27 June 2019
EMA/447330/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Victoza

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/001026/II/0049

Note

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

Table of contents

List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AUC	area under the concentration-time curve
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum concentration at steady state
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin A1c
HDL	high-density lipoprotein
HLGT	high level group term
HLT	high level term
HOMA-B	homeostatic model assessment of beta-cell function
HOMA-IR	homeostatic model assessment of insulin resistance
ICH	International Conference on Harmonisation
IDF	International Diabetes Federation
LDL	low-density lipoprotein
MMRM	mixed model for repeated measurements
PDCO	Paediatric Committee
PIP	paediatric investigation plan
PMM	pattern mixture model
PSUR	periodic safety update report
PT	preferred term
PYE	patient years of exposure
SAE	serious adverse event
SD	standard deviation

SDS	standard deviation score
seq	sequence
SMPG	self-measured plasma glucose
SMQ	standard medical query
SOC	system organ class

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 21 November 2018 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 of children and adolescents (age 10-17 years) with T2D based on Study NN2211-1800; a Phase 1 clinical pharmacology, multi-centre, randomised, double-blind placebo controlled trial, and Study NN2211-3659; a Phase 3a efficacy and safety, multi-centre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 5.2 of the SmPC are being updated and the Package Leaflet is updated accordingly. Additionally, in accordance with the guideline from 2017 about excipients, the MAH took the opportunity to include sodium in SmPC section 4.4 and the Package Leaflet. An updated RMP version 30 was provided as part of the application.

The requested variation proposed 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/0218/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0218/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0218/2017.

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 applicant 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

On 29 June 2018, the MAH submitted a request for Scientific Advice to the EMA regarding clinical aspects of Study 3659. A response from the EMA was received by the MAH on 20 September 2018 (EMA/CHMP/SAWP/599380/2018).

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: Sinan B. Sarac

Timetable	Actual dates
Submission date	21 November 2018
Start of procedure	29 December 2018
CHMP Rapporteur Assessment Report	5 March 2019
CHMP Co-Rapporteur Assessment Report	21 February 2019
PRAC Rapporteur Assessment Report	5 March 2019
PRAC Outcome	14 March 2019
CHMP members comments	19 March 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 March 2019
Request for supplementary information (RSI)	28 March 2019
CHMP Rapporteur response Assessment Report	8 June 2019
PRAC Rapporteur response Assessment Report	8 June 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 June 2019
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	27 June 2019

2. Scientific discussion

2.1. Introduction

T2D is a progressive metabolic disease primarily characterised by abnormal glucose metabolism, resulting in hyperglycaemia. Uncontrolled hyperglycaemia is associated with adverse long-term consequences such as microvascular and macrovascular complications (e.g., retinopathy, nephropathy, neuropathy and cardiovascular disease). The aetiology, pathophysiology and clinical manifestation of T2D in the paediatric population are similar to that in adults. The recommended treatment approach for paediatric T2D is similar to that in adults, namely the achievement and maintenance of glycaemic control in order to prevent long-term complications. Given the similar pathophysiology and progression of adult and paediatric T2D, the paediatric treatment guidelines also recommend a step-wise approach starting with lifestyle modifications followed by pharmacologic monotherapy and later by combination therapy. Metformin and insulin are currently the only approved pharmacologic treatment options for paediatric subjects with T2D in most countries. However, more than half of youth with T2D experience a loss of glycaemic control with metformin alone or when combined with lifestyle intervention. Although insulin is highly effective in lowering blood glucose, its acceptance and use by paediatric subjects with T2D may be limited by such drawbacks as weight gain, high risk of hypoglycaemia, complex titration and need for coordination with meals. Given the

above-mentioned limitations of currently approved therapies, there is a need for new efficacious, durable, safe and tolerable treatment options for paediatric patients with T2D.

Regulatory guidance

The aim of this application is to extend the indication for liraglutide (Victoza) for the treatment of T2D in children and adolescents aged 10 years and above.

The liraglutide (Victoza) paediatric development programme was designed in agreement with the FDA and the EMA. Key binding elements for the programme were included in the paediatric investigation plan (PIP) agreed upon with the EMA (EMEA-000128-PIP01-07-M08). The EMA granted a waiver for the investigation of liraglutide (Victoza) in children with T2D less than 10 years of age, as such investigation would be highly impractical or impossible due to the very low prevalence of T2D in this age range.

The MAH did receive EMA Scientific Advice regarding the PIP request for Trial 3659: "At least 30% of study patients should be included from EU countries or countries with lifestyle and diabetes care similar to those of the EU member states"(EMA/CHMP/SAWP/599380/2018) specifying an approach of comparing WHO lifestyle parameters of other countries to the range of these parameters in the EU and considering ISPAD guidelines to assure comparability of the treatment recommendations across the non-EU countries included.

2.1. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2. Clinical aspects

GCP

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

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

- Tabular overview of clinical studies: see table 1

Introduction

The paediatric clinical development programme for liraglutide builds on the data already available for liraglutide in adults. Liraglutide was investigated in children and adolescents (age 10-17 years) with T2D in two trials (Table 1):

- a clinical pharmacology trial (Trial NN2211-1800, referred to as Trial 1800)
- a Phase 3a efficacy and safety trial (Trial NN2211-3659, referred to as Trial 3659)

Both trials were designed and conducted in accordance with the Declaration of Helsinki[4] and ICH Good Clinical Practice[5].

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

Trial	Title	Timing
(NN2211-1800; completed)	A randomised, double-blind, placebo-controlled trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in paediatric subjects (10–17 years) with T2D	Last subject last visit: 30 September 2011
(NN2211-3659; main part	Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children	Last subject last visit was 23 May 2018, which denoted end-of-treatment in the

Trial	Title	Timing
completed)	and adolescents with T2D. A 26-week double-blind, randomised, parallel group, placebo controlled multi-centre trial followed by a 26-week open-label extension.	main part of the trial. Subjects treated with liraglutide for >3 months were asked to return for safety follow-up visits 1 and 2 years after stopping treatment (the follow-up is currently ongoing).

Abbreviations: PIP = paediatric investigation plan, T2D = type 2 diabetes

The execution of the paediatric clinical development programme was challenging, mainly due to the slow and difficult subject recruitment. The recruitment period for Trial 1800 spanned approximately 2 years. A total of 14 sites in 4 countries randomised subjects (N=21). Two (2) of the protocol amendments for Trial 1800 were implemented to aid recruitment. The recruitment period for Trial 3659 spanned 4 years and 4 months. A total of 84 sites in 25 countries screened subjects and 57 of these sites randomised subjects (N=135). Three (3) of the protocol amendments for Trial 3659 were done in order to facilitate recruitment and/or reduce the sample size.

2.2.1. Pharmacokinetics

The main objectives of the clinical pharmacology program for the use of liraglutide in paediatric subjects aged 10-17 years with T2D were to assess the safety and tolerability and pharmacokinetic properties in this population and compare exposure to exposure in the corresponding adult population.

The short-term clinical pharmacology trial (Trial 1800) provided evidence of safety and tolerability in paediatric subjects and that pharmacokinetics in paediatric subjects were consistent with pharmacokinetics in adults. In Trial 1800 the half-life was approximately 12 h and CL/F was 1.7 L/h assessed for liraglutide 1.8 mg at steady state, in accordance with pharmacokinetics in adults. This trial also indicated dose proportionality for AUC0–24h and Cmax for liraglutide doses up to 1.8 mg. Based on the safety/tolerability results, and the PK data from this trial and the knowledge that the body weight range is similar for adolescents and adults with T2D in the patient population, the adult dose range (0.6-1.8 mg) was chosen for the phase 3a trial (Trial 3659).

The phase 3a efficacy/safety trial (Trial 3659) was designed to test the same dose regimen in paediatric subjects as used in adults: a starting dose of 0.6 mg for 1 week, thereafter escalating the dose to 1.2 mg and 1.8 mg according to individual glucose level and safety/tolerability.

Population pharmacokinetic analysis of a combined data set that included data from Trial 3659, data from Trial 1800, and data from two historical clinical pharmacology trials in adults with T2D (NN2211-3534 and NN2211-3673) showed as expected (based on previous findings in paediatric and adult trials) that exposure was inversely correlated with body weight (the covariate of most importance), that males have lower body weight-adjusted exposure than females, and that no clinically relevant difference in exposure was observed for the paediatric population versus adults when adjusted for effects of covariates.

Simulated steady-state concentration-time profiles following liraglutide 1.8 mg once-daily in paediatric subjects and adults showed similar body-weight adjusted liraglutide concentrations over the dosing interval.

Additionally, the exposure in Trial 3659 was compared to exposure in a previous phase 3a trial conducted in adults with T2D (NN2211-1573, referred to as Trial 1573). The exposure levels were comparable between the paediatric subjects in Trial 3659 and the adults in Trial 1573 (Figure 1) as a result of the similar body weights for the subjects in these trials. The body weight range in Trial 1573 (43.7-163.3 kg) was consistent with the range observed across several liraglutide trials in adults with T2D (40.3-170.0 kg).6 It is expected, therefore, that in general, paediatric subjects aged 10-17 years with T2D will have a similar body weight range as compared to adults with T2D.

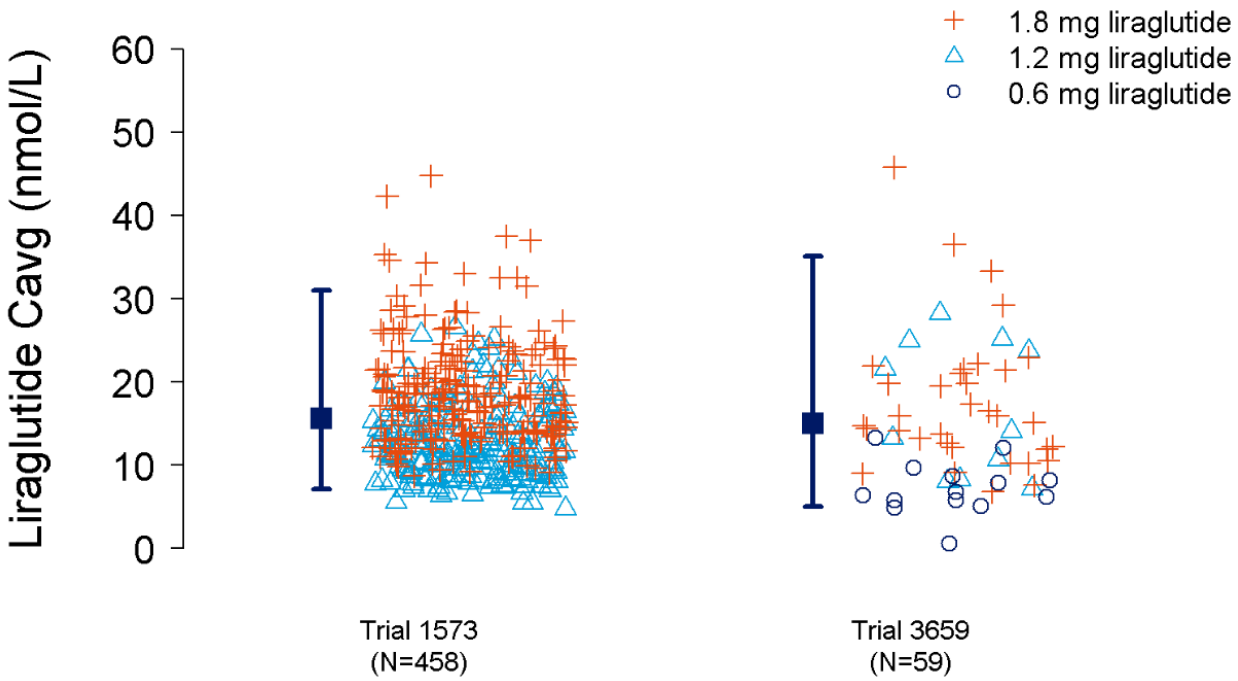


Figure 1 Individual average steady-state concentrations in adults (Trial 1573) and paediatric subjects (Trial 3659)

Data are individual model-derived Cavg (symbols) and geometric mean (90% range [5th - 95th percentile, blue square with bars]). Cavg estimates from a population PK analysis of Trial 1573 and from the full model for Trial 3659. Trial 1573: maintenance dose (1.2 and 1.8 mg). Trial 3659: highest achieved maintenance dose (0.6, 1.2 or 1.8 mg).

Cavg: average concentration

Cross-reference: Modified from Trial 3659 (M 5.3.3.5) Modelling Report, Figure 5-13

The exposure-response analysis for change in HbA1c at week 26 in Trial 3659 showed a larger reduction in HbA1c with higher exposure, despite factors that could suppress the magnitude of HbA1c reduction: individual dose escalation based on FPG and tolerability, use of rescue medication, and suspected possible non-compliance.

In conclusion, the pharmacokinetic data supports the same liraglutide dose regimen for paediatric patients aged 10-17 years with T2D, as used by adult patients with T2D.

2.2.2. Discussion on clinical pharmacology

The main objectives of the clinical pharmacology program for the use of liraglutide in paediatric subjects aged 10-17 years with T2D were to assess the safety and tolerability and pharmacokinetic properties in this population and compare exposure to exposure in the corresponding adult population. In Trial 1800 the half-life was approximately 12 h and CL/F was 1.7 L/h assessed for liraglutide 1.8 mg at steady state, in accordance with pharmacokinetics in adults.

Of the 14 subjects treated with liraglutide, one subject stayed on 0.3 mg liraglutide, and three subjects stayed on 0.6 mg liraglutide. In the study report, the Applicant has justified the non-escalation by the protocol-specified stop in dose escalation if the 3-day average FPG was ≤ 6.1 mmol/L. Overall, the study seems well conducted.

AUC, C_{max} and C_{trough} increased with increasing dose until 1.8 mg, which is indicative of dose proportionality, which is further supported by the dose proportionality analysis provided by the Applicant. C_{max} and AUC is

markedly lower in children than what is stated in the SmPC. This is likely due to a higher body weight in the paediatric studies than the adult studies on which the SmPC values are based on, as body weight was a significant covariate for exposure. In the SmPC section 5.2, it is therefore now stated that the exposure (C_{max} and AUC) is dependent on body weight, and the body mean weight that corresponds to the C_{max} and AUC is reported. T_{max} was approximately 8-10 hours for all selected doses with no apparent dose dependency. This is acceptable. T_{max} in children was similar to T_{max} in adults (8-12 hours). Clearance was 1.7 L/h, which is comparable to the clearance in adults (1.2 L/h). This is acceptable. $T_{½}$ was assessed at the final dose, that is 0.6 mg (n=2) and 1.8 mg (N=9).

No pharmacokinetic interaction studies were conducted in children. This is considered acceptable as no differences in drug-drug interactions are expected between children and adults.

The Applicant presented data on secondary efficacy parameters from Trial 1800, which showed statistically significantly decreases in HbA1c and fructosamine in the Liraglutide treated subjects. The Applicant has not shown any dose-response results from study 1800. This would have been appreciated in order to evaluate the selection of the liraglutide dose in children. However, as the Applicant has shown dose response curves based on modelled data from study 3659, the lack of information regarding dose-response analysis in study 1800 is acceptable.

The Applicant has conducted two population PK (popPK) analyses: 1) a covariate analysis combining data from the two paediatric trials with data from two trials in adults with type 2 diabetes (Trial 3534 and Trial 3673); and 2) comparing exposure in the paediatric population (trial 4659) with exposure in adults with type 2 diabetes (Trial 1573).

Regarding 1), the covariate analysis: in the two adult studies included in this analysis, concomitant treatment with glucose lowering drugs were allowed. This is not considered to affect the pharmacokinetics of liraglutide and is thus acceptable. The full model included effects of body weight (centred at 90 kg), sex and age group on CL/F and on V/F, which is considered relevant.

Regarding 2), the exposure comparison: the comparability between the paediatric and adult studies seems reasonable.

Dose proportionality analysis from trial 1800 showed a linear increase AUC with increasing dose from 0.3 mg liraglutide up to 1.8 mg. This is endorsed. Based on trial 3659, exposure increased with increasing dose in a weight adjusted model, which is endorsed.

The popPK model showed that exposure increased with lower body weight, that males have lower body weight-adjusted exposure than females, and that no clinically relevant difference in exposure was observed for the paediatric population versus adults when adjusted for effects of covariates. The SmpC in section 5.2 now reflects that exposure depends on body weight. The Applicant has included age as a binary variable in the model and has thus combined all age groups within the range 10-17 years to one parameter and age above 17 years to the other parameter. There were no marked differences between the 10-14 year age group and 14-17 year age group regarding exposure.

Based on simulated steady-state concentration-time profiles following 1.8 mg liraglutide, no marked differences between adults and children were observed. This is endorsed.

Data from the paediatric Trial 3659 and the adult Trial 1573 indicate similar distribution and range of body weight and similar concentrations at steady state in adults and paediatric subjects, which is endorsed.

The exposure response curve shows a decrease in HbA1c with increasing liraglutide concentrations, which is endorsed.

In the SmPC section 4.2 it is stated that some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg. This was found to be acceptable. Moreover, in section 5.1, the proportion of patients in

study 3659 who escalated to 1.2 mg and 1.8 mg respectively, as well who stayed at 0.6 mg, are now mentioned.

2.2.3. Conclusions on clinical pharmacology

The pharmacokinetic data supports the same liraglutide dose regimen for paediatric patients aged 10-17 years with T2D, as used by adult patients with T2D. As body weight is an important covariate for exposure, this is reflected in the SmPC.

2.3. Clinical efficacy

2.3.1. Dose response study(ies)

N/A

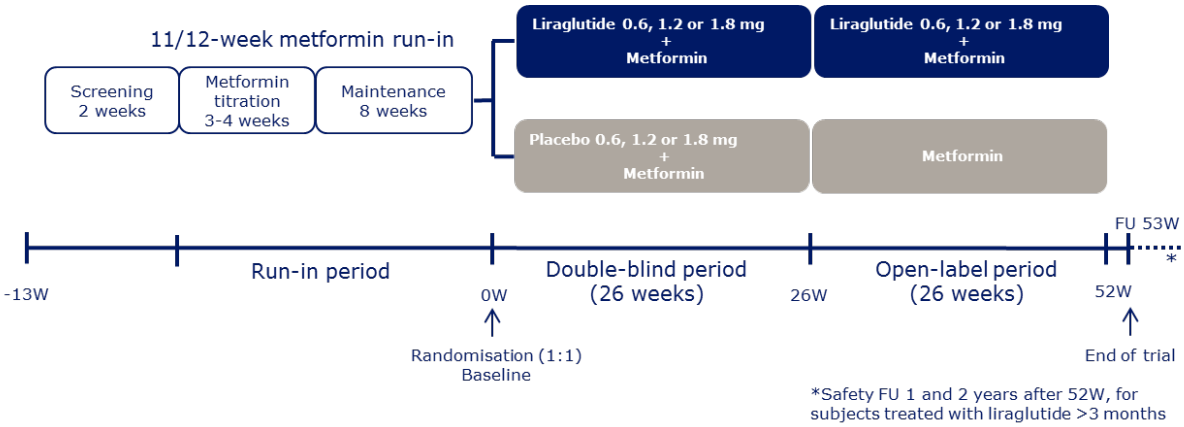
2.3.2. Main study

There was one Phase 3a efficacy and safety trial (Trial NN2211-3659, referred to as Trial 3659)

Methods

Trial design

Trial 3659 was a multinational, multi-centre, randomised, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension in subjects with T2D aged 10−17 years. The trial design is shown schematically Figure 2.



Key inclusion criteria

- Children and adolescents between the ages of 10 –17 years
- Diagnosis of type 2 diabetes mellitus and treated for at least 30 days
- HbA_{1c}
  - ≥7.0% and ≤11% if diet and exercise treated
  - ≥ 6.5% and ≤ 11% if treated with metformin as monotherapy, basal insulin as monotherapy or metformin and basal insulin in combination
- BMI >85th percentile

Randomisation criteria

- FPG ≥ 7.0 mmol/L and ≤ 12.2 mmol/L
- Stable dose for at least 56 days of metformin ≥1000 mg
- Subjects treated with basal insulin must be on a stable dose for at least 56 days

Key exclusion criteria

- Type 1 diabetes
- Fasting C-peptide < 0.6 ng/ml
- Maturity onset diabetes of the young (MODY)
- Use of any antidiabetic agent other than metformin and/or basal insulin 90 days prior to screening
- Previous treatment with liraglutide
- History of pancreatitis
- Screening calcitonin value ≥ 50 ng/L
- Subjects with personal or family history MTC or MEN 2

Figure 2 Trial design and main in- and exclusion criteria
Abbreviations: BMI = body mass index, FPG = fasting plasma glucose, FU = follow-up, HbA_{1c} = glycosylated haemoglobin A_{1c}, MEN 2 = multiple endocrine neoplasia type 2, MTC = medullary thyroid carcinoma

The data from the 1- and 2-year safety follow-up (currently ongoing) will be described in a separate clinical trial report after the completion of the last follow-up visit by the last trial subject.

The main part of the trial consisted of a 2-week screening period, an 11- to 12-week run-in period (consisting of 3-4 weeks of metformin titration and 8 weeks of metformin maintenance treatment), a 26-week double-blind treatment, a 26-week open-label period and a one week follow-up period. A 26-week double-blind period was considered adequate to demonstrate an effect on long-term glycaemic control (HbA_{1c}) and the 26-week open-label period was implemented to assess the longer-term safety of liraglutide treatment.

The current standard of care for children and adolescents with T2D is metformin treatment or insulin, if needed. To ensure adequate care, subjects were treated with metformin at the approved MTD (≥1000 mg) throughout the trial. The aim of metformin titration during the run-in period was to reach a daily dose of 2000 mg. Placebo was chosen as the comparator, as combination therapy with metformin was applied, and because no other antidiabetic medication, except for insulin, is widely approved for use in the paediatric T2D population.

In the open-label period, unblinding was done to enable discontinuation of the placebo injections, which are considered a burden for children and adolescents. During the open-label treatment period, subjects treated with liraglutide continued their treatment regimen unchanged, whereas subjects treated with placebo continued treatment with the MTD of metformin (with or without basal insulin).

For subjects experiencing confirmed hyperglycaemia and meeting the rescue criterion, rescue treatment (basal insulin addition or up-titration; followed by addition of rapid-acting insulin, if needed) was allowed. Subjects on rescue treatment were to remain in the trial unless hyperglycaemia persisted and they met the applicable withdrawal criteria.

Trial population

The trial was conducted at 84 sites in 25 countries on 5 continents, thereby ensuring representation of children and adolescents from different ethnical and cultural backgrounds.

Treatments

At randomisation, liraglutide dosing was started at 0.6 mg daily during the first week and escalated in weekly increments of 0.6 mg over the following 2-3 weeks to a maximum dose of 1.8 mg daily. Subjects randomised to placebo received doses of equivalent volume.

Dose escalation was based on:

- tolerability (the dose was not to be increased in case of severe intolerability, as judged by the investigator);
- the average of 3 measurements of fasting SMPG on the 3 consecutive days preceding the dose escalation visit had to be >6.1 mmol/L (110 mg/dL).

After the dose escalation period, no further dose escalation was to be performed. If a subject experienced severe intolerance or recurrent hypoglycaemia, as judged by the investigator (such as, ≥3 unexplained minor hypoglycaemic events, or 1 severe unexplained hypoglycaemic event in a week), the liraglutide/placebo dose was to be lowered to the next lower dose. If a subject on liraglutide 0.6 mg/day (or placebo dose-volume equivalent) experienced severe intolerance or recurrent hypoglycaemia the subject had to be withdrawn from the trial.

Duration of treatment

The duration of treatment was 52 weeks for the subjects randomised to liraglutide and 26 weeks for the subjects randomised to placebo.

All subjects received metformin (with or without basal insulin) for the duration of the trial.

Objectives

The primary objective was to confirm the superiority of liraglutide at its maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg daily) versus placebo when added to metformin, with or without basal insulin treatment, in controlling glycaemia in children and adolescents (aged 10–17 years) with T2D.

The secondary objectives were to assess and compare the effect of liraglutide versus placebo (both in combination with metformin, with or without basal insulin treatment) on parameters of glycaemic control, beta-cell function, body composition, vital signs, growth velocity, safety and tolerability.

Outcomes/endpoints

The primary endpoint was the change from baseline to week 26 in HbA1c.

The primary endpoint and confirmatory secondary endpoints were analysed in a hierarchical manner in the following order:

- Primary endpoint (change in HbA1c from baseline to week 26)
- Change from baseline in FPG after 26 weeks of treatment
- HbA1c < 7.0% after 26 weeks of treatment (yes/no)
- Change from baseline in BMI SDS after 26 weeks of treatment

To conclude on superiority for an endpoint in the list above, the results for that endpoint and for the endpoints higher up in the hierarchy had to show superiority of liraglutide over placebo.

Sample size

Two protocol amendments were issued to reduce the sample size, from 172 subject to 150 subjects and from 150 subjects to 94 subjects, due to the difficulties in recruiting subjects to the trial.

The sample size was determined to evaluate whether liraglutide was superior to placebo with regards to the primary endpoint. The primary endpoint was evaluated using a two-sided test and a significance level of 5%.

Assumptions for the final calculations were as follows:

- Change in HbA_{1c} from baseline to week 26: a mean difference of 0.9%-point and a standard deviation of 1.2%-point were assumed for liraglutide versus placebo, both in combination with metformin with or without basal insulin. This mean difference was chosen based on the effect of liraglutide versus placebo observed in the adult population (LEAD-1, -2, -4 and -5 trials)[4-7] and Trial 1800, in which the change in HbA_{1c} after 5 weeks of treatment was an exploratory endpoint.
- The assumed subject withdrawal rates were based on the withdrawal rates in the LEAD-2 trial[5] (approximately 40% in the placebo group and approximately 20% in the active groups). A slightly higher withdrawal rate was expected in a paediatric population, therefore, the withdrawal rate for the liraglutide group was assumed to be 22%. The primary analysis imputed values for withdrawn placebo subjects based on those in placebo completers, and thus the sample size was not adjusted for the withdrawal rate in the placebo group.

A sample size of 47 subjects per treatment arm of the FAS was calculated to yield a power of 80%. Assuming a screening failure rate of 65%, 269 subjects needed to be screened

Randomisation/Blinding (masking)

After the run-in period, subjects who fulfilled the randomisation criteria listed below were randomised 1:1 to either liraglutide or placebo:

- the average of fasting SMPG values taken on the 3 consecutive days leading up to the randomisation visit was ≥7.0 mmol/L (126 mg/dL) and ≤12.2 mmol/L (220 mg/dL)
- subjects had to have been on a stable dose of metformin ≥1000 mg and ≤2000 mg per day for at least 56 days (subjects who entered the trial on >2000 mg continued with that dose at randomisation)
- subjects treated with basal insulin had to have been on a stable dose for at least 56 days (stable dose of basal insulin was defined as basal insulin adjustments up to 15%).

Randomisation was performed using centralised allocation via IV/WRS; subjects were stratified by sex and age at end of trial (≤14 years or >14 years; ≤14 years was defined as not reaching 14 years and 11 months at week 52).

Subjects randomised to placebo received doses of equivalent volume as liraglutide during the dose escalation period and thereafter, to maintain blinding. In the 26-week open-label period, treatment allocation was unblinded to all subjects and site staff but was to remain blinded to the Novo Nordisk personnel assessing outcomes. The subjects randomised to placebo discontinued placebo injections in the open-label period.

Statistical methods

Efficacy variables and analysis sets

The primary objective of Trial 3659 was to confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin treatment in controlling glycaemia, in children and adolescents (aged 10–17 years) with T2D.

A superiority design was chosen based on the beneficial results observed with liraglutide (doses up to 1.8 mg) in adults with T2D and the exploratory results for pharmacodynamic endpoints in the paediatric Trial 1800. The safety and tolerability profile of liraglutide in children and adolescents with T2D in Trial 1800 was consistent with that observed in adults with T2D.

The secondary objectives were to assess and compare the effect of liraglutide versus placebo (both in combination with metformin with or without basal insulin treatment) on other parameters of glycaemic control, beta-cell function, body composition, vital signs, growth (i.e., height velocity), safety and tolerability.

As pre-specified in the protocol, the efficacy analyses were conducted on the full analysis set, defined as including all randomised subjects receiving at least one dose of liraglutide or placebo.

Primary and secondary statistical analyses

The primary analysis of the primary efficacy endpoint, the confirmatory secondary endpoints and supportive secondary endpoints was based on a PMM using multiple imputations and including data collected after initiation of rescue medication or discontinuation of treatment for all subjects in the full analysis set. The imputed data sets were analysed using an ANCOVA model with treatment and stratification group (sex*age group) as fixed effects and baseline parameter value as a covariate. A pre-specified secondary analysis was performed for all endpoints analysed statistically. This analysis was based on a MMRM and excluded data

collected after initiation of rescue medication or discontinuation of treatment. Fixed effects in the model were treatment and stratification group (sex*age group) and baseline parameter value was a covariate, all nested within visit. The dichotomous endpoints were analysed using a logistic regression model with missing data imputed from either the PMM or MMRM. Furthermore, for the primary endpoint, five additional sensitivity analyses were performed that used different approaches to account for the missing data. The statistical analyses were performed with a significance level of 5% (two-sided test).

In order to conclude on superiority for a confirmatory endpoint, the primary analysis (PMM) results for that endpoint and for the endpoints higher up in the hierarchy had to show superiority of liraglutide treatment over placebo treatment.

A p-value of <0.05 was considered to be statistically significant.

In the following sections, the evaluation of clinical efficacy is based on the results of the PMM analysis.

Study participants

Key selection criteria

Key inclusion criteria:

- children and adolescents between the ages of 10 –17 years
- diagnosis of T2D and treated for at least 30 days
- HbA_{1c}: ≥7.0% and ≤11%, if diet and exercise-treated
- HbA_{1c}: ≥ 6.5% and ≤ 11%, if treated with metformin as monotherapy, basal insulin as monotherapy or metformin and basal insulin in combination
- BMI >85th percentile for age and gender
- Randomisation criteria are detailed above.

Key exclusion criteria:

- type 1 diabetes
- fasting C-peptide <0.6 ng/ml
- maturity onset diabetes of the young (MODY)
- use of any antidiabetic agent other than metformin and/or basal insulin 90 days prior to screening
- previous treatment with liraglutide
- history of pancreatitis
- screening calcitonin value ≥ 50 ng/L
- subjects with personal or family history MTC or MEN 2

Results

Participant flow

In Trial 3659, 135 of 307 screened subjects were randomised (1:1); 66 subjects to the liraglutide group and 69 subjects to placebo group (

Table 2). One (1) subject in the placebo group withdrew before being exposed to treatment and was excluded from both the full analysis set (FAS) and the safety analysis set.

The majority (87.4%; 60 randomised to liraglutide and 58 randomised to placebo) of the 134 exposed subjects completed the 26-week double-blind period. A higher proportion of subjects in the liraglutide group (86.4%) than in the placebo group (66.7%) completed this period without rescue medication. A total of 56 (84.8%) subjects randomised to liraglutide and 53 (76.8%) subjects randomised to placebo completed the trial (52-week period and 1-week follow-up).

Of the 10 liraglutide subjects and 16 placebo subjects who withdrew, 6 and 8 subjects, respectively, did so due to meeting a withdrawal criterion, and 4 subjects in each group withdrew due to non-compliance. One subject randomised to placebo withdrew due to an AE and 3 others for a reason 'other'. One of the subjects in the liraglutide group who withdrew due to non-compliance discontinued liraglutide treatment permanently due to an AE ('hyperglycaemia').

Table 2 Subject disposition – total population

	Liraglutide		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Screened subjects					307	
Screening failures					152	
Withdrew before randomisation					20	
Randomised	66	(100.0)	69	(100.0)	135	(100.0)
Exposed	66	(100.0)	68	(98.6)	134	(99.3)
Completed treatment week 26	60	(90.9)	58	(84.1)	118	(87.4)
Completed treatment week 26 without rescue medication	57	(86.4)	46	(66.7)	103	(76.3)
Completed treatment week 52	56	(84.8)	53	(76.8)	109	(80.7)
Completed treatment week 52 without rescue medication	47	(71.2)	35	(50.7)	82	(60.7)
Completed trial	56	(84.8)	53	(76.8)	109	(80.7)
Did not complete the trial	10	(15.2)	16	(23.2)	26	(19.3)
Withdrawal criteria	6	(9.1)	8	(11.6)	14	(10.4)
Non-compliance	4	(6.1)	4	(5.8)	8	(5.9)
Adverse events			1	(1.4)	1	(0.7)
Other			3	(4.3)	3	(2.2)
Full analysis set	66	(100.0)	68	(98.6)	134	(99.3)
Safety analysis set	66	(100.0)	68	(98.6)	134	(99.3)

Abbreviations: N: Number of subjects, %: Percentages are based on randomised subjects. Completed treatment week 26: entered open label period, Completed treatment week 52: completed treatment, Completed trial: completed treatment and completed week 53 follow-up visit. Full analysis set: includes all randomised subjects receiving at least one dose of the trial product, Safety analysis set: includes all subjects receiving at least one dose of the trial product.

Dosing

The planned duration of treatment was 52 weeks for subjects randomised to liraglutide and 26 weeks for those randomised to placebo. Subjects initiated liraglutide (and placebo) at a daily dose of 0.6 mg and then increased their dose by weekly 0.6 mg increments over 2−3 weeks. The dose escalation was based on tolerability, as judged by the investigator, and having FPG >6.1 mmol/L (110 mg/dL; average of 3

consecutive daily SMPGs preceding each dose escalation visit). Once subjects completed their dose escalation period, they were to continue on their maximum tolerated dose for the rest of the trial.

By week 3, 28.6% of the subjects in the liraglutide group were on the 0.6 mg dose, 15.9% were on the 1.2 mg dose and 55.6% were on the 1.8 mg dose. From week 3 and throughout the duration of the trial (up to week 48 in the liraglutide group and up to week 26 in the placebo group), the doses of liraglutide and placebo remained relatively constant. The main reason for not escalating the dose to the next level at weeks 1 and 2 was the attainment of the FPG value of ≤6.1 mmol/L (more frequent in the liraglutide group than in the placebo group). Importantly, throughout dose escalation, less than 10% of the subjects in either treatment group (6 subjects in the liraglutide group and 4 subjects in the placebo group) refrained from increasing their dose due to intolerance. In the liraglutide group, intolerance primarily involved gastrointestinal AEs (i.e., nausea and/or vomiting; 4 out of 6 subjects).

Exposure

During the double-blind period, cumulative exposure to liraglutide and placebo was 31.0 and 31.4 years, respectively, with a mean exposure of 0.47 and 0.46 years per subject, respectively; 38 subjects in the liraglutide group and 54 subjects in the placebo group reached the maximum daily dose of 1.8 mg with a mean exposure at this maximum dose of 0.39 and 0.40 years per subject, respectively. Subjects in the liraglutide group accumulated 59.6 years of exposure over 52 weeks of treatment (mean of 0.90 years per subject); accumulated exposure by dose was 17.7 years (0.6 mg), 11.6 years (1.2 mg) and 29.9 years (1.8 mg).

Baseline data

Baseline subject characteristics

In general, demographics were well balanced between the treatment groups (Table 3). The subjects' mean age was 14.6 years, ranging from 10.0 to 16.9 years at baseline; 30% of the subjects were 10−14 years old (age at end of treatment) and 62% of the subjects were female. The subjects had had diabetes for a mean of 1.9 years. Mean HbA_{1c} was 7.78 % and mean BMI was 33.9 kg/m^2.

Most subjects resided in North America (35.1%) or Europe (defined in this trial as including Belgium, Hungary, Israel, Macedonia, Poland, Portugal, Russia, Spain, Turkey and the United Kingdom; 33.6%), with the rest residing in South America (i.e., Mexico), Asia, Oceania and Africa. The proportion of subjects from EU and EU-like countries (i.e., countries with lifestyle and diabetes care similar to the EU member states) was 45%; countries included in this classification are: Australia, Belgium, Canada, Hungary, Israel, Poland, Portugal, Macedonia, Mexico, Russia, Spain and United Kingdom. Approximately two-thirds (64.9%) of the subjects were White. Racial and ethnic minorities were also represented: 13.4% of the subjects were Asian, 11.9% were Black/African American and 29.1% were of Hispanic or Latino ethnicity.

The subject demographic and baseline characteristics were similar between EU countries and EU-like countries. Likewise, the subject demographic and baseline characteristics were similar between the US and the non-US countries, with the exception of weight-related parameters, which were higher in the US than in the non-US countries.

Table 3 Summary of demographics and baseline characteristics for Trial 3659 - FAS

	Liraglutide	Placebo	Total
N	66	68	134
Age (years), mean, [min;max]	14.57 [10.0;16.9]	14.57 [10.4;16.9]	14.57 [10.0;16.9]
Female, N (%)	41 (62.1)	42 (61.8)	83 (61.9)
HbA_{1c} (%), mean [min;max]	7.87 [5.1;11.5]	7.69 [5.1;11.0]	7.78 [5.1;11.5]
FPG (mmol/L), mean [min;max]	8.70 [4.80;16.30]	8.15 [4.30;14.90]	8.42 [4.30;16.30]

Body weight (kg), mean [min;max]	93.23 [41.80;201.70]	89.83 [48.00;141.70]	91.50 [41.80;201.70]
BMI (kg/m^2), mean [min;max]	34.55 [20.90;81.16]	33.27 [21.91;57.05]	33.90 [20.90;81.16]
BMI SDS, mean [min;max]	3.03 [1.00;9.29]	2.86 [1.07;6.32]	2.94 [1.00;9.29]
Duration of diabetes (years), mean [min;max]	1.85 [0.3;10.1]	1.93 [0.2;6.2]	1.89 [0.2;10.1]
Basal insulin at baseline, N (%)			
Yes	15 (22.7)	10 (14.7)	25 (18.7)
No	51 (77.3)	58 (85.3)	109 (81.3)
Race, N (%)			
White	42 (63.6)	45 (66.2)	87 (64.9)
Black or African American	9 (13.6)	7 (10.3)	16 (11.9)
Asian	10 (15.2)	8 (11.8)	18 (13.4)
American Indian or Alaska Native	2 (3.0)	1 (1.5)	3 (2.2)
Other	3 (4.5)	7 (10.3)	10 (7.5)
Ethnicity: Hispanic or Latino, N (%)	16 (24.2)	23 (33.8)	39 (29.1)
Age 10-14 at EOT, N (%)	21 (31.8)	19 (27.9)	40 (29.9)
Tanner Stage[a], N (%)	66 (100.0)	67 (98.5)	133
I	3 (4.5)	3 (4.5)	6 (4.5)
II	3 (4.5)	0 (0.0)	3 (2.3)
III	8 (12.1)	10 (14.9)	18 (13.5)
IV	14 (21.2)	25 (37.3)	39 (29.3)
V	38 (57.6)	29 (43.3)	67 (50.4)
Region, N (%)			
Asia	6 (9.1)	6 (8.8)	12 (9.0)
Europe	24 (36.4)	21 (30.9)	45 (33.6)
North America	19 (28.8)	28 (41.2)	47 (35.1)
South America	9 (13.6)	7 (10.3)	16 (11.9)
Rest of the world	8 (12.1)	6 (8.8)	14 (10.4)
EU/EU-like countries, N (%)	34 (51.5)	26 (38.2)	60 (44.8)

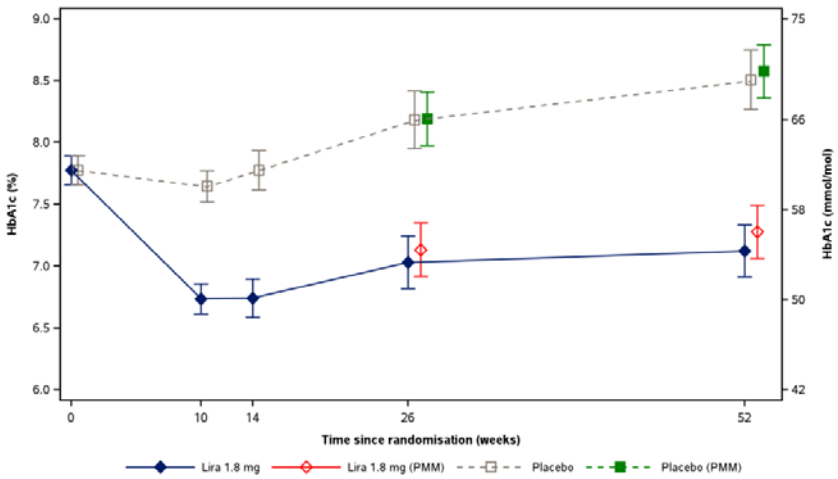
[a]Tanner staging was based on pubic hair development.

Liraglutide refers to all doses (0.6, 1.2 and 1.8 mg); Baseline is at randomisation (week 0); **Asia**: India, Malaysia, Taiwan, Thailand; **Europe**: Belgium, Hungary, Israel, Poland, Portugal, Macedonia, Russia, Spain, Turkey, United Kingdom; **North America**: Canada, USA; **South America**: Mexico; **Rest of the world**: Australia, Lebanon, Morocco, New Zealand; **EU/EU-like countries** (EU countries or countries with lifestyle and diabetes care similar to EU member states): Australia, Belgium, Canada, Hungary, Israel, Poland, Portugal, Macedonia, Mexico, Russia, Spain, United Kingdom; **EU member countries**: Belgium, Hungary, Poland, Portugal, Spain and United Kingdom.

HbA1c

HbA1c

Treatment with liraglutide led to a reduction in HbA1c from baseline to week 26 (-0.64%), with this reduction being maintained in the open-label period up to week 52 (-0.50%); with placebo, HbA1c increased from baseline to weeks 26 (0.42%) and 52 (0.80%), as shown in Figure 3 and summarised in Table 4.. The estimated treatment differences (ETDs) were statistically significantly in favour of liraglutide both at weeks 26 and 52 and superiority of liraglutide over placebo at week 26 was confirmed.



Abbreviations: Lira 1.8 mg: liraglutide all doses, error bars: +- standard error (mean)

Means are estimated from a mixed model of repeated measurements (MMRM) containing treatment (sex*age) group as fixed effects and baseline value as covariate, all nested within visit. Results from a pattern mixture model (PMM) are shown at weeks 26 and 52.

For MMRM results data collected after treatment discontinuation or initiation of rescue medication were handled as missing data.

Figure 3 HbA1c - change from baseline at weeks 26 and 52-PMM-FAS

Table 4 HbA1c – change from baseline at weeks 26 and 52-PMM-FAS

		Estimated change from baseline		Estimated difference	95% CI	p-value
		liraglutide	placebo			
HbA_{1c}						
baseline	% (mmol/mol)	7.87 (62.5)	7.69 (60.5)			
week 26*	%-points	-0.643	0.415	-1.058	[-1.653; -0.464]	<0.001
	mmol/mol	-7.030	4.538	-11.57	[-18.07; -5.066]	
week 52	%-points	-0.499	0.801	-1.299	[-1.895; -0.704]	<0.001
	mmol/mol	-5.451	8.751	-14.20	[-20.71; -7.695]	

*primary endpoint

The robustness of the conclusions based on the primary analysis of the primary endpoint (change from baseline in HbA1c at week 26) was confirmed by six sensitivity analyses. The sensitivity analyses consistently showed statistically significant estimated treatment differences in favour of liraglutide (Figure 4).

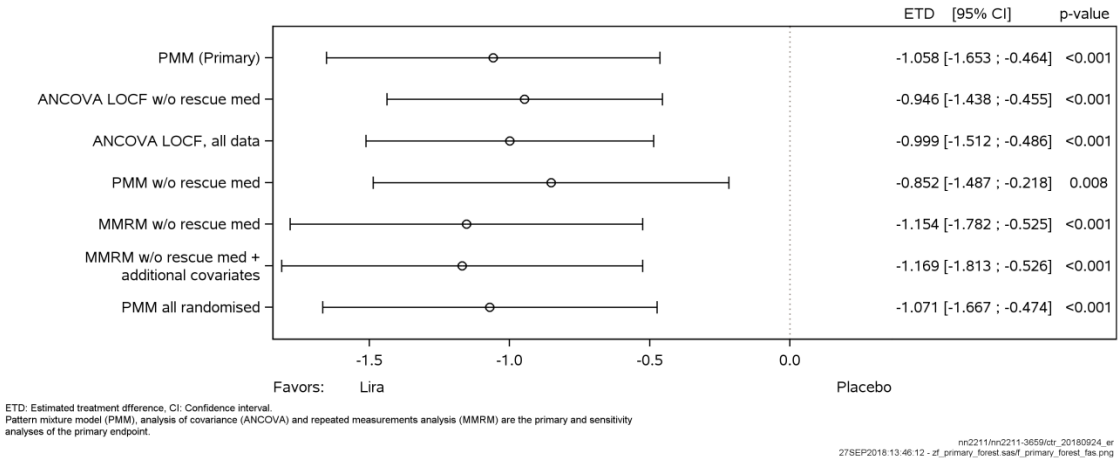


Figure 4 **Analyses of the primary endpoint – forest plot – FAS**

HbA1c treatment targets

At baseline, the proportions of subjects who had achieved various treatment targets were relatively high, reflecting the fact that all subjects had to have had at least 8 weeks of treatment with metformin at their MTD prior to randomisation (baseline). Thus, some subjects had already improved their HbA_{1c} in the run-in period between screening and randomisation. In addition, subjects with HbA_{1c} ≥ 6.5% and ≤ 11%, were allowed in the trial, if they were being treated with metformin, or basal insulin, or both. Nevertheless, treatment with liraglutide resulted in consistently greater proportions of responders (of all categories) than with placebo, both at weeks 26 and 52, with statistically significant odds ratios (except for HbA_{1c} <7.0% without severe or minor hypoglycaemic episodes at week 52, for which p=0.072) (Table 5).

Similar results were obtained using the MMRM imputation.

Table 5 Responders – HbA_{1c} treatment targets at weeks 26 and 52 – logistic regression with imputation from PMM – FAS

		Liraglutide (%)	Placebo (%)	Odds ratio [95% CI]	p-value
HbA_{1c} <7.0%	baseline[a]	21.2	32.4		
	week 26*	63.7	36.5	5.353 [2.105; 13.615]	<.001
	week 52	44.5	26.6	3.754 [1.447; 9.741]	0.007
HbA1c <7.0% w/o minor or severe hypos	week 26	50.1	33.6	2.627 [1.151; 5.997]	0.022
	week 52	36.9	26.6	2.282 [0.929; 5.603]	0.072
HbA_{1c} ≤6.5%	baseline[a]	13.6	23.5		
	week 26	44.7	29.8	2.793 [1.167; 6.682]	0.021
	week 52	40.5	21.2	5.064 [1.775; 14.453]	0.002
HbA_{1c} <7.5%	baseline[a]	40.9	41.2		
	week 26	69.2	46.3	4.095 [1.653; 10.147]	0.002
	week 52	59.3	38.1	4.228 [1.615; 11.073]	0.003

[a]observed means; *confirmatory secondary endpoint

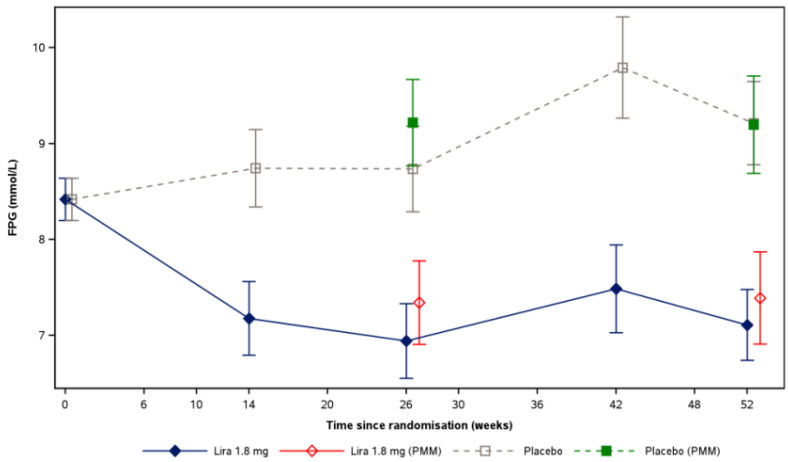
Abbreviations: w/o: without; hypos: hypoglycaemic episodes

Plasma glucose

Fasting plasma glucose

Treatment with liraglutide led to a reduction from baseline to week 26 in FPG (-1.08 mmol/L), with this reduction being maintained in the open-label period up to week 52 (-1.03 mmol/L); with placebo, FPG increased from baseline to week 26 (0.80 mmol/L) and week 52 (0.78 mmol/L), as shown in Figure 5 and summarised in

Table 6 Thus, the ETDs were statistically significantly in favour of liraglutide both at weeks 26 and 52, and superiority of liraglutide over placebo at week 26 was confirmed.



Abbreviations: Lira 1.8 mg: liraglutide all doses, error bars: +- standard error (mean)

Means are estimated from a mixed model of repeated measurements containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit. Results from a pattern mixture model (PMM) are shown at weeks 26 and 52.

Figure 5 Fasting plasma glucose by treatment week – PMM and MMRM – FAS

Table 6 FPG – change from baseline at weeks 26 and 52 – PMM – FAS

	Estimated change from baseline		Estimated difference	95% CI	p-value
	liraglutide	placebo			
Fasting plasma glucose					
baseline[a] mmol/L (mg/dL)	8.7 (156.8)	8.1 (146.8)			
week 26* mmol/L	-1.076	0.801	-1.878	[-3.093; -0.662]	0.002
mg/dL	-19.39	14.439	-33.83	[-55.74; -11.92]	0.002
week 52 mmol/L	-1.028	0.780	-1.808	[-3.175; -0.441]	0.010
mg/dL	-18.52	14.057	-32.58	[-57.21; -7.946]	0.010

[a] observed means; *confirmatory secondary endpoint

Self-measured plasma glucose (SMPG)

Subjects were instructed to perform a 7-point SMPG profile prior to the randomisation visit and visits at weeks 14, 26 and 52. The SMPG levels were to be recorded before breakfast, 90 minutes after start of

breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 minutes after start of dinner and at bedtime.

The mean plots of the 7-point SMPG profiles indicated a greater improvement in the liraglutide group than in the placebo group at week 26, which is also reflected in the results of the analysis of the mean of the 7-point SMPG presented in Table 7. There were no statistically significant differences between the treatment groups in the mean of meal increments (

Table 8).

Table 7 Mean of 7-point SMPG – change from baseline at weeks 26 and 52 – PMM – FAS

		Estimated change from baseline		Estimated difference	95% CI	p-value
		liraglutide	placebo			
Mean of 7-point SMPG						
baseline[a] mmol/L (mg/dL)		10.3 (185.1)	9.3 (167.2)			
week 26	mmol/L	-1.520	0.126	-1.646	[-2.580; -0.711]	<0.001
	mg/dL	-27.38	2.276	-29.66	[-46.50; -12.82]	<0.001
week 52	mmol/L	-1.870	-1.399	-0.471	[-1.322; 0.381]	0.279
	mg/dL	-33.70	-25.22	-8.480	[-23.82; 6.862]	0.279

[a] observed means Cross-reference:

Table 8 Mean of post-prandial increments of 7-point SMPG (all meals) – change from baseline at weeks 26 and 52 – PMM – FAS

	Estimated change from baseline		Estimated difference	95% CI	p-value
	liraglutide	placebo			
Post-prandial increments 7-point SMPG					
baseline[a] mmol/L (mg/dL)	1.98 (35.6)	1.74 (31.4)			
week 26 mmol/L	-0.357	-0.446	0.089	[-0.561; 0.740]	0.788
mg/dL	-6.432	-8.043	1.611	[-10.12; 13.339]	0.788
week 52 mmol/L	-0.696	-0.394	-0.303	[-0.981; 0.376]	0.382
mg/dL	-12.55	-7.097	-5.452	[-17.69; 6.782]	0.382

[a] observed means Cross-reference:

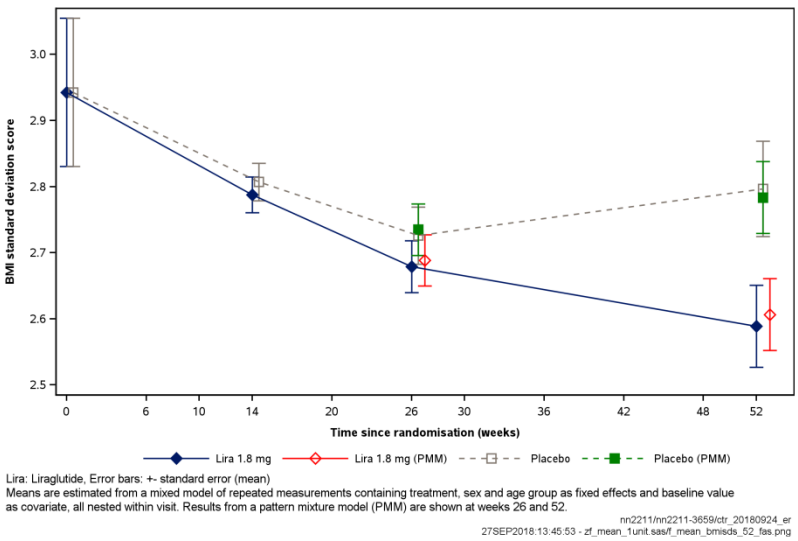
It may be noted that the proportion of missing data for the SMPG endpoints was larger than for the fasting plasma glucose endpoints, probably attributable to the fact that the SMPG assessments were performed at home whereas the fasting glucose samples were taken at site. Home assessments are expected to be a greater challenge than site assessments in this trial population, in turn leading to greater variation in the results based on self-measured data.

Body weight-related parameters

BMI SDS

Treatment with liraglutide led to a reduction in BMI SDS from baseline to week 26 (-0.254), with a further reduction in the open-label period up to week 52 (-0.336); with placebo, BMI SDS decreased less than with liraglutide (-0.208 at week 26 and -0.159 at week 52), as shown Figure 6 and summarised in

Table 9.



Abbreviations: Lira 1.8 mg: liraglutide all doses, error bars: +- standard error (mean)

Means are estimated from a mixed model of repeated measurements containing treatment, sex and age group as fixed effects and baseline value as covariate, all nested within visit. Results from a pattern mixture model (PMM) are shown at weeks 26 and 52.

Figure 6 BMI SDS by treatment week – PMM and MMRM – FAS

The ETD was statistically significantly in favour of liraglutide at week 52 only, thus, superiority of liraglutide over placebo at week 26 was not demonstrated.

Table 9 BMI SDS – change from baseline at weeks 26 and 52 – PMM – FAS

	Estimated change from baseline		Estimated difference	95% CI	p-value
	liraglutide	placebo			
BMI SDS					
baseline[a]	3.03	2.86			
week 26*	-0.254	-0.208	-0.047	[-0.153; 0.060]	0.392
week 52	-0.336	-0.159	-0.177	[-0.327; -0.027]	0.021

[a] observed means; *confirmatory secondary endpoint

BMI, body weight and waist circumference

The results for the weight-related parameters BMI, body weight and waist circumference were all consistent with those for BMI SDS; the ETDs favoured liraglutide both at weeks 26 and 52, but were statistically significant for BMI and body weight at week 52 only (

Table 10).

Table 10 BMI, body weight and waist circumference – change from baseline at weeks 26 and 52 – PMM – FAS

	Estimated change from baseline		Estimated difference	95% CI	p-value
	liraglutide	placebo			
BMI (kg/m^2)					
baseline[a]	34.5	33.3			
week 26	-1.121	-0.813	-0.308	[-0.932; 0.317]	0.334
week 52	-1.105	-0.185	-0.920	[-1.718; -0.123]	0.024
Body weight (kg)					
baseline[a]	93.2	89.8			
week 26	-2.304	-0.986	-1.318	[-3.013; 0.377]	0.128
week 52	-1.905	0.869	-2.774	[-5.014; -0.535]	0.015
Waist circumference (cm)					

baseline[a]	106.1	104.3			
week 26	-1.886	-1.814	-0.072	[-2.347; 2.203]	0.951
week 52	-2.314	-0.748	-1.566	[-4.399; 1.268]	0.279

[a] observed mean Cross-reference:

Blood pressure

The ETD in systolic blood pressure at week 52 favoured liraglutide, as did the ETDs in diastolic blood pressure at weeks 26 and 52; however, none of the ETDs were statistically significant (Table 11).

Table 11 Blood pressure – change from baseline at weeks 26 and 52 – PMM – FAS

		Estimated change from baseline		Estimated difference	95% CI	p-value
		liraglutide	placebo			
SBP (mmHg)						
	baseline[a]	118.4	115.3			
	week 26	-1.084	-1.118	0.034	[-3.404; 3.472]	0.985
	week 52	-0.317	1.756	-2.073	[-5.477; 1.332]	0.233
DBP (mmHg)						
	baseline[a]	73.2	71.2			
	week 26	-0.795	0.286	-1.081	[-3.778; 1.616]	0.432
	week 52	0.682	0.940	-0.257	[-3.112; 2.598]	0.860

[a] observed means

Fasting lipid profile

Greater reductions in VLDL cholesterol and triglycerides were observed with liraglutide than with placebo, with statistically significant ETDs at week 26. For the rest of the fasting lipid endpoints, the changes were generally small and the ETDs not statistically significant (Table 12).

Table 12 Fasting lipids at weeks 26 and 52 – PMM – FAS

		Ratio to baseline[a] (SE)		**Treatment ratio [95% CI]**	**p-value**
		liraglutide	placebo		

Total cholesterol					
	at week 26	0.972 (0.017)	1.017 (0.018)	0.956 [0.912; 1.003]	0.066
	at week 52	1.004 (0.020)	1.035 (0.020)	0.970 [0.919; 1.025]	0.282
HDL cholesterol					
	at week 26	0.997 (0.021)	0.982 (0.021)	1.015 [0.957; 1.076]	0.625
	at week 52	1.025 (0.022)	1.018 (0.022)	1.007 [0.948; 1.069]	0.823
LDL cholesterol					
	at week 26	0.994 (0.028)	0.995 (0.028)	0.999 [0.925; 1.079]	0.980
	at week 52	1.020 (0.037)	1.037 (0.037)	0.984 [0.892; 1.085]	0.745
VLDL cholesterol					
	at week 26	0.878 (0.044)	1.069 (0.053)	0.822 [0.716; 0.943]	0.005
	at week 52	0.955 (0.055)	1.007 (0.058)	0.949 [0.809; 1.113]	0.519
Triglycerides					
	at week 26	0.887 (0.044)	1.069 (0.053)	0.830 [0.723; 0.952]	0.008
	at week 52	0.948 (0.058)	1.047 (0.064)	0.905 [0.764; 1.072]	0.249
Free fatty acids					
	at week 26	0.999 (0.054)	1.000 (0.053)	0.999 [0.862; 1.159]	0.991
	at week 52	0.914 (0.051)	0.878 (0.050)	1.041 [0.893; 1.214]	0.607

[a] Estimated geometric mean ratio

Basal insulin

Fewer subjects in the liraglutide group (5 subjects) than in the placebo group (20 subjects) initiated basal insulin treatment during the trial.

The observed geometric mean daily dose of basal insulin decreased from 23.3 units at baseline to 22.4 units at week 26 in the liraglutide group and increased from 23.0 units to 27.1 units in the placebo group.

Summary of main study

The following tables summarise the efficacy results from the main study 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 12: Summary of efficacy table for Trial NN2211-3659

Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes. A 26-week double-blind, randomised, parallel group, placebo controlled multi-centre trial followed by a 26-week open-label extension.				
Study identifier	NN2211-3659			
Design	A 26-week double-blind, randomised, parallel group, placebo controlled multi-centre trial followed by a 26-week open-label extension.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 11-12 weeks 26 weeks		
Hypothesis	Superiority			
Treatments groups	Treatment	liraglutide dosing was started at 0.6 mg/day during the first week and escalated in weekly increments of 0.6 mg to a maximum dose of 1.8 mg/day over the next 2−3 weeks. 66 patients randomised.		
	Placebo	placebo was administered and dose/volume-escalated in the same manner as liraglutide. 68 patients randomised		
Endpoints and definitions	Change in HbA1c	%	from baseline to week 26	
	Change in FPG and BMI standard deviation score (SDS),	mmol/L and	from baseline to week 26	
	HbA1c <7.0% (yes/no)	proportion	Assessed at week 26	
Database lock	27 June 2018.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Liraglutide	Placebo	
	Number of subject	66	68	
	HbA1c	-0.64	+0.42	

		estimated treatment difference of -1.058 % [-1.653; -0.464]95% CI		
	Fasting plasma glucose	-1.08	+0.80	
		estimated treatment difference of -1.878 mmol/L [-3.093; -0.662]95% CI		
	HbA1c <7.0% (yes/no)	63.7%	36.5%	
		Odds ratio of 5.353 [2.105; 13.615]95% CI		
	BMI-SDS	-0.254	-0.208	
		estimated treatment difference -0.047 [-0.153; 0.060]95% CI		

Clinical studies in special populations

This trial was not powered to show differences by subgroups and the number of subjects in the subgroups 10-14 years was low, therefore, all results should be interpreted with caution.

Age

The observed mean changes over time in HbA1c by age group (10-14 years and >14 years) suggest a similar difference between liraglutide and placebo treatment in the two age subgroups.

The difference in the observed mean change from baseline in BMI SDS between liraglutide and placebo treatment appeared to be greater in the subgroup >14 years old than in the subgroup 10-14 years old (the liraglutide subgroup aged >14 had the largest reduction, and the placebo group aged >14 had the smallest reduction, in BMI SDS at week 52).

Basal insulin

The influence of treatment with basal insulin at baseline (yes/no) on the change from baseline in HbA1c was investigated in a pre-specified exploratory analysis. The treatment difference between liraglutide and placebo was larger in the subjects who took basal insulin (in addition to metformin) at baseline than in the subjects who did not. However, in both groups there was a clinically relevant and statistically significant difference on hbA1c.

Analysis of clinical information relevant to dosing recommendations

The clinical pharmacology trial, Trial 1800, provided evidence that the pharmacokinetics and exposure in paediatric subjects aged 10 to 17 years with a body weight ranging between 57 kg and 214 kg were similar to those in adults. Based on an evaluation of tolerability, safety and the exposure levels in Trial 1800, a starting dose of liraglutide 0.6 mg daily, with subsequent weekly increments of 0.6 mg over 2-3 weeks to the maximum dose 1.8 mg daily, was chosen for Trial 3659.

Dose escalation in Trial 3659 was not forced, but dependent both on tolerability (as judged by the investigator) and glycaemic control in the individual subject (as assessed by SMPG). By week 3, 28.6% of the subjects in the liraglutide group were on the 0.6 mg dose, 15.9% were on the 1.2 mg dose and 55.6% were on the 1.8 mg dose. From week 3 and throughout the duration of the trial (up to week 48 in the liraglutide group and up to week 26 in the placebo group), the doses of liraglutide and placebo remained relatively constant

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Trial 3659 was a multinational, multi-centre, randomised, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension in subjects with T2D aged 10−17 years. The main part of the trial consisted of a 26 week double-blind treatment period and a 26-week open-label period.

The design of the trial is acceptable and was in line with the PIP. However, a randomised treatment period of 26 weeks is relatively short for a medicine that is intended to be used for many decades.

The indication as approved in adults was not supported in full by the paediatric data. Liraglutide monotherapy has not been investigated in paediatric subjects. During the procedure, therefore the question was raised to what extent extrapolation (from adult data and/or from the paediatric data available) is possible. In addition, with regard to combined therapy, it should be noted that liraglutide has not been studied in combinations other than metformin ±insulin.

The doses of liraglutide were similar to those used in adults. Given the results of pharmacokinetic trial (Trial 1800), this is acceptable.

Efficacy data and additional analyses

The subjects' mean age was 14.6 years, ranging from 10.0 to 16.9 years at baseline; 30% of the subjects were 10−14 years old (age at end of treatment) and 62% of the subjects were female. The subjects had had diabetes for a mean of 1.9 years. Mean HbA1c was 7.78 % and mean BMI was 33.9 kg/m2 (with a mean body weight of 91.5 kg).

Of the 307 screened subjects, 135 were randomised (1:1); 66 subjects to the liraglutide group and 69 subjects to placebo group. A higher proportion of subjects in the liraglutide group (90.9%) than in the placebo group (84.1%) completed the 26-week double-blind period, and the proportion was higher in the oldest age group. In general, demographics were well balanced between the treatment groups.

In the liraglutide group total and mean exposure to 0.6 and 1.2 mg liraglutide were higher and total exposure to 1.8 mg was lower compared with the placebo group. This reflects the observation that a smaller proportion in the liraglutide group increased their dose to the next level at weeks 1 and 2 compared with the placebo group. The main reason for no dose escalation was a fasting plasma glucose of 6.1 mmol/l or lower. This is acceptable. Less than 10% of the subjects in either treatment group refrained from increasing their dose due to intolerance.

HbA1c

Treatment with liraglutide led to a reduction in HbA1c from baseline to week 26 (-0.64%), with this reduction being maintained in the open-label period up to week 52 (-0.50%); with placebo, HbA1c increased from baseline to weeks 26 (0.42%) and 52 (0.80%). The estimated treatment difference was -1.058 % [-1.653; -0.464]95%CI (p=<0.001). In addition, treatment with liraglutide resulted in consistently greater proportions of hbA1c <7.0% responders (of all categories) than with placebo, both at weeks 26 and 52, with statistically significant odds ratios.

Glucose

Treatment with liraglutide led to a reduction from baseline to week 26 in FPG (-1.08 mmol/L), with this reduction being maintained in the open-label period up to week 52 (-1.03 mmol/L); with placebo, FPG increased from baseline to week 26 (0.80 mmol/L) and week 52 (0.78 mmol/L).

The mean plots of the 7-point SMPG profiles indicated a greater improvement in the liraglutide group than in the placebo group at week 26.

BMI

During the blinded treatment period, treatment with liraglutide did not lead to a significant decrease in BMI SDS compared to placebo (placebo adjusted change in BMI SDS -0.047[CI -0.153; 0.060]; p-value 0.392). This corresponded to a non-significant change in body weight of -1.3 kg [CI -3.013; 0.377]; p=0.128). After deblinding, liraglutide was associated with a significant decrease in BMI SDS of -0.177 [CI -0.327; -0.027]; p-value 0.021. This corresponded to a change in body weight of -2.8 kg [CI -5.014; -0.535]; p=0.015).

Other outcome measures

There were no relevant changes in blood pressure. There were no significant changes in total cholesterol and HDL cholesterol. Greater reductions in VLDL cholesterol and triglycerides were observed with liraglutide than with placebo, with statistically significant differences at week 26.

The observed geometric mean daily dose of basal insulin decreased from 23.3 units at baseline to 22.4 units at week 26 in the liraglutide group and increased from 23.0 units to 27.1 units in the placebo group.

Subgroups

There were no relevant differences by subgroups age and insulin at baseline. However, the number of subjects in the subgroups was low. In adults, efficacy was not significantly different between men and women.

2.3.4. Conclusions on the clinical efficacy

In paediatric subjects treated with metformin with or without basal insulin, six months of treatment with the maximum tolerated dose of liraglutide (0.6, 1.2 or 1.8 mg) was associated with a clinically relevant decrease in HbA1c compared to placebo (-1.1 %). After deblinding, the treatment effect of liraglutide on HbA1c was sustained up to one year.

Compared to placebo, small reductions in BMI SDS were seen with liraglutide at 6 months, corresponding to a treatment difference of -1.3 kg in body weight. This difference was not statistically significant, hence superiority of liraglutide over placebo was not confirmed. After deblinding, the effect of liraglutide on BMI SDS increases corresponding to a treatment difference of -2.8 kg after 1 year. This effect was not statistically significant, but this may be due to the small number of subjects. The point estimate is in line with effects of liraglutide 1.2 and 1.8 mg in the larger adult study LEAD-2 (trial 1572). In addition, in the paediatric study, approximately 30% of the patient were using the lowest dose of liraglutide (0.6 mg).

More subjects in the liraglutide group were not escalated in dose to 1.8 mg due to reach of target or intolerability. There were no marked differences with regards to age, which supports a similar posology of the youngest and oldest age group. There was however a tendency that those with the lowest body weight did not escalate in dose to liraglutide 1.8 mg. The SmPC is now reflecting the influence of body weight on liraglutide plasma concentration. There were no relevant differences by subgroups age and insulin at baseline. However, the number of subjects in the subgroups was low.

The design of the trial was acceptable and in line with the PIP.

2.4. Clinical safety

Introduction

In the evaluation of safety, results from the larger phase 3a trial (Trial 3659) are given primary focus and are described in the following sections. The safety results from the phase 1 trial (Trial 1800) showed that liraglutide (0.3−1.8 mg) was safe and well tolerated in paediatric subjects with T2D aged 10−17 years, with a safety profile similar to that in adults with T2D.

In Trial 3659, all safety endpoints addressed the secondary objective and included AEs, hypoglycaemic episodes, laboratory parameters related to safety, clinical evaluations, height/growth-related parameters and pubertal progression. Medical events of special interest (MESI) are also described. A MESI is an event which, in the evaluation of safety, has a special focus. The protocol-defined areas of interest for MESI reporting in Trial 3659 are listed in Trial 3659. In addition, MedDRA searches based on SMQs, SOCs, HLGTs, HLTs and/or PTs were specified for pre-defined safety areas of interest (Trial 3659). Hypoglycaemic episodes were also classified according to the Novo Nordisk classification (minor hypoglycaemia) and the ADA classification (Trial 3659). The ADA-classified hypoglycaemic episodes included all reported hypoglycaemia.

The AEs, hypoglycaemic episodes and MESI described in this document are treatment emergent. An event (or episode) was defined as treatment emergent if it had an onset on or after the first day of exposure to randomised treatment and no later than 7 days (1 day for hypoglycaemic episodes) after the last day on randomised treatment (in the placebo group, events in the open-label period were defined as treatment emergent although the subjects were only treated with metformin, with or without insulin). All AEs were coded using MedDRA version 21.0. Event rates were calculated as events per 1000 PYE.

All safety parameters were summarised descriptively using the safety analysis set, which included all subjects receiving at least one dose of the investigational product or its comparator. In addition, resting pulse was analysed in the same manner as other supportive secondary endpoints using a PMM with multiple imputations and an MMRM model only including data before initiation of rescue medication.

The safety evaluation mainly refers to the blinded treatment period (weeks 0 to 26) and the entire treatment period (weeks 0 to 52). The open-label treatment period comprised treatment weeks 27−52.

Patient exposure

Of the 307 screened subjects, 135 were randomised (1:1); 66 subjects to the liraglutide group and 69 subjects to placebo group. One subject in the placebo group withdrew before exposure to trial treatment and was excluded from both the full analysis set and the safety analysis set. The majority (118) of the 134 exposed subjects (60 randomised to liraglutide and 58 randomised to placebo) completed treatment in the blinded period. A higher proportion of subjects in the liraglutide (86.4%) versus placebo (66.7%) group completed this period without rescue medication. A total of 56 (84.8%) subjects treated with liraglutide and 53 (76.8%) subjects randomised to placebo completed the entire 52-week treatment period. Of the 10 liraglutide subjects and 16 placebo subjects who discontinued, most were withdrawn for meeting a withdrawal criterion (6 and 8 subjects in the two groups, respectively) followed by non-compliance (4 subjects in each group). One subject randomised to placebo withdrew as a result of an AE and 3 others for a reason of ‘other’. In the liraglutide group, one subject discontinued liraglutide treatment permanently due to an AE of ‘hyperglycaemia’; however the primary reason for withdrawal was non-compliance.

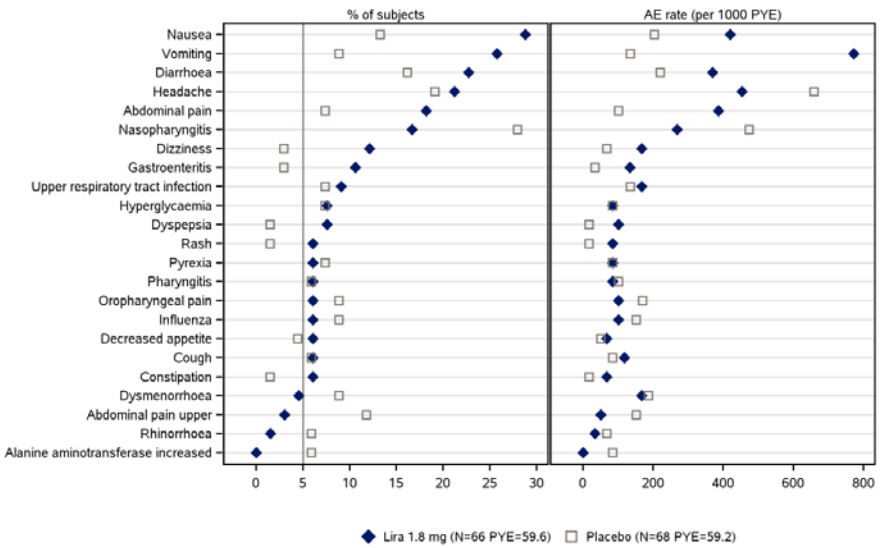
Adverse events

A total of 310 and 230 AEs were reported for the liraglutide and placebo groups, respectively, during the blinded treatment period. The majority of AEs in both treatment groups were non-serious, mild in severity, judged as unlikely to be related to trial product by the investigator and had an outcome of resolved. Although the proportions of subjects who experienced AEs were similar in the liraglutide and placebo groups (78.8% versus 76.5%, respectively), the rate of AEs was higher in the liraglutide group (9992 versus 7330 events per 1000 PYE). The difference in the rate of all adverse events in the liraglutide and placebo groups appeared primarily to be driven by the higher rates of GI AEs (primarily nausea, vomiting, diarrhoea and abdominal pain) in the liraglutide group.

During the entire treatment period, 426 and 321 AEs were reported in the liraglutide and placebo groups, respectively. The majority of these occurred during the blinded treatment period: ~73% (310/426) in the liraglutide group and ~72% (230/321) in the placebo group. The AE pattern during the entire treatment period was very similar to that in the blinded treatment period.

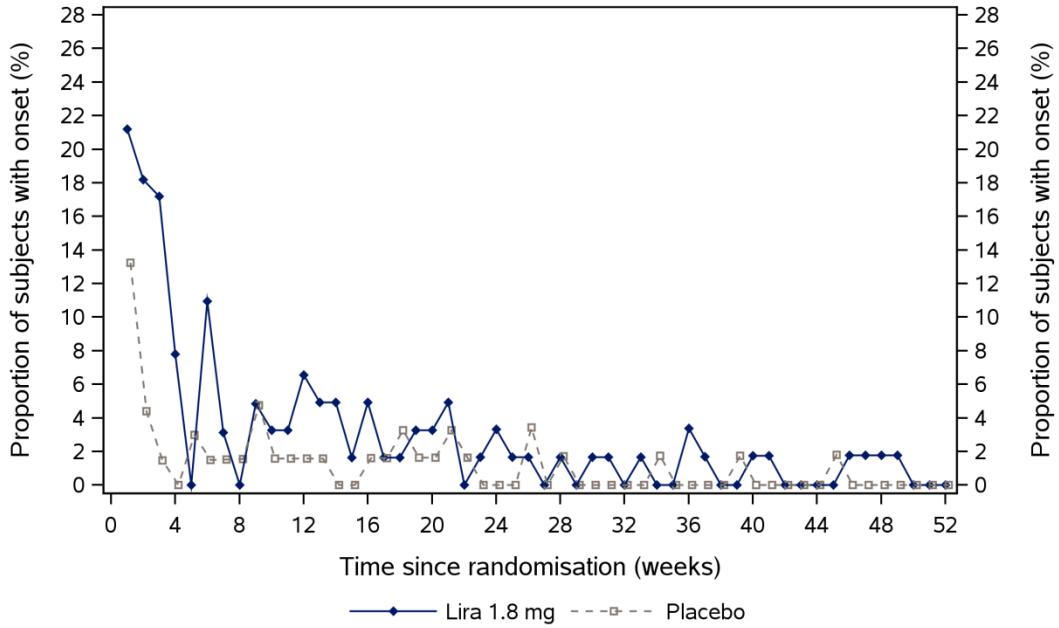
Common adverse events

The nature and frequency of the most commonly reported AEs during the entire treatment period were very similar to those seen during the blinded treatment period. The most common AEs (occurring in ≥5% of subjects) in the liraglutide group during the entire treatment period belonged to the SOC gastrointestinal disorders (Figure 7). 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: 56.1% and 2381 events per 1000 PYE versus 36.8% and 896 events per 1000 PYE, respectively (Trial 3659). This imbalance was mainly driven by the PTs 'nausea', 'vomiting', 'diarrhoea' and 'abdominal pain', all more prevalent in the liraglutide group (28.8%, 25.8%, 22.7% and 18.2% of subjects, respectively). The incidence of all GI AEs was mainly higher in the liraglutide group than in the placebo group during the initial 8 weeks of treatment and then remained comparable between the treatment groups until the end of the entire treatment period (Figure 8). The prevalence of ongoing GI AEs declined in the placebo group during the open-label period (i.e., after treatment allocation unblinding); Trial 3659.



Abbreviations: Lira 1.8 mg: liraglutide all doses. Left panel: % subjects. Solid vertical line indicates a 5% of subjects cut-off. Right panel: AE rate (per 1000 patient years of exposure)

Figure 7 Reported AEs during the entire treatment period



Lira: Liraglutide
Every subject is counted in the week of onset of any gastrointestinal event. Placebo-patients stopped randomized treatment at week 26.

Figure 8 Gastrointestinal adverse events - proportion of subjects with onset of event per treatment week - safety analysis set

Serious adverse event / deaths / other significant events

No deaths were reported in Trial 3659.

A total of 15 SAEs occurred during the entire treatment period. Of the 10 SAEs reported in the liraglutide group during the entire treatment period, the majority of events (7) occurred during the blinded treatment period. The proportion of subjects with SAEs, as well as the event rate, was higher in the liraglutide group than in the placebo group during both the blinded and the entire treatment periods (Table 13). An examination of individual PTs did not reveal clear drivers of this imbalance. In the liraglutide group, the SAEs occurred as single events and were distributed throughout different SOCs with no apparent clustering. In the liraglutide group, all SAEs had an outcome of 'resolved' and the majority were considered unlikely to be related to treatment by the investigator.

Table 13 Summary of serious adverse events during the blinded and the entire treatment periods – safety analysis set

Treatment period	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Blinded	6	9.1	7	226	3	4.4	4	127
Entire	9	13.6	10	168	4	5.9	5	85

Abbreviations: % = percent of subjects with one or more events, 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)

During the blinded treatment period, in the liraglutide group, 2 PTs were within the SOC 'Gastrointestinal disorders' ('diarrhoea' and 'abdominal pain'), whereas the rest of the SOCs each contained a single PT ('glycosylated haemoglobin increased', 'vertigo', 'abscess neck', 'fibroadenoma of breast',

'hyperglycaemia'). In the placebo group, 3 out of 4 SAEs were related to loss of glycaemic control ('diabetes mellitus inadequate control' in 1 subject; 'hyperglycaemia' and 'glycosylated haemoglobin increased' in another subject. The 3 SAEs in 3 liraglutide-treated subjects reported during the open-label treatment period were distributed among different PTs ('viral infections', 'nervous system disorders' and 'scoliosis') and did not change the conclusion of 'no SAE clustering within SOCs' based on the blinded treatment period

Other significant adverse events

Medical events of special interest

The vast majority of MESI in the liraglutide group (9 out of 10 events) and the majority of MESI in the placebo group (2 out of 3 events) were reported during the blinded treatment period). The reported MESI in both groups were primarily single events (Table 14). In the liraglutide group, approximately a third of the events (3 out of 10) related to accidental overdose and suspicion of overdose and another third of the events (3 out of 10) related to elevated clinical laboratory parameters. Three (3) related MESI ('pancreatic enzymes increased', 'overdose' and 'blood creatinine increased') were reported for 1 liraglutide-treated subject. The detected elevations in laboratory parameters led to a suspicion of overdose in this subject (reported as a MESI 'overdose').

Table 14 Medical events of special interest by system organ class and preferred term in the entire treatment period – safety analysis set

	Liraglutide				Placebo			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Total subjects	66				68			
Total Events	6	9.1	10	168	3	4.4	3	51
Investigations	2	3.0	3	50	2	2.9	2	34
Amylase increased	0	0	0	0	1	1.5	1	17
Lipase increased	1	1.5	1	17	0	0	0	0
Pancreatic enzymes increased	1	1.5	1	17	0	0	0	0
Glycosylated haemoglobin increased	0	0	0	0	1	1.5	1	17
Blood creatinine increased	1	1.5	1	17	0	0	0	0
Injury, poisoning and procedural complications	3	4.5	3	50	0	0	0	0
Overdose	1	1.5	1	17	0	0	0	0
Accidental overdose	2	3.0	2	34	0	0	0	0
Eye disorders	1	1.5	1	17	0	0	0	0
Conjunctivitis allergic	1	1.5	1	17	0	0	0	0
Neoplasms benign, malignant and unspecified	1	1.5	1	17	0	0	0	0
Fibroadenoma of breast	1	1.5	1	17	0	0	0	0

Renal and urinary disorders	0	0	0	0	1	1.5	1	17
Proteinuria	0	0	0	0	1	1.5	1	17
Skin and subcutaneous tissue disorders	1	1.5	2	34	0	0	0	0
Rash	1	1.5	2	34	0	0	0	0

Abbreviations: % = percent of subjects with one or more events, 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)

The results of the MedDRA search for AEs related to allergic reactions showed a numerical imbalance in disfavour of liraglutide, although the number of events in both treatment groups was low (liraglutide group: 12 AEs in 10 subjects, placebo group: 5 AEs in 4 subjects).

Adverse event leading to withdrawal

A total of 3 AEs leading to permanent treatment discontinuations were reported (all in the blinded treatment period): 1 AE in the liraglutide group and 2 AEs in 1 subject in the placebo group . All 3 AEs were related to loss of glycaemic control (liraglutide: 'hyperglycaemia', placebo: 'hyperglycaemia' and 'glycosylated haemoglobin increased'). The AE in the liraglutide group occurred on study day 23 and was non-serious, mild in severity and had an outcome of 'not resolved'. The subject was withdrawn from the trial; however, the primary reason for withdrawal was non-compliance. In the placebo group, the subject withdrew from the trial due to the AEs.

Adverse events leading to dose reduction or temporary treatment discontinuation

In total, 2 AEs leading to dose reduction were reported, 1 in each group. Both AEs were reported during the blinded treatment period, were within the SOC gastrointestinal disorders and were considered to be probably related to trial product (liraglutide or placebo) by the investigator. In the liraglutide group, the event leading to dose reduction, 'diarrhoea', occurred on study day 176 and was serious, moderate in severity and had an outcome of 'resolved'. The daily liraglutide dose was reduced from 1.8 mg to 0.6 mg due to the SAE and the subject received the 0.6 mg dose for the remainder of the trial.

Few AEs leading to temporary discontinuation of liraglutide or placebo were reported (8 AEs in 4 subjects in the liraglutide group and 2 AEs in 1 subject in the placebo group), all in the blinded treatment period.

Hypoglycaemic episodes

Both in the blinded and the entire treatment periods, the proportion of subjects experiencing hypoglycaemic episodes (both minor and ADA-classified) and the episode rates, were higher in the liraglutide group than in the placebo group (Table 15). The vast majority of ADA-classified episodes in both treatment groups were classified as either asymptomatic or documented symptomatic. Both the proportion of subjects experiencing asymptomatic and documented symptomatic hypoglycaemic episodes and the episode rates, were higher in the liraglutide group than in the placebo group (Table 16). No severe hypoglycaemic episodes occurred in the liraglutide group. One (1) severe hypoglycaemic episode was reported in a 15-year-old male subject in the placebo group. In addition to placebo, the subject received concomitant daily treatment with metformin 2000 mg and 35 IU of basal insulin (insulin glargine).

Table 15 Summary of hypoglycaemic episodes in the blinded and entire treatment periods – safety analysis set

Treatment period	Liraglutide				Placebo			
Hypo classification	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Blinded								
Minor	12	18.2	18	580	6	8.8	9	287
ADA (total)	23	34.8	92	2965	14	20.6	43	1370
Entire								
Minor	16	24.2	23	386	7	10.3	13	220
ADA (total)	30	45.5	160	2683	17	25.0	63	1065

Minor hypoglycaemia: blood glucose < 3.1 mmol/L (56 mg/dL) with or without symptoms

Abbreviations: % = percent of subjects with one or more events, ADA = American Diabetes Association, 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)

The observed results for hypoglycaemia should be interpreted in the context of better glycaemic control with liraglutide.

Table 16 Hypoglycaemic episodes during the blinded period of treatment – Trial 3659 - summary - safety analysis set

	Lira 1.8 mg				Placebo			
	N	%	E	R	N	%	E	R
Number of subjects	66				68			
PYE	31.03				31.38			
Minor	12	(18.2)	18	580	6	(8.8)	9	287
ADA classification	23	(34.8)	92	2965	14	(20.6)	43	1370
Severe	0				1	(1.5)	1	32
Asymptomatic	17	(25.8)	42	1354	10	(14.7)	16	510
Documented symptomatic	13	(19.7)	37	1193	6	(8.8)	19	606
Relative	1	(1.5)	8	258	0			
Probable symptomatic	1	(1.5)	1	32	2	(2.9)	2	64
Unclassifiable	2	(3.0)	4	129	2	(2.9)	5	159

Abbreviations: Lira 1.8 mg: Liraglutide all doses, Minor: Blood glucose < 3.1 mmol/L (56 mg/dL) with or without symptoms, N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events, R: Rate (number of events divided by patient years of exposure multiplied by 1000), PYE: Patient years of exposure (1 PYE = 365.25 days). The blinded period is from randomisation to week 26 visit, including both days.
nn2211/nn2211-3659/ctr_20180924_e 27SEP2018:13:42:24 - t_hypo_class.sas/t_hypo_class_all_26.t

Insulin use within 24 hours prior to the hypoglycaemic episode was associated with higher rates of minor and ADA-classified episodes in both treatment groups. However, the proportion of subjects experiencing hypoglycaemic episodes, as well as the episode rate, were higher in the liraglutide group than in the placebo group irrespective of insulin use prior to the hypoglycaemic episode (

Table 17).

Table 17 Hypoglycaemic episodes on/off insulin treatment during the blinded and entire period of treatment – Trial 3659 - treatment emergent - summary - safety analysis set

Insulin taken before hypo	ADA classification	Lira 1.8 mg					Placebo				
		n	PYE	N	%	E	R	n	PYE	N	%	E	R
Blinded treatment period													
	Total subjects	66						68					
	Total PYE		31.03						31.38				
No	Minor	54	24.98	7	(13.0)	7	280	59	24.75	3	(5.1)	3	121
	ADA total			18	(33.3)	67	2682			9	(15.3)	18	727
Yes	Minor	16	6.05	5	(31.3)	11	1819	24	6.62	3	(12.5)	6	906
	ADA total			7	(43.8)	25	4134			5	(20.8)	25	3775
Entire treatment period													
	Total subjects	66						68					
	Total PYE		59.63						59.17				
No	Minor	54	47.55	8	(14.8)	8	168	59	42.00	3	(5.1)	4	95
	ADA total			22	(40.7)	125	2629			9	(15.3)	23	548
Yes	Minor	20	12.08	8	(40.0)	15	1242	30	17.17	4	(13.3)	9	524
	ADA total			10	(50.0)	35	2897			8	(26.7)	40	2330

Liraglutide 1.8 mg: liraglutide all doses, n: Total number of subjects, N: Number of subjects with one or more events per category, %: Percentage of subjects with one or more events (calculated from total number of subjects per subgroup), E: Number of events, R: Rate (number of events divided by patient years of exposure multiplied by 1000), PYE: Patient years of exposure (1 PYE = 365.25 days). Insulin treatment is set to yes if it was taken within 24 hours before the hypoglycaemic episode.

Laboratory findings

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

At week 26, the amylase activity in the liraglutide group was slightly higher compared to baseline and compared to that in the placebo group (liraglutide: 55.28 U/L versus placebo: 49.84 U/L). At week 52, the amylase activity in the liraglutide group was also slightly higher compared to that in the placebo group (liraglutide: 53.49 U/L versus placebo: 51.47 U/L).

At weeks 26 and 52, lipase activity in the liraglutide group was higher compared to baseline and compared to that in the placebo group at these time points: week 26 (liraglutide: 29.16 U/L versus placebo: 24.30 U/L), week 52 (liraglutide: 29.33 U/L versus placebo: 26.60 U/L)The clinical significance of pancreatic enzyme elevations with liraglutide is unknown in the absence of other signs and symptoms of pancreatitis.

At week 53 (after the end of the entire treatment period), anti-liraglutide antibodies were detected in 5 (8.5%) subjects in the liraglutide group. The levels of anti liraglutide antibodies in terms of % B/T in the 5 subjects were low (< 5.3). None were cross reacting with native GLP-1 or were in vitro neutralising antibodies. Although the low number of subjects who developed anti-liraglutide antibodies precludes firm conclusions, 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. This is supported by the observation that HbA1c and FPG response patterns were similar in the subjects who developed antibodies and in those who did not.

Vital signs, physical findings, pubertal progression and other observations related to safety

There were no clinically relevant changes from baseline or differences between the liraglutide and placebo groups in resting pulse, physical examination, electrocardiogram, as well as parameters related to pubertal progression and growth/height during the entire treatment period.

Safety in special populations

Aside from the paediatric population, no other subgroups were defined.

Discontinuation due to adverse events

A total of 3 AEs leading to permanent treatment discontinuations were reported (all in the blinded treatment period): 1 AE in the liraglutide group and 2 AEs in 1 subject in the placebo group. All 3 AEs were related to loss of glycaemic control (liraglutide: ‘hyperglycaemia’, placebo: ‘hyperglycaemia’ and ‘glycosylated haemoglobin increased’). The AE in the liraglutide group occurred on study day 23 and was non-serious, mild in severity and had an outcome of ‘not resolved’. The subject was withdrawn from the trial; however, the primary reason for withdrawal was non-compliance. In the placebo group, the subject withdrew from the trial due to the AEs.

Post marketing experience

Liraglutide is not approved for use in the paediatric population.

2.4.1. Discussion on clinical safety

In general, the results of Trial 3659 have demonstrated that liraglutide has a safety profile comparable to that in adults with T2D. However, a randomised treatment period of 26 weeks is relatively short for a drug that is intended to be used for many decades.

Total and mean exposure to the 0.6 mg and 1.2 mg doses was higher in the liraglutide group than in the placebo group. Fewer subjects in the liraglutide group than in the placebo group (38 versus 54, respectively) reached the maximum daily dose of 1.8 mg, hence total exposure to the 1.8 mg dose was lower in the liraglutide group than in the placebo group. There was a tendency toward an increased frequency of adverse events with increasing dose.

Adverse events

Although the proportions of subjects who experienced AEs were similar in the liraglutide and placebo groups (78.8% versus 76.5%, respectively), the rate of AEs was higher in the liraglutide group (9992 versus 7330 events per 1000 PYE). The difference in the rate of all adverse events in the liraglutide and placebo groups appeared primarily to be driven by the higher rates of GI AEs (primarily nausea, vomiting, diarrhoea and abdominal pain) in the liraglutide group.

A total of 3 AEs leading to permanent treatment discontinuations were reported (all in the blinded treatment period): 1 AE in the liraglutide group and 2 AEs in 1 subject in the placebo group.

Serious averse events

The proportion of subjects with SAEs, as well as the event rate, was higher in the liraglutide group than in the placebo group during both the blinded (9.1% vs 4.4%) and the entire treatment periods (13.6% vs 5.9%). There was no SAE clustering within SOCs.

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: 56.1% and 2381 events per 1000 PYE versus 36.8% and 896 events per 1000 PYE, respectively (Trial 3659). 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 proportion of children and adolescents experiencing at least one episode of diarrhoea with liraglutide treatment are markedly higher than in adults treated with liraglutide. This might reflect a higher risk of diarrhoea among children and adolescents, as the proportion of subjects in the placebo group with an episode of diarrhoea is also higher among children than among adults .

Other adverse events

The proportion of subjects with medical events of special interest was higher in the liraglutide group than in the placebo group (during the entire treatment periods 9.1% vs 4.4%).

Both in the blinded and the entire treatment periods, the proportion of subjects experiencing hypoglycaemic episodes and the episode rates, were higher in the liraglutide group than in the placebo group. During the blinded period, ADA defined total hypoglycaemia was 34.8% in the liraglutide group vs. 20.6% in the placebo group. In addition, during the blinded treatment period, the proportion of subjects experiencing documented symptomatic hypoglycaemic episodes (ADA defined) was also higher in the liraglutide group than in the placebo group (19.7% vs. 8.8%). No severe hypoglycaemic episodes occurred in the liraglutide group. The proportion of subjects experiencing hypoglycaemic episodes, as well as the episode rate, were higher in the liraglutide group than in the placebo group irrespective of insulin use prior to the hypoglycaemic episode (OC). This risk is described in the SmPC.

There were no clinically relevant changes from baseline or differences between groups in safety laboratory parameters (haematology, biochemistry, hormones, urinalysis and bone metabolism), although, small increases in geometric mean pancreatic enzyme levels were observed in the liraglutide group. The clinical significance of pancreatic enzyme elevations with liraglutide is unknown, but current evidence does not suggest negative long term effects.

Heart rate increased by 4.23 beats/min during the first 6 weeks and declined to near baseline values by week 52. As increased heart rate is associated with worse cardiovascular outcome, current evidence does not suggest negative long-term effects.

At week 53 (after the end of the entire treatment period), anti-liraglutide antibodies were detected in 5 (8.5%) subjects in the liraglutide group. This is in line with the information in the SmPC (8.6%). 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. HbA1c response patterns were similar in the subjects who developed antibodies and in those who did not.

2.4.2. Conclusions on clinical safety

In general, the results of Trial 3659 have demonstrated that liraglutide has a safety profile comparable to that in adults with T2D. However, a randomised treatment period of 26 weeks is relatively short for a medicine that is intended to be used for many decades. 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.

In contrast to adults, the proportion of subjects experiencing hypoglycaemic episodes were higher in the liraglutide group than in the placebo group, irrespective of insulin use prior to the hypoglycaemic episode. This is different from the findings with liraglutide in adults. In adults, liraglutide was associated with hypoglycaemia in individuals in combination with insulin (or SU), but it was not associated with hypoglycaemia without use of insulin (or SU). This risk is described in the SmPC.

The clinical significance of elevations in pancreatic enzymes, anti-liraglutide antibodies and heart rate increase with liraglutide are unknown, but current evidence does not suggest negative long term effects.

2.4.3. 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.

2.5. Risk management plan

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

The PRAC considered that the risk management plan version 30.1 for liraglutide (Victoza in T2DM and Saxenda in Weight Management) is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 30.1 with the following content:

Safety concerns

Liraglutide in T2DM (Victoza)

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Off-label use, including abuse due to weight-lowering potential

Liraglutide in Weight Management (Saxenda)

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

Pharmacovigilance plan

Liraglutide in T2DM (Victoza)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
NN2211-3965 MTC registry (MTC-22341) Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Protocol submission	28 May 2010
			Final report	15 Sep 2026

Liraglutide in Weight Management (Saxenda)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
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	December 2019
NN8022-4241 PASS Ongoing	In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study	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	November 2019

Risk minimisation measures

Liraglutide in T2DM (Victoza)

Safety concern	Risk minimisation measures
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the***

Safety concern	Risk minimisation measures
	Product Information: None ***Additional risk minimisation measures*** None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Off-label use, including abuse due to weight-lowering potential	***Routine risk communication:*** • The approved indication is described in Section 4.1 of the SmPC and Section 1 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** • By the legal status of the product; prescription only

Liraglutide in Weight Management (Saxenda)

Safety concern	Risk minimisation measures
Important potential risk Neoplasms (including melanoma)	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None

Safety concern	Risk minimisation measures
	Additional risk minimisation measures None
Important potential risk Medullary thyroid cancer (C-cell carcinogenicity)	***Routine risk communication:*** • Nonclinical findings are described in Section 5.3. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL ***Other risk minimisation measures beyond the Product Information:*** None
Important potential risk Pancreatic cancer	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information *Patients with a history of major depression or other severe psychiatric disorders*	***Routine risk communication:*** None proposed ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Concomitant use of other weight lowering products	***Routine risk communication:*** • The lack of data supporting co-administration with other products for weight management is included in Section 4.4 of the SmPC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None proposed ***Other risk minimisation measures beyond the Product Information:*** None
Missing information Off-label use	***Routine risk communication:*** • The approved indication is described in Section 4.1 of the SmPC and Section 1 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:***

Safety concern	Risk minimisation measures
	None proposed ***Other risk minimisation measures beyond the Product Information:*** By the legal status of the product; prescription only

2.6. 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 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

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

2.6.1. 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

T2D is a progressive metabolic disease primarily characterised by abnormal glucose metabolism, resulting in hyperglycaemia. Uncontrolled hyperglycaemia is associated with adverse long-term consequences such as microvascular and macrovascular complications (e.g., retinopathy, nephropathy, neuropathy and cardiovascular disease). The aetiology, pathophysiology and clinical manifestation of T2D in the paediatric population are similar to those in adults.

3.1.2. Available therapies and unmet medical need

The recommended treatment approach for paediatric T2D is similar to that in adults, namely the achievement and maintenance of glycaemic control in order to prevent long-term complications. Given the similar pathophysiology and progression of adult and paediatric T2D, the paediatric treatment guidelines also recommend a step-wise approach starting with lifestyle modifications followed by pharmacologic monotherapy and later by combination therapy. Metformin and insulin are currently the only approved pharmacologic treatment options for paediatric subjects with T2D in most countries. However, more than half of youth with T2D experience a loss of glycaemic control with metformin alone or when combined with lifestyle intervention. Although insulin is highly effective in lowering blood glucose, its acceptance and use by paediatric subjects with T2D may be limited by such drawbacks as weight gain, high risk of hypoglycaemia, complex titration and need for coordination with meals. Given these considerations, there is a medical need to have alternative treatment options for adolescents with type 2 diabetes that optimize diabetes control and reduce complications. Efforts to enrich the currently limited therapeutic armamentarium with newer drugs for youth with type 2 diabetes are welcomed.

The aim of this application was to extend the indication for liraglutide (Victoza) for the treatment of T2D in children and adolescents aged 10 years and above.

3.1.3. Main clinical studies

The pivotal trial 3659 was a multinational, multi-centre, randomised, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension in subjects with T2D aged 10−17 years. The main part of the trial consisted of a 26 week double-blind treatment period and a 26-week open-label period. The design of the trial was acceptable and in line with the PIP.

The subjects' mean age was 14.6 years, ranging from 10.0 to 16.9 years at baseline; 30% of the subjects were 10−14 years old (age at end of treatment) and 62% of the subjects were female. The subjects had had diabetes for a mean of 1.9 years. Mean HbA1c was 7.78 % and mean BMI was 33.9 kg/m2 (with a mean body weight of 91.5 kg).

Of the 307 screened subjects, 135 were randomised (1:1); 66 subjects to the liraglutide group and 69 subjects to placebo group. A higher proportion of subjects in the liraglutide group (90.9%) than in the placebo group (84.1%) completed the 26-week double-blind period.

3.2. Favourable effects

HbA1c

Treatment with liraglutide led to a reduction in HbA1c from baseline to week 26 (-0.64%), with this reduction being maintained in the open-label period up to week 52 (-0.50%); with placebo, HbA1c increased from baseline to weeks 26 (0.42%) and 52 (0.80%). The estimated treatment difference was -1.058 % [-1.653; -0.464]95%CI (p=<0.001). In addition, treatment with liraglutide resulted in consistently greater proportions of HbA1c <7.0% responders (of all categories) than with placebo, both at weeks 26 and 52, with statistically significant odds ratios.

Glucose

Treatment with liraglutide led to a reduction from baseline to week 26 in FPG (-1.08 mmol/L), with this reduction being maintained in the open-label period up to week 52 (-1.03 mmol/L); with placebo, FPG increased from baseline to week 26 (0.80 mmol/L) and week 52 (0.78 mmol/L).The mean plots of the 7-point SMPG profiles indicated a greater improvement in the liraglutide group than in the placebo group at week 26.

Other end points

The observed geometric mean daily dose of basal insulin decreased from 23.3 units at baseline to 22.4 units at week 26 in the liraglutide group and increased from 23.0 units to 27.1 units in the placebo group.

There were no relevant changes in blood pressure. There were no significant changes in total cholesterol and HDL cholesterol. Greater reductions in VLDL cholesterol and triglycerides were observed with liraglutide than with placebo, with statistically significant differences at week 26

3.3. Uncertainties and limitations about favourable effects

The Applicant performed a trial in paediatric subjects (treated with metformin with or without basal insulin). The indication of the SmPC comprises the use of liraglutide as monotherapy when metformin is considered inappropriate (due to intolerance or contraindications) and in addition to other medicinal products for the

treatment of diabetes, and refers for study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, to sections 4.4, 4.5 and 5.1 of the SmPC.

The indication as approved in adults was not supported directly in all respects by available paediatric data. Liraglutide monotherapy has not been investigated in paediatric subjects, but due to the similarities regarding pharmacology, efficacy and adverse events in adolescents and children aged 10 years and above treated with liraglutide on top of metformin, extrapolation to this population regarding monotherapy with liraglutide when metformin is not tolerated or contraindicated was found to be acceptable by CHMP. With regard to combination therapy, it should be noted that liraglutide has not been studied in combination with glucose-lowering agents other than metformin ±insulin, but it should be noted that none of these other glucose-lowering agents are currently approved for a paediatric population.

The doses of liraglutide were similar to those used in adults. Given the results from the pharmacokinetic trial data, this was acceptable. However, the liraglutide dose of 1.8 mg was not used in several cases due to low glucose levels. It is therefore possible that a dose of 1.2 mg liraglutide is sufficient in most of the individuals, and that a dose of 1.8 mg liraglutide is only necessary in a minority of the subjects.

It is uncertain if treatment with liraglutide is associated with reductions in body weight and BMI. During the blinded treatment period, treatment with liraglutide did not lead to a significant decrease in BMI SDS compared to placebo (placebo adjusted change in BMI SDS -0.047[CI -0.153; 0.060]; p-value 0.392). This corresponded to a non-significant change in body weight of -1.3 kg [CI -3.013; 0.377]; p=0.128). After deblinding, liraglutide was associated with a significant decrease in BMI SDS of -0.177 [CI -0.327; -0.027]; p-value 0.021. This corresponded to a change in body weight of -2.8 kg [CI -5.014; -0.535]; p=0.015).

With respect to the effect of liraglutide on HbA1c, there were no relevant differences by subgroups age and insulin at baseline. However, the number of subjects in the subgroups was low. In addition, efficacy was similar in male and female patients.

A higher proportion of subjects in the youngest age group did not complete the trial, and the difference between age groups in the proportion of completers was more pronounced in the liraglutide group than the placebo group, which is a limitation to the favourable effects of liraglutide.

3.4. Unfavourable effects

In general, the results of Trial 3659 have demonstrated that liraglutide has a safety profile comparable to that in adults with T2D.

Adverse events

Although the proportions of subjects who experienced AEs were similar in the liraglutide and placebo groups (78.8% versus 76.5%, respectively), the rate of AEs was higher in the liraglutide group (9992 versus 7330 events per 1000 PYE). The difference in the rate of all adverse events in the liraglutide and placebo groups appeared primarily to be driven by the higher rates of GI AEs (primarily nausea, vomiting, diarrhoea and abdominal pain) in the liraglutide group.

A total of 3 AEs leading to permanent treatment discontinuations were reported (all in the blinded treatment period): 1 AE in the liraglutide group and 2 AEs in 1 subject in the placebo group.

Serious adverse events

The proportion of subjects with SAEs, as well as the event rate, was higher in the liraglutide group than in the placebo group during both the blinded (9.1% vs 4.4%) and the entire treatment periods (13.6% vs 5.9%). There was no SAE clustering within SOCs.

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: 56.1% and 2381 events per 1000 PYE versus 36.8% and 896 events per 1000 PYE, respectively (Trial 3659). 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.

Other adverse events

The proportion of subjects with medical events of special interest was higher in the liraglutide group than in the placebo group (during the entire treatment periods 9.1% vs 4.4%).

Both in the blinded and the entire treatment periods, the proportion of subjects experiencing hypoglycaemic episodes and the episode rates, were higher in the liraglutide group than in the placebo group. During the blinded period, ADA defined total hypoglycaemia was 34.8% in the liraglutide group vs. 20.6% in the placebo group. In addition, during the blinded treatment period, the proportion of subjects experiencing documented symptomatic hypoglycaemic episodes (ADA defined) was also higher in the liraglutide group than in the placebo group (19.7% vs. 8.8%). No severe hypoglycaemic episodes occurred in the liraglutide group. The proportion of subjects experiencing hypoglycaemic episodes, as well as the episode rate, were higher in the liraglutide group than in the placebo group irrespective of insulin use prior to the hypoglycaemic episode.

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

At week 53 (after the end of the entire treatment period), anti-liraglutide antibodies were detected in 5 (8.5%) subjects in the liraglutide group. 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. HbA1c response patterns were similar in the subjects who developed antibodies and in those who did not.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile in paediatric subjects was largely comparable to that in adults with T2D. However, a randomised treatment period of 26 weeks is relatively short for a medicine that is intended to be used for many decades.

The clinical significance of pancreatic enzyme elevations with liraglutide is unknown. Long term effects of liraglutide on the developing pancreas are unknown. As seen in adult patients, anti-liraglutide antibodies were observed in 8.5% of subjects. While this might not have an effect on efficacy, anti-liraglutide antibodies could be still a concern in children. As seen in adult patients, an increase in heart rate was observed. As higher heart rate is known to be associated with worse cardiovascular outcome, the higher heart rate observed in this high risk population might be still of relevance.

In contrast to adults, the proportion of subjects experiencing hypoglycaemic episodes was higher in the liraglutide group than in the placebo group, irrespective of insulin use prior to the hypoglycaemic episode. This is different from the findings with liraglutide in adults. In adults, liraglutide was associated with hypoglycaemia in individuals in combination with insulin (or SU), but is was not associated with hypoglycaemia without use of insulin (or SU).

A higher proportion of subjects in the liraglutide group did not increase dose to the maximal dose of 1.8 mg. The frequency of adverse events by liraglutide dose is therefore unknown.

3.6. Effects Table

Table 16: Effects Table for Victoza® (data cut-off: 30 June 2018)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	Change from baseline at week 26	%	-0.64	+0.42	treatment difference -1.058 % [95% CI 1.653; 0.464](p<0.001)	Trial 3659
BMI	Change from baseline at week 26	SDS	-0.254	-0.208	treatment difference -0.047[95% CI -0.153; 0.060]; p-value 0.392	Trial 3659
Body weight	Change from baseline at week 26	kg	-2.304	-0.986	treatment difference -1.3 kg [95% CI -3.013; 0.377]; p=0.128	Trial 3659
Unfavourable Effects						
AE	During blinded period (26 weeks)	%	78.8	76.5	primarily driven by the higher rates of GI AEs	Trial 3659
SAE	During blinded period (26 weeks)	%	9.1	4.4	no SAE clustering within SOCs	Trial 3659
Hypoglycaemia	ADA defined during blinded period (26 weeks)	%	34.8	20.6	irrespective of prior insulin use	Trial 3659
Amylase	At week 26	U/L	55.28	49.84	no events of pancreatitis	Trial 3659
Lipase	At week 26	U/L	29.16	24.30		Trial 3659

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The Applicant proposed an extension of indication to include treatment of children and adolescents (age 10-17 years) with T2D. The subjects' mean age was 14.6 years and mean BMI was 33.9 kg/m2, suggesting that most of these young patients have severe obesity. Metformin and insulin are currently the only approved pharmacologic treatment options for paediatric subjects with T2D. However, more than half of youth with T2D experience a loss of glycaemic control with metformin alone. Although insulin is highly effective in lowering blood glucose, its acceptance and use by paediatric subjects with T2D may be limited. There is an unmet medical need for these very obese patients when metformin (with or without insulin) does not provide adequate glycaemic control.

Although liraglutide has not been studied in monotherapy in children, extrapolation from adult studies was found to be acceptable by CHMP. With regard to combination therapy, it should be noted that liraglutide has not been studied in combination with glucose-lowering agents other than metformin ±insulin, but none of these other glucose-lowering agents are currently approved for a paediatric population with T2D. This was therefore considered to be adequate by CHMP. In the text of the indication, reference is made to section 5.1 of the SmPC with regard to the combinations and populations studied in trials, where it is stated that liraglutide in paediatric subjects was only investigated in combination with metformin ± insulin. Accordingly,

the posology in section 4.2 of the SmPC specifically reflects that the combination therapy with a sulfonylurea or thiazolidinediones are only valid in adult patients.

In these paediatric subjects (treated with metformin with or without basal insulin), six months of treatment with the maximum tolerated dose of liraglutide (0.6, 1.2 or 1.8 mg) was associated with a decrease in HbA1c compared to placebo (-1.1 %). After deblinding, the treatment effect of liraglutide on HbA1c was sustained up to one year. This effect is clinically relevant and in line with findings in adults.

Compared to placebo, only small reductions in BMI SDS were seen with liraglutide at 6 months, corresponding to a treatment difference of -1.3 kg in body weight. This difference was not statistically significant, hence superiority of liraglutide over placebo was not confirmed. This may be due to the small number of subjects. The point estimate is in line with effects of liraglutide 1.2 and 1.8 mg in the larger adult study LEAD-2 (trial 1572). In addition, in the paediatric study, approximately 30% of the patients were using only the lowest dose of liraglutide (0.6 mg).

There was an increased risk of both asymptomatic and documented symptomatic hypoglycaemic 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, irrespective of insulin use prior to the episode. This risk is now described in the SmPC.

It is uncertain whether a dose of 1.8 mg is necessary in the majority of the children, as based on the dose-response analysis, limited additional benefit in terms of HbA1c decrease was observed between liraglutide doses of 1.2 mg and 1.8 mg. Furthermore, a part of the population did not reach the highest dose due to reaching acceptable glucose values with a lower dose or adverse events.

A double-blind randomised treatment period of 26 weeks is relatively short for a medicine that is intended to be used for many decades. Long-term effects in children may be different from adults due to the fact that their organs are still in a developmental state. Although long-term safety in children is unknown, current evidence does not suggest negative long term effects.

3.7.2. Balance of benefits and risks

Positive effects on HbA1c are in line with what could be expected from data in adults and the adverse events appeared to be acceptable. Weight loss after 26 weeks was not statistically significant, but this may be due to the smaller number of subjects in the paediatric study. The point estimate is in line with effects of liraglutide in adult studies. There was an increased risk of hypoglycaemia irrespective of insulin use prior to the hypoglycaemic episode. This risk is described in the SmPC. The benefit/risk balance is considered positive in these subjects. Furthermore, the benefit /risk is considered positive for monotherapy, as it is accepted that the results from adults with regards to liraglutide monotherapy can be extrapolated to children. As the only approved glucose-lowering agents for paediatric use currently are metformin and insulin, the posology in section 4.2 regarding combination therapy reflects that the combination therapy with a sulfonylurea or thiazalidinediones are only valid in adult patients.

3.8. Conclusions

The overall B/R of liraglutide (Victoza) for the extension of indication to adolescents and children aged 10 years and above is positive.

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 of children and adolescents aged 10 years and above with type 2 diabetes mellitus based on Study NN2211-1800; a Phase 1 clinical pharmacology, multi-centre, randomised, double-blind placebo controlled trial, and Study NN2211-3659; a Phase 3a efficacy and safety, multi-centre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 5.2 of the SmPC are being updated and the Package Leaflet is updated accordingly.
Additionally, in accordance with the excipients guideline from 2017, the MAH took the opportunity to include sodium in SmPC section 4.4 and the Package Leaflet. Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).
An updated RMP version 30.1 was agreed during the procedure.

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Risk management plan (RMP)

The 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/0218/2017 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 8b "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Victoza-H-C-1026-II-49'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 27 June 2019.