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Human Medicines Division

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

Victoza

liraglutide

Procedure no: EMEA/H/C/001026/P46/038

Note

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

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

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1. Introduction

On 20 November 2020, the MAH submitted a completed paediatric study for Victoza, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the ELLIPSE trial (study NN2211-3659) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Victoza (liraglutide) is a human glucagon-like peptide-1 (GLP-1) analogue developed for the treatment of type 2 diabetes mellitus (T2D) with pharmacokinetic properties suitable for once daily injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for liraglutide in combination with metformin

- 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.

2.3.2. Clinical study

Description

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.

Methods

Objective(s)

The objectives of the 1-and 2-year safety follow-up period were to assess any potential long-term effect of liraglutide on growth, pubertal development and general safety.

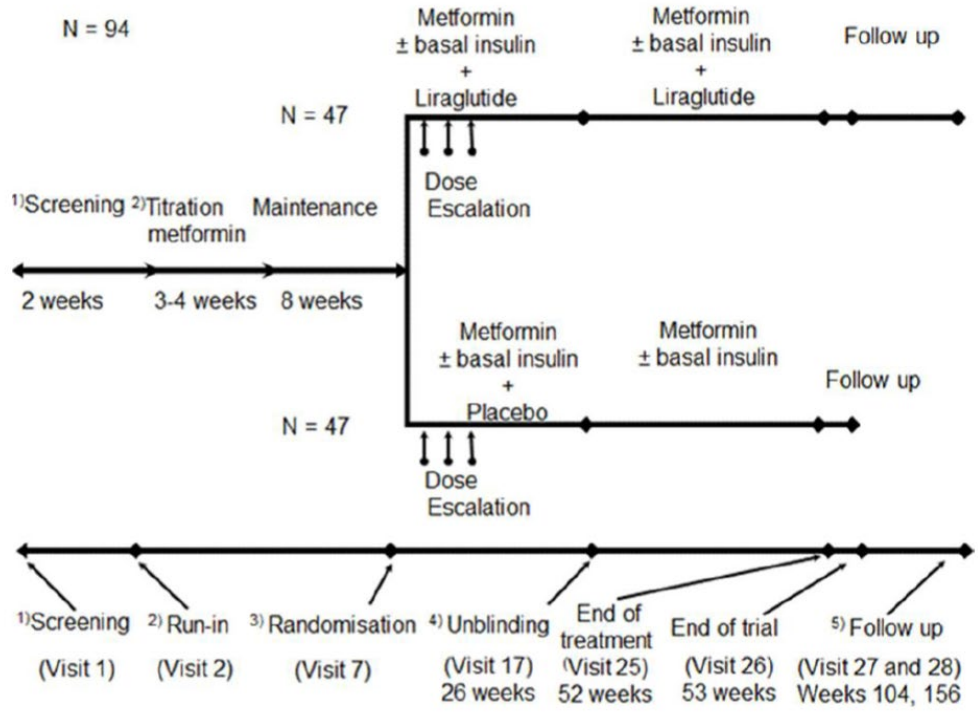
Study design

Trial NN2211-3659 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 consisted of a 2-week screening period followed by an 11−12-week run-in period (3−4 weeks of metformin titration and 8 weeks of metformin maintenance). After the run-in period, subjects who fulfilled the randomisation criteria were randomised 1:1 to either liraglutide or placebo (in combination with metformin with or without basal insulin treatment, on a background of diet and exercise) for 26 weeks. Subjects already treated with a stable metformin dose of ≥ 2000 mg/day for ≥ 56 days at screening could skip the run-in period and advance directly to randomisation. Subjects treated with basal insulin were to be on a stable dose of basal insulin for ≥ 56 days (in addition to being on a stable dose of metformin) in order to advance directly to randomisation.

At the end of the 26-week double-blind treatment period, the treatment allocation was unblinded. Subjects treated with liraglutide in the double-blind period continued their treatment regimen unchanged during the 26-week open-label period. Subjects treated with placebo during the double-blind period discontinued the placebo treatment at week 26, and continued treatment with the maximum tolerated dose (MTD) of metformin (with or without basal insulin) during the open-label period. The maximum duration of the trial, including screening and one week of follow-up (after 52 weeks of treatment) was ≤ 67 weeks. Rescue treatment was allowed for subjects in both treatment groups experiencing confirmed hyperglycaemia. Subjects on rescue treatment were to remain in the trial unless hyperglycaemia persisted, and they met the specified withdrawal criteria.

Subjects treated with liraglutide (active treatment) for more than 3 months were asked to return for follow-up visits one and two years (visit 27 at week 104, and visit 28 at week 156) after the subject completed the open-label part of the trial (after trial drug cessation at week 52).



1) Screening prior to metformin titration

2) Run-in: metformin titration to 2000 mg daily, if possible, or a MTD ≥1000 mg and ≤2000 mg after verification of eligibility according to the inclusion and exclusion criteria. Subjects already treated with a stable dose ≥ 2000 mg of metformin or more for at least 56 days at the time of screening could skip the run-in period and advance directly to randomisation. Subjects who were treated with basal insulin should in addition to the stable dose of metformin have had a stable dose of basal insulin for at least 56 days to advance directly to visit 7.
3) Randomised treatment: Escalation of liraglutide in weekly 0.6 mg increments over 2-3 weeks to 1.8 mg, if possible, or a MTD. Subjects on basal insulin had their insulin dose decreased by 20% at randomisation.
4) All subjects were unblinded at visit 17. Subjects treated with liraglutide continued with unchanged doses of metformin ± basal insulin and their treatment with liraglutide. Subjects treated with placebo discontinued placebo and continued on metformin ± basal insulin.
5) All subjects were to complete visit 26. Subjects treated with liraglutide for more than 3 months were to also complete visits 27 and 28.

Abbreviations: MTD = maximum tolerated dose; N = number of subjects

Rationale

A randomised, double-blind design was chosen in order to limit the bias in the trial conduct and interpretation of the results for the primary endpoint and efficacy/safety endpoints assessed at week 26. The 26-week open-label extension was implemented in order to assess the longer-term safety of liraglutide treatment in the paediatric population.

The 1- and 2-year follow-up for subjects treated with liraglutide for more than 3 months was implemented in order to assess any potential long-term effects on growth, pubertal development and general safety.

Study population/Sample size

Subjects treated with liraglutide for more than 3 months in trial NN2211-3659 were to be included for follow-up visits one and two years after the end of the open-label period (after trial drug cessation at week 52).

Treatments

Liraglutide (Victoza) 6.0 mg/mL, 3mL pre-filled pen injector and the maximum tolerated dose of metformin or placebo.

Outcomes/endpoints

Endpoints to address the objectives of the 1- and 2-year safety follow-up period are:

- AEs and SAEs
- Growth (i.e., height velocity) in cm/year (if subject is still growing)
- Height velocity SDS (if subject is still growing)

Change in:

- height SDS
- pubertal assessment/progression (Tanner staging)
- bone age assessment (x-ray of left hand and wrist).

Results of all other objectives and endpoints for the main part (0-52 weeks) of the trial NN2211-3659 are described in a separate CTR Dated 02 November 2018.

Statistical Methods

This 1-and 2-year safety follow-up period included subjects from the Safety Analysis Set (SAS) from the main part of the trial NN2211-3659, who were treated with liraglutide (active treatment) for more than 3 months.

Efficacy assessments were not evaluated during the 1-and 2-year safety follow up period. Body weight and height measurements were collected in relation to safety.

All safety endpoints were summarised using descriptive statistics.

The safety areas of interest were defined by MAH's Global Safety. At the follow-up visits (visits 27 and 28), sites were to record reported AEs and SAEs (based on the subject's memory) and any associated concomitant medication. In addition, subjects were to be asked at each contact with the trial site staff (site visits and telephone contacts) whether they had any AEs (including any changes in concomitant illness or new illnesses).

Results

Recruitment/Number analysed

Subjects treated with liraglutide (active treatment) for more than 3 months were asked to return for follow-up visits at 1- and 2-year (visit 27 at week 104, and visit 28 at week 156) after the subject completed the open-label period of the trial (after trial drug cessation at week 52). Of the 66 subjects who were randomised and exposed to liraglutide group during the main part of the trial (0-52 weeks), 61 subjects completed more than 3 months of active liraglutide treatment and were eligible for the 1- and 2-year safety follow-up period. Of eligible subjects, 50 subjects (82.0%) attended the 1-year follow-up visit, and 48 subjects (78.7%) attended the 2-year follow-up visit.

	Lira 1.8 mg	
	N	(%)
Randomised	66	
Exposed	66	
Subjects who are eligible for safety follow up (completed more than 3 months of treatment)	61	(100.0)
Subjects who did not attend any follow up visit and no data available	9	(14.8)
Subjects who provided safety follow up data	52	(85.2)
Subjects who did not attend follow up visits but have AE records available	2	(3.3)
Subjects who attended 1 year* follow up (Visit 27)	50	(82.0)
Did not attend the 1 year follow up (Visit 27)	11	(18.0)
Lost to follow up	9	(14.8)
Withdrawal criteria	2	(3.3)
Subjects who attended 2 year** follow up (Visit 28)	48	(78.7)
Did not attend the 2 year follow up (Visit 28)	13	(21.3)
Lost to follow up	11	(18.0)
Withdrawal criteria	2	(3.3)

Lira: Liraglutide, N: Number of subjects, %: Percentages are based on subjects eligible for safety follow up
Lira 1.8 mg refers to subjects who were on any dose of liraglutide for more than 3 months
* 1 year follow up at week 104
** 2 year follow up at week 156

Baseline data

In total, 61 subjects were eligible for the safety follow-up period; of these, 50 subjects attended the 1-year follow-up visit, and 48 subjects attended the 2-year follow-up visit. Key demographic and other baseline characteristics for the trial population that participated in the 1-and 2-year safety follow-up are as follows: The mean age (standard deviation (SD)) at baseline was 14.6 years (1.57), whereas the mean bone age was higher (16.6 years, SD: 2.05). There were more female subjects (53.8%) than male subjects (46.2%). The mean height (SD) at baseline was 1.64 m (0.12), ranging between 1.34 m and 1.92 m. The mean height SDS (SD) at baseline was 0.23 (1.36).

Efficacy results

Although not a pre-specified endpoint, weight was collected at the week 104 and 156 visits. At baseline, the mean weight (SD) for the 52 subjects who provided safety information at follow-up was 91.05 kg (27.19 kg), at week 52 was 88.68 kg (28,77 kg), and on treatment without rescue medication 86.37 kg (28.86 kg). At the 1-year follow-up (week 104), the mean weight (SD) for 50 subjects was 88.56 kg (27.10 kg), and at 2-year follow-up (week 156), the mean weight (SD) for 45 subjects was 85.04 kg (21.75 kg). Although the numbers are small, there appears to be a trend in this cohort for weight maintenance at the 1-year follow-up visit. There also appears in this cohort to be weight loss from end of main part of the trial at 52 weeks to week 156 (at end of 2-years follow-up period).

Safety results

Adverse events

During the 1-and 2-year safety follow-up period, 20 subjects (38.5%) out of 52 subjects who provided safety follow-up data experienced 47 AEs. The majority of the AEs were reported within the SOCs Gastrointestinal disorders and Infections and infestations. The majority of AEs in the follow-up period were nonserious (38 AEs in 18 subjects), mild (30 AEs in 15 subjects) or moderate (15 AEs in 10 subjects) in severity. The majority were judged as unlikely to be related to trial product by the investigator (37 AEs in 16 subjects) and had an outcome of resolved (36 AEs in 17 subjects).

Within the SOC Gastrointestinal disorders, the majority of the subjects (11.5%) reporting AEs covered by HLGT Gastrointestinal signs and symptoms (7 AEs in 6 subjects), including PTs of 'vomiting', 'nausea', 'dyspepsia', 'faecaloma' and 'abdominal pain'.

Within the SOC Infections and infestations, the majority of the subjects (13.5%) reporting AEs covered by the HLGT Infections- pathogen unspecified (12 AEs in 7 subjects).

The SOC Metabolism and nutrition disorders (5 AEs in 5 subjects) and the SOC Psychiatric disorders (3 AEs in 3 subjects) accounted for 9.6% and 5.8% of subjects, respectively.

CHMP comment: Reported adverse events do not differ from the ADRs mentioned in the product information.

No fatal events were reported during the safety follow-up period. Eight (8) subjects (15.4%), experienced 9 SAEs during the 1- and 2- year safety follow-up period. There was no clustering of SAEs in a specific system-organ class (SOC), and the majority of the SAEs had an outcome of resolved (6 SAEs) or resolving (1 SAE). All SAEs were deemed unlikely related to trial product. Only one severe SAE of persistent hyperglycaemia was reported, which had the outcome of 'resolved'.

The most frequently reported moderate AEs in the 1 and 2 year safety follow-up period were events within the SOC infections and infestations (6 AEs in 4 subjects) and GI disorders (3 AEs in 3 subjects). The most frequently reported mild AEs in the 1 and 2 year safety follow-up period were events within the SOC infections and infestations (9 AEs in 6 subjects) and GI disorders (8 AEs in 6 subjects).

As reported in the main part of the trial NN2211-3659 (week 0-52), during the blinded treatment period (week 0-26), the rates of all mild and moderate AEs (including serious and nonserious events) were higher in the liraglutide treatment group (1708 and 8090 events per 1000 PYE, respectively) than in the placebo group (892 and 6311 events per 1000 PYE, respectively). The observed imbalance was mainly driven by the higher rates of mild and moderate GI AEs in the liraglutide group. The most frequently reported mild or moderate AEs in the liraglutide group were events within the SOC gastrointestinal disorders. The findings for all mild and moderate AEs (including serious and nonserious events) in the entire treatment period (week 0-56) were very similar to those in the blinded treatment period, since the majority of these AEs in both groups occurred during the blinded treatment period.

Table 12-4 Serious adverse events during the follow-up period – non-treatment-emergent

Subject	SOC/Preferred term	Severity/Outcome	Relation to liraglutide[a]
	Metabolism and nutrition disorders/Hyperglycaemia	Severe/Recovered	Unlikely
	Infections and infestations/Appendicitis	Moderate/Recovered	Unlikely
	Metabolism and nutrition disorders/Hyperglycaemia	Moderate/Recovered	Unlikely
	Infections and infestations/Subcutaneous abscess	Moderate/Recovered	Unlikely
	Gastrointestinal disorders/Malocclusion	Moderate/Recovering	Unlikely
	Gastrointestinal disorders/Abdominal pain	Mild/Recovered	Unlikely
	Surgical and medical procedures/Fasciotomy	Mild/Recovered	Unlikely
	Psychiatric disorders/Depressive symptom	Mild/Unknown	Unlikely
	Surgical and medical procedures/Metabolic surgery	–/Recovered	Unlikely

[a]Based on the investigator's assessment

During the 1- and 2-year safety follow-up period, 1 subject reported 1 MESI of 'autoimmune thyroiditis' which was mild in severity and had an outcome of not resolved. The AE was reported to have occurred on study day 490. The event was nonserious, mild in severity, judged to be unlikely related to the trial product (liraglutide) by the investigator and had an outcome of 'not resolved'. Upon the cessation of liraglutide treatment, the event onset latency period (event onset date – last date of liraglutide treatment) was approximately 4 months.

CHMP comment:

Causality is assessed as unlikely related to liraglutide and metformin by the investigator. Based on the information provided, it can be considered that this case occurred by incidence and is unlikely related to the study drugs.

Two (2) AEs in 2 subjects ('hyperglycaemia' and 'persistent hyperglycaemia') were reported as SAEs. The SAE 'Persistent hyperglycaemia' was reported as severe, whereas the 'hyperglycaemia' was reported as moderate in severity. The remaining 2 AEs were reported as nonserious (hyperglycaemia and acute hyperglycaemia). Both of these AEs were mild in severity. All 4 AEs were judged to be unlikely related to the trial product (liraglutide) by the investigator. Three (3) AEs had an outcome of 'recovered', whereas the nonserious AE of 'acute hyperglycaemia' had an outcome of 'recovering'.

CHMP comment:

The two cases of hyperglycaemia concerned patients who had besides type 2 diabetes also obesity (BMI 47.2 and 31.8). Both took other anti-diabetic drugs like insulin or sitagliptin and still had high blood glucose levels and a high HbA1c. These patients had high glucose levels over a longer period of time. The investigators considered causality for liraglutide and metformin as unlikely.

In the 1-and 2-year safety follow-up period, the pre-defined MedDRA search for AEs related to depression and suicide/self-injury identified 2 AEs in 2 subjects: 'depression' and 'depressive symptoms'. The event of 'depressive symptom' was reported as serious, whereas the event of depression was reported as nonserious. Both of the events were mild in severity and were judged to be unlikely related to the trial product (liraglutide) by the investigator. The PT of 'depression' for one subject was also identified as 'nonserious AE deemed to be significant in the judgement of the trial study group'.

CHMP comment:

The investigator considered causality with liraglutide and metformin as unlikely for the patient reported with the event 'depressive symptoms'.

Table 12-6 Other significant non-serious AEs

Subject	SOC/Preferred term	Severity/Outcome	Relation to liraglutide[a]
	Reproductive system and breast disorders /Menorrhagia	Moderate/Recovered	Unlikely
	Reproductive system and breast disorders /Oligomenorrhoea	Mild/Recovered	Unlikely
	Psychiatric disorders/Anxiety	Mild/Recovered	Unlikely
	Psychiatric disorders/Depression	Mild/Not Recovered	Unlikely

[a]Based on the investigator's assessment;

Overall, the results of safety follow-up period for AE severity were in line with the main part of the trial (0-52 weeks).

Height/growth

Height SDS, growth (i.e., height velocity) and height velocity SDS were calculated.

Mean (SD) Height SDS at baseline and at week 52 was 0.23 (1.36) and 0.018 (1.37), respectively. A slight decrease in height SDS (mean (SD)) was noted, at week 104 (−0.14 (1.37)) and 156 (−0.22 (1.44)). Height velocity (mean (SD)) at week 104 for 50 subjects was 1.15 (1.78) and at week 156 for 45 subjects was 1.10 (1.50). A slight decrease in height velocity at these two-time points (week 104 and week 156) was also noted compared to week 52, as could be expected in subjects approaching or having reached final height. Height velocity SDS (mean (SD)) at week 104 for 41 subjects was −0.52 (1.47) and at week 156 for 27 subjects was 0.14 (1.16). Mean (SD) height velocity SDS was reported to be slightly increased at week 104 and week 156 compared to week 52. However, no notable difference was observed in change in mean (SD) height velocity SDS from week 52 to week 104 (0.469 (1.36)) and from week 104 to week 156 (0.48 (0.64)).

The safety follow-up results for height SDS, growth (i.e., height velocity) and height velocity SDS are in line with the main part of the trial.

Pubertal assessment/progression

Tanner staging

At weeks 104 and 156, none of the subjects was Tanner stages I or II or III with respect to breast development. Five (31.3%) subjects at week 104 and 3 (21.4%) subjects at week 156 were Tanner stage IV with respect to breast development. At weeks 104 and 156, the majority of female subjects (68.8% and 78.6%, respectively) were Tanner stage V with respect to breast development. Smaller or comparable proportions of female subjects progressed to higher Tanner stages with respect to breast development at weeks 104 and 156 compared to baseline and week 52.

At weeks 104 and 156, the majority of male subjects were Tanner stages IV (35.7% and 23.1%, respectively) or V (57.1% and 69.2%, respectively) with respect to penis development. Smaller proportions of male subjects progressed to higher Tanner stages with respect to penis development at weeks 104 and 156 compared to baseline and week 52.

At weeks 104 and 156, very few female subjects were Tanner Stage IV (12.5% and 15.4%, respectively) and the majority of female subjects were Tanner stages V (81.3% and 84.6%, respectively) with respect to pubic hair development. At weeks 104 and 156, the majority of male subjects were Tanner stages IV (28.6% and 21.4%, respectively) or V (64.3% and 71.4%, respectively) with respect to pubic hair development. Smaller or comparable proportions of subjects progressed to higher Tanner stages with respect to pubic hair development at weeks 104 and 156 compared to baseline and week 52.

Overall, there was no evidence of abnormal pubertal progression at follow-up (weeks 104 and 156) with respect to any of the three assessed areas (breast, penis and pubic hair development).

Testicular volume

At week 104, mean (SD) testicular volume of 15 subjects was 18.93 (5.38) mL and at week 156 mean (SD) testicular volume of 14 subjects was 20.36 mL (5.12). Testicular volume at follow-up period (week 104 and 156) was reported to be slightly increased compared to the observations at baseline and week 52. The mean (SD) change in testicular volume at week 104 with respect to week 52 was 2.54 mL (2.33) and at week 156 with respect to week 52 was 4.15 mL (3.83). The mean change in testicular volume at week 104 and week 156 was 1.50 mL (2.41). Overall, there was no evidence of abnormal pubertal progression with respect to testicular volume.

Bone Age

Bone age was determined for 16 subjects (9 males and 7 females) at week 104 and for 10 subjects (6 males and 4 females) at week 156.

At week 104, a mean bone age for 9 males was 17.22 years (1.99) and for 7 females was 16.29 years (2.14). At week 156, a mean bone age for a total of 6 males was 17.00 years (2.01) and for a total of 4 females was 15.50 years (1.00). A mean bone age (SD) for a total of 16 subjects at week 104 was 16.81 years (2.04) and for a total of 10 subjects at week 156 was 16.40 years (1.84).

At week 104, a mean chronological age (SD) for a total of 23 males was 16.74 years (1.49) and for a total of 27 females was 16.51 years (1.72). At week 156, a mean chronological age (SD) for a total of 22 males was 17.69 years (1.53) and for a total of 26 females 17.47 years (1.75).

The mean (min−max) bone age was similar at baseline (week 0), week 52, week 104, and week 156 and no notable differences were observed in mean bone age at these time points.

CHMP comment:
Growth, pubertal progression and bone development did not show differences compared to the general population in these age groups.

Overall, the results of the 1- and 2-year safety follow-up period are in line with the main part of the trial. During the 1- and 2-year follow-up period:

- The majority of the subjects (17.3%) reporting AEs were within the SOC Gastrointestinal disorders (11 AEs in 9 subjects) followed by the SOC Infections and infestations (15.4% of subjects, 15 AEs in 8 subjects).
- The majority of AEs were nonserious, mild or moderate in severity, judged as unlikely to be related to the trial product by the investigator and had an outcome of resolved (with a minority recovered /resolving, or not recovered/not resolved).
- No fatal events occurred during the follow-up period.
- Nine (9) SAEs were reported in 8 subjects. There was no clustering of SAEs within a SOC and all SAEs had outcome of resolved, except for 2 SAEs (of which, the SAE of malocclusion was reported as 'resolving' and the outcome for the SAE of depressive symptom was reported as 'unknown'). All SAEs were deemed unlikely related to trial product.
- With respect to height: at weeks 104 and 156, there was a small decrease in height SDS. There was also a slight decrease in height velocity, which could be due to subjects nearing or attaining final height.
- Bone age obtained at weeks 104 and 156 indicated that some subjects were near or at the final height.
- No abnormalities in pubertal progression were observed.

2.3.3. Discussion on clinical aspects

This 1-and 2-year safety follow-up period was intended to assess any potential long-term effect of liraglutide on growth, pubertal development and general safety. This report evaluated 1-and 2-year safety data after trial drug cessation at week 52 and included data from subjects who were treated with liraglutide for more than 3 months during the main part of the trial (0-52 weeks). The 1-and 2-year safety follow-up was conducted at 35 sites in 18 countries.

In total, 61 subjects were eligible for the 1-and 2-year safety follow-up period. Fifty (50) subjects (82.0%) attended the 1-year follow-up visit (week 104, visit 27) and 48 subjects (78.7%) attended the 2-year follow-up visit (week 156, visit 28). Safety endpoints were evaluated at both visits.

During 1-and 2-year safety follow-up period, a total of 47 AEs were reported in 20 subjects (38.5%). The majority of the AEs reported were within the SOC Gastrointestinal disorders and the SOC Infections and infestations. The majority of AEs in the follow-up period were nonserious, mild or moderate in severity, judged to be unlikely related to the trial product by the investigator and had an outcome of 'resolved'.

No fatal events were reported during the 1-and 2-year safety follow-up period. Eight (8) subjects treated with liraglutide for more than 3 months in the main part of the trial experienced 9 SAEs in the follow-up period. Of these 9 SAEs, one was severe, and the remaining 8 were of mild or moderate in severity. All SAEs were deemed unlikely related to trial product. There was no clustering of SAEs in a specific SOC. All SAEs had an outcome of resolved, except for 2 SAEs (of which, the SAE of malocclusion was 'resolving' and the outcome for the SAE of depressive symptom was reported as 'unknown'). During the 1-and 2-year safety follow-up period, one MESI of autoimmune thyroiditis which was mild in severity and had an outcome of resolved was reported in one subject.

The results for height parameters are consistent with a cohort that had a mean bone age at week 156 of 17.00 years for boys and 15.50 years for girls, indicating that some subjects were approaching or had achieved their final height by the end of the 2-year follow-up period. A slight decrease in height SDS (mean (SD)) was noted, at week 104 (-0.14 (1.37)) and 156 (-0.22 (1.44)). A slight decrease in height velocity at these two-time points was also noted, as could be expected in subjects approaching or having reached the final height.

With respect to pubertal development of subjects in the safety follow-up period: at the end of the 1-and 2-year safety follow-up period, the majority of female subjects were Tanner stage V with respect to breast development and pubic hair development and the majority of male subjects were Tanner stage V with respect to penis development and pubic hair development. There was no evidence of abnormal pubertal progression. In the 1-and 2-year follow-up period, there were no clinically relevant changes in pubertal progression (i.e., Tanner staging) and in growth/height. The results of these parameters during 1 and 2 follow-up period were in line with the main part of the trial (baseline to week 52).

No notable differences were observed in mean bone age at week 104 and week 156 compared to baseline and week 52. Overall, the mean bone age at 1-and 2-year safety follow-up period was in line with the main part of the trial.

Although not a pre-specified endpoint, weight was collected at the week 104 and 156 visits. There appears to be a trend for weight maintenance at the 1-year follow-up visit with a small difference in mean weight compared to week 52. There also appears in this cohort to be some weight loss from the end of main part of the trial at 52 weeks to week 156 (at the end of 2-years follow-up period).

Overall conclusions

- Following exposure of paediatric subjects with T2D with liraglutide for more than 3 months during the main part of the trial, the results from the 1-and 2-year safety follow-up period did not reveal any new apparent safety concerns with respect to: AEs and SAEs, growth (height velocity), pubertal development (by Tanner staging) or bone age.
- Eight (8) subjects treated with liraglutide in the main phase, experienced 9 non-treatment emergent SAEs in the follow-up period with no clustering in any SOC.

- Weight was maintained at week 104, with an observed mean weight loss demonstrated at week 156 (non-pre-specified endpoint).

3. Rapporteur's CHMP overall conclusion and recommendation

The MAH has submitted the results of the long-term extension of a double-blind study of liraglutide with or without metformin in children aged 10-17 years. Efficacy was determined in the main study. Long-term safety did not reveal new safety issues. Most of the reported adverse events are included in the product information, and several single cases, such as autoimmune thyroiditis are considered unlikely related to liraglutide or metformin.

Growth parameters and pubertal assessment did not show differences compared to the general population of these age groups.

Based on the results of among others the main study, the indication of liraglutide was previously extended to children of 10 years and older (procedure EMEA/H/C/001026/II/0049).

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Not applicable.