25 March 2021
EMA/217044/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Saxenda

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/003780/II/0026

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
BMI	body mass index
BMI-SDS	body mass index, standard deviation score
BOCF	baseline observations carried forward
BP	blood pressure
CI	confidence interval
CTD	common technical document
CTR	clinical trial report
DP	drug product
DS	drug substance
EEA	European Economic Area
EEC	European Economic Community
FFA	free fatty acids
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GMP	good manufacturing practice
HbA_{1c}	glycosylated haemoglobin A_{1c}
HCP	health care professional
HDL	high-density lipoprotein
hsCRP	high sensitivity C-reactive protein
ICH	International conference on harmonisation
IWQoL-Lite	Impact of Weight on Quality of Life-Lite version
LDL	low-density lipoprotein
Lira 3.0 mg	liraglutide 3.0 mg
LoQ	list of questions
MAA	marketing authorization application
N/A	not applicable
NaOH	sodium hydroxyde
OGTT	oral glucose tolerance test
OR	odds ratio
PG	plasma glucose
PYE	patient years of exposure
s.c.	subcutaneous(ly)
SAE	serious adverse event
SCALE	Satiety and Clinical Adiposity – Liraglutide Evidence in non-diabetic and diabetic subjects
SCE	Summary of Clinical Efficacy (CTD module 2.7.3)
SD	standard deviation
SmPC	summary of product characteristics
T2DM	type 2 diabetes mellitus
VLDL	very low-density lipoprotein

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 4 February 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with obesity (BMI corresponding to ≥30 kg/m2 for adults) and body weight above 60 kg, based on Study NN8022-4180 that evaluated the efficacy of liraglutide 3.0 mg in adolescents aged 12 to less than 18 years with obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are being updated and the Package Leaflet is updated in accordance.
The application relates to paediatric studies submitted according to Article 46 of the paediatric regulation.
The application included an updated RMP version 32.0.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0383/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0383/2019 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP EMEA-C2-000128-PIP02-09-M03.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kirstine Moll Harboe

Timetable	Actual dates
Submission date	4 February 2020
Start of procedure:	29 February 2020
CHMP Rapporteur Assessment Report	22 April 2020
CHMP Co-Rapporteur Assessment Report	22 April 2020
PRAC Rapporteur Assessment Report	22 April 2020
PRAC Outcome	14 May 2020
CHMP members comments	22 May 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	28 May 2020
Request for supplementary information (RSI)	28 May 2020
CHMP Rapporteur Assessment Report	17 September 2020
PRAC Rapporteur Assessment Report	17 September 2020
PRAC members comments	24 September 2020
PRAC Outcome	1 October 2020
CHMP members comments	2 October 2020
Updated CHMP Rapporteur Assessment Report	9 October 2020
Request for supplementary information (RSI)	15 October 2020
CHMP Rapporteur Assessment Report	28 December 2020
CHMP members comments	18 January 2021
Updated CHMP Rapporteur Assessment Report	27 January 2021
Request for supplementary information (RSI)	28 January 2021
CHMP Rapporteur Assessment Report	12 March 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	25 March 2021

2. Scientific discussion

2.1. Introduction

Obesity is a global public health challenge. The prevalence of obesity in children and adolescents, as well as in adults, has been increasing steadily during the past three decades and has reached alarming proportions worldwide. According to an International Association for the Study of Obesity and International Obesity Task Force analysis, over 20% of school-aged children in the EU were estimated to be either overweight or obese. Childhood overweight or obesity is also an independent risk factor for obesity in adulthood and its associated comorbid conditions as well as reduced life expectancy. The American Medical Association (AMA) as well as a number of leading institutions such as the National Institutes of Health (1998), the Obesity Society (2008) and the American Association for Clinical Endocrinology (2012) now classify obesity as a disease, calling for dedicated efforts in prevention, diagnosis and treatment.

Paediatric obesity is associated with a number of comorbid conditions including hypertension, type 2 diabetes mellitus (T2D), early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems. Effective weight loss, subsequent weight maintenance as well as treatment and prevention of these comorbidities are of particular importance in the treatment of obesity. In studies conducted in paediatric subjects with obesity, weight loss has been associated with improvements in cardiometabolic risk factors, including measures of glycaemic control, beta-cell function, insulin sensitivity/resistance, lipid profile, systolic/diastolic blood pressure and metabolic syndrome. Paediatric obesity remains a major public health challenge, as treatment options are limited. Although lifestyle modification is the recommended first-line treatment, widespread adoption of this treatment method and long-term compliance are problematic, and therefore treatment intensification may be needed.

2.1.1. About the product

Liraglutide is a once-daily glucagon-like peptide-1 (GLP-1) analogue classified as a 'GLP-1 receptor agonist', with 97% homology to human GLP-1. GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. Liraglutide lowers body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than subcutaneous fat loss. Liraglutide regulates appetite by increasing feelings of fullness and safety, while lowering feelings of hunger and prospective food consumption, thereby leading to reduced food intake. Liraglutide has unique therapeutic potential for the treatment of obesity, due to its combined effects not only on body weight but also on glycaemic control and other weight-related comorbidities.

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

The aim of this application is to support the extension of the indication of Saxenda for use in the adolescent population (aged 12 to less than 18 years) with obesity (BMI corresponding to ≥30 kg/m2 for adults by international cut-off points and ≥95th percentile for age and gender).

The paediatric development programme for liraglutide 3.0 mg was designed in agreement with the EMA PDCO. Key binding elements for the programme were included in the paediatric investigation plan (PIP) agreed upon with the EMA (EMEA-000128-PIP02-09-M03).

The MAH did not seek Scientific advice at the CHMP.

2.2. Non-clinical aspects

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

2.2.1. Introduction

One nonclinical study was submitted with the current application, which was also submitted previously, and assessed in 2015 as part of a type II variation for Victoza (EMEA/H/C/001026/II/0032), namely a 10-week repeated dose toxicity study in juvenile rats, including a 4 week recovery period. The juvenile toxicity study was conducted to fulfil the request in the paediatric investigation plan (PIP) Opinion for liraglutide in the weight management indication (EMEA-000128-PIP02-09). Although the study has previously been submitted, that submission was not regarding a paediatric indication, and no inclusion of any data regarding juvenile study findings were included in the SmPC at that time. However, with the current indication extension for Saxenda, the data has been considered relevant for inclusion in the SmPC, hence, are included in section 5.3.

A dose range study in juvenile animals (Study No JLY0395, or report number NN212267) was performed and submitted previously with the original MAA for Saxenda.

Four literature references (Kennedy and Mitra 1963, Leonhardt et al. 2003, Carney et al. 2004 and McShane and Wise 1996) were quoted in the nonclinical overview and submitted in order to allow for secondary assessment.

2.2.2. Toxicology

Reproduction toxicity

In the non-GLP dose range finding study (Study no NN212267) previously submitted the following was concluded by the MAH:

Subcutaneous administration of 0.1, 0.25 or 1 mg liraglutide/kg/day to juvenile Sprague Dawley rats from Day 21 to Day 55 of age resulted in a treatment-related reduction in food consumption and bodyweight gain, with males being more affected than females. Sexual maturation assessed as vaginal opening and balano-preputial separation was delayed in a dose-dependent manner at all tested dose levels. Ovary weights were also slightly reduced.

As a consequence, the low dose was lowered to 0.05 mg/kg/day in the definitive study.

In the definitive juvenile animal study in rats (report NN 212291), doses of 0, 0.05, 0.25 and 1.0 mg/kg/day was administered subcutaneously to juvenile Sprague Dawley Crl:CD(SD) rats. The animals were 21 days old at start of treatment, and dosing was performed daily until 90 days of age.

Three groups of ten male and ten female rats received liraglutide for ten weeks at doses of 0.05, 0.25 or 1.0 mg/kg/day at a volume-dose of 1 mL/kg. A similarly constituted Control group received the vehicle, at the same volume-dose. These animals comprised the Main phase of the study. A further twenty males and twenty females were assigned to each group: these animals comprised the

Recovery/Reproductive phase and were treated for 10 weeks at the same dose levels as the Main phase animals followed by a four week period without treatment to assess recovery from any treatment-related effects prior to a reproductive assessment. For the reproductive assessment Control males were paired with Control females, previously treated males were paired with specifically acquired untreated females, and previously treated females were paired with stock males. All females were allowed to litter and rear their offspring to Day 7 of age.

An additional nine males and nine females were assigned to each treated group, and three males and three females to the Control group; these animals comprised the Single Dose TK phase. Animals received a single dose on Day 21 of age, and blood samples were taken for toxicokinetic evaluation only.

During the study, clinical observations, post-dose observations, body weight, food consumption, limb measurements, haematology, blood chemistry, urinalysis, organ weight, macropathology and histopathology investigations were performed for Main phase and Recovery/Reproductive phase animals. In addition, for the Recovery/Reproductive phase animals, investigations of toxicokinetics, sexual maturation, neurobehaviour, oestrous cycles, mating performance and fertility, gestation length and parturition were undertaken. The clinical condition, litter size and survival, sex ratio, body weight and ano-genital distance of offspring were assessed, and macropathology investigations were undertaken at necropsy.

Results

Systemic exposure to liraglutide in the dosed animals was confirmed. The t_{max} was in the range of 2-4 hours post-dosing on Day 1 and 2-8 hours during Week 10 of dosing. C_{max} and AUC_{0-24hr} increased with dose for both male and female animals. The increase in exposure seemed proportional to the increase in dose. Minor accumulation was observed for both males and females. No clear sex differences were observed.

There were no unscheduled deaths related to the administration of liraglutide, and no treatment-related changes in the clinical condition of the animals.

Mean body weight gain of males receiving 0.25 or 1 mg/kg/day, was generally lower than control throughout the 10-week dosing period, particularly from Day 21-28 of age (20% and 39% lower than Control) and from Day 84-91 of age (26% and 39% lower than Control), with a dose-response apparent; during the recovery period overall mean body weight gains of these animals were greater than in Controls. The mean body weight gain of females receiving 0.25 or 1 mg/kg/day was lower than Control during the first week of dosing but thereafter body weight gain was generally similar to or slightly greater than in Controls until the end of the recovery period. There was no effect of previous treatment on body weight gain during gestation or lactation. The overall body weight gain of males and females receiving 0.05 mg/kg/day during the 10-week dosing period was 5% and 4% lower than Control, respectively, with statistical significance attained for the males.

Mean food consumption of males receiving 0.25 or 1 mg/kg/day was lower than Controls throughout the 10-week dosing period but higher than Controls during the first week of recovery. Mean food intake for males receiving 0.05 mg/kg/day was slightly lower than Control during Week 1 of dosing (Days 21 to 23 of age) and marginally but statistically significantly low during Weeks 8 and 9 of dosing. Mean food consumption of females receiving 0.25 or 1 mg/kg/day was lower than Controls during the first week or first two weeks of dosing respectively, but higher than Controls during the first week of recovery. There was no effect of previous treatment on food consumption during gestation or lactation.

Mean ulna length and growth of the ulna between Day 21 and Day 35 of age for males and females

receiving 0.25 or 1 mg/kg/day was shorter than Control.

Among females receiving 0.25 or 1 mg/kg/day, a marked dose-dependent delay in the age of attainment of vaginal opening was evident when compared to Controls.

Treatment did not affect the condition or behaviour of the animals when observed in week 8-9 of treatment in the hand or in an arena, or their motor activity or learning and memory capacity in the Morris water maze.

There were no adverse effects of treatment on haematology, blood chemistry or urinalysis parameters at any dose level investigated.

There was a slightly extended oestrous cycle length among females receiving 1 mg/kg/day during Weeks 6-8 of treatment; cycles had returned to normal length after two weeks of recovery, before pairing.

Organ weight analysis after 10 weeks of treatment revealed low absolute and body weight-relative ovary weights among females receiving 0.25 or 1 mg/kg/day; this difference was not apparent at the end of the recovery period, and no treatment-related macroscopic or microscopic changes were detected in the ovaries. There were no other toxicologically significant or treatment-related effects on organ weights.

There were no treatment-related macropathology findings at the end of treatment or during recovery.

Microscopic examination of a full list of tissues revealed that changes related to treatment with liraglutide were limited to minimal hypertrophy in the duodenum's Brunner's gland in both sexes receiving 1 mg/kg/day; this change was not apparent at the end of the recovery period.

Mating performance and fertility of both sexes and gestation length and gestation index were unaffected by previous treatment with liraglutide.

The mean number of implantations and subsequent litter size was slightly low among females previously treated at 1 mg/kg/day which were mated with untreated stock males during the recovery period compared with those in the other six groups of litters on the study, although the differences from Control did not attain statistical significance. There was no effect of previous treatment of males at 1 mg/kg/day on the number of implantations or litter size in untreated females following mating.

There was no effect of previous maternal or paternal treatment on offspring clinical condition, survival, ano-genital distance, sex ratio, body weight, body weight gain or macropathology findings.

Discussion by MAH

The repeated daily subcutaneous administration of liraglutide to juvenile rats for 10 weeks (from Day 21 to Day 90 of age) at doses up to and including 1 mg/kg/day was well tolerated. There were no unscheduled deaths related to the administration of liraglutide, and no treatment-related changes in the clinical condition of the animals. In general, the treatment-related effects observed mirrored those seen in the preliminary study in juvenile rats, and predominantly related to pharmacologically-induced reductions in body weight gain and food intake throughout the dosing period in males receiving 0.25 or 1 mg/kg/day, and in females in these groups predominantly during Week 1 of dosing. A concomitant reduction in ulna growth was apparent in these males and females during the first two weeks of dosing, and among the males receiving 0.25 or 1 mg/kg/day a body weight-related dose-dependent slight delay in the onset and completion of balano-preputial separation was observed.

Sexual maturation - group mean age and body weight (g) at attainment for Recovery/Reproductive phase animals

Group		Vaginal opening (Day of age)	Body weight (g) at Vaginal opening	Preputial separation (Day of age)		Body weight (g)	
				Onset	Completion	Onset	Completion
Statistical test:		lWi	Wi	Wi	Wi	Wi	Wi
1	Mean	32.3	115	36.1	43.6	166	238
	SD	1.8	13.1	0.9	1.8	16.7	19.3
	N	20	20	20	20	20	20
2	Mean	32.9	122	36.5	43.9	168	239
	SD	1.5	9.4	1.0	2.9	18.1	23.3
	N	20	20	20	20	20	20
3	Mean	37.1**	134**	37.2**	44.9	161	233
	SD	3.2	20.3	1.5	2.4	16.8	21.0
	N	20	20	20	20	20	20
4	Mean	40.1**	145**	37.7**	46.5**	150**	228
	SD	2.9	14.1	1.1	2.8	15.8	18.6
	N	20	20	20	20	20	20

Treatment of juvenile female rats from Day 21 of age with 0.25 or 1 mg/kg/day liraglutide affected the reproductive system, as indicated by:

- Markedly delayed vaginal opening among females receiving 0.25 or 1 mg/kg/day – these groups of females showed a statistically significant and dose-related decrease in mean body weight gain during Week 1 of treatment (Day 21-28 of age) of 26% and 39% respectively when compared to Control.
- Slightly extended oestrous cycles among females receiving 1 mg/kg/day during Weeks 6-8 of treatment - cycles had returned to normal two weeks after the cessation of treatment, before pairing.
- Low absolute and body weight-relative ovary weights among females receiving 0.25 or 1 mg/kg/day - a similar difference was not apparent at the end of the recovery period and no treatment-related macroscopic or microscopic changes were detected in the ovaries.

Mating performance and fertility of both sexes were unaffected by previous treatment with liraglutide, but the mean number of implantations (and subsequent litter size) was slightly low among females who had received 1 mg/kg/day and were mated with untreated stock males during the recovery period. Although the differences from Control did not attain statistical significance, mean numbers of implantations and offspring were slightly low compared with those in the other six groups of litters on the study, and in view of this, and the previously detailed indications that treatment had affected the integrity of the female reproductive system, a relationship between these findings and previous treatment with liraglutide could not be discounted. This finding was not apparent when males previously treated at 1 mg/kg/day were mated with untreated females. There was no effect of previous maternal or paternal treatment on offspring clinical condition, survival, ano-genital distance, sex ratio, body weight or weight gain or macropathology findings.

Following ten weeks of dosing, treatment-related minimal hypertrophy was found in the Brunner's glands of the duodenum; similar histopathological changes were not apparent after the recovery/reproductive period. Brunner's glands are located only in the most proximal portion of the duodenum adjacent to the gastric pylorus in rats and produce mucin and bicarbonate-containing secretum in order to increase the luminal pH of the duodenum from the acidic pH of the stomach (Pritam et al, 2013). The glands have been shown to have high GLP 1 receptor expression (Meike Korner et al., 2007). Since this subtle finding was not associated with any inflammation or cellular changes, the finding is considered to be of no toxicological relevance and can be regarded as a consequence of altered function rather than a pathological alteration.

The incidence of procedure-related microscopic changes at the injection sites was generally similar in control and test substance treated groups and not considered related to treatment with liraglutide.

Treatment did not affect the condition or performance of the animals when observed in the hand or in an arena, or their motor activity or learning and memory capacity in the Morris water maze; an indication of faster trial times and lower numbers of sector entries and failed trials was evident in liraglutide-treated males and females, however, due to the direction of change relative to the Controls (improved performance) this observation was considered to be of no toxicological significance.

Some minor differences were recorded in haematology, blood chemistry or urinalysis parameters, the majority of which were within the historical control data range. In view of this, and since there were no supporting treatment-related microscopic pathology changes or effects on the clinical condition or survival of the animals, these differences were considered not to represent an adverse effect of treatment.

The MAH concluded that daily subcutaneous administration of liraglutide to juvenile Sprague Dawley rats for 10 Weeks produced adverse signs of toxicity among females at a dose level of 0.25 and above, resulting in a marked delay in the attainment of sexual maturation at 0.25 and 1 mg/kg/day and slightly low implantation counts and post-partum litter size following mating at 1 mg/kg/day, for which a relationship to treatment could not be discounted. The No-Observed-Adverse-Effect level (NOAEL) for juvenile female rats was therefore considered to be 0.05 mg/kg/day. There were no toxicologically significant changes observed among liraglutide-treated males, and it was therefore considered that the NOAEL for juvenile male rats was 1 mg/kg/day.

Toxicokinetic data

Appendix A **Juvenile rat exposure at NOAEL in relation to exposure in obese children aged 7-11 years and adolescents aged 12-17 at 3.0 mg/day**

Type of study	**Mean $AUC_{(0-24h)}$ (nmol•h/L)**		**Mean C_{max} and (C_{avg}) (nmol/L)**	
	Male	Female	Male	Female
Rat: Juvenile animals				
NOAEL male:1.0 mg/kg	3,870		267	
Exposure level ratio: rat/human – children	3.3		5.5	
Exposure level ratio: rat/human – adolescents	5.5		7.9	
NOAEL female: 0.05 mg/kg		196		16.2
Exposure level ratio: rat/human - children		0.2		0.3
Exposure level ratio: rat/human - adolescent		0.2		0.4)
Human clinical trials - Maximal human dose: 3.0 mg/day	**$AUC_{(0-24h)}$ (nmol•h/L)[a]**		**C_{avg} (nmol/L)[b]**	
Exposure in obese children aged 7−11 years at steady-state (5.3.5.1, NN8022-4181).	1161		48.4	
Exposure in obese adolescents aged 12−17 years at steady-state (5.3.5.1, NN8022-3967). Males	699		33.7	
Exposure in obese adolescents aged 12−17 years at steady-state (5.3.5.1, NN8022-3967). Females	883		36.8	

[a] $AUC_{(0-24h)}$ derived from population kinetics analysis and stated as geometric mean. [b] C_{max} was not calculation in clinical trials using a population kinetic analysis model. Stated as geometric mean.

2.2.3. Ecotoxicity/environmental risk assessment

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

Therefore, in accordance with the guidance (EMEA/CHMP/SWP/4447/00 corr [21*]), liraglutide is exempted from performing ERA studies, under the expectation that e.g. due to their nature they are unlikely to result in a significant risk to the environment. Any increase in consumption of liraglutide, is

considered not to have any impact on the environment.

2.2.4. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

No new target organs were observed in juvenile animals. The females were most sensitive to delayed sexual maturation, as attainment of vaginal opening was significantly delayed in the mid and high dose females. The mean body weight at attainment of vaginal opening, was higher for the mid and high dose group females, compared to the control group.

In the males, only slight delays were observed in the onset and completion of balano-preputial separation. The age at which the males attained separation of balano-preputium was within the historical control range for the CRO. The slight delays observed were directly correlated with slightly lower absolute body weight, and the mean body weight in the treated groups at completion of balano-preputial separation was comparable to the control group mean body weight.

None of the observations from the juvenile animal study has been initially included in the SmPC. The MAH stressed that food restriction during early postnatal development is well known to delay sexual maturation and ovary weight in rats (Kennedy and Mitra (1963), Leonhardt et al. (2003), Carney et al. (2004)) and prolong oestrous cycle length (McShane and Wise (1996)). As the animals fully recovered after cessation of treatment, the findings were therefore not considered of toxicological concern by the MAH. However, the MAH included the information regarding delayed sexual maturation of the females, especially considering the low exposure (fractional) compared to the clinically relevant exposure in children in SmPC section 5.3 which is agreed by the CHMP.

2.2.5. Conclusion on the non-clinical aspects

The performed juvenile animal study showed delayed attainment of vaginal opening in females treated with 0.25 or 1.0 mg/kg/day liraglutide administered subcutaneously. In addition, the oestrus cycle activity was slightly extended during weeks 6-8 of treatment (4-5 or 5-day cycles in 9/20 high dose females). This change was not evident after 2 weeks recovery.

Considering that liraglutide is a peptide with a fatty acid, is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The paediatric clinical development programme for liraglutide 3.0 mg builds on the data already available for liraglutide 3.0 mg in adults.

Liraglutide 3.0 mg was investigated in adolescents (aged 12 years to less than 18 years) with obesity in 2 trials (Table):

- NN8022-3967, referred to as Trial 3967: a phase 1 clinical pharmacology trial to assess the safety, tolerability and PK of liraglutide 3.0 mg in adolescents aged 12−17 years with obesity
- Trial 4180: referred to as Trial 4180: a phase 3a efficacy and safety trial in adolescents aged 12 years to less than 18 years with obesity.

Both trials were designed and conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice. This clinical trial report for study NN8022-3967 was already submitted and assessed in 2014 under the Victoza, liraglutide 1.8 mg procedure (EMEA/H/C001026) and the Saxenda, liraglutide 3.0 mg), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended (EMA/H/C/003780/P46).

Table 1: Trials in the liraglutide (Saxenda) paediatric clinical development programme

Trial ID	Type of Study	Trial design and type of control	Number of subjects
NN8022-3967; Completed	Clinical pharmacology	Single-centre, randomised, double-blind, parallel-group, placebo-controlled trial to assess safety, tolerability and pharmacokinetics of liraglutide in adolescent subjects with obesity	Liraglutide 3.0 mg: 14 Placebo: 7
NN8022-4180; completed	Efficacy and safety	Double-blind, randomised, parallel-group, placebo-controlled multi-national 56-week trial followed by a 26-week period off study-drug for weight management in pubertal adolescent subjects with obesity	Liraglutide 3.0 mg: 125 Placebo: 126

Apart from the above 2 trials, liraglutide 3.0 mg was also investigated in children (aged 7-11 years) with obesity (NN8022-4181, referred to as Trial 4181). Trial 4181 is not part of this submission and the data from this trial has been included only for population PK analyses.

2.3.2. Pharmacokinetics

Dose proportionality and time dependencies

The dose proportionality of liraglutide exposures was assessed based on Ctrough. This was done by estimating the slope β in a linear normal regression model with the logarithm of Ctrough as a dependent variable, a common intercept as a fixed factor and log dose as a fixed covariate. Furthermore, a subject-specific intercept was included as random effect. The estimated quantity 2β with 95% confidence interval (CI) was reported 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).

Population pharmacokinetic analysis

The objective of the analyses is to investigate the population pharmacokinetics and exposure-response relationship for weight management in adolescent subjects (12 to <18 years) with obesity treated with

liraglutide in **trial 4180** and to investigate if the assumption of similarity between adult and adolescent populations with regards to PK and exposure-response relationship can be supported.

The population PK meta-analyses will include historical data from both adult (trial **3630**, ≥ 18 years) and paediatric populations (trial **3967**, 12 to <18 years and trial **4181**, 6 to <12 years) with obesity to compare exposure across age groups. The analysis is an update of a previous analysis that included all the historical data, now with the additional data from trial **4180**.

Trial 4181:

The trial was a multicentre, randomised, double-blind, placebo-controlled safety and tolerability, PK and PD trial in children with obesity aged 6 to <12 years at Tanner stage 1. 21 subjects were randomised 2:1 to receive either liraglutide or placebo. Treatment duration was at least 7 week (with 6 optional flex weeks). BMI (body mass index) corresponded to ≥30 kg/m2 for adults by international cut-off points and BMI ≤45 kg/m2 as well as BMI ≥95th percentile for age and sex at the time of signing informed consent. Treatment was initiated with liraglutide 0.3 mg daily for one week and increased as tolerated in weekly steps of 0.3 mg until a dose of 1.2 mg was reached, and then 0.6 mg until a dose of maximum 3.0 mg liraglutide was reached. The dose was escalated over 7 weeks with flexibility for up to 13 weeks.

Trial 3630:

The trial was 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. In total, 49 subjects were randomised in the trial. 29 subjects were randomised and exposed to liraglutide 3.0 mg and included in this analysis. In brief, the subjects included in the trial were adult (aged 18 to 75 years) males and females with a BMI ≥ 30.0 kg/m2 and < 40.0 kg/m2 and a FPG < 7.0 mmol/L (126 mg/dL). Treatment with liraglutide was started at a dose of 0.6 mg/day. The dose was gradually increased with 0.6 mg once weekly until maintenance doses of either 1.8 or 3.0 mg/day were reached but for this analysis, only data from 3.0 mg liraglutide was used.

Table 2: Summary of trial designs for trials included in the population PK analysis

Group	Trial 4180[3]	Trial 4181[3]	Trial 3967[3]	Trial 3630[3]
Clinical stage	Phase 3	Phase 1	Phase 1	Phase 1
N	121	13	13	29[8]
No of adults with obesity	-	-	-	29
No of adolescents (11-17 years) with obesity	121	-	13	-
No of children (7-11 years) with obesity	-	13	-	-
Weekly dose escalation steps (mg/day)	0.6, 1.2, 1.8, 2.4, 3.0[4]	0.3, 0.6, 0.9, 1.2, 1.8, 2.4, 3.0[5]	0.6, 1.2, 1.8, 2.4, 3.0[7]	0.6, 1.2, 1.8, 2.4, 3.0
Actual maintenance doses (mg/day)[1]	0.6 (n=1) 1.2 (n=1) 1.8 (n=2) 2.4 (n=10) 3.0 (n=107)	2.4 (n=1) 3.0 (n=12)	2.4 (n=1) 3.0 (n=12)	3.0
Treatment duration (weeks)[2]	56 weeks	7 weeks	5–6 weeks	35 days
Sparse PK sampling weeks	8, 12, 16, 30, 42, 56	NA	NA	NA
Number of pre-dose (trough) PK samples during dose escalation	NA	7[6]	4	NA
Number of PK samples after last dose	NA	5	6	12
Nominal timing of PK sampling after the last dose	NA	Pre-dose, 1h, 2h, 3h, 24h, 72h	Varying according to assigned sequence	Pre-dose, 2h, 4h, 1h, 13h, 15h, 18h, 20h, 24h, 36h, 48h, 60h

*Numbers refer to the final data files following data cleaning. [1]Dose levels for the longest durations in trial 4180. [2]Including dose-escalation. [3]Actual numbers in the PK population, i.e. subjects on active treatment. [4]Dose escalation was flexible (5–8 weeks). [5]Dose escalation was flexible (7–13 weeks). [6]Including one trough sample before last dose. [7]Dose escalation over 5 weeks with flexibility. [8]Subjects exposed to 3.0 mg liraglutide.

Table 3: summary of demographics across trials

Category	Group	Trial 4180	Trial 4181	Trial 3967	Trial 3630
All	N (on active treatment, included in pop-PK analysis)	251*	13	13	29
Population	Adults with obesity	-	-	-	29
	Adolescents with obesity	251*	-	13	-
	Children with obesity	-	13	-	-
Race	White	220 (87.6%)	6 (46.2%)	12 (92.3%)	25 (86.2%)
	Black or African American	20 (8%)	7 (53.8%)	-	-
	Other	11 (4.4%)	-	1 (7.7%)	4 (13.8%)
Ethnicity	Not Hispanic or latino	195 (77.7%)	10 (76.9%)	13 (100%)	26 (89.7%)
	Hispanic or latino	56 (22.3%)	3 (23.1%)	-	3 (10.3%)
Sex	Female	149 (59.4%)	7 (53.9%)	10 (76.9%)	11 (37.9%)
	Male	102 (40.6%)	6 (46.1%)	3 (23.1%)	18 (62.1%)
BW	Mean (SD)	100.8 (20.7)	69.08 (10.9)	102.05 (12.17)	102.28 (15.6)
	Range	[62.1-178.2]	[53.9-86.8]	[79.9-119.2]	[74.2-131.6]
Age	Mean (SD)	14.5 (1.6)	9.85 (0.9)	15.08 (0.95)	47.76 (13.8)
	Range	[12-17]	[8-11]	[13-16]	[20-72]
BMI	Mean (SD)	35.60 (5.40)	31.82 (2.85)	35.89 (3.09)	34.15 (2.74)
	Range	[26.60-58.80]	[26.73-37.75]	[31.62-40.62]	[30.27-40.03]

*Including placebo subjects

Liraglutide population PK has been studied for two indications: T2D (Victoza) and weight management (Saxenda), both for adult and paediatric subjects. Body weight has been shown to be the most important covariate, being inversely related to exposure. In the population PK analysis of phase 3 data in adults with obesity, a small sex effect was found with higher exposure in females compared with males. The population PK was consistent across indications, however with a tendency for lower exposure in subjects with T2D.

The first-order conditional estimation (FOCE-I) method implemented in the NONMEM software was used for the population PK analysis. A base model without covariates was developed based on prior knowledge of liraglutide PK. Next, a full model, which was the base model with all investigated covariates included, was estimated for the covariate analysis. All investigated covariates were significant except for age group. The full model could therefore not be reduced, and so, the full model was adopted as the final model.

As compliance can be challenging in the adolescent population, necessary action was taken to account for this. For the population PK analysis, the aim was to estimate PK parameters that are relevant for a compliant population; hence data records with missing concentration values and data records with concentration values below the lower limits of quantification (LLOQ) were flagged in the data file and excluded from the analysis.

A standard one-compartment model with first-order absorption and elimination was the starting point for the description of liraglutide PK. The structural model was parameterized in terms of the following parameters:

- Ka (absorption rate constant)
- CL/F (apparent clearance)
- V/F (apparent volume of distribution)

Between-subject variability was included for CL/F and V/F, assuming log-normal distributions without correlation between parameters. Furthermore, CL/F and V/F were estimated with a full variance-covariance matrix. No between-subject variability was included for ka. Within-subject variability (residual) was described by a proportional error model.

Results

Pharmacokinetics of study 3967

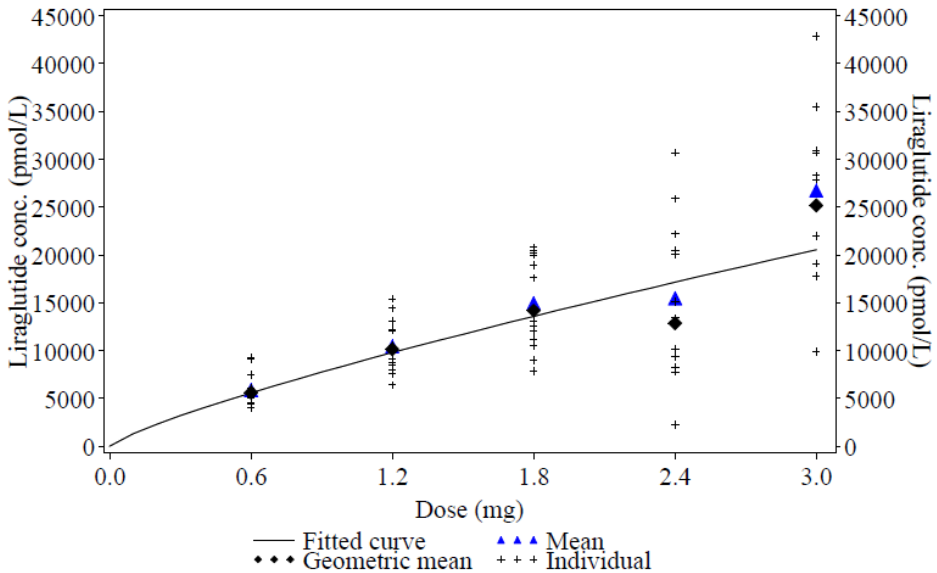
Dose proportionality

In the table below (Table) the mean C_{trough} values are listed of the subjects measured on each visiting day (escalating doses) in this study and in Figure 1. the individual data are presented and fitted to estimate the dose proportionality of the pharmacokinetics of liraglutide.

Table 4: 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 1: Dose proportionality based on Ctrough 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.

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

Population Pharmacokinetic Analysis:

The final dataset from study 4180 comprised 646 PK observations from 121 subjects. A total of 22 PK observations were excluded, due to missing times or inadequate dosing history, corresponding to 3.3% of the data. A total of 94 observations were below the LLOQ, corresponding to 14.6% of the final dataset.

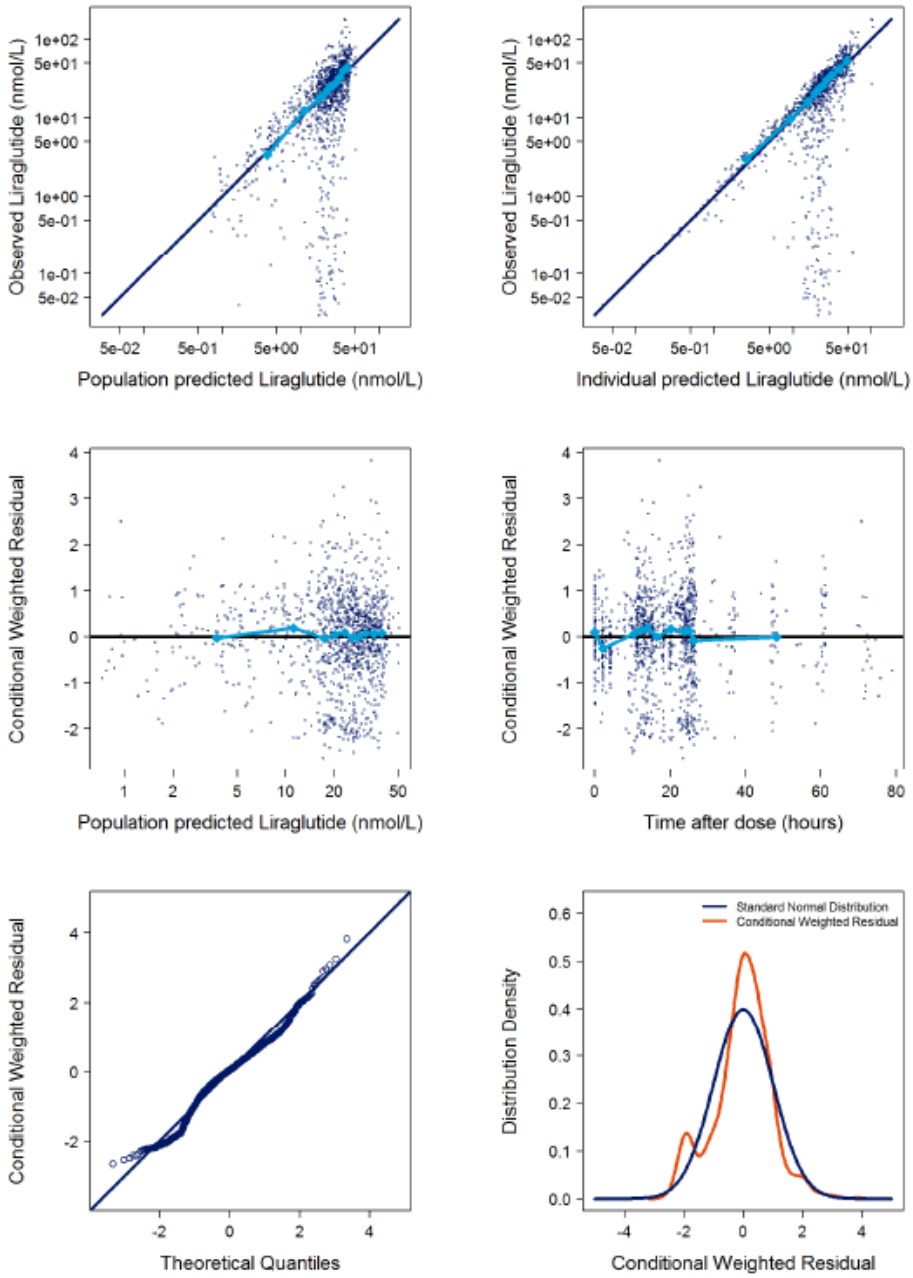
Building on previous population PK analysis of liraglutide, a one-compartment model with first-order absorption and elimination was applied with values of ka, and V/F fixed to previously estimated values, to allow for estimation of CL/F in trial 4180 with sparse PK sampling. A confirmatory approach was used regarding covariates with the estimation of a base model without covariates, a full model with all investigated covariates and a final model including only significant covariates. In the current analysis, all covariates included in the full model were statistically significant except for age group. As age group was the covariate under investigation for this analysis, the full model was also used as the final model, and a reduced model with exclusion of non-significant covariates was not estimated.

Table 5: parameter estimates from the final PK model

Parameter	Parameter name [unit]	Estimate	95% CI Lower bound	95% CI Upper bound	RSE (%)	IIV (%CV)	Shrinkage (%)
Absorption rate constant	KA [1/h]	0.0813	Fixed	Fixed	Fixed	NA	NA
Apparent Clearance	CL/F [L/h]	1.01	0.922	1.09	4.25	31.2	10.2
Apparent Volume of Distribution	V/F [L]	13.8	Fixed	Fixed	Fixed	31.7	19.2
Body weight exponent on CL/F	CL-BW	0.762	0.565	0.958	13.2	NA	NA
Sex contrast (MALE/FEMALE) on CL/F	CL-Male	1.12	0.993	1.24	5.64	NA	NA
Age contrast (CHILD/ADULT) on CL/F	CL-Child	1.11	0.89	1.34	10.2	NA	NA
Age contrast (ADOLE/ADULT) on CL/F	CL-Adole	1.06	0.931	1.19	6.24	NA	NA
Body weight exponent on V/F	V-BW	0.587	0.475	0.7	9.75	NA	NA
NA	Prop. Error	43.3	NA	NA	NA	NA	6.4

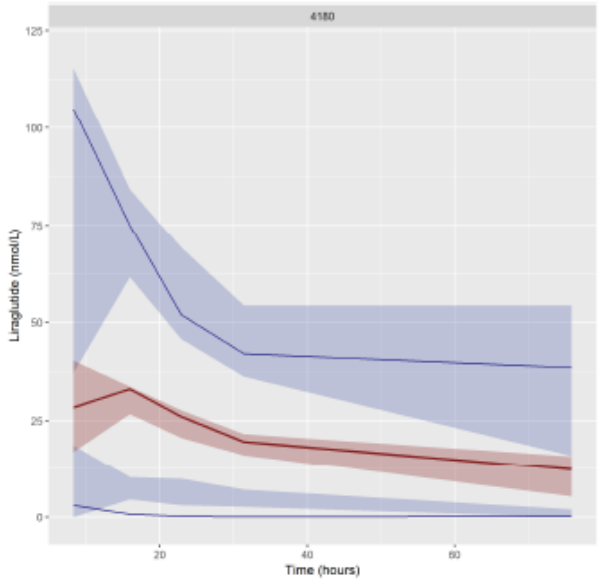
CI: confidence interval. RSE: relative standard error. CV: coefficient of variation

Figure 2: diagnostic plots for the final population PK model



Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of conditional weighted residuals and distribution plot of conditional weighted residuals. Data from trials 4180, 3967, 3630 and 4181.

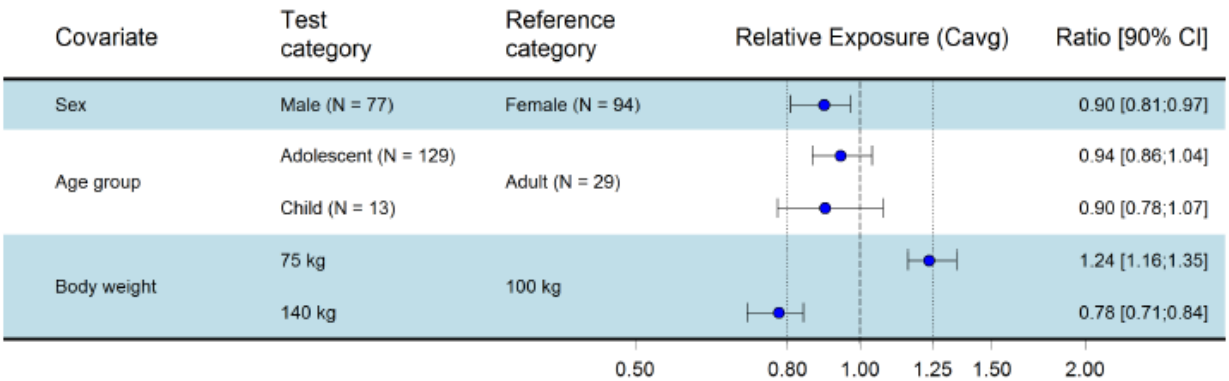
Figure 3: visual predictive check for the final population PK model



Data are observed (lines) and simulated (shaded area, n=2000) medians and 5th and 95th percentiles for concentrations after the first dose. Data from trial 4180.

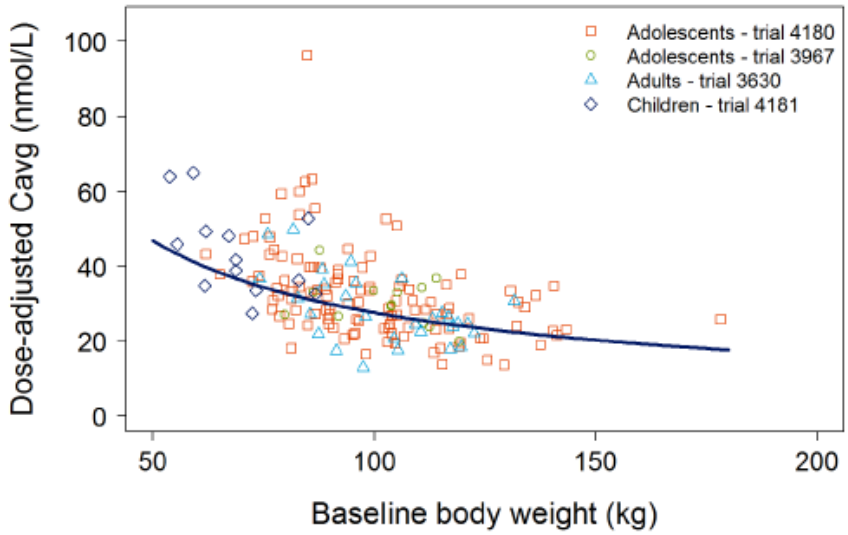
The population pharmacokinetic analysis has sufficiently been described, and model diagnostics seem to demonstrate adequate model performance. The Applicant additionally discussed the occurrence of the second peak in the conditional weighted residuals (CWRES) and provided the outcome file of the final model run which demonstrated acceptable results and showed convergence of the model.

Effects of intrinsic covariates on liraglutide exposure are shown in below. In accordance with previous findings in adults, body weight was the main intrinsic covariate for liraglutide exposure with lower exposure at higher body weights. Age group and sex were of no or little importance.



The reference category profile was a female adult subject with a body weight of 100 kg. The column to the right shows numerical means and 90% CI for the relative exposures. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80–1.25). Data from trials 4180, 3967, 3630 and 4181.

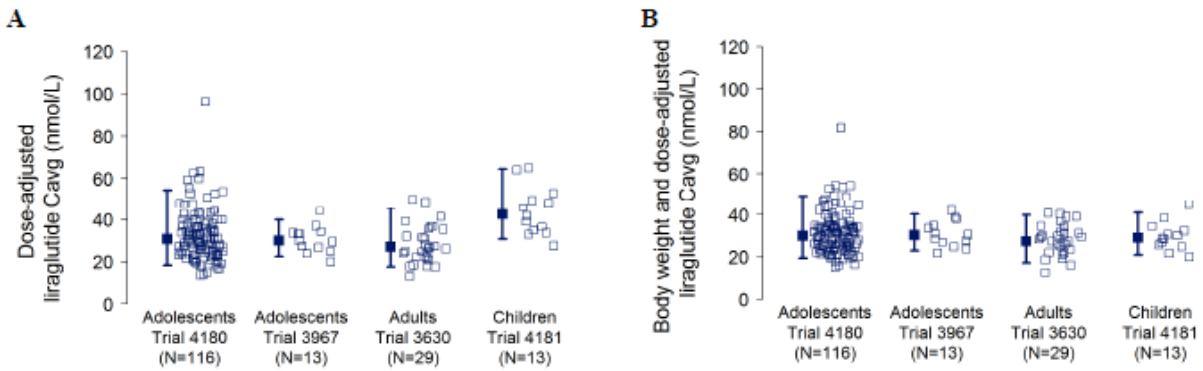
Figure 4: forest plot of covariate analysis for liraglutide exposure in subjects with obesity



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

Individual and mean liraglutide Cavg values were similar in adolescents and adults when adjusted to 3.0 mg dose whereas children had slightly higher concentrations. When adjusting for differences in body weight, exposures were similar across trials and age groups (figures below).

Figure 5: Liraglutide steady-state exposure across trials in subjects with obesity, without (A) and with (B) adjustment for body weight.



Data are individual (open symbols) and geometric mean C_{avg} estimates adjusted to 3.0 mg dose with 95% CI (closed symbols with error bars) from the final PK model for each trial. Data from trials 4180, 3967, 3630 and 4181.

A table of the summary of model-derived clearance (CL/F) values and average exposures across trials is provided below. Both the individual clearance and exposure estimates (CL/F and Cavg) were comparable between paediatric and adult subjects except for children who had slightly lower clearance and higher exposure. This difference can be partly explained by differences in body weight and the distribution of sex.

Table 6: summary of clearance and exposure (Cavg) estimates across trials included in the population PK analysis, liraglutide 3.0 mg

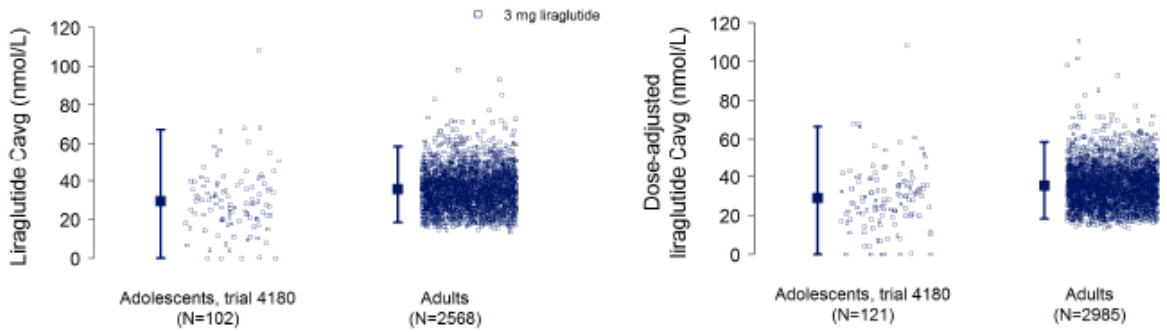
Trial	Clearance (CL/F) (L/h)	C_{avg}[a] (nmol/L), 90% CI
4180 - adolescents	1.09 [1.02, 1.16]	30.7 [28.8, 32.7]
3967 - adolescents	1.11 [0.98, 1.26]	30.0 [26.4, 34.0]
3630 - adults	1.23 [1.09, 1.40]	27.0 [23.9, 30.5]
4181 - children	0.78 [0.67, 0.92]	42.6 [36.4, 49.9]

Data are geometric means of individual model-derived estimates with 95% CI.

[a] average concentrations estimated for 3.0 mg dose of liraglutide.

The mean exposure in the exposure-response population for liraglutide dosed at 3.0 mg was similar in adolescents (trial 4180) and in adults (trials 1807, 1839 and 1922) with a large overlap of individual exposures between the two age groups, figure below. Exposures were numerically smaller in adolescents compared to adults, likely due to a lower degree of treatment compliance in adolescents.

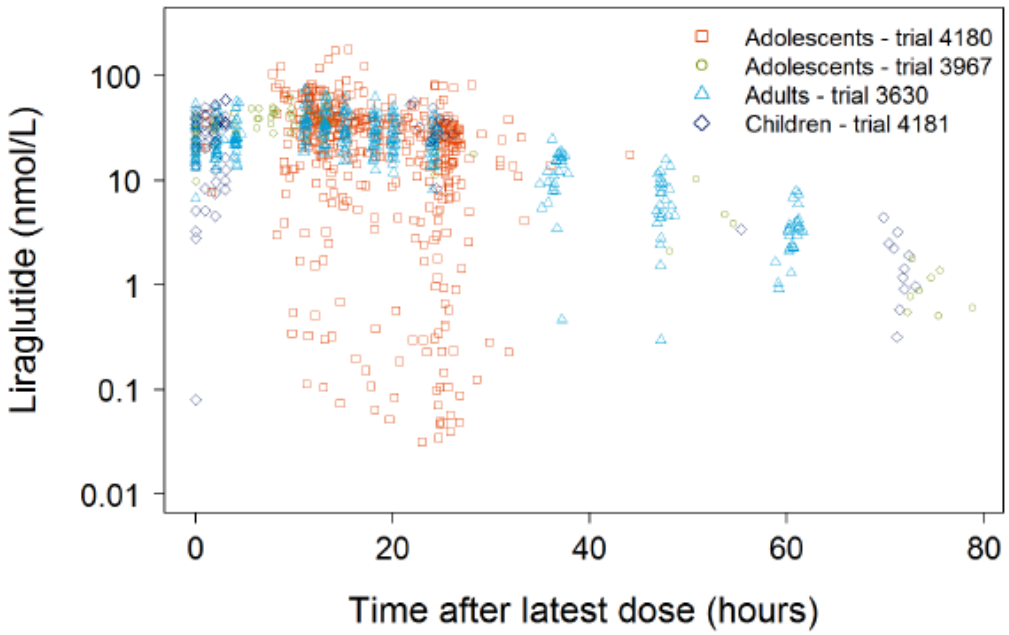
Figure 6: liraglutide steady-state exposure across trials in subjects treated with 3.0 mg liraglutide (A) and in all subjects with doses adjusted to 3.0 mg liraglutide (B).



Data are individual (open symbols) and geometric mean C_{avg} estimates with 95% CI (closed symbols with error bars) from the final PK model. Data from trial 4180 (including BLQ values) and trials 1807, 1839 and 1922 (not including BLQ values).

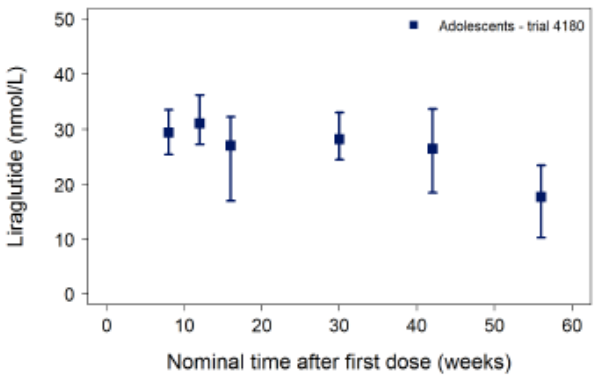
Individual observed liraglutide concentrations versus time since the latest dose revealed a number of lower than expected values in trial 4180. These observations could indicate compliance issues with some of the subjects in trial 4180. The possible lack of compliance by some subjects is also reflected in the summary concentrations over time as shown in the below figure. Instead of the expected constant exposure during steady-state maintenance dosing, exposures appeared to decrease, thus indicating a possible lack of compliance over time.

Figure 7: graphical analysis of PK and demographic data



Data from trials 4180, 3967, 3630 and 4181.

Figure 8: observed liraglutide concentrations in trial 4180 versus time since first dose



Data are median observed concentrations with 95% CIs for each time point for 3.0 mg dose. Data from trial 4180.

2.3.3. Discussion on clinical pharmacology

Regarding pharmacokinetics, the study results and population pharmacokinetic analysis indeed demonstrate that the exposure largely overlaps between the adolescent and adult study population. It is agreed that exposure associated with 3.0 mg liraglutide was found to be comparable between adolescent subjects in trial 4180 and previous findings of exposures across age groups.

Model-derived clearance (CL/F) values and average exposures (Cavg) were comparable between age groups, except for younger children (< 12 years) who had slightly lower clearance and a higher exposure, which is partly explained by differences in body weight and distribution of sex.

Steady-state exposure across trials in subjects treated with 3.0 mg liraglutide demonstrated quite a number of lower than expected values. The reasoning by the applicant, that it is due to compliance issues in this population and that in other trials a less stringent data cleaning was applied, can be agreed. Although it does not necessarily fully explain all lower than expected observed concentrations, it also very difficult to further investigate this issue.

2.3.4. Conclusions on clinical pharmacology

Regarding pharmacokinetics, overall, it can be agreed that the study results and population pharmacokinetic analysis demonstrate that the exposure is comparable between the adolescent and adult study population.

2.4. Clinical efficacy

2.4.1. Main study(ies)

There was one Phase 3a efficacy and safety trial of liraglutide 3.0mg in adolescents with obesity (Trial 4180).

Trial 4180

Methods

Trial design

Trial 4180 was a 56-week double-blind, multi-centre, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week off study-drug follow up period. The trial design is shown schematically in

.

The trial was conducted in pubertal adolescents with obesity aged 12 to less than 18 years. Subjects were randomised 1:1 to receive liraglutide or placebo as a once-daily s.c. injection. Randomisation was stratified according to pubertal development (Tanner staging) and glycaemic status. The trial consisted of a 12-week run-in period, followed by a 56-week double-blind treatment period and a 26-week off study drug follow-up period.

All subjects underwent counselling in healthy nutrition and physical activity for weight loss and were prescribed a structured programme from the beginning of the 12-week run-in period and continuing through the 26-week off study drug follow-up period.

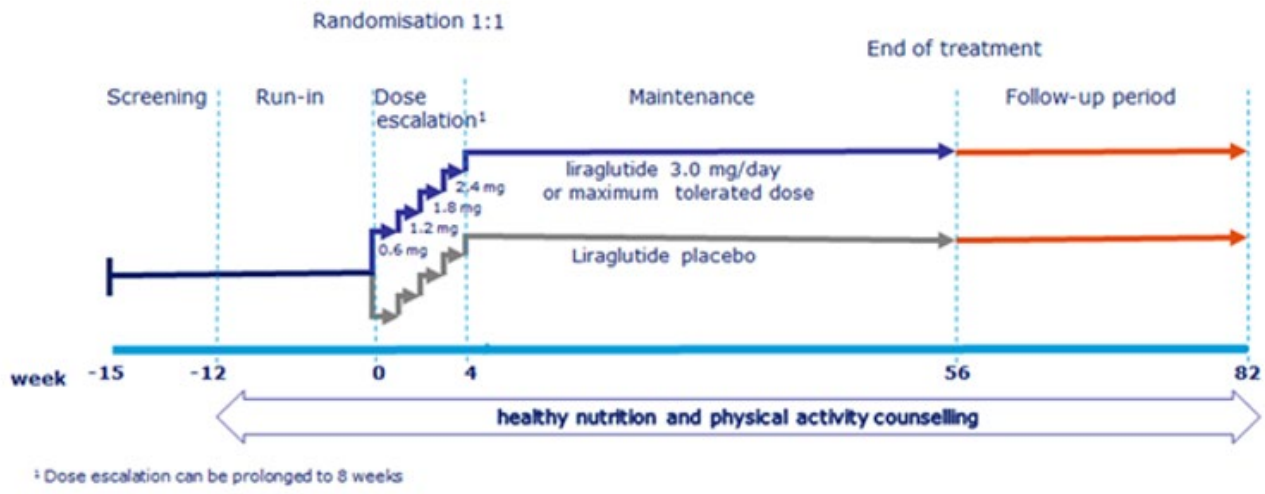


Figure 9: Study 4180 Trial design

Study participants

The population in the Trial 4180 included pubertal adolescent male and female subjects aged 12 to less than 18 years with obesity (BMI corresponding to ≥30 kg/m2 for adults by international cut-off points and ≥95th percentile for age and gender). Table provides details on the international cut off points for body mass index for obesity by sex between 12 and 18 years, defined to pass-through body mass index of 30 kg/m2 at age 18, obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and the United States.

The trial was conducted at 32 sites in 5 countries (Belgium, Sweden, Russia, Mexico and USA) which allowed for the inclusion of subjects with different racial and ethnic backgrounds. In accordance with regulatory commitment in the Paediatric Investigational Plan, at least 30% of the randomised subjects were from countries with a lifestyle and nutrition comparable to those in the European Union.

Table 7: International cut off points for body mass index for obesity by sex between 12 and 18 years

Age (years)	Body mass index 30 kg/m^2	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

Randomisation criteria

- BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥the 95th percentile for age and sex (for diagnosis of obesity).
- Compliance with run-in procedures and visit schedule as judged by the investigator.
- PHQ-9 score < 15 at randomisation
- No suicidal ideation of type 4 or 5 since last visit based on the C-SSRS questionnaire at randomisation.

Key inclusion criteria

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.

- Male or female, age 12 to less than 18 years at the time of signing informed consent and less than 18 years at date of randomisation
- BMI corresponding to ≥30 kg/m^2 for adults by international cut-off points and ≥ the 95th percentile for age and sex (for diagnosis of obesity)
- Stable body weight during the previous 90 days before screening V2 (<5 kg self-reported weight change)
- History of failing to lose sufficient weight with lifestyle modification as judged by the investigator and documented in subject's medical record.

Key exclusion criteria

- Pre-pubertal subjects (Tanner stage 1) at screening visit 2
- Body weight ≤60 kg
- Type 1 diabetes mellitus (T1DM)
- Family or personal history of multiple endocrine neoplasia type 2 (MEN2)
- Medullary thyroid carcinoma (MTC)
- History of pancreatitis (acute or chronic)
- Subjects with secondary causes of obesity (i.e., hypothalamic, genetic or endocrine causes)
- Treatment with medications within 90 days before screening visit 2 that, based on the investigator's judgement, may cause significant weight change. This should also include treatment with any of the following medications: pramlintide, orlistat, zonisamide, topiramate, lorcaserin, phenteremine, bupropion, naltrexone, glucagon-like peptide-1 (GLP-1) receptor agonists, or metformin (used as treatment for obesity)
- Anti-diabetic treatment other than metformin
- History of major depressive disorder within 2 years before screening visit 2.

Treatments

Treatment with liraglutide was initiated with 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until the 3.0 mg dose of liraglutide (highest allowed liraglutide dose) or a maximum tolerated dose was reached. Dose escalation was based on safety and tolerability as judged by the investigator. Dose escalation of the trial product was not allowed if the subject had a SMPG <3.1 mmol/L (56 mg/dL) or <3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia during the week prior to or during the dose-escalation visits, or during contacts (i.e., via telephone).

Objectives

The primary objective of Trial 4180 was to compare the efficacy of liraglutide versus placebo on weight loss in adolescent subjects with obesity after 56 weeks of treatment.

The secondary objectives of the trial were to compare the efficacy of liraglutide versus placebo on glycaemic control, cardiovascular risk factors and Impact of Weight on Quality of Life-Kids (IWQOL-Kids) in adolescent subjects with obesity after 30 and 56 weeks of treatment. Safety was also assessed at these time points. Additionally, the potential rebound effect from end of treatment at week 56 to week 82 was to be examined.

Outcomes/endpoints

Primary endpoint

- Change in BMI SDS from baseline (randomisation) to 56 weeks

Supportive secondary efficacy endpoints

- Percent of subjects achieving ≥5% reduction in baseline BMI at weeks 30, 56 and 82
- Percent of subjects achieving ≥10% reduction in baseline BMI at weeks 30, 56 and 82
- Change in BMI SDS from baseline to 30 and 82 weeks and change from 56 weeks to 82 weeks
- Change in BMI SDS (%) from baseline to 30 and 56 weeks
- Change from baseline to 30 and 56 weeks and change from 56 weeks to 82 weeks in:
- BMI
- Body weight (kilogram [kg], and percent [%])
- Waist circumference
- Waist-to-hip circumference ratio
- Cardiovascular risk factors: high sensitivity C-reactive protein (hsCRP) and fasting lipids:
- total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein
- (HDL)-cholesterol, non-HDL cholesterol, very low density lipoprotein (VLDL)-cholesterol,
- triglycerides and free fatty acids
- Systolic and diastolic blood pressure
- Glucose metabolism: glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG),
- fasting insulin, fasting C-peptide, glycaemic category and homeostasis model assessment of
- beta-cell function and insulin resistance parameters (HOMA-B and HOMA-IR)
- Patient reported outcome (PRO) assessed by Impact of Weight on Quality of Life-Kids
- (IWQOL-Kids)[a]

[a]Not assessed at week 82 and does not have associated endpoints.

Exploratory efficacy endpoint

- Change in BMI (%) from baseline to 56 weeks.

Sample size

The sample size was calculated to ensure a marginal statistical power of at least 90% for the primary endpoint (change in BMI SDS from baseline to 56 weeks) to confirm the superiority of liraglutide to placebo. Based on different sample size scenarios, it was considered realistic and conservative to assume a treatment difference of -0.26 and SD of 0.35 with the randomised subjects. Therefore, a sample size of 228 subjects were planned to be randomised in order to ensure 90% power.

Randomisation

At randomisation (week 0), eligible subjects were randomised in a 1:1 manner to one of the 2 treatment groups (liraglutide or placebo), using an interactive web response system (IWRS).
The randomisation of subjects was stratified according to Tanner staging, to enable the examination of treatment effect across trial population subgroups. Further, dysglycaemia was expected to occur frequently in this trial population. As a result, stratification was also performed according to glycaemic status: normoglycaemia versus dysglycaemia (pre-diabetes and T2D as described below in Table8.

Table 8: Glycaemic category

Normoglycaemia	FPG <5.6 mmol/L (<100 mg/dL) and/or HbA_{1c} <5.7%
Pre-diabetes	FPG 5.6−6.9 mmol/L (both inclusive), FPG 100–125 mg/dL (both inclusive) or HbA_{1c} 5.7−6.4% (both inclusive)
Type 2 diabetes (T2D)	FPG ≥7.0 mmol/L (≥126 mg/dL) and/or HbA_{1c} ≥6.5%

Placebo treatment was used as a comparator in this trial to evaluate the safety and efficacy of liraglutide 3.0 mg. Both treatment arms were in combination with healthy nutrition and physical activity counselling.

Blinding (masking)

As liraglutide was administered by s.c. injections, the same route of administration was also used for placebo to maintain blinding. Subjects, investigators and the Novo Nordisk clinical study group were blinded to subject treatment until after database lock. There were no cases of unblinding of members of the clinical study group prior to breaking the randomisation code.

Statistical methods

The full analysis set (FAS) was used in the analysis of the efficacy endpoints and the safety analysis set (SAS) was used in the evaluation of safety endpoints.

- **Full analysis set (FAS)** – all randomised subjects who had received at least one dose of trial product and had any post-randomisation data (according to the ITT principle). Subjects in the FAS were analysed as randomised.
- **Safety analysis set (SAS)** – all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS were analysed as treated.

The primary endpoint of change from baseline in BMI SDS after 56 weeks of treatment was analysed using an ANCOVA model with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage, and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, and with baseline BMI SDS and age as covariates. Missing observations were imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach.

Efficacy analyses

Results from the statistical analysis were generally presented by two-sided confidence intervals (CIs) with a confidence level of 95%. Superiority was claimed if the two-sided p-value was less than 5% and the treatment estimate favoured liraglutide. If the upper limit was below 0, superiority of liraglutide against placebo was concluded.

The FAS was used in the analysis of the efficacy endpoints.

The primary endpoint of change from baseline in BMI SDS after 56 weeks of treatment was analysed using an analysis of covariance (ANCOVA) model with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, with baseline BMI SDS and age as covariates. Missing observations were imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach.

The following sensitivity analyses were done to address the robustness of the primary approach for handling of missing values:

- ANCOVA with the last observation carried forward (LOCF) method,
- ANCOVA with the baseline observation carried forward (BOCF) method,
- ANCOVA without imputation by including only treatment completers, and
- Mixed model for repeated measurements (MMRM)

The changes in BMI SDS from baseline to 30 weeks and 82 weeks and from 56 weeks to 82 weeks were analysed using the same statistical method as used for the main analysis of the primary endpoint. Categorical endpoints related to BMI (percentage of subjects achieving ≥5% or ≥ 10% reduction in baseline BMI at 30, 56 and 82 weeks) were analysed using a logistic regression model. For the other supportive secondary efficacy endpoints and an exploratory efficacy endpoint, changes from baseline to 30 weeks or 56 weeks were analysed using the same type of ANCOVA with MI as used for the main analysis of the primary endpoint, but with the baseline value of the corresponding variable instead of the baseline BMI SDS as covariate.

Trial 4180 was a 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug in pubertal adolescents with obesity aged 12 to less than 18 years. The main part of the trial consisted of a 56-week double-blind treatment period and a 26-week follow-up period. The design of the trial is acceptable and in line with the PIP and the EMA guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev. 1) addendum on weight control in children. However, a randomised treatment period of 56 weeks is relatively short for a drug that is intended to be used for many decades. In adults, data are available from a double-blind, randomised trial with a treatment duration of 3.8 years. However, long term effects in children may be different due to the fact that organs are still in a developmental state.

The statistical analyses in the trial design are based on an intention to treat analysis. It was requested also to perform a per-protocol analysis to be informed of the magnitude of the effect of liraglutide on obesity in treatment completers. The applicant performed an additional per-protocol analysis to observe the efficacy in treatment completers separately. This is in line with the previous described results and showed a statistically significant change of SDS BMI -0.27 with liraglutide 3.0 mg treatment.

Results

Participant flow

A total of 299 subjects were screened across 32 sites in 5 countries. Of these, 40 subjects were screen failures. There were 259 subjects who entered the run-in period. Of these, 8 subjects were run-in failures, and 251 subjects were randomised; 125 subjects were randomised to the liraglutide 3.0 mg group, and 126 subjects were randomised to the placebo group. All randomised subjects were exposed to randomised treatment.

Of the 251 randomised subjects, 198 subjects (78.9%) (99 subjects each in the liraglutide and placebo groups) completed the trial (i.e. completed 56 weeks treatment on the trial product and did not withdraw from the trial at any timepoint), also termed as trial completers (Table).

Treatment completers: A total of 201 subjects (80.1%) remained on treatment and completed the end-of-treatment visit (week 56) without discontinuation of the trial product. These included 101 subjects (80.8%) from the liraglutide group and 100 subjects (79.4%) from the placebo group.

Premature discontinuation of the trial product (with or without withdrawing from the trial): A total of 50 subjects (19.9%) discontinued the trial product prematurely (24 subjects (19.2%) from the liraglutide group and 26 subjects (20.6%) from the placebo group).

AEs leading to premature discontinuation of trial product: 13 subjects from the liraglutide 3.0 mg group experienced AEs that led to premature discontinuation of trial product. Of these 6 subjects discontinued the trial product as well as withdrew from the trial and 7 subjects discontinued the trial product without withdrawing from the trial. The most common AEs that led to discontinuation of trial product were vomiting (6 subjects) and nausea (4 subjects).

The most frequent reasons for withdrawal from the trial were 'withdrawal by subject' (5 subjects in the liraglutide group and 15 subjects in the placebo group) and 'lost to follow up' (3 subjects in the liraglutide group and 6 subjects in the placebo group). Further, 1 subject in the liraglutide 3.0 mg group had discontinued due to a protocol violation; this subject had started a treatment that based on the investigator's judgement could have affected subject's weight.

Subjects randomised to liraglutide took doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg or MTD based on their individual tolerability.

Table 9: Subject disposition - summary - all subjects

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Screened			299
Screening failures			40
Run-in failures			8
Withdrawn before randomisation			0
Randomised	125	126	251
Exposed	125 (100.0)	126 (100.0)	251 (100.0)
Completed week 56 visit without discontinuation of trial product (treatment completers)	101 (80.8)	100 (79.4)	201 (80.1)
Premature discontinuation of trial product and/or withdrawn from trial during treatment period	24 (19.2)	26 (20.6)	50 (19.9)
Premature discontinuation of trial product			
1. Without withdrawing from the trial	13 (10.4)	4 (3.2)	17 (6.8)
Adverse event	7 (5.6)	0	7 (2.8)
Other	6 (4.8)	4 (3.2)	10 (4.0)
2. Withdrawing from the trial	11 (8.8)	22 (17.5)	33 (13.1)
Adverse event	6 (4.8)	0	6 (2.4)
Protocol violation	1 (0.8)	0	1 (0.4)
Other	4 (3.2)	22 (17.5)	26 (10.4)
Trial Completers	99 (79.2)	99 (78.6)	198 (78.9)
Completed trial product and withdrawn from the trial	2 (1.6)	1 (0.8)	3 (1.2)
Withdrawn from trial	13 (10.4)	23 (18.3)	36 (14.3)
Lost to follow-up	3 (2.4)	6 (4.8)	9 (3.6)
Withdrawal by subject	5 (4.0)	15 (11.9)	20 (8.0)
Withdrawal by parent/guardian	2 (1.6)	1 (0.8)	3 (1.2)
Other	3 (2.4)	1 (0.8)	4 (1.6)
Full analysis set	125 (100.0)	126 (100.0)	251 (100.0)
Safety analysis set	125 (100.0)	126 (100.0)	251 (100.0)

N: Number of subjects, %: Percentages are based on randomised subjects.
Only reasons for discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.
Run-in failures are not included in screen failures.

In the safety analysis set rows, subjects are summarised according to the actual treatment received and not randomised treatment.

One subject committed suicide after visit 23 (week 46).

No difference was observed in premature discontinuation rates between the liraglutide group and placebo. A total of 80.1% completed the 56-week visit without discontinuation of the trial product. This is a higher percentage compared to adult studies among liraglutide indicated for obesity (~70% treatment completers). It is acceptable that the stopping rule was not applied during the 4180 trial. Although not specific for liraglutide treatment, "early responders" (in general) seem to have a larger BMI decrease after 56 weeks. However, a stopping rule was asked to be applied, comparable to adults stated in the therapeutic indications (section 4.1) of the current SmPC and according to the recommendations of the European Society of Endocrinology and the Paediatric Endocrine Society: "*Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.*".

Conduct of the study

Dosing

In Trial 4180, liraglutide was initiated at a dose of 0.6 mg daily during the first week. The dose was increased in weekly steps of 0.6 mg until the 3.0 mg dose of liraglutide (highest allowed liraglutide dose), or a maximum tolerated dose was reached. Dose escalation was based on tolerability as judged by the investigator. The dose was not increased if the subject had a self-measured plasma glucose (SMPG) <3.1 mmol/L (56 mg/dL) or <3.9 mmol/L (70 mg/dL) in the presence of symptoms of hypoglycaemia during the week prior to or during the dose-escalation visits, or during contacts (i.e., via telephone). The duration of the dose-escalation varied from 4−8 weeks.

Of the 251 randomised subjects, 125 subjects were exposed to liraglutide and 126 subjects were exposed to placebo. Overall, the mean duration of exposure was comparable between the treatment groups (52.4 weeks in the liraglutide 3.0 mg group and 51.7 weeks in the placebo group, respectively) during the on-treatment period.

Of the 125 subjects in the liraglutide group, 103 subjects (82.4%) were escalated to 3.0 mg dose (the highest dose level) and remained on liraglutide 3.0 mg for a median time of 92.8% through the 56 weeks double-blind treatment period. Among the remaining 22 subjects (17.6%), 11 subjects (8.8%) did not reach the liraglutide 3.0 mg dose at any time point during the trial (mainly due to tolerability issues), and 11 subjects (8.8%) reached the liraglutide 3.0 mg dose but could not remain on the same dose level due to tolerability issues and the dose was subsequently lowered by the investigator (Table10).

Table 10: Exposure - summary - full analysis set

	Lira 3.0mg		Placebo	
Dose	n (%)	Median (%)	n (%)	Median (%)
Number of subjects	125		126	
0.6mg	3 (2.4)	62.5	0	
1.2mg	4 (3.2)	68.6	1 (0.8)	29.4
1.8mg	4 (3.2)	86.0	1 (0.8)	14.3
2.4mg	11 (8.8)	87.2	0	
3.0mg	103 (82.4)	92.8	124 (98.4)	92.8

The doses of liraglutide were similar to those used in adults. Given the high average body weight of 100.8kg, which was comparable to the body weight of the adult population, this was acceptable. The majority of the subjects could be escalated to liraglutide 3.0mg (82.4%) and remained on this dose throughout the trial duration of 56-weeks (92.8%), which is a higher percentage than in the adult study population.

Baseline data

Baseline subject characteristics

In general, the demographic and baseline characteristics were well-balanced between treatment groups (Table11,
Table12). The mean age at baseline was 14.5 years. There were more female subjects (59.4%) than male subjects (40.6%), with a comparable distribution in both treatment groups. The subjects were predominantly White (Caucasian) (87.6%). Most of the subjects were in the BMI subgroup of 30.0−<35.0 kg/m2 (45.8%) followed by BMI subgroup of 35.0−<40.0 (27.9%) at baseline. The majority of male and female subjects in both the treatment groups were pubertal and had reached full sexual maturity (Tanner stage 5) (51.8%).

Overall, the mean body weight was 100.8 kg and the mean BMI was 35.6 kg/m2. The mean height at baseline was 1.68 m, and the mean waist circumference was 105.93 cm. The mean BMI SDS at baseline was 3.17. Overall, the mean HbA1c was 5.3%, the fasting plasma glucose was 5.2 mmol/L, and overall, most subjects were normoglycaemic (74.1%). Systolic and diastolic blood pressures were noted to be
117 mmHg and 72 mmHg, respectively, at baseline, with no pronounced differences between both the treatment groups.

In accordance with regulatory commitment in the Paediatric Investigational Plan, at least 30% of the randomised subjects were from countries with a lifestyle and nutrition comparable to those in the European Union.

Table 11: Demographics and baseline characteristics - summary - full analysis set

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	125	126	251
Sex			
Female	71 (56.8)	78 (61.9)	149 (59.4)
Male	54 (43.2)	48 (38.1)	102 (40.6)
Country			
Belgium	15 (12.0)	18 (14.3)	33 (13.1)
Mexico	26 (20.8)	20 (15.9)	46 (18.3)
Russian Federation	30 (24.0)	38 (30.2)	68 (27.1)
Sweden	19 (15.2)	25 (19.8)	44 (17.5)
United States	35 (28.0)	25 (19.8)	60 (23.9)
Ethnicity			
Hispanic or Latino	32 (25.6)	24 (19.0)	56 (22.3)
Not Hispanic or Latino	93 (74.4)	102 (81.0)	195 (77.7)
Race			
American Indian or Alaska Native	0	1 (0.8)	1 (0.4)
Asian	2 (1.6)	0	2 (0.8)
Black or African American	14 (11.2)	6 (4.8)	20 (8.0)
Native Hawaiian or Other Pacific Islander	0	0	0
White	105 (84.0)	115 (91.3)	220 (87.6)
Other	4 (3.2)	4 (3.2)	8 (3.2)
BMI subgroup (kg/m^2)			
25.0-<30.0	11 (8.8)	12 (9.5)	23 (9.2)
30.0-<35.0	57 (45.6)	58 (46.0)	115 (45.8)
35.0-<40.0	39 (31.2)	31 (24.6)	70 (27.9)
>=40.0	18 (14.4)	25 (19.8)	43 (17.1)
Overall Tanner stage			
Stage 2	6 (4.8)	8 (6.3)	14 (5.6)
Stage 3	16 (12.8)	13 (10.3)	29 (11.6)
Stage 4	38 (30.4)	40 (31.7)	78 (31.1)
Stage 5	65 (52.0)	65 (51.6)	130 (51.8)
Dysglycaemia status			
Yes	32 (25.6)	33 (26.2)	65 (25.9)
No	93 (74.4)	93 (73.8)	186 (74.1)

N: Number of subjects, %: Percentages are based on number of subjects.
BMI: Body Mass Index (kg/m^2).
For parameters not measured at baseline, screening value is used.
Overall Tanner stage for each subject is calculated as maximum Tanner stage combining all the categorical questions per visit. Baseline value is defined as the latest pre-dosing value.

Table 12: Baseline characteristics (for continuous data) - full analysis set

	Lira 3.0 mg	Placebo	Total
Number of subjects	125	126	251
Mean age (years)	14.6	14.5	14.5
Mean BMI SDS	3.14	3.20	3.17

	Lira 3.0 mg	Placebo	Total
Mean BMI (kg/m^2)	35.3	35.8	35.6
Mean body weight (kg)	99.3	102.2	100.8
Mean HbA_{1c} (%)	5.3	5.3	5.3
Mean FPG (mmol/L)	5.2	5.2	5.2
Mean LDL (mmol/L)	2.29	2.24	2.27
Mean triglyceride (mmol/L)	1.36	1.40	1.38

BMI: body mass index, BMI SDS: body mass index standard deviation Score, FPG: fasting plasma glucose, HbA1c: glycosylated haemoglobin, LDL: low density lipoprotein

In general, demographics were well balanced between the treatment groups. However, there were some racial differences between the groups, with a higher percentage of white subjects in the placebo group compared to liraglutide (91.3 vs 84.0%). In total, there were more female subjects (59.4%) than male subjects (40.6%), with a comparable distribution in both treatment groups. The placebo group had a slightly higher BMI SDS compared to liraglutide (3.20 vs 3.14) with no differences in glycaemic parameters. No absolute numbers of the number of subjects with diabetes are given.

Outcomes and estimation

Primary outcome

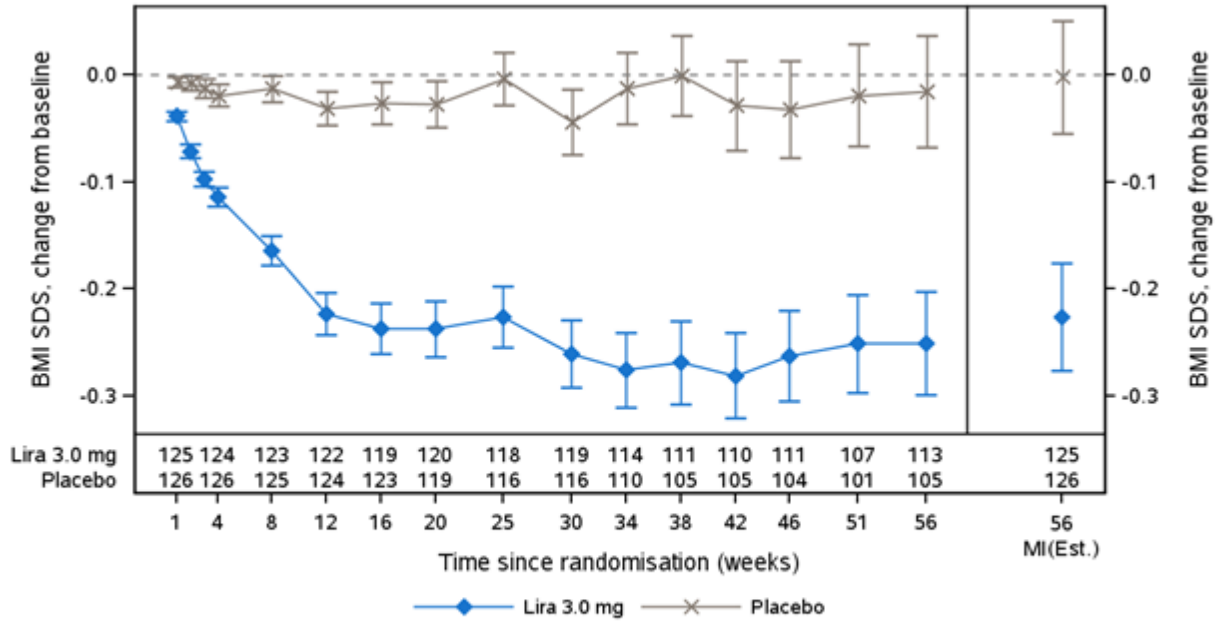
Change in BMI SDS

Change in BMI SDS from baseline (randomisation) to week 56 was the primary endpoint in Trial 4180.

Treatment with liraglutide 3.0 mg led to a significant reduction in BMI SDS from baseline (randomisation) to week 56. The superiority of liraglutide 3.0 mg over placebo in reducing mean BMI SDS from baseline to week 56 was confirmed with an ETD of -0.22 $[-0.37; -0.08]_{95\% CI}$, p=0.0022 No statistically significant difference in BMI SDS from baseline was observed between the treatment groups at week 82 (TableTable 13: Change in BMI SDS from baseline - ANCOVA - MI - full analysis set). The estimated treatment difference was statistically significant in favour of liraglutide 3.0 mg when compared with placebo. The robustness of the primary analysis results (i.e. superiority of liraglutide 3.0 mg to placebo in reducing BMI SDS at week 56 from baseline) was supported by sensitivity analyses Figure.

Treatment with liraglutide 3.0 mg also resulted in a statistically significant reduction in BMI SDS from baseline to week 30 compared to placebo (ETD at week 30: -0.21 $[-0.30; -0.12]_{95\% CI}$, p<0.0001).

The observed mean BMI SDS at baseline was 3.14 in the liraglutide 3.0 mg group and 3.20 in the placebo group. After 56 weeks of treatment, the observed mean BMI SDS was 2.88 in the liraglutide 3.0 mg group and 3.14 in the placebo group. The observed mean change in BMI SDS from baseline to week 56 was -0.25 in the liraglutide 3.0 mg group and -0.02 in the placebo group. The mean change in BMI SDS by treatment week is plotted in Figure.



BMI SDS: Body Mass Index (kg/m^2) Standard Deviation Score.
Baseline is defined as latest pre-dosing value.
Mean values based on all in-trial observations. MI(Est.): Estimated treatment difference from ANCOVA model (Lira 3.0 mg - Placebo).
Bottom panel: Numbers of contributing subjects by treatment arm.
Error bar is: +/- standard error of mean.
Data from subjects discontinued trial product before week 30 (Visit 19) and subjects discontinued after week 30 (Visit 19) and before week 56 (Visit 25) and returned for week 30 (Visit 19x) and week 56 (Visit 25x) respectively are included.

Figure 10: Change in BMI SDS by treatment week - mean plot - full analysis set

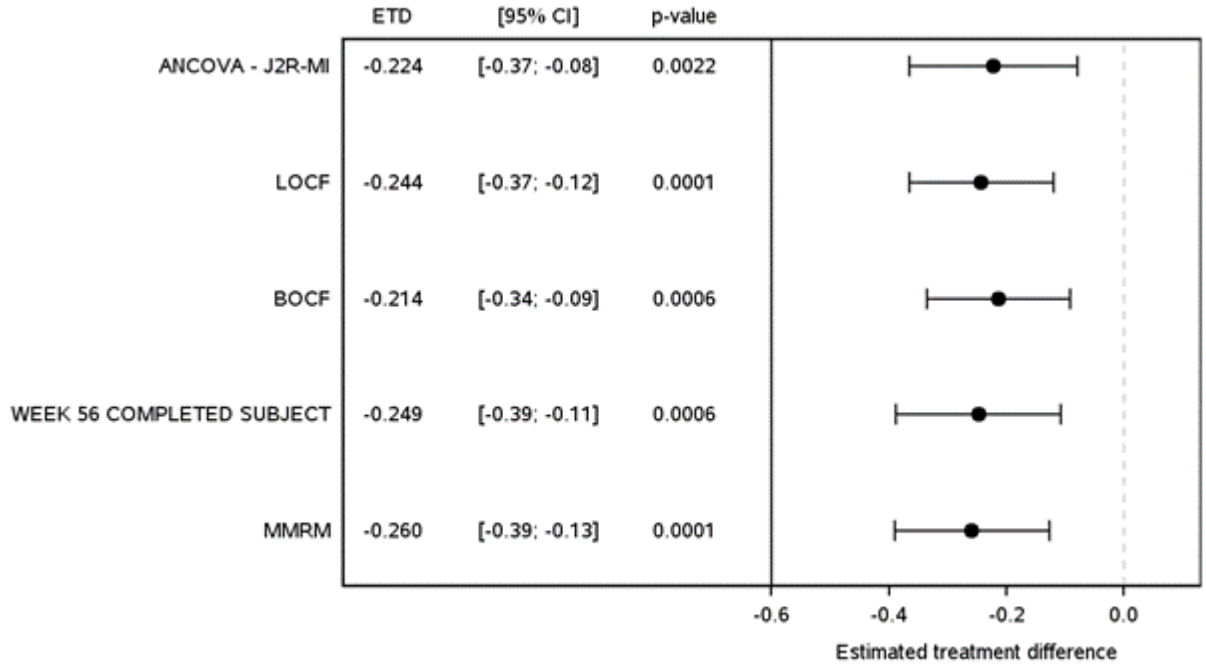
Table 13: Change in BMI SDS from baseline - ANCOVA - MI - full analysis set

BMI SDS	Baseline BMI SDS		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
week 30	3.14	3.20	-0.25	-0.04	-0.21 [-0.30; -0.12]	<.0001
week 56[a]			-0.23	-0.00	-0.22 [-0.37; -0.08]	0.0022
week 82			-0.03	0.08	-0.11 [-0.28; 0.06]	0.1913

Baseline value is defined as latest pre-dosing value.

[a]Primary endpoint

CI: confidence interval, ETD: estimated treatment difference, N: number of subjects contributing to analysis Jump to reference-MI: Analysis of in-trial data with missing observations imputed from the placebo arm based on a jump to reference multiple (x100) imputation approach. Responses at week 30, 56, 82 were analysed using an analysis of covariance model with treatment, sex, region, baseline glycaemic category, stratification factor for Tanner stage and interaction between baseline glycaemic category and stratification factor for Tanner stage as fixed effects, baseline BMI SDS, age as covariates.



ETD: Estimated treatment difference (Lira 3.0 m.g - Placebo) at week 56. CI: Confidence interval. BMI SDS: Body Mass Index (kg/m^2) Standard Deviation Score.
Baseline is defined as latest pre-dosing value.
Estimated treatment difference for primary and sensitivity analysis model.
LOCF: Last Observation Carried Forward, BOCF: Baseline Observation Carried Forward, MMRM: Mixed Model for Repeated Measures.

Figure 11: Change in BMI SDS from baseline - statistical analysis - primary and sensitivity analysis - forest plot - full analysis set

Change in BMI SDS from week 56 to week 82 (off-study-drug follow-up period)

At week 56, the observed mean BMI SDS for treatment completers was 2.87 in the liraglutide 3.0 mg group and the 3.10 in the placebo group. In the off-study-drug follow-up period, the observed mean change in BMI SDS was +0.22 in the liraglutide 3.0 mg group and +0.08 in the placebo group.

In the off-study-drug follow-up period, the estimated mean change in BMI SDS was 0.22 in the liraglutide 3.0 mg group and 0.07 in the placebo group. The ETD for the change in BMI SDS from week 56 to week 82 was 0.15 $[0.07; 0.23]_{95\%CI}$, p=0.0002. Thus, a significant increase in BMI SDS (weight regain) was seen from week 52 to week 82 for liraglutide 3.0 mg vs. placebo after drug discontinuation

Change in BMI SDS (%)

The ETD for the change from baseline in BMI SDS percentage was statistically significant in favour of liraglutide 3.0 mg versus placebo at weeks 30 and 56:

- ETD at week 30: -7.04% [-9.98; -4.09]95% CI, p<0.0001
- ETD at week 56: -7.64% [-12.41; -2.87]95% CI, p=0.0017

Treatment with liraglutide led to a reduction BMI SDS from baseline to week 56 (-0.23), corresponding to a change in body weight of -2.26kg. This reduction did not maintain during the 26-week follow-up period (-0.03). In the placebo group, BMI SDS did not change after 56-weeks and slightly increased during the follow-up period (0.08). The clinical relevance of the reduction in BMI SDS in the treatment group is uncertain. In general, improvement in body composition and cardiometabolic risk can be seen with BMI SDS reductions of ≥0.25 in obese adolescents, while greater benefits accrue from losing at least 0.5 BMI SDS (Ford et al. 2010). In this study, the authors observed no improvement in mean waist circumference SDS or body fat SDS with a BMI SDS reduction of >0 to <0.25. Improvement by ≥0.25 was associated with small reductions in mean waist circumference SDS and body fat SDS. Concomitant with these findings, they observed significant improvements in the key metabolic risk factors triglyceride, LDL-C and hs-CRP levels (30%, 15% and 45%, respectively) with a minimum loss of ≥0.5 BMI SDS. Improvements were also seen (13%, 12% and 11%) for losses of between ≥0.25 and <0.5. A similar picture emerged with insulin sensitivity and blood pressure with losses of ≥0.25 BMI SDS associated with a significant reduction. The applicant was requested to discuss the clinical relevance of the observed reduction in BMI SDS and should discuss whether there is a prespecified subgroup with relevant clinical benefit from treatment of liraglutide or not. Moreover, it was not clear whether the observed weight reduction is only seen in subjects suffering from gastro-intestinal side effects, suggesting that the beneficial effect is mainly caused by adverse effects of liraglutide. A subgroup analysis in subjects with and without gastrointestinal side effects was warranted. The sub-group analyses showed that treatment with liraglutide 3.0 in subjects with GI adverse events resulted in a change in BMI SDS -0.26 compared with placebo treatment. A comparable result was observed in the group without GI adverse events, i.e. BMI SDS -0.23, and the interaction test was not significant. We therefore conclude that also without GI symptoms a comparable treatment effect is achieved.

Additionally, a per-protocol analysis was requested to observe the effect of liraglutide in subjects who completed the treatment period successfully. The applicant performed an additional per-protocol analysis to observe the efficacy in treatment completers separately. This is in line with the previous described results and showed a statistically significant change of SDS BMI -0.27 with liraglutide 3.0 mg treatment.

BMI, body weight, waist circumference and waist-to-hip circumference ratio

The results for the weight-related parameters (BMI, body weight and waist circumference) were all consistent with those for BMI SDS. Treatment with liraglutide 3.0 mg resulted in a statistically significant reduction in BMI (kg/m^2), body weight (% and kg) and waist circumference from baseline to weeks 30 and 56 compared to placebo (Table14). However, the change from baseline in waist-to-hip circumference ratio was not statistically significant between the treatment groups at weeks 30 and 56.

Table 14: Change in BMI, body weight, waist circumference and waist-to-hip circumference ratio from baseline - ANCOVA - MI - full analysis set

Endpoint	Baseline values		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
BMI (kg/m^2) at week 30	35.3 kg/m^2	35.8 kg/m^2	-1.68 kg/m^2	-0.18 kg/m^2	-1.50 kg/m^2 [-2.07; -0.93]	<0.0001
BMI (kg/m^2) at week 56			-1.39 kg/m^2	0.19 kg/m^2	-1.58 kg/m^2 [-2.47; -0.69]	0.0005

Endpoint	Baseline values		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
Body weight (%) at week 30	N/A	N/A	-4.03 %	0.42 %	-4.45% [-6.09; -2.81]	<.0001
Body weight (%) at week 56			-2.65 %	2.37 %	-5.01% [-7.63; -2.39]	0.0002
Body weight (kg) at week 30	99.3 kg	102.2 kg	-3.69 kg	0.42 kg	-4.11 kg [-5.79; -2.44]	<.0001
Body weight (kg) at week 56			-2.26 kg	2.25 kg	-4.50 kg [-7.17; -1.84]	0.0009
Waist circumference (cm) at week 30	104.87 cm	106.99 cm	-4.46 cm	-1.98 cm	-2.48 cm [-4.10; -0.86]	0.0027
Waist circumference (cm) at week 56			-4.35 cm	-1.42 cm	-2.93 cm [-5.24; -0.63]	0.0126
Waist-to-hip circumference ratio at week 30	0.908	0.915	-0.02	-0.02	-0.00 [-0.01; 0.01]	0.9870
Waist-to-hip circumference ratio at week 56			-0.02	-0.02	-0.00 [-0.02; 0.01]	0.5214

CI: confidence interval, ETD: estimated treatment difference, N: number of subjects contributing to analysis, N/A: not applicable

Change in BMI, body weight, waist circumference and waist-to-hip circumference ratio from week 56 to 82 (off-study-drug follow-up period)

The observed mean changes in BMI, body weight, waist circumference and waist-to-hip circumference ratio in the off-study-drug follow-up period (from week 56 to week 82) are presented in Table 15.

Table 15: Change in BMI, body weight, waist circumference and waist-to-hip circumference ratio from week 56 to 82 - descriptive statistics - full analysis set

Endpoint	Observed values at week 56		Observed mean change from week 56 to week 82	
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126
BMI (kg/m^2)	33.7 kg/m^2	35.3 kg/m^2	+1.5 kg/m^2	+0.7 kg/m^2
Body weight (%)	N/A	N/A	5.3 %	2.3 %
Body weight (kg)	96.3 kg	102.0 kg	+4.7 kg	+2.4 kg
Waist circumference (cm)	100.07 cm	104.45 cm	+3.58 cm	+1.24 cm
Waist-to-hip circumference ratio	0.887	0.894	0.010	0.003

Note: Actual number of subjects contributing to the observed values and change in mean values may vary depending on the number of subjects available at that timepoint

N: total number of subjects, N/A: not applicable

Change in BMI (%)

Change in BMI (%) at week 56 was analysed as an exploratory endpoint. The ETD for the change in BMI (%) from baseline to week 56 was statistically significant in favour of liraglutide 3.0 mg versus placebo (Table).

Table 16: Change in BMI (%) at week 56 - statistical analysis - full analysis set

Endpoint	Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126		
BMI (%) at week 56	-4.29	0.35	-4.64 [-7.14; -2.14]	0.0003

BMI (%): body mass index (percentage), CI: confidence interval, ETD: estimated treatment difference, N: number of subjects contributing to analysis

Percent of subjects achieving ≥5% or ≥10% reduction in baseline BMI

At weeks 30, 56 and 82, the estimated proportion of subjects who achieved a reduction in BMI of ≥5% or ≥10% from baseline was greater in the liraglutide 3.0 mg group than in the placebo group. The odds for reaching a ≥5% or ≥10% reduction in BMI at weeks 30 and 56 were statistically significantly greater with liraglutide 3.0 mg than with placebo. There was no statistically significant reduction (≥5% or ≥10%) in BMI at week 82 (Tabl).

Table 17: Subjects losing at least 5% or 10% of baseline BMI after 30, 56 or 82 weeks of treatment – statistical analysis – logistic regression – MI – full analysis set

Endpoint	Lira 3.0 mg Probability (%)	Placebo Probability (%)	Odds ratio [95% CI] Lira 3.0 mg/Placebo	p-value
≥5% reduction in BMI at week 30	44.51	13.68	5.06 [2.64; 9.71]	<.0001
≥5% reduction in BMI at week 56	43.25	18.73	3.31 [1.78; 6.16]	0.0002
≥5% reduction in BMI at week 82	27.46	18.79	1.64 [0.85; 3.13]	0.1377
≥10% reduction in BMI at week 30	21.98	4.41	6.11 [2.38; 15.72]	0.0002
≥10% reduction in BMI at week 56	26.08	8.11	4.00 [1.81; 8.83]	0.0006
≥10% reduction in BMI at week 82	15.84	9.72	1.75 [0.78; 3.92]	0.1748

CI: confidence interval, J2R-MI: jump to reference-multiple imputation

During the treatment period liraglutide 3.0 mg resulted in a statistically significant reduction in BMI (kg/m^2) (ETD: -1.58 kg/m^2 [-2.47; -0.69]), body weight (ETD: -4.50 kg [-7.17; -1.84]) and waist circumference (ETD: -2.93 cm [-5.24; -0.63]) compared to placebo. The estimated proportion of subjects who achieved a reduction in BMI of ≥5% or ≥10% from baseline was greater in the liraglutide 3.0 mg group than in the placebo group (≥5%: 43.25 vs 18.73% and ≥10%: 26.08 vs 8.11% at 56-weeks). However, these numbers were lower compared to the adult population whereas 63.5% of the subjects in the liraglutide 3.0mg group received a reduction in BMI of ≥5% and 32.8% ≥10% after 56-weeks (SCALE Obesity & Pre-Diabetes – Trial 1839). In contrast with the adult study, no early response in BMI reduction was measured after 12 weeks which is defined as early responders and was a predictive factor for long-term weight reduction in adults.

Cardiometabolic parameters

No statistically significant differences in high sensitivity C-reactive protein (hsCRP), fasting lipid values and blood pressure were observed between the treatment groups from baseline to weeks 30 and 56 (Table18, Table).

Table 18: Change from baseline in fasting lipids (mmol/L) – ANCOVA – MI- full analysis set

Endpoint	Baseline values (mmol/L)		Estimated ratio to baseline values		Treatment ratio (Liraglutide 3.0 mg/ Placebo) Estimate [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
Total cholesterol at week 30	4.05	4.01	1.00	0.98	1.02 [0.99; 1.05]	0.2444
Total cholesterol at week 56			1.00	0.99	1.01 [0.97; 1.04]	0.6451
LDL cholesterol at week 30	2.29	2.24	1.00	0.99	1.01 [0.95; 1.07]	0.7531
LDL cholesterol at week 56			1.00	1.00	1.00 [0.94; 1.05]	0.8816
HDL cholesterol at week 30	1.13	1.14	1.04	1.00	1.04 [1.00; 1.08]	0.0809
HDL cholesterol at week 56			1.04	1.01	1.02 [0.97; 1.07]	0.3998
Non-HDL cholesterol at week 30	2.92	2.88	0.98	0.97	1.01 [0.97; 1.06]	0.5758
Non-HDL cholesterol at week 56			0.98	0.98	1.00 [0.95; 1.05]	0.9977

Endpoint	Baseline values (mmol/L)		Estimated ratio to baseline values		Treatment ratio (Liraglutide 3.0 mg/ Placebo) Estimate [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
VLDL cholesterol at week 30	0.62	0.63	0.91	0.91	1.00 [0.91; 1.10]	0.9802
VLDL cholesterol at week 56			0.92	0.93	0.98 [0.89; 1.08]	0.7025
Triglycerides at week 30	1.36	1.40	0.91	0.92	0.99 [0.90; 1.09]	0.8609
Triglycerides at week 56			0.92	0.93	0.98 [0.89; 1.08]	0.7273
Free fatty acids at week 30	0.46	0.51	0.92	0.89	1.03 [0.92; 1.16]	0.5732
Free fatty acids at week 56			0.97	0.97	1.00 [0.90; 1.10]	0.9472

ETD: estimated treatment difference, N: number of subjects contributing to analysis

Table 19: Change from baseline in blood pressure (mmHg) - ANCOVA - MI - full analysis set

Endpoint	Baseline values (mmHg)		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
SBP at week 30	116	117	-2.03	-0.19	-1.84 [-4.08; 0.41]	0.1085
SBP at week 56			-1.21	0.84	-2.05 [-4.53; 0.43]	0.1056
DBP at week 30	72	73	-0.51	-0.50	-0.02 [-1.95; 1.92]	0.9867
DBP at week 56			0.77	-0.46	1.24 [-0.66; 3.14]	0.2018

CI: confidence interval, DBP: diastolic blood pressure, ETD: estimated treatment difference, N: number of subjects contributing to analysis, SBP: systolic blood pressure

Glucose metabolism parameters

Treatment with liraglutide 3.0 mg resulted in a statistically significant reduction in HbA_{1c} and fasting plasma glucose (FPG) from baseline to week 30 compared to placebo. No statistically significant differences in HbA_{1c} and FPG were observed between the treatment groups at week 56 (Table20).

Table 20: Change from baseline in HbA_{1c} (%) and FPG (mmol/L) - ANCOVA - MI - full analysis set

Endpoint	Baseline values		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
HbA_{1c} (%) at week 30	5.3%	5.3%	-0.12	-0.01	-0.10%-points [-0.17; -0.04]	0.0018
HbA_{1c} (%) at week 56			-0.10	-0.03	-0.06%-points [-0.14; -0.01]	0.0914

Endpoint	Baseline values		Estimated mean change from baseline		ETD (Lira 3.0 mg - Placebo) [95% CI]	p-value
	Lira 3.0 mg N=125	Placebo N=126	Lira 3.0 mg N=125	Placebo N=126		
FPG (mmol/L) at week 30	5.2 mmol/L	5.2 mmol/L	-0.22	-0.02	-0.20 mmol/L [-0.30; -0.10]	0.0002
FPG (mmol/L) at week 56			-0.11	-0.01	-0.10 mmol/L [-0.23; 0.03]	0.1253

CI: confidence interval, ETD: estimated treatment difference, FPG: fasting plasma glucose, HbA_{1c}: glycosylated haemoglobin, N: number of subjects contributing to analysis

At week 56, the observed mean HbA_{1c} was 5.2% in the liraglutide 3.0 mg group and 5.3% in the placebo group. In the off-study-drug follow-up period, the observed mean change in HbA_{1c} was 0.1%-points in both the liraglutide 3.0 mg and placebo groups.

At week 56, the observed mean FPG was 5.1 mmol/L in the liraglutide 3.0 mg group and 5.2 mmol/L in the placebo group. In the off-study-drug follow-up period, the observed mean change in FPG was +0.1 mmol/L in both the liraglutide 3.0 mg and placebo groups.

Fasting C-peptide, Fasting insulin, HOMA-B and HOMA-IR

No statistically significant treatment differences in fasting C-peptide, fasting insulin, homeostasis model assessment of beta-cell function (HOMA-B) and homeostasis model assessment of insulin resistance (HOMA-IR) were observed between the liraglutide 3.0 mg and placebo groups at weeks 30 and 56.

Glycaemic category

At baseline (week -2), the proportion of subjects who were normoglycaemic was comparable between the liraglutide 3.0 mg and placebo groups (74.4% vs. 73.8%). The estimated proportion of subjects who were normoglycaemic was higher in the liraglutide 3.0 mg group than in the placebo group at week 30 (86.72% vs. 76.16%) and week 56 (84.60% vs. 74.66%). However, the odds of being normoglycaemic at weeks 30 and 56 were not statistically significant between the treatment groups.

The proportion of subjects who were normoglycaemic at baseline (week -2) and progressed to a pre-diabetic state was lower in the liraglutide 3.0 mg group compared to the placebo group at week 30 (5.6% vs. 10.3%) and this proportion was similar between the treatment groups at week 56 (8.0% vs. 7.1%).

The proportion of subjects who were pre-diabetic at baseline (week -2) and reverted to a normoglycaemic state was higher in the liraglutide 3.0 mg group compared to placebo group at week 30 (13.6% vs. 10.3%) and week 56 (12.8% vs. 7.1%).

The proportion of subjects who were pre-diabetic at baseline (week -2) and progressed to a type 2 diabetic state at weeks 30 and 56 was lower (range of 0−0.8%) and did not differ between the treatment groups.

Greater reductions in HbA_{1c} and fasting plasma glucose (FPG) were observed with liraglutide than with placebo at week 30 (ETD: -0.10%-points [-0.17; -0.04]). After 56-weeks of treatment, the ETD in HbA1c was not statistically significant (ETD: -0.06%-points [-0.14; -0.01]). There were no significant changes in fasting C-peptide, fasting insulin, homeostasis model assessment of beta-cell function

(HOMA-B) and homeostasis model assessment of insulin resistance (HOMA-IR). No differences were observed regarding shifts in glycaemic categories during the treatment period between liraglutide and placebo. However, no absolute numbers of diabetic subjects are shown.

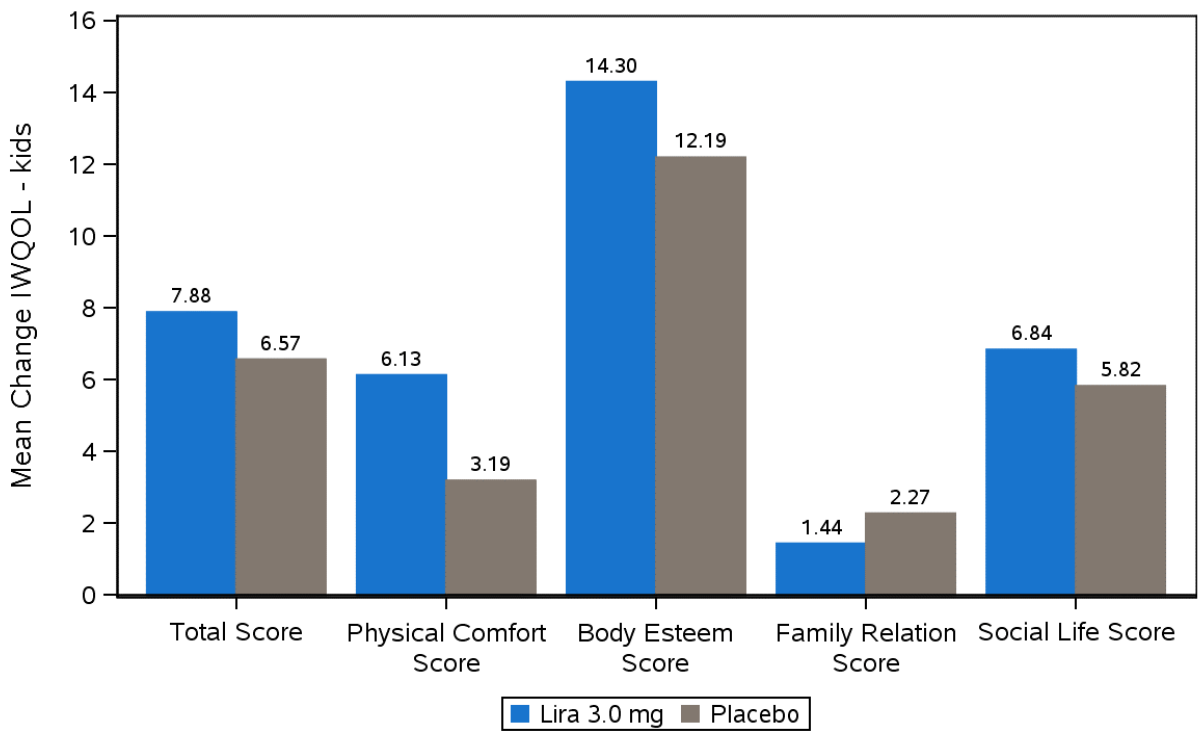
Patient reported outcome - Impact of Weight on Quality of Life-Kids (IWQOL Kids)

The IWQOL-Kids questionnaire was used to assess the weight-related quality of life in adolescents. The following four domain scores and a total score was calculated:

- Physical comfort
- Body esteem
- Social life
- Family relations.

There were no statistically significant differences between the treatment groups in any of the 4 domain scores or in the total score of IWQOL-kids from baseline to week 30 and week 56 (Figure12).

Figure 12: Change in IWQOL-kids score from baseline at week 56 - full analysis set



Bar graph is estimated mean change from baseline at week 56. No statistically significant difference was found for all category.

Ancillary analyses

Specific subgroup analysis are discussed above.

Summary of main study(ies)

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

Table 21: Summary of Efficacy for trial NN8022-4180

Title: Effect of Liraglutide for Weight Management in Pubertal Adolescent Subjects with Obesity: A 56-week, double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug				
Study identifier	NN8022-4180			
Design	A 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	56 weeks 12 weeks 26 weeks		
Hypothesis	Superiority			
Treatments groups	Treatment	Treatment with liraglutide was initiated with 0.6 mg daily for one week and increased in weekly steps of 0.6 mg until the 3.0 mg dose of liraglutide (highest allowed liraglutide dose) or a maximum tolerated dose was reached. 125 subjects randomised.		
	Placebo	Placebo was administered once daily by s.c. injection. Subjects randomised to placebo took volume corresponding to 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg or MTD based on their individual tolerability. 126 subjects randomised.		
Endpoints and definitions	Change in BMI standard deviation score (SDS)		From baseline to week 56	
	Change in Hba1c, FPG	%, mmol/l	From baseline to week 56	
	Impact of Weight on Quality of Life-Kids	IWQOL-kids	From baseline to week 56	
Database lock	11-09-2019			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Liraglutide 3.0mg	Placebo	
	Number of subjects	125	126	
	BMI SDS	-0.23	-0.00	
		ETD at week 56: -7.64% [-12.41; -2.87] p=0.0017		
	Body weight (kg)	-2.26 kg	2.25 kg	
		ETD -4.50 kg [-7.17; -1.84] p= 0.0009		
	⩾5% reduction in BMI at week 56	43.25	18.73	
		OR 3.31 [1.78; 6.16]		

Clinical studies in special populations

In this trial no subgroup analyses in special populations were performed with respect to age, (pre)diabetes, Tanner stage, gender, BMI groups etc. The applicant was requested to perform subgroup analyses in different age and BMI groups, gender, underlying (pre) diabetes, and Tanner stages which are essential to give more insight of the effects of liraglutide in different subgroups. Subgroup analyses were performed for different parameters at baseline (age group, BMI category, ethnicity, glycaemic status, waist circumference, race, sex, and Tanner stage) and the results indicated that there were no significant subgroup interactions.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Trial 4180 was a 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug in pubertal adolescents with obesity aged 12 to less than 18 years. The main part of the trial consisted of a 56-week double-blind treatment period and a 26-week follow-up period.

The design of the trial is acceptable and in line with the PIP and the EMA guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev. 1) addendum on weight control in children. However, a randomised treatment period of 56 weeks is relatively short for a drug that potentially is for long-term use.

The statistical analyses in the trial design are based on an intention to treat analysis. It was requested to also perform a per protocol analysis to be informed of the magnitude of the effect of liraglutide on obesity in treatment completers.

The doses of liraglutide were similar to those used in adults. Given the high average body weight of 100.8kg, which is comparable to the adult study population, this was acceptable. The majority of the subjects could be escalated to liraglutide 3.0mg (82.4%) and remained on this dose throughout the trial duration of 56-weeks (92.8%), which is a higher percentage than in the adult population.

Efficacy data and additional analyses

Assessment of paediatric data on clinical efficacy

In general, the demographic and baseline characteristics were well-balanced between treatment groups. The mean age at baseline was 14.5 years. There were more female subjects (59.4%) than male subjects (40.6%), with a comparable distribution in both treatment groups. The subjects were predominantly White (Caucasian) (87.6%). Most of the subjects were in the BMI subgroup of 30.0−<35.0 kg/m2 (45.8%) followed by BMI subgroup of 35.0−<40.0 (27.9%) at baseline. The majority of male and female subjects in both the treatment groups were pubertal and had reached full sexual maturity (Tanner stage 5) (51.8%).

Overall, the mean body weight was 100.8 kg, and the mean BMI was 35.6 kg/m2. The mean height at baseline was 1.68 m, and the mean waist circumference was 105.93 cm. The mean BMI SDS at baseline was 3.17. Mean HbA1c was 5.3%, the fasting plasma glucose was 5.2 mmol/L, and overall, most

subjects were normoglycaemic (74.1%).

Of the 299 screened subjects, 251 were randomised (1:1); 125 subjects to the liraglutide group and 126 subjects were exposed to placebo. No difference was observed in premature discontinuation rates between the liraglutide group and placebo. A total of 80.1% completed the 56-week visit without discontinuation of the trial product. This is a higher percentage compared to adult studies among liraglutide indicated for obesity (~70% treatment completers). The stopping rule: *"Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight."* stated in the therapeutic indications (section 4.1) of the current SmPC for adults has not been applied in trial 4180 but a similar statement is now included in the final SmPC. This was adapted to a slightly lower percentage, i.e. 4% according to the Endocrine Society Guidelines (Styne et al. J Clin Endocrinol Metab, March 2017), taking in account the growth of adolescents and the change in weight-related to that.

BMI SDS

Treatment with liraglutide led to a reduction in BMI SDS from baseline to week 56 (-0.23), corresponding to a change in body weight of -2.26kg. This reduction was not maintained during the 26-week follow-up period (-0.03).

In the placebo group, BMI SDS did not change after 56-weeks and slightly increased during the follow-up period (0.08). In general, improvement in body composition and cardiometabolic risk can be seen with BMI SDS reductions of ≥0.25 in obese adolescents, while greater benefits accrue from losing at least 0.5 BMI SDS (Ford et al. 2010). The applicant was requested to discuss the clinical relevance of the observed reduction in BMI SDS and whether there is a prespecified subgroup with relevant clinical benefit from treatment of liraglutide.

The observed reduction in BMI SDS was evident after 2−4 weeks of treatment with nadir reached after approximately 42 weeks, whereas a subsequent increase in BMI SDS seemed to be evident from nadir to week 56. The MAH discussed the reason for and potential clinical relevance of the observed increase in BMI SDS following week 42 in patients randomised to liraglutide 3.0 mg. The MAH explained that the observed increase in BMI SDS following week 42 could be explained by the decrease in adherence of treatment of liraglutide 3.0 mg. This was supported by the data showing the liraglutide concentrations and a larger proportion of the subjects that reach the lower limit of quantification at 56 weeks compared to at 8 weeks of treatment with liraglutide. In addition, the MAH discussed the clinical relevance of the rebound effect in terms of weight regain observed after cessation of liraglutide treatment. Based on current knowledge, it is not possible to predict whether treatment with liraglutide 3.0 mg could be discontinued after a certain amount of time in adolescents, especially keeping in mind the chronic nature of the disease. Therefore, it is important that a patient population that will benefit most from the treatment is identified and added stopping rule used.

Another uncertainty was whether the observed weight reduction is only seen in subjects suffering from gastro-intestinal side effects, concluding that the beneficial effect is mainly caused by adverse effects of liraglutide. A subgroup analysis in subjects with and without gastro-intestinal side effects was warranted to explore this possibility. The sub-group analyses showed that treatment with liraglutide 3.0 in subjects with GI adverse events resulted in a change in BMI SDS -0.26 compared with placebo treatment. A comparable result was observed in the group without GI adverse events, i.e. BMI SDS -0.23, and the interaction test was not significant. Therefore it was concluded that also without GI symptoms a comparable treatment effect was achieved.

In adults, liraglutide is possibly less effective in males and in subjects with underlying diabetes regarding the treatment effect for obesity. The applicant was requested to perform subgroup analyses

in different age and BMI groups, gender, underlying (pre)diabetes, and Tanner stages which are essential to give more insight of the effects of liraglutide in different subgroups. Subgroup analyses were performed for different parameters at baseline (age group, BMI category, ethnicity, glycaemic status, waist circumference, race, sex, and Tanner stage) and the results indicated that there were no significant subgroup interactions.

Change in BMI and body weight

During the treatment period liraglutide 3.0 mg resulted in a statistically significant reduction in BMI (kg/m^2) (ETD: -1.58 kg/m^2 [-2.47; -0.69]), body weight (ETD: -4.50 kg [-7.17; -1.84]) and waist circumference (ETD: -2.93 cm [-5.24; -0.63]) compared to placebo. The estimated proportion of subjects who achieved a reduction in BMI of ≥5% or ≥10% from baseline was greater in the liraglutide 3.0 mg group than in the placebo group (≥5%: 43.25 vs 18.73% and ≥10%: 26.08 vs 8.11% at 56-weeks). However, these numbers were lower compared to the adult population whereas 63.5% of the subjects in the liraglutide 3.0mg group received a reduction in BMI of ≥5% and 32.8% ≥10% after 56-weeks (SCALE Obesity & Pre-Diabetes - Trial 1839).

In contrast with the adult study, no early response in BMI reduction was measured after 12 weeks which is defined as early responders and which shows to be a predictive factor for long-term weight reduction in adults.

Glycaemic parameters

Greater reductions in HbA_{1c} and fasting plasma glucose (FPG) were observed with liraglutide than with placebo at week 30 (ETD: -0.10%-points [-0.17; -0.04]). After 56-weeks of treatment, the ETD in HbA1c was not statistically significant (ETD: -0.06%-points [-0.14; -0.01]). There were no significant changes in fasting C-peptide, fasting insulin, homeostasis model assessment of beta-cell function (HOMA-B) and homeostasis model assessment of insulin resistance (HOMA-IR). No differences were observed regarding shifts in glycaemic categories during the treatment period between liraglutide and placebo. However, no absolute numbers of diabetic subjects are shown.

Other outcome measures

There were no statistically significant changes in cardiometabolic parameters. There were no statistically significant differences in IWQOL-kids with liraglutide compared to placebo.

In adults, efficacy may be different between men and women and in patients with underlying diabetes. Efficacy was not reported in paediatric males and females separately. There were no subgroup analyses performed with respect to age, (pre)diabetes, Tanner stage, gender and BMI groups and these were requested and provided; the results indicated that there were no significant subgroup interactions.

2.4.3. Conclusions on the clinical efficacy

In 251 adolescent subjects with obesity, 56-weeks of treatment with the maximum tolerated dose of liraglutide (3.0mg) was associated with a reduction in BMI SDS compared to placebo (ETD: -0.22 [-0.37; -0.08]), corresponding with a weight loss of -2.26kg in the liraglutide group. The results for the weight-related parameters (BMI, body weight and waist circumference) were all consistent with those for the BMI SDS. The clinical relevance of the observed reduction in BMI SDS was uncertain as no statistically significant cardiometabolic improvement is observed and the differences in weight loss are small compared to adults (body weight: -7.8 kg with liraglutide 3.0 mg vs. -2.5 kg with placebo). The applicant was requested to further justify the benefit-risk and discuss which patients would benefit most from this treatment. In addition to the stopping rule added, subgroup analyses were performed

for different parameters at baseline (age group, BMI category, ethnicity, glycaemic status, waist circumference, race, sex, and Tanner stage) and the results indicated that there were no significant subgroup interactions.

A subgroup analysis in subjects with and without gastrointestinal side effects was warranted to explore whether the reduction observed in BMI SDS is solely dependent on gastrointestinal side effects from treatment with liraglutide. The sub-group analyses showed that treatment with liraglutide 3.0 in subjects with GI adverse events resulted in a change in BMI SDS -0.26 compared with placebo treatment. A comparable result was observed in the group without GI adverse events, i.e. BMI SDS -0.23, and the interaction test was not significant. Therefore it was concluded that also without GI symptoms a comparable treatment effect was achieved.

The observed reduction in BMI SDS was evident after 2−4 weeks of treatment with nadir reached after approximately 42 weeks, whereas a subsequent increase in BMI SDS seemed to be evident from nadir to week 56. The MAH discussed the reason for and potential clinical relevance of the observed increase in BMI SDS following week 42 in patients randomised to liraglutide 3.0 mg. The MAH explained that the observed increase in BMI SDS following week 42 could be explained by the decrease in adherence of treatment of liraglutide 3.0 mg. This was supported by the data showing the liraglutide concentrations and a larger proportion of the subjects that reach the lower limit of quantification at 56 weeks compared to at 8 weeks of treatment with liraglutide.

In addition, the MAH discussed the clinical relevance of the rebound effect in terms of weight regain observed after cessation of liraglutide treatment. Based on current knowledge, it is not possible to predict whether treatment with liraglutide 3.0 mg could be discontinued after a certain amount of time in adolescents, especially keeping in mind the chronic nature of the disease. Therefore, it is important that a patient population that will benefit most from the treatment is identified and added stopping rule used.

Compared to the largest trial performed in adults (SCALE Obesity & Pre-Diabetes – trial 1839), the effects of liraglutide on obesity in adolescents are lower with 63.5% of the adult subjects losing ≥ 5% body weight after 56-weeks compared to 43.25% in adolescents, corresponding with a reduction of -2.26kg in adolescents vs. -7.8kg in adults in the liraglutide 3.0mg group after 56 weeks. The difference in an achieved weight reduction of Saxenda between adults in the SCALE trial 1839 and adolescent in the 4180 trial was discussed. In adolescents, a lower percentage achieved a BMI reduction of $\geqslant$ 5%, but the mean percentage of BMI reduction was comparable. i.e. trial 4180 5.01% vs. trial 1839 5.39%. It was conceivable that the difference in population, i.e. growing adolescents, and difference in trial protocol with the use of a maximum tolerated dosage, may explain part of these findings in adolescents.

Small reductions in glycaemic parameters were seen with liraglutide at 30-weeks compared to placebo. However, at 56-weeks of treatment, these effects remained no longer statistically significant. No absolute numbers of the account of diabetic subjects are given, and no subgroup analysis in this special population is performed. Therefore, the MAH provided data regarding the prevalence of (pre)diabetes in both treatment groups and the distribution between the group was equal. Additionally, no subgroup analyses have been performed in different age groups, BMI groups, Tanner stage and with respect to gender. Efficacy analyses were asked and reported in these different subgroups with no significant subgroup interactions noted.

There were no statistically significant differences regarding cardiometabolic parameters and IWQOL-kids measurement.

A randomised treatment period of 56 weeks is relatively short for a drug that potentially is for long-term use. Additionally, a per-protocol analysis was warranted to observe the efficacy in treatment

completers separately**.** The applicant performed an additional per-protocol analysis to observe the efficacy in treatment completers separately. This is in line with the previous described results and showed a statistically significant change of SDS BMI -0.27 with liraglutide 3.0 mg treatment.

In line with the adult indication the applicant added a similar stopping rule in the SmPC for adolescents as well.

2.5. Clinical safety

Introduction

In the evaluation of safety, results from the larger phase 3a trial (Trial 4180) are given primary focus and are described in the following sections. Trial 3967 showed that liraglutide (0.6−3.0 mg) was safe and well-tolerated in adolescent subjects with obesity aged 12−17 years, with a safety profile similar to that in adults with obesity.
In Trial 3967, treatment with liraglutide was initiated at a dose of 0.6 mg/day, and the dose was escalated by 0.6 mg in weekly steps over a period of 5 weeks to a maximum of 3.0 mg/day. Dose escalation was based on tolerability as judged by the investigator (Trial 3967).

Both Trial 3967 and Trial 4180 were conducted in a representative sample of the patient population expected to be treated with liraglutide 3.0 mg.

The secondary safety objective of the Trial 4180 was to compare the safety of liraglutide versus placebo in adolescent subjects with obesity after 30 and 56 weeks of treatment. All safety endpoints in this trial addressed the secondary objective and included adverse events, anti-liraglutide antibodies, bone age assessment, laboratory parameters related to safety, clinical evaluations, height/growth-related parameters, vital signs, pubertal progression and mental health assessed by Columbia Suicidality Severity Rating Scale (C-SSRS) and Patient-Reported Health Questionnaire 9 (PHQ-9). The MedDRA searches based on standardised MedDRA queries (SMQs), SOCs, HLGTs, HLTs and/or PTs were specified for pre-defined safety areas of interest (Trial 4180).

Hypoglycaemia episodes described in this document are treatment-emergent. An event (or episode) was defined as treatment-emergent if the onset of the episode occurred on or after the first day of trial product administration, and no later than 14 days after the last day on trial product. Hypoglycaemic episodes were also classified according to the American Diabetes Association (ADA)/ international society for paediatric and adolescent diabetes (ISPAD) and Novo Nordisk classification. The ADA/ISPAD classified hypoglycaemic episodes included all reported hypoglycaemia.

All AEs were coded using MedDRA version 22.0. Event rates were calculated as events per 1000 PYE.

Patient exposure

Of the 299 screened subjects, 251 were randomized (1:1); 125 subjects were randomized to the liraglutide 3.0 mg arm and 126 subjects to the placebo arm. All randomised subjects were exposed to the randomised treatment. A total of 201 subjects (80.1%) remained on treatment and completed the end-of-treatment visit (week 56) without discontinuation of the trial product. These included 101 subjects (80.8%) from the liraglutide group and 100 subjects (79.4%) from the placebo group.

The majority of subjects in the liraglutide 3.0 mg group (103 out of 125 subjects, 82.4%) were escalated to a 3.0 mg dose and remained on the same dose for 92.8% of median time through the 56 weeks double-blind treatment period, suggesting that liraglutide was overall well-tolerated in the adolescent population. Among the remaining 22 subjects (17.6%), 11 subjects (8.8%) did not reach the liraglutide 3.0 mg dose at any time point during the trial (mainly due to tolerability issues), and 11 subjects (8.8%) reached the liraglutide 3.0 mg dose but could not remain on the same dose level due to tolerability issues and the dose was subsequently lowered by the investigator.

A total of 50 subjects (19.9%) discontinued the trial product prematurely (24 subjects (19.2%) from the liraglutide group and 26 subjects (20.6%) from the placebo group).

Overall, a total of 198 subjects (78.9%) (99 subjects each in the liraglutide 3.0 mg and placebo groups) completed the trial (i.e. completed 56 weeks on trial product and did not withdraw from the trial), indicating a higher than expected retention rate in this trial population.

Adverse events

The AE data was categorised based on the following time points:

On-treatment period: Events with an onset date between the first day of trial product administration and any of the following date, whichever came first:

- 14 days after the last day on the trial product, or
- follow-up visit (Visit 26) for subjects with trial product discontinued, or
- last study visit (subjects withdrawn without follow-up visit)

In trial period: Events with an onset date between the first day of trial product administration and the last study visit.

During the 'on-treatment period', a total of 777 and 627 treatment-emergent adverse events (TEAEs) were reported in the liraglutide 3.0 mg and the placebo groups, respectively (T). The majority of TEAEs in both treatment groups were non-serious, mild or moderate in severity, judged as unlikely to be related to the trial product by the investigator and had an outcome of 'recovered' or 'recovering'. A higher number of TEAEs judged by the investigator as probably or possibly related to treatment occurred in liraglutide treated, compared to placebo-treated subjects. This imbalance was primarily driven by gastrointestinal AEs (GI TEAEs) (primarily nausea, vomiting and diarrhoea) in the liraglutide 3.0 mg group. The proportion of subjects with TEAEs and the rate of AEs were higher in the liraglutide 3.0 mg group compared to the placebo group (6187.8 versus 5018.5 events per 1000 PYE). During the 'in-trial period', 910 and 752 AEs were reported in the liraglutide 3.0 mg and placebo groups, respectively (Trial 4180). Overall, the AE pattern/distribution in both treatment groups was similar for the 'in-trial' period and the 'on treatment' period.

Table 22: Trial 4180 - Adverse events - overview -on-treatment- safety analysis set

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	125				126			
Patient years of exposure	125.6				124.9			
Events	111	(88.8)	777	6187.8	107	(84.9)	627	5018.5
Serious								
Yes	3	(2.4)	3	23.9	5	(4.0)	6	48.0
No	111	(88.8)	774	6163.9	107	(84.9)	621	4970.5
Severity								
Severe	2	(1.6)	2	15.9	3	(2.4)	3	24.0
Moderate	59	(47.2)	161	1282.2	48	(38.1)	104	832.4
Mild	109	(87.2)	614	4889.7	98	(77.8)	520	4162.1
Relationship to trial product								
Probable	46	(36.8)	116	923.8	20	(15.9)	29	232.1
Possible	57	(45.6)	249	1983.0	39	(31.0)	125	1000.5
Unlikely	100	(80.0)	402	3201.4	104	(82.5)	462	3697.9
Missing	8	(6.4)	10	79.6	9	(7.1)	11	88.0
Outcome								
Fatal	1	(0.8)	1	8.0	0			
Recovered	111	(88.8)	731	5821.5	106	(84.1)	571	4570.3
Recovering	6	(4.8)	7	55.7	4	(3.2)	16	128.1
Recovered with Sequelae	0				0			
Not Recovered	29	(23.2)	38	302.6	31	(24.6)	39	312.2
Unknown	0				1	(0.8)	1	8.0
Leading to								
Premature treatment discontinuation of trial product	12	(9.6)	18	143.3	0			
Temporary interruption of trial product	9	(7.2)	16	127.4	5	(4.0)	6	48.0
Dose reduction of trial product	17	(13.6)	32	254.8	0			

MedDRA version 22.0. N: Number of subjects experiencing at least one event, %: Percentages of subjects experiencing at least one event, E: Number of events, R: Event rate per 1000 years of exposure time.

Common adverse events

The nature and frequency of the most commonly reported TEAEs during the 'on-treatment period' were very similar to AEs seen during the in-trial period. The following preferred terms were more frequently reported in the liraglutide 3.0 mg group than the placebo group: nausea, vomiting, diarrhoea, gastroenteritis and dizziness (
Figure13). Of the most frequently reported AEs, none were serious, most were of mild to moderate severity and the majority of AEs had an outcome of 'recovered' or 'recovering'. Gastrointestinal disorders were reported by a higher proportion of subjects in the liraglutide 3.0 mg group compared to the placebo group during the on- treatment period (64.8%, 2540.4 events per 100 PYE and 36.5%, 968.5 events per 100 PYE, respectively). The following preferred terms were more frequently reported in the liraglutide 3.0 mg group than the placebo group: nausea, vomiting, diarrhoea, gastroenteritis and dizziness. The other frequently reported AEs were either more frequently reported in the placebo group or there was no difference between the treatment groups. Although, the AE rate was found to be high within the SOC gastrointestinal disorders, the GI tolerability to the trial product (liraglutide 3.0 mg) improved over the course of the trial (Figure 14).

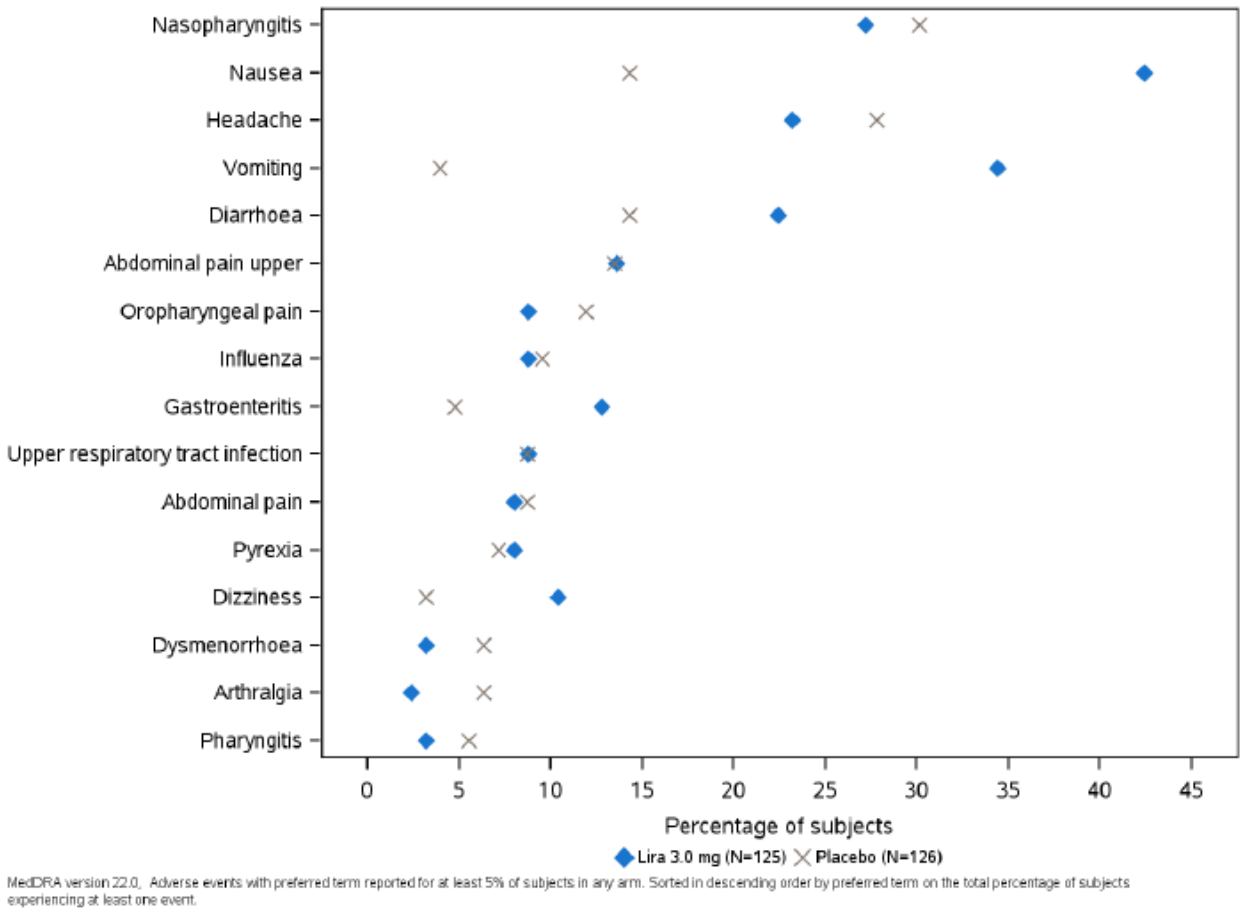


Figure 13: Trial 4180 - Adverse events by preferred term - most frequent (≥ 5%) - plot - on-treatment - safety analysis set

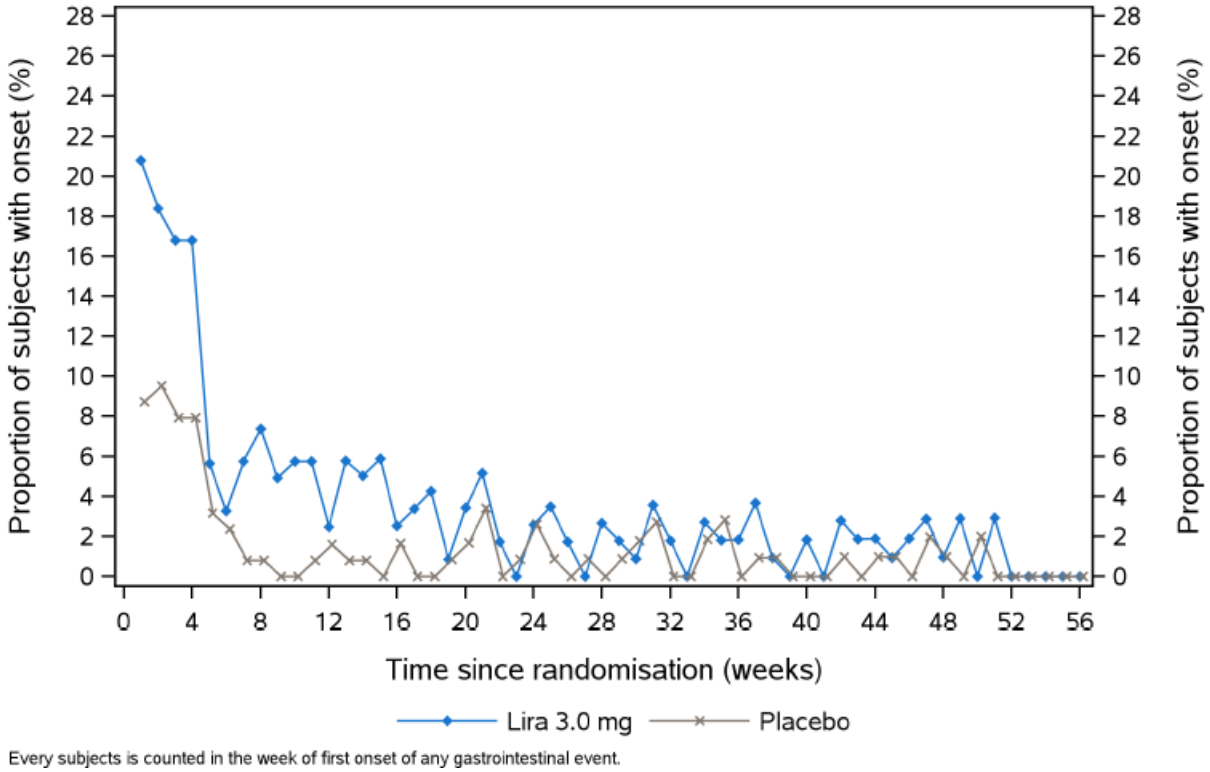


Figure 14: Trial 4180: Gastrointestinal adverse events - plot - safety analysis set

The proportion of subjects with AEs within the SOC gastrointestinal disorders, as well as the AE rate, were higher in the liraglutide group compared to the placebo group during the entire treatment period: 64.8%, 2540.4 events per 100 PYE and 36.5%, 968.5 events per 100 PYE, respectively (Trial 4180). The incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment. It then remained comparable between the treatment groups until the end of the entire treatment period.

Serious adverse event/deaths/other significant events

One subject in the liraglutide 3.0 mg group died by suicide after ~339 days of exposure to the trial product, during the 'on-treatment' period. This was the only SAE with a fatal outcome during the trial (Trial 4180). The Columbia Suicidality Severity Rating Scale (C-SSRS) assessment did not indicate any suicidal ideation/behaviour in this subject prior to the occurrence of the SAE. The event was considered to be unlikely related to the trial product as judged by the investigator.

Serious adverse events

The proportion of subjects with SAEs, as well as the event rate was higher in the placebo group than in the liraglutide 3.0 mg group during both the on-treatment and in-trial periods (Trial 4180, Table).

A total of 15 SAEs (4 SAEs in liraglutide 3.0 mg group and 11 SAEs in the placebo group) were reported during the 'in-trial' period.

During the 'on-treatment' period, 3 SAEs were reported in the liraglutide 3.0 mg group and were all assessed as unlikely related to the trial product by the investigator. One (1) non-treatment-emergent SAE of suicide attempt (unlikely related to the trial product) was reported in the placebo group on trial day 484, during the 26-weeks off-study-drug follow-up period. One (1) non treatment-emergent SAE

of suicide attempt (unlikely related to the trial product) was reported in the liraglutide 3.0 mg group on trial day 489, during the 26-weeks off study-drug follow-up period.

Table 23: Summary of serious adverse events during 'on-treatment period' and 'in-trial period'– safety analysis set

Treatment period	Liraglutide				Placebo			
	N	%	E	R	N	%	E	R
On-treatment	3	2.4	3	23.9	5	4.0	6	48.0
In-trial	4	3.2	4	21.2	9	7.1	11	59.0

E: number of events, N: number of subjects with one or more events, R: rate (number of events divided by patient years of exposure multiplied by 1000), %: percent of subjects with one or more events,

Most treatment-emergent SAEs were single events, with no specific event driving the small numerical imbalance. Since the number of subjects with treatment-emergent SAEs was low overall, any numerical differences should be interpreted with caution. Except for the fatal outcome resulting from the SAE of 'completed suicide', all of the remaining 8 treatment-emergent SAEs in either treatment group were reported as recovered. None of the other treatment-emergent SAEs led to permanent discontinuation of the trial product and/or trial withdrawal.

All of the non-treatment-emergent SAEs had an outcome of 'recovered' and were judged to be unlikely related to the trial product by the investigator (including the 2 suicide attempts).

Laboratory findings

There were no clinically relevant changes from baseline or differences between groups in safety laboratory parameters (haematology, biochemistry, hormones and bone metabolism).

Anti-liraglutide antibodies were measured at the following timepoints in subjects randomized and treated with liraglutide in Trial 4180:

- week 0 (baseline)
- week 30
- week 56 (end of the double-blind treatment period)
- week 58 (2 weeks after cessation of the trial product)
- week 70
- week 82 (end of the follow-up period).

A small number of subjects (14 subjects) developed anti-liraglutide antibodies at some point during the clinical trial.

- At week 56, 5 subjects (4.9%) were antibody positive.
- In the follow-up period, two weeks after cessation of trial product (week 58), 11 subjects (9.7%) were antibody positive.
- By the end of the follow-up period, at week 82, 2 subjects remained antibody positive (2.0%).

Both the small number of subjects (14 subjects) with anti-liraglutide antibodies and the low antibody levels (<9.1% B/T) preclude a conclusion regarding the effect of the observed immune response. Given the low antibody levels and the lack of *in vitro* neutralising effect, it is unlikely that antibody development had an impact on the efficacy and safety of liraglutide during 1 year of treatment.

There were no clinically relevant changes from baseline or differences between the liraglutide 3.0 mg and placebo groups in hormonal levels (luteinising hormone [LH], follicle stimulating hormone [FSH] and oestradiol). There were no apparent clinically relevant changes from baseline or differences between the treatment groups in bone age assessments and other safety laboratory parameters.

Pancreatic enzymes (amylase and lipase)
It is well-described that GLP-1 RAs are associated with increased levels of pancreatic enzymes (amylase and lipase). In Trial 4180, minor elevations in the mean amylase and lipase levels, compared to baseline and to placebo, were seen during 56 weeks of treatment with liraglutide 3.0 mg. No subjects had amylase levels >3×ULN in this trial. There were 4 subjects (2 subjects in the liraglutide 3.0 mg group and 2 subjects in the placebo group) with increased levels of lipase (above 3×ULN). The clinical significance of pancreatic enzyme small elevations with liraglutide is unknown in the absence of other signs and symptoms of pancreatitis.

Vital signs, physical findings, mental health assessment and other observations related to safety

There was a statistically significant difference observed between the liraglutide 3.0 mg and placebo groups with respect to change in the resting pulse from baseline to week 30, however, there was no statistically significant difference observed between the liraglutide 3.0 mg and placebo groups with respect to change in the resting pulse from baseline to week 56.

There were no 'acute gallstone disease' related AEs reported in the liraglutide 3.0 mg group. There were 5 acute gallstone disease' related AEs reported in 3 subjects in the placebo group during the in-trial period.

There were no clinically relevant changes from baseline or differences between the liraglutide 3.0 mg and placebo groups in physical examination, electrocardiogram, as well as parameters related to pubertal progression, growth/height and mental health assessment during the trial.

Discontinuation due to adverse events

Adverse event leading to premature trial product discontinuation

The most common AEs in the liraglutide 3.0 mg group that led to trial product discontinuation were vomiting and nausea. Other reported AEs that led to discontinuation included abdominal pain upper, abdominal discomfort, pancreatitis, depression, retching, injection site pain, and pancreatic enzymes increased.

During the 'on-treatment' period, 6 subjects in the liraglutide 3.0 mg experienced TEAEs that led to premature discontinuation of trial product and withdrawal from the trial. Seven subjects in the liraglutide 3.0 mg group experienced an AE that led to premature discontinuation of the trial product but did not withdraw from the trial. All AEs that led to premature discontinuation of the trial product had an outcome of 'recovered' with the exception of the SAE with a fatal outcome due to 'completed suicide'.

There were no AEs that led to premature discontinuation of the trial product in the placebo group.

Adverse events leading to dose reduction

In total, 17 subjects experienced AEs that led to dose reduction of trial product (during the 'on-treatment' period), all in the liraglutide 3.0 mg group. The most commonly reported AE belonged to

the SOC of gastrointestinal (GI) disorders and primarily included events of vomiting and nausea. These GI AEs were considered to be possibly or probably related to trial product (liraglutide 3.0 mg) by the investigator. Most of these GI AEs and other reported AEs leading to dose reduction primarily occurred during dose escalation (the first 4-8 weeks of treatment) with the exception of 2 events (abdominal discomfort and irritable bowel syndrome) that had a late onset (beyond 8 weeks).

Adverse events leading to temporary treatment discontinuation

Few AEs leading to temporary discontinuation of liraglutide 3.0 mg or placebo were reported on treatment period (9 subjects [7.2%] reported 16 AEs in the liraglutide 3.0 mg group and 5 subjects [4.0%] reported 6 AEs in the placebo group).

The most frequent AEs leading to dose reductions in the liraglutide 3.0 mg group were from the SOC 'Gastrointestinal disorders'.

Hypoglycaemic episodes

Both in the on-treatment and in-trial period, the proportion of subjects experiencing hypoglycaemic episodes (per ADA/ISPAD and Novo Nordisk classification) and the episode rates, were higher in the liraglutide 3.0 mg group than in the placebo group (Table24).

A higher proportion of subjects in the liraglutide 3.0 mg group (78 events in 26 subjects, 20.8% of subjects, event rate was 621.2 episodes per 1000 PYE) reported hypoglycaemic episodes (per ADA/ISPAD and Novo Nordisk classification) compared to the placebo group (28 events in 18 subjects, 14.3% of subjects, event rate was 224.1 episodes per 1000 PYE.

As per the ADA/ISPAD classification, there were 31 documented symptomatic hypoglycaemic episodes in 19 subjects (15.2%) in the liraglutide 3.0 mg group and 6 documented symptomatic hypoglycaemic episodes in 5 subjects (4.0%) in the placebo group. As per the Novo Nordisk classification, there were 4 symptomatic BG confirmed episodes in 3 subjects (2.4%) in the liraglutide 3.0 mg group and none in the placebo group. No severe hypoglycaemic episodes occurred in the liraglutide 3.0 mg or placebo group.

Table 24: Treatment emergent hypoglycaemic episodes by classification - summary - in-trial - safety analysis set

Treatment period	Liraglutide 3.0 mg				Placebo			
Hypo classification	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Hypoglycaemic episodes	26	20.8	78	412.9	18	14.3	28	150.2
ADA classification								
Severe hypoglycaemia	0				0			
Asymptomatic hypoglycaemia	8	6.4	12	63.5	14	11.1	17	91.2
Symptomatic hypoglycaemia	19	15.2	31	164.1	5	4.0	6	32.2

ADA: American Diabetes Association, E: number of events, N: number of subjects experiencing at least one event, %: percentage of subjects experiencing at least one event, R: event rate per 1000 years of observation time.

Post marketing experience

The post-marketing safety data for liraglutide received by Novo Nordisk A/S are made available in Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports (PSUR/PBRER) according to the regulatory requirements.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

In general, the results of Trial 4180 have demonstrated that liraglutide has a safety profile comparable to that in obese adults. However, a randomised treatment period of 56 weeks is relatively short for a drug that could be used used long-term. Long term effects in children may be different due to the fact that organs are still in a developmental state.

Adverse events

The proportions of subjects who experienced AEs were slightly higher in the liraglutide group versus the placebo group (88.8% versus 84.9%, respectively) with a higher rate of AEs in the liraglutide group (6187.8 versus 5018.5 events per 1000 PYE). The difference of all adverse events in the liraglutide and placebo groups appeared primarily to be driven by the higher rates of GI AEs in the liraglutide group (nausea, vomiting, diarrhoea, gastroenteritis and dizziness).

TEAEs leading to premature discontinuation of the trial product, during the 'on-treatment' period, were reported in 13 subjects in the liraglutide 3.0 mg group versus 0 subjects in the placebo group. The most common AEs that led to trial product discontinuation in the liraglutide 3.0 mg group were vomiting (6 subjects) and nausea (4 subjects).

Serious adverse events

In trial 4180 there was one fatal outcome during the trial in the liraglutide group caused by suicide. The event was considered to be unlikely related to the trial product by the applicant. The proportion of subjects with SAEs, as well as the event rate was higher in the placebo group than in the liraglutide 3.0 mg group during both the on-treatment (2.4% vs 4.0%) and in-trial periods (3.2% vs 7.1%).

Gastrointestinal adverse events

The proportion of subjects with AEs within the SOC gastrointestinal disorders, as well as the AE rate, were higher in the liraglutide group compared to the placebo group during the entire treatment period: 64.8%, 2540.4 events per 100 PYE and 36.5%, 968.5 events per 100 PYE, respectively (Trial 4180). The incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment and then remained comparable between the treatment groups until the end of the entire treatment period.

The frequency of vomiting in subjects treated with liraglutide 3.0 mg (34.4% of subjects and 676.9 events per 1000 PYE) was quite high. This issue has been addressed by the MAH in section 4.8 of the proposed SmPC with the wording "*Vomiting occurred with a 2-fold higher frequency in adolescents compared to adults*". The MAH was requested to clarify the reasons(s) for the high frequency of the AE vomiting in the adolescent population and discuss the potential clinical impact of this issue. This was discussed and resolved with proposed changes in SmPC.

Hypoglycaemic adverse events

Both in the on-treatment and in-trial period, the proportion of subjects experiencing hypoglycaemic episodes (per ADA/ISPAD and Novo Nordisk classification) and the episode rates, were higher in the liraglutide 3.0 mg group than in the placebo group.

The ADA/ISPAD classification that defines plasma glucose ≤3.9 mmol/l as documented hypoglycaemia is considered to be clinically relevant. The observation of 31 documented symptomatic hypoglycaemic episodes in 19 subjects (15.2%) in the liraglutide 3.0 mg group compared to 6 such episodes in 5 subjects (4.0%) in the placebo group is worrying and somewhat surprising when considering the glucose-dependent mechanisms of GLP-1. Section 4.8 of the proposed SmPC includes the wording regarding hypoglycaemia in patients without type 2 diabetes mellitus "*Symptoms of hypoglycaemic events were reported by 1.6 % of patients treated with Saxenda and 1.1% of patients treated with placebo; however, these events were not confirmed by blood glucose measurements*".

The MAH was requested to clarify the reasons(s) for the high frequency of documented symptomatic hypoglycaemia in the adolescent population, and in addition, sufficiently address this issue in the SmPC**.** The risk of hypoglycaemia was addressed and added in the SmPC section 4.4 "Special warnings and precautions for use", with a warning for adolescents and in 4.8. under Description of selected adverse reactions.

Other adverse events

There were no clinically relevant changes from baseline or differences between groups in safety laboratory parameters (haematology, biochemistry, hormones and bone metabolism), although, small increases in mean pancreatic enzyme levels were observed in the liraglutide group. The clinical significance of pancreatic enzyme elevations with liraglutide is unknown in the absence of other signs and symptoms of pancreatitis.

A small number of subjects (14 subjects) developed anti-liraglutide antibodies at some point during the clinical trial. Given the low antibody levels and the lack of *in vitro* neutralising effect, it is unlikely that antibody development had an impact on the efficacy and safety of liraglutide during 1 year of treatment.

There were no 'acute gallstone disease' related AEs reported in the liraglutide 3.0 mg group. There were 5 acute gallstone disease' related AEs reported in 3 subjects in the placebo group during the in-trial period.

2.5.2. Conclusions on clinical safety

In general, the results of Trial 4180 have demonstrated that liraglutide has a safety profile comparable to that in obese adults and adolescents with type 2 diabetes. However, a randomised treatment period of 56 weeks is relatively short for a drug that potentially is for long-term use. Long term effects in children may be different due to the fact that organs are still in a developmental state.

There was one fatal outcome during the trial in the liraglutide group caused by suicide. The event was considered to be unlikely related to the trial**.**

Similar to adults, the incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment and then remained comparable between the treatment groups. The higher liraglutide dose in comparison to Victoza seems to have little effect on the AE rate, except for gastrointestinal events which were more frequent. A discrepancy with the adult population was observed in regarding the higher frequency of vomiting. The MAH was requested to clarify the reason(s) for the high frequency of the AE vomiting in the adolescent population and discuss

the potential clinical impact of this issue. This was discussed and resolved with proposed changes in SmPC.

Hypoglycaemic events appeared to be evident in adolescents compared to adults. The MAH was requested to clarify the reason(s) for the high frequency of documented symptomatic hypoglycaemia in the adolescent population, and in addition, sufficiently address this issue in the SmPC. The risk of hypoglycaemia was addressed and added in the SmPC section 4.4 "Special warnings and precautions for use", with a warning for adolescents and in 4.8. under Description of selected adverse reactions.

The clinical significance of pancreatic enzyme elevations with liraglutide is unknown, but long-term negative effects on the pancreas may be serious, especially when liraglutide is started in paediatric subjects with a developing pancreas. The company discussed the pancreatic safety of liraglutide in children and it was considered that pancreatic safety in adolescents will be monitored in the PSURs as an important potential risk for which the MAH should provide comparative analysis.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 32.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 32.0 with the following content:

The MAH has submitted RMP version 32.0 with Data lock point for this RMP 31 Oct 2019 and date of final sign off: 24 January 2020.

Rational for submitting the updated RMP: Submission in connection with the variation application for indication extension of Saxenda for use in adolescents of 12 year and older.

The proposed indication is: Saxenda can be used as an adjunct to a healthy nutrition and physical activity counselling for weight management in adolescent patients aged 12 years and above with:

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

PART II modules SI-SVII were updated with new information regarding use in adolescents.

Safety concerns

Module SVIII was not amended. The list of safety concerns remained.

Pharmacovigilance plan

The ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan – Liraglutide in weight management - Saxenda are presented below.

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk)				
None	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit−risk)				
None	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA)				
NN2211-3965 MTC registry (MTC-22341) Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Protocol submission	18 Jun 2015
			Final report	15 Sep 2026
NN8022-4246 PASS Ongoing	In-market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database	Off-label use (Victoza® used for treatment of weight management and Saxenda® not used correctly according to approved label)	Protocol submission	01 Dec 2015
			Final report	September 2022

The study NN8022-4241 has been removed from the table. The study results of NN8022-4241 have been submitted in November 2019 and have been assessed in procedure EMEA/H/C/003780/II/0025. This procedure was finalised in February 2020.

The final report of NN8022-4246 due date was amended from December 2019 to September 2022.

Risk minimisation measures

No changes are proposed for risk minimisation measure.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Paediatric or childhood obesity is the most prevalent nutritional disorder among children and adolescents worldwide. Paediatric obesity is associated with a number of complications, including hypertension, type 2 diabetes mellitus (T2D), early puberty, menstrual irregularities, polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, musculoskeletal disorders and psychological problems. Over 90% of obesity cases are idiopathic, and less than 10% of obesity cases are associated with genetic and hormonal causes. A number of factors contribute to paediatric obesity. Genetic factors have a significant impact on individual predisposition, but other factors of behaviour and environment can also play a vital role in paediatric obesity.

In the past 30 years, paediatric obesity has more than doubled in children and tripled in adolescents worldwide. It is a chronic, refractory, and relapsing disease, afflicting, approximately 158 million children and adolescents aged between 5−19 years. By 2025, these numbers per forecast will climb to 206 million before surpassing 250 million in 2030. Paediatric obesity requires long-term management. With the dramatic rise in the number of children affected by obesity, there is an unmet need of effective methods for the prevention and treatment of paediatric obesity.

3.1.2. Available therapies and unmet medical need

Three major types of treatment options are available for obesity – lifestyle intervention, pharmacotherapy, and bariatric surgery. Lifestyle intervention in the form of diet and exercise is the first-line treatment, but most people with obesity struggle to achieve and maintain their weight loss, and often fail. Pharmacotherapy is an option to fill the therapeutic gap between lifestyle intervention and surgery. Pharmacotherapy may serve as a valuable adjunct to lifestyle intervention in achieving and sustaining weight loss, improving comorbid conditions and facilitating healthier lifestyle habits. There is a need for efficacious, safe and tolerable medications for paediatric patients with obesity, especially medications that facilitate a maintained weight loss and also target the obesity-related comorbidities. While pharmacotherapy may not be appropriate for all paediatric patients with obesity, the addition of weight loss medication to lifestyle modification may result in improved weight loss. Currently, bariatric surgery is primarily used for the treatment of severe obesity in childhood.

Currently, orlistat, naltrexone/bupropion, and liraglutide 3.0 mg are the approved treatment options for the long-term management of obesity in the adult population in the EU as well.

While most of these approved obesity medications have the potential to reduce weight and weight-related comorbidities, the majority have not been adequately tested for safety and efficacy among paediatric population. There has been a lack of long-term experience (and data) with weight management drugs in the paediatric population. Finding treatments that are safe and effective for paediatric patients with obesity is, therefore, crucial to improving their health and well-being.

Liraglutide treatment could potentially be an important treatment option for weight management in paediatric patients with obesity.

Liraglutide 3.0 mg represents a new drug class within weight management. The effects of liraglutide are mediated via specific activation of the GLP-1 receptor in the brain and peripheral tissues. Due to the combined actions on appetite regulation, glucose metabolism and cardiometabolic risk factors, liraglutide 3.0 mg has unique potential for weight management in adolescent population.

3.1.3. Main clinical studies

Trial 4180 was a 56-week double-blind, randomised, parallel-group, placebo-controlled, multi-national trial followed by a 26-week period off study-drug in pubertal adolescents with obesity aged 12 to less than 18 years. The main part of the trial consisted of a 56-week double-blind treatment period and a 26-week follow-up period.

The doses of liraglutide were similar to those used in adults. The majority of the subjects could be escalated to liraglutide 3.0mg (82.4%) and remained on this dose throughout the trial duration of 56-weeks (92.8%), which is a higher percentage than in the adult population.

The mean age at baseline was 14.5 years. There were more female subjects (59.4%) than male subjects (40.6%), with a comparable distribution in both treatment groups. The subjects were predominantly White (Caucasian) (87.6%). Most of the subjects were in the BMI subgroup of 30.0−<35.0 kg/m2 (45.8%) followed by BMI subgroup of 35.0−<40.0 (27.9%) at baseline. The majority of male and female subjects in both the treatment groups were pubertal and had reached full sexual maturity (Tanner stage 5) (51.8%).

Overall, the mean body weight was 100.8 kg and the mean BMI was 35.6 kg/m2. The mean height at baseline was 1.68 m, and the mean waist circumference was 105.93 cm. The mean BMI SDS at baseline was 3.17. Overall, the mean HbA1c was 5.3%, the fasting plasma glucose was 5.2 mmol/L, and overall, most subjects were normoglycaemic (74.1%).

Of the 299 screened subjects, 251 were randomised (1:1); 125 subjects to the liraglutide group and 126 subjects were exposed to placebo. No difference was observed in premature discontinuation rates between the liraglutide group and placebo. A total of 80.1% completed the 56-week visit without discontinuation of the trial product.

3.2. Favourable effects

BMI SDS

Treatment with liraglutide led to a reduction BMI SDS from baseline to week 56 (-0.22; ETD: -0.22 [-0.37; -0.08]). This reduction did not sustain during the 26-week follow-up period (-0.03; ETD: -0.11 [-0.28; 0.06]). In the placebo group, BMI SDS did not change after 56-weeks and slightly increased during the follow-up period (0.08).

Change in BMI and body weight

During the treatment period liraglutide 3.0 mg resulted in a statistically significant reduction in BMI (kg/m^2) (ETD: -1.58 kg/m^2 [-2.47; -0.69]), body weight (ETD: -4.50 kg [-7.17; -1.84]) and waist circumference (ETD: -2.93 cm [-5.24; -0.63]) compared to placebo. The estimated proportion of subjects who achieved a reduction in BMI of ≥5% or ≥10% from baseline was greater in the liraglutide 3.0 mg group than in the placebo group (≥5%: 43.25 vs 18.73% and ≥10%: 26.08 vs 8.11% at 56-weeks).

Glycaemic parameters

Greater reductions in HbA1c and fasting plasma glucose (FPG) were observed with liraglutide than with placebo (ETD: -0.10%-points [-0.17; -0.04]) with a statistically significant difference at week 30. However, this effect did not remain after 56-weeks of treatment.

3.3. Uncertainties and limitations about favourable effects

It is not clear if and how long the benefits of liraglutide on weight-related parameters will persist after long term treatment which is proposed in children. In trial 4180 subjects were treated for 56 weeks demonstrating a modest beneficial effect on BMI SDS and other weight-related parameters in the liraglutide group compared to placebo. This effect did not remain after discontinuation of the liraglutide during the 26-week follow-up duration. In addition, the decrease in BMI SDS of -0.22 during treatment with liraglutide was not paralleled by improvements in health-related outcomes. After 56 weeks, there were no significant changes in blood pressure, serum lipids, HbA1c or quality of life.

In general, improvement in body composition and cardiometabolic risk can be seen with BMI SDS reductions of ≥0.25 in obese adolescents, while greater benefits accrue from losing at least 0.5 BMI SDS (Ford et al. 2010). The MAH referred to several papers that support a reduction in BMI z score of 0.20 to 0.25 in adolescents as a suitable threshold for clinical relevance. However, this threshold is based on weight loss in adolescents that was achieved with lifestyle interventions.

In trial 4180, in a subgroup analysis of treatment effects of liraglutide 3.0 mg in subjects who adhered to the protocol and completed the 56 weeks of treatment, a somewhat larger decrease in BMI SDS of -0.27 was observed. The MAH, therefore, stated that adolescents with obesity who have not achieved enough weight loss with lifestyle modification, are motivated to be compliant with taking a pharmacologic agent are the best candidates for Saxenda. However, we assume that this should have been represented in the outcomes of the total population of the 4180 trial. It is not clear how this will improve the outcomes in clinical practice compared to the findings of the current study. Furthermore, it is proposed that the treatment effects in these obese adolescents may be larger in the long term than the observed BMD SDS -0.22 in 4180 trial, by considering an alternative scenario of continued weight gain in this population without treatment, thus adding to the risk of obesity-related comorbidities. However, based on the trials in adults, further weight loss cannot be expected after the investigated 56 weeks, but only the maintenance of weight loss that was achieved in the first 3 months. In addition, a significant increase in BMI SDS (weight regain) was observed in the liraglutide 3.0 mg group from the time of treatment cessation at week 56 to week 82, thereby resulting in no statistically significant difference in BMI SDS change from baseline between the treatment groups at week 82.

The MAH provided results of a comparison between "early responders" and "early non-responders" to further investigate whether this could help select patients that benefit most. In the total group, the placebo adjusted treatment effect of liraglutide was -0.22 BMI SDS. The placebo adjusted treatment effects of liraglutide in early non-responders and early responders were -0.18 and -0.27, respectively (p=0.5). The reduction in BMI SDS in early responders is higher than that in the total population (-0.27 vs -0.22). In the total group, the placebo adjusted treatment effect of liraglutide on body weight was -4.5 kg. The placebo adjusted treatment effect of liraglutide in early non-responders and early responders was -3.9 and -5.3 kg, respectively(p=0.6). The reduction in body weight in early responders is higher than that in the total population (-5.3 vs -4.5 kg). Subgroup analyses indicated that there were no significant subgroup interactions (age group, BMI category, ethnicity, glycaemic status, waist circumference, race, sex, and Tanner stage).

3.4. Unfavourable effects

In general, the results of Trial 4180 have demonstrated that liraglutide has a safety profile comparable to that in obese adults. However, a randomised treatment period of 56 weeks is relatively short for a drug that is potentially can be used long-term. Long term effects in children may be different due to the fact that organs are still in a developmental state.

Adverse events

The proportions of subjects who experienced AEs were slightly higher in the liraglutide group versus the placebo group (88.8% versus 84.9%, respectively) with a higher rate of AEs in the liraglutide group (6187.8 versus 5018.5 events per 1000 PYE). The difference of all adverse events in the liraglutide and placebo groups appeared primarily to be driven by the higher rates of GI AEs in the liraglutide group (nausea, vomiting, diarrhoea, gastroenteritis and dizziness).

TEAEs leading to premature discontinuation of the trial product, during the 'on-treatment' period, were reported in 13 subjects in the liraglutide 3.0 mg group versus 0 subjects in the placebo group. The most common AEs that led to trial product discontinuation in the liraglutide 3.0 mg group were vomiting (6 subjects) and nausea (4 subjects).

Serious adverse events

In trial 4180 there was one fatal outcome during the trial in the liraglutide group caused by suicide. The event was considered to be unlikely related to the trial product. The proportion of subjects with SAEs, as well as the event rate was higher in the placebo group than in the liraglutide 3.0 mg group during both the on-treatment (2.4% vs 4.0%) and in-trial periods (3.2% vs 7.1%).

Gastrointestinal adverse events

The proportion of subjects with AEs within the SOC gastrointestinal disorders, as well as the AE rate, were higher in the liraglutide group compared to the placebo group during the entire treatment period: 64.8%, 2540.4 events per 100 PYE and 36.5%, 968.5 events per 100 PYE, respectively (Trial 4180). The incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment and then remained comparable between the treatment groups until the end of the entire treatment period.

Hypoglycaemic adverse events

More treatment-emergent hypoglycaemic episodes were reported in the liraglutide 3.0 mg groups compared to the placebo groups in the both trials. In trial 4180, 31 documented symptomatic hypoglycaemic episodes in 19 subjects (15.2%) was reported in the liraglutide 3.0 mg group compared to 6 such episodes in 5 subjects (4.0%) in the placebo group, which is considered to be much higher compared to the reported frequencies in previous clinical trials with liraglutide 3.0 mg in adults. Using the criteria by International Hypoglycaemia Study Group (IHSG) 2017/ADA2018/ISPAD2018 for clinically significant hypoglycaemia (i.e. plasma glucose confirmed <3.0 mmol/L), the percentage of patients reporting at least one episode of clinically significant hypoglycaemia were higher with liraglutide (1.6%) compared to placebo (0.8%). No severe hypoglycaemic episodes occurred in the trial.

Other adverse events

There were no clinically relevant changes from baseline or differences between groups in safety laboratory parameters (haematology, biochemistry, hormones and bone metabolism), although, small increases in mean pancreatic enzyme levels were observed in the liraglutide group. The clinical

significance of pancreatic enzyme elevations with liraglutide is unknown in the absence of other signs and symptoms of pancreatitis.

A small number of subjects (14 subjects) developed anti-liraglutide antibodies at some point during the clinical trial. Given the low antibody levels and the lack of *in vitro* neutralising effect, it is unlikely that antibody development had an impact on the efficacy and safety of liraglutide during 1 year of treatment.

There were no 'acute gallstone disease' related AEs reported in the liraglutide 3.0 mg group. There were 5 acute gallstone disease' related AEs reported in 3 subjects in the placebo group during the in-trial period.

3.5. Uncertainties and limitations about unfavourable effects

In general, the results of Trial 4180 have demonstrated that liraglutide has a safety profile comparable to that in obese adults and adolescents with type 2 diabetes. However, a randomised treatment period of 56 weeks is relatively short for a drug that may be used long-term. Long term effects in children may be different due to the fact that organs are still in a developmental state.

Similar to adults, the incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment and then remained comparable between the treatment groups. The higher liraglutide dose in comparison to Victoza seems to have little effect on the AE rate, except for gastrointestinal events which were more frequent.

The observation of 31 documented symptomatic hypoglycaemic episodes in 19 subjects (15.2%) in the liraglutide 3.0 mg group compared to 6 such episodes in 5 subjects (4.0%) in the placebo group is surprising when considering the glucose-dependent mechanisms of GLP-1. The proportion of adult subjects reporting AEs of hypoglycaemia was low, both with liraglutide 3.0 mg (1.6% of subjects) and placebo (1.1% of subjects).

The clinical significance of pancreatic enzyme elevations with liraglutide is unknown, but long-term negative effects on the pancreas are uncertain if can be serious, especially when liraglutide is started in paediatric subjects with a developing pancreas. The company discussed the pancreatic safety of liraglutide in children and it was considered that pancreatic safety in adolescents will be monitored in the PSURs as an important potential risk for which the MAH should provide comparative analysis.

3.6. Effects Table

Table 25: Effects Table for Saxenda for weight management in (data cut-off: Sept. 2019)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
BMI SDS	Change from baseline at week 56	SDS	-0.23	-0.00	**SoE:** ETD of -0.22 [-0.37; - 0.08] 95% CI, p=0.0022 **Unc:** magnitude clinically not relevant	Trial 4180
Body weight	Change from baseline at week 56	kg	-2.26	2.25	**SoE:** ETD of -4.50 kg [-7.17; -1.84] 95% CI, p= 0.0009	Trial 4180
≥ 5% BMI	Change from baseline at	%	43.25	18.73	**SoE:** OR of 3.31 [1.78; 6.16] 95% CI,	Trial 4180

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
reduction	week 56				p= 0.0002 **Unc:** discrepancy with adult population	
Hba1c	Change from baseline at week 56	%	-0.10	-0.03	ETD of -0.06%-points [-0.14; -0.01] 95% CI, p= 0.0914	Trial 4180
Unfavourable Effects						
AE	On treatment period	%	88.8	84.9	primarily driven by the higher rates of GI AEs	Trial 4180
SAE	On treatment period	%	2.4	4.0	No SAE clustering within SOCs	Trial 4180
Death	On treatment period	n	1	0	Suicide unlikely related to the trial product	Trial 4180
Symptomatic hypoglycemia	ADA defined during in trial period	%	15.2	4.0	Increased number compared to obese adults	Trial 4180

Abbreviations: AE, adverse events; BMI, body mass index; ETD, estimated treatment difference; n, number; OR, odds ratio; SAE, serious adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applicant proposed an extension of the indication of liraglutide for use in adolescents (aged 12 years to less than 18 years) with obesity (BMI corresponding to ≥30 kg/m² for adults by international cut-off points). The subjects' mean age at baseline was 14.5 years, and mean BMI was 35.6kg/m2, suggesting that most of the subjects had severe obesity. Mean Hba1c was 5.3% with most subjects in the normoglycaemic range (74.1%). Obesity in adolescents is currently a global problem with three major types of treatment options available: lifestyle intervention, pharmacotherapy and bariatric surgery. However, lifestyle interventions often fail in the long term, and bariatric surgery is only indicated for severe obesity in childhood. With regard to pharmacotherapy, none of the approved treatment options for the long-term management of obesity in the adult populations is approved in adolescents in the EU as they have not been adequately tested for safety and efficacy in the adolescent population. So, there is an unmet medical need for adolescent subjects with obesity who fail lifestyle interventions.

In these adolescent subjects (n = 251), 56 weeks of treatment with the maximum tolerated dose of liraglutide (82.4% could be escalated to 3.0mg), was associated with a statistically significant decrease in BMI SDS (ETD of -0.22 [-0.37; - 0.08] 95% CI, p=0.0022) compared to placebo. Bodyweight was statistically significantly reduced -2.26kg in the liraglutide group compared to +2.25kg in the placebo group (ETD of -4.50 kg [-7.17; -1.84] 95% CI, p= 0.0009) as well as BMI (kg/m^2) (ETD: -1.58 kg/m^2 [-2.47; -0.69] 95% CI, p=0.0005), and waist circumference (ETD: -2.93 cm [-5.24; -0.63] 95% CI, p=0.0126). After treatment discontinuation and deblinding the treatment effect of liraglutide did not sustain.

Although the responder analyses showed that a larger percentage of adolescents achieved weight loss >10% with liraglutide compared to placebo (26 vs 8%), there remain uncertainties with regards to the clinical relevance of the reduction observed in BMI SDS in the total adolescent obese population. In

contrast to the lifestyle-based weight loss in adolescents and liraglutide-induced weight loss in adults, there are no data available with regards to improvements in health-related outcomes with liraglutide in adolescents. This is important, especially because the treatment can be long-term. Based on the trials in adults, a further weight loss after the investigated 56 weeks is not expected, but only the maintenance of the weight loss that was achieved in the first months. In addition, the adherence in adolescents may become less in the following years, as was also observed in trial 4180 after 42 weeks. This could further decrease the treatment effect.

Given the uncertainties regarding the clinical relevance of the overall achieved reduction in BMI/body weight in the total population, introducing a stopping rule in the context of goal-driven weight management should help in the selection of adolescent patients that benefit most and may protect patients from unnecessary long-term treatment. A similar stopping rule as included for Saxenda in adults, has been included for adolescents. In addition, a stopping rule is in line with the Endocrine Society Guidelines (Styne et al. J Clin Endocrinol Metab, March 2017), i.e. the percentage (4%) is slightly lower than for adults, taking in account the growth of adolescents and the change in weight-related to that. The effects of Saxenda on weight-related endpoints were higher in "early responders" compared to "early non-responders" when adjusted for placebo. As requested, subgroup analyses were performed for different parameters at baseline (age group, BMI category, ethnicity, glycaemic status, waist circumference, race, sex, and Tanner stage). The results indicate that there were no significant subgroup interactions.

There was an increased risk of both asymptomatic and documented hypoglycaemia episodes with liraglutide. In contrast to adults, the proportion of subjects experiencing hypoglycaemic episodes was higher in the liraglutide group than in the placebo group. As requested, the risk of hypoglycaemia is added to the SmPC section 4.4 "Special warnings and precautions".

3.7.2. Balance of benefits and risks

Although the efficacy is considered modest, demonstrated effects, in combination with the stopping rule, unmet medical need and safety profile which seemed similar to the one observed in adults, the benefit risk is considered to be positive.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R balance for Saxenda is considered to be positive in the following proposed extension of the indication:

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

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

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

4. Recommendations

Outcome

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

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

Extension of indication to include treatment as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with obesity (BMI corresponding to ≥30 kg/m2 for adults) and body weight above 60 kg, based on Study NN8022-4180 that evaluated the efficacy of liraglutide 3.0 mg in adolescents aged 12 to less than 18 years with obesity. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are being updated and the Package Leaflet is updated in accordance.
The application relates to paediatric studies submitted according to Article 46 of the paediatric regulation.
The application included an updated RMP version 32.0.

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

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0383/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0383/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Saxenda-H-C-3780-II-26'.