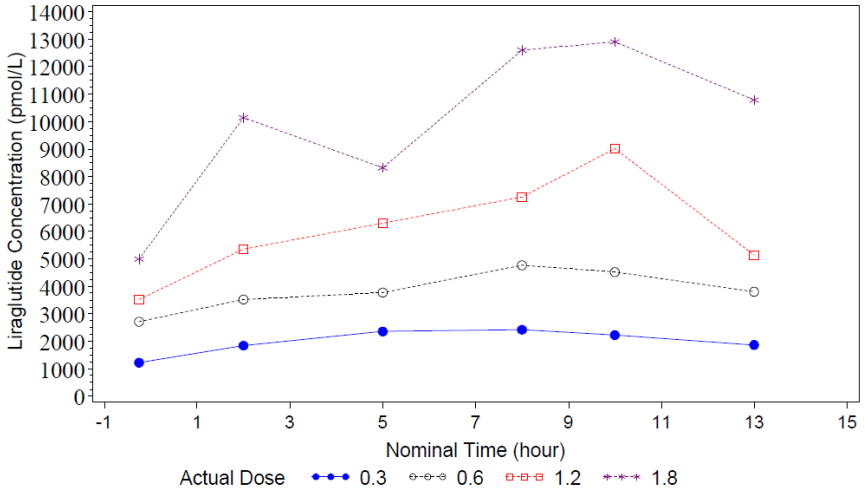

Figure PK 1 Geometric mean profile of 13 hours liraglutide concentrations.

Dose Proportionality

In the population pharmacokinetic analysis the dose proportionality was modelled and in Figure PK 2 this proportionality is given.

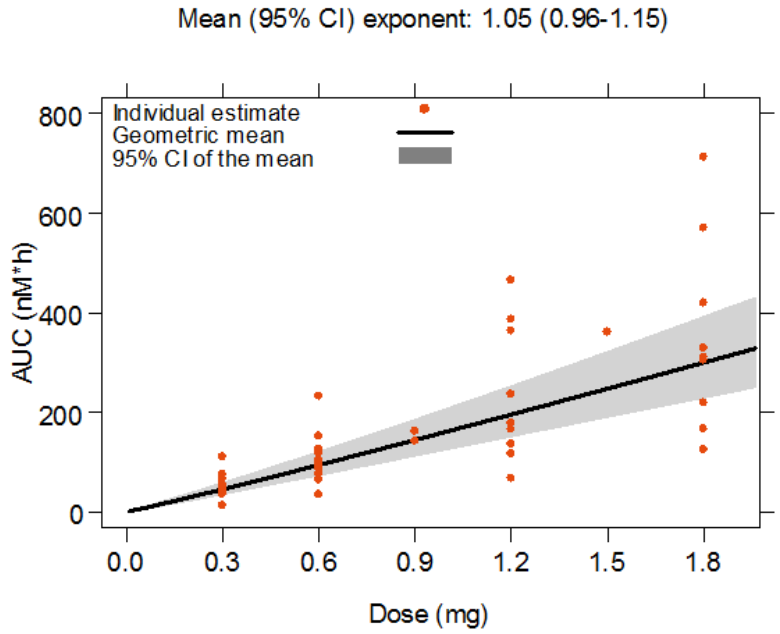

Figure PK 2 Dose proportionality test based on model-estimated AUC_{SS0-24}.

Estimates for CL/F for each individual and the corresponding dose level were used to estimate AUC_{SS0-24}. The individual estimates are shown as red dots. The solid black line is AUC_{SS0-24} as estimated by the log-log linear mixed effects model used for the dose proportionality test, back-transformed to normal scale as geometric mean and plotted versus dose.

Weight

Body weight and gender are significant covariates for liraglutide clearance (and, thus, AUCSS0-24). The effects on AUC_{SS0-24} of minimum and maximum observed body weight, age category (i.e., paediatric: 10-17 years), and gender (i.e., male) in comparison to a reference subject (a 90 kg adult female with type 2 diabetes) are presented in Figure PK 3. The mean (90% CI) change in AUC_{SS0-24} for minimum (53 kg) and maximum (216 kg) observed body weights were 63% (44 to 84%) higher and 56% (46 to 64%) lower, respectively, than for the median body weight of 90 kg.

The mean (90% CI) change in AUC_{SS0-24} for paediatric subjects was 10% (-6 to 24%) lower than that for adults, and males had an AUC_{SS0-24} 31% (17 to 42%) lower than females.

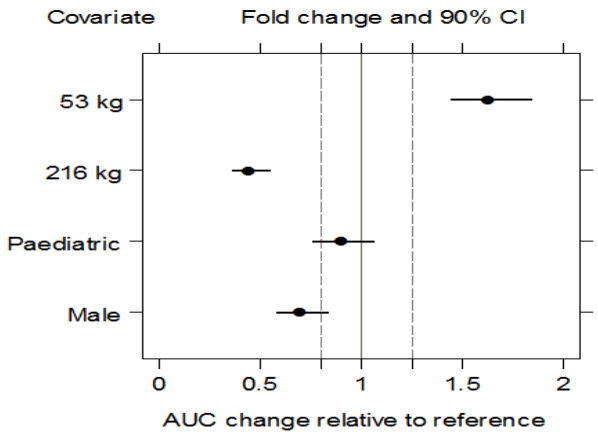

Figure PK 3 Mean and 90% CI for effects of demographic covariates on AUC_{SS0-24} relative to a reference subject (90 kg adult female). The dotted lines indicate bioequivalence limits of 0.8-1.25.

Comparison paediatric to adults patients

The estimated CL/F and volume of distribution (V/F) for the liraglutide 1.8 mg dose in paediatric subjects (10-17 years) fall within the same range as the estimated CL/F and V/F for an identical liraglutide dose in adults, leading to similar exposure in the two age categories. This is illustrated by the modelled steady-state liraglutide concentration-time profiles for paediatric and adult subjects with type 2 diabetes receiving 1.8 mg liraglutide once-daily (Figure PK 4). As the data indicate dose proportionality for the paediatric subjects in this trial, and similar results have been previously found in adults, it can be assumed that the PK in the paediatric subjects is similar to that in adults for the investigated liraglutide dose range of 0.3-1.8 mg.

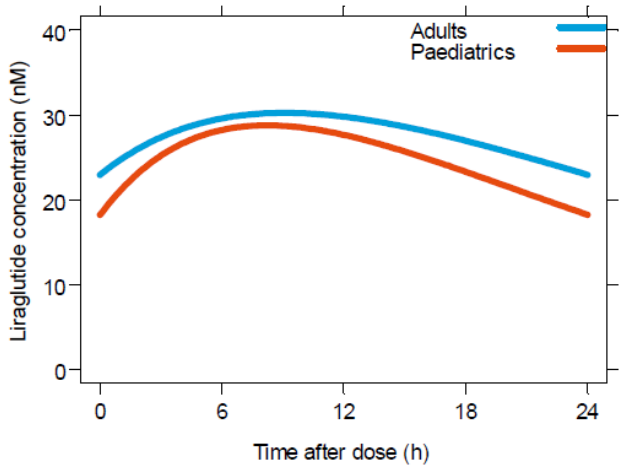

Figure PK 4. Model-derived, typical steady-state concentration-time profiles for paediatric and adult simulated populations (both with 50% females and body weight of 90 kg) receiving 1.8 mg liraglutide once-daily

In Conclusion

Population pharmacokinetic analysis showed:

- Dose proportionality based on estimated AUC_{SS0-24} (slope: 1.05 (95% CI 0.96 - 1.15)

- Body weight and gender are significant covariates for liraglutide clearance, as previously demonstrated in adult subjects. Age category (i.e., paediatric, adult) is not a significant covariate for liraglutide clearance
- Liraglutide PK in paediatric subjects (age: 10-17 years) with type 2 diabetes is similar to that in adult subjects with type 2 diabetes.

Assessors Comments

The population pharmacokinetic analysis as performed by Applicant did show that liraglutide exposure in children is dose proportional and body weight is a significant covariate in the clearance of liraglutide. The analysis was of good quality.

However, the number of subjects in the study was rather small, in most dose groups no more than 10 subjects were included. Furthermore, the subjects were recruited in several countries. This may be an explanation of the high variability seen in the estimated pharmacokinetic variables. Especially with respect to the influence of weight on the pharmacokinetics of liraglutide, the extreme differences in (from 55 to 214 kg) in this small group, the extent of the contribution of weight on the clearance of liraglutide should be interpreted with caution.

The main conclusion of the population pharmacokinetic analysis may be that the exposure in children from 10 - 17 years is comparable with adults.

III.3 Pharmacodynamics

Evaluation of pharmacodynamic effect of liraglutide in the paediatric population was a secondary objective in this trial. Glycaemic control and glucose metabolism were evaluated using the following endpoints: HbA1c, fructosamine, FPG (glucometer) and body weight. In addition, 7-point SMPG, self-monitored FPG (3 consecutive days per week), fasting serum glucose, fasting serum insulin, 2-hour post-prandial plasma glucose, insulin, glucagon were measured; however, these parameters were evaluated after initiation of trial drug, so there were no baseline values for these parameters.

Results are presented in Table 6.

Mean HbA1c and fructosamine decreased during this short-term treatment period with the decrease being statically significantly larger during liraglutide treatment compared to placebo treatment.

Mean FPG (obtained at site by glucometer) also decreased during the treatment period with liraglutide but the decrease was not statistically different compared to placebo treatment.

Mean body weight with liraglutide did not change significantly compared to placebo.

Post-meal glucose, 7-point SMPG and self-monitored FPG levels were lower for liraglutide-treated subjects versus placebo-treated subjects and there was no discernible difference between liraglutide and placebo in post-meal glucagon and insulin. These parameters were evaluated after the subjects were on trial drug, with the postprandial glucose, insulin, and glucagon levels being drawn during pharmacokinetic sampling visits.

It should be noted that the limited duration and power of this trial preclude the drawing of clear conclusions regarding the exploratory pharmacodynamic parameter.

Table 6: ANCOVA of change in HbA1c, fructosamine, FPG and body weight from baseline to end of treatment – full analysis set.

		Change from baseline		Treatment difference (Lira - Pla)		
Treatment/Comparison	N	LS mean	SE	LS mean	95% CI	p
HbA1c (%)						
Liraglutide	13	-0.86	0.12	-0.90	-1.36; -0.45	0.0007
Placebo	6	+0.04	0.18			
fructosamine (µmol/L)						
Liraglutide	13	-40.3	6.84	-50.9	-79.1; -22.8	0.0016
Placebo	5	+10.67	11.15			
FPG (glucometer; mmol/L)						
Liraglutide	14	-1.27	0.558	-1.44	-3.61; 0.73	0.1797
Placebo	6	+0.16	0.857			
Body weight (kg)						
Liraglutide	14	-0.50	0.58	0.04	-2.19; 2.27	0.9703
Placebo	6	-0.54	0.88			

Assessor's comments
It is agreed with the MAH that the limited duration and power of this trial preclude clear conclusions. The presented data are suggestive that liraglutide may have positive effects on glucose control in paediatric subjects.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

As part of the Paediatric Investigation Plan, and in accordance with article 46 of Regulation (EC) No 1901/2006, the MAH has submitted the final Clinical Trial Report for Trial NN2211-1800, a paediatric study. Primary endpoint was safety and tolerability. In general liraglutide was well tolerated and there were no unexpected safety issues. GI disorders were the most commonly recorded TEAEs, especially occurring after initiation of treatment. That's the reason why these were seen most frequently with the lower doses of 0.3 and 0.6 mg, as treatment was started with 0.3 mg. Four subjects were not escalated unto 1.8 mg as FPG was ≤110 mg/dL [6.1 mmol/L]. This is an argument for a prudent dose escalation with a low starting dose.

The majority of subjects were post-pubertal. Only three subjects (2 liraglutide, 1 placebo) were below 12 years of age. Therefore, the experience in children below 12 years and pubertal stage I-III is very limited.

PD parameters are suggestive for a positive effect in paediatric subjects. However, the study duration and power is too limited to draw clear conclusions.

The main conclusion of the population pharmacokinetic analysis may be that the exposure in children from 10 - 17 years is comparable with adults. However, in this study there was a high variability in the estimated pharmacokinetic variables. Especially with respect to the influence of weight on the pharmacokinetics of liraglutide, the extreme differences in (from 55 to 214 kg) in this small group, the extent of the contribution of weight on the clearance of liraglutide should be interpreted with caution.

This study is part of the Paediatric Investigation Plan. Aiming at an efficient assessment procedure in which clear conclusions can be drawn, it is recommended to submit all paediatric studies performed as part of the PIP in one package, unless safety data give rise to earlier announcement to the authorities.