EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2023
EMA/CHMP/21654/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trulicity

International non-proprietary name: dulaglutide

Procedure No. EMEA/H/C/002825/II/0065

Note

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

Table of contents

List of abbreviations

Term	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
Cmax	maximum observed drug concentration
CSR	clinical study report
CV	cardiovascular
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ETD	estimated treatment difference
FBG	fasting blood glucose
GCP	good clinical practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IFU	Instructions for Use
ITT	intent-to-treat
KA	absorption rate constant
LDL	low-density lipoprotein
LS	least squares
LSC	Lilly Search Categories
MedDRA	Medical Dictionary for Regulatory Activities: a standard coding terminology for adverse events used globally in compliance with International Council for Harmonisation guidelines.
nGLP-1	native GLP-1
PD	pharmacodynamic(s)
PG	plasma glucose
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PSP	paediatric study plan
PT	preferred term

QTcB	corrected time from the start of the Q wave to the end of the T wave interval – Bazett formula
QTcB	corrected time from the start of the Q wave to the end of the T wave interval – Fridericia formula
RA	receptor agonist
SAE	serious adverse event
SC	subcutaneous
SDP	single-dose pen
SDS	standard deviation score
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SMQ	Standardised MedDRA query
TE	treatment-emergent
TEAE	treatment-emergent adverse event
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 27 May 2022 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 type 2 diabetes mellitus (T2DM) in children and adolescents aged 10 to less than 18 years based on final results from study H9X-MC-GBGC; this is a phase 3, double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open label extension to evaluate safety. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0409/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0409/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0409/2021.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise   Co-Rapporteur: Ondřej Slanař

Timetable	Actual dates
Submission date	27 May 2022
Start of procedure	16 July 2022
CHMP Rapporteur preliminary Assessment Report	8 September 2022
PRAC Rapporteur preliminary Assessment Report	16 September 2022
CHMP Co-Rapporteur Critique	21 September 2022
PRAC members comments	21 September 2022
Updated PRAC Rapporteur Assessment Report	22 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 October 2022
Request for supplementary information (RSI)	13 October 2022
CHMP Rapporteur(s) (Joint) preliminary response Assessment Report	19 December 2022
PRAC Rapporteur preliminary response Assessment Report	3 January 2023
PRAC members comments	4 January 2023
Updated PRAC Rapporteur response Assessment Report	5 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur(s) (Joint) response Assessment Report	n/a
Opinion	26 January 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Trulicity (dulaglutide) is currently approved for the treatment of type 2 diabetes mellitus in adults.

The modified wording of the indication will extend the use of dulaglutide to children and adolescents aged 10 to less than 18 years with T2DM and is proposed by the applicant as follows:

Type 2 Diabetes Mellitus
Trulicity is indicated for the treatment of ~~adults~~ **patients 10 years and above** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
• as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
• in addition to other medicinal products for the treatment of diabetes.
For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Proposed paediatric dosing
The starting dose for paediatric patients 10 years and above is 0.75 mg once weekly. If needed, the dose can be increased to 1.5 mg once weekly after at least 4 weeks. The maximum dose is 1.5 mg once weekly.

Epidemiology

The incidence of T2DM in children and adolescents is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100,000.

Biologic features

Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA). In Phase 3 studies in adults, once weekly subcutaneous injection of dulaglutide (both 0.75 mg and 1.5 mg) was associated with clinically relevant long-term decreases in glucose concentration (as measured by HbA1c) and body weight, low risk of hypoglycemia, low risk of immunogenicity, and no new safety observations compared to the approved agents from the GLP-1 RA class (Edwards and Minze 2015).

Because of the pathophysiological similarities between type 2 diabetes mellitus (T2DM) in adults and children and adolescents aged 10 to less than 18 years, it is hypothesized that dulaglutide will also have efficacy in this paediatric population with a similar safety profile.

Diagnosis

Four diagnostic tests for type 2 diabetes mellitus are currently recommended, including measurement of fasting plasma glucose, 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT), HbA1c and a random blood glucose in the presence of signs and symptoms of diabetes.

People with fasting plasma glucose values of ≥7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), HbA1c ≥ 6.5% (48 mmol/mol) or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes (WHO 2019).

Management

The recommended treatment for paediatric type 2 diabetes is similar to that in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise, followed by the use of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

For a long time, the only two approved treatment options for paediatric patients with type 2 diabetes in most countries were metformin and insulin. Recently, additional treatment options have become available in the EU for children and adolescents aged 10 to less than 18 years with type 2 diabetes, e.g. the GLP-1 receptor agonist liraglutide (Victoza), exenatide extended-release once-weekly injection (Bydureon) and the SGLT-2 inhibitor dapagliflozin (Forxiga).

2.1.2. About the product

Dulaglutide (Trulicity) is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist with 90% amino acid sequence homology to endogenous human GLP-1 that exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying and inhibition of appetite/ weight loss.

Dulaglutide received initial marketing authorization on 18 Sept 2014 in the US and on 21 Nov 2014 in the EU as a once-weekly SC injection to improve glycemic control in adult patients with T2DM.

One of the post-marketing requirements received with the initial approval was to conduct a study on the efficacy, safety and PK/PD of Trulicity for treatment of T2DM in paediatric patients aged 10 to less than 18 years.

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

The following Table summarizes the non-clinical and clinical studies of the of the paediatric investigation plan (PIP) that contributed data to the present application of Trulicity (dulaglutide) for the treatment of type 2 diabetes mellitus in children and adolescents aged 10 to less than 18 years.

Table 1: Summary of studies in the paediatric investigation plan (PIP)

PIP Measure	Application reference in which PIP results are included and status	Dossier location of PIP results
Study 1 Development of a pre-filled pen for subcutaneous use.	Partial PIP compliance check, ref. EMEA-C2-000783-PIP01-09-M05 Compliance assessment compete	eCTD sequence 00149; Module 5.3.5.4: Other Study Reports; Human Factors Engineering Reports
Study 2 Juvenile toxicity study to evaluate potential effects on sexual maturation, reproductive function, and neurobehavioral development and function in immature rats exposed to dulaglutide.	Partial PIP compliance check, ref. EMEA-C2-000783-PIP01-09-M05 Compliance assessment compete	eCTD sequences 00014 and 00149; Module 4.2.3.5.4: Studies in which the offspring (juvenile animals) are dosed and/or further evaluated; WIL-353304
Study 3 Comparative analysis of the tumerigenic potential of dulaglutide versus liraglutide. Comparative analysis of affinity (IC50) and potency (EC50) for the GLP-1 receptor binding of dulaglutide versus liraglutide.	Partial PIP compliance check, ref. EMEA-C1-000783-PIP01-09-M02 Compliance assessment compete	eCTD sequence 00149; Module 4.2.3.7: Other Toxicity Studies; Lira-Dula Comparison Report
Study 4- H9X-MC-GBGC Double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open-label extension to evaluate safety.	Full PIP compliance check, ref. EMEA-C-000783-PIP01-09-M06 Compliance assessment ongoing, submitted 14 April 2022	eCTD sequence 00149; Module 5.3: Clinical Study Reports

Scientific advice from the EMA's Paediatric Committee (PDCO) was obtained on the paediatric phase 3 study (H9X-MC-GBGC) during their review of the paediatric investigation plan (PIP Number: EMEA-000783-PIP01-09-M06).

2.1.4. General comments on compliance with GCP

The paediatric Study H9X-MC-GBGC was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical guidelines, the ICH Good Clinical Practice (GCP) guideline [E6] and applicable laws and regulations. Assessment of the paediatric Study H9X-MC-GBGC did not reveal concerns regarding GCP non-compliance.

2.2. Non-clinical aspects

2.2.1. Introduction

The dulaglutide non-clinical program undertaken to support the clinical trials and the marketing authorization in paediatric patients was designed prior to the finalization of the ICH S11 guideline "Nonclinical safety testing in support of development of paediatric pharmaceuticals" (ICH 2020); however, the need for, and design of, the juvenile rat toxicity study is consistent with the principles in the final guideline. There were no findings in the non-clinical data package that raised special concerns for the paediatric development except for potential effects on learning and memory in a rat pre- and postnatal development (PPND) study. In that study, memory deficits in F1 female rats were observed. To support paediatric clinical trials and the consequential MAA for children with type 2 diabetes mellitus from 10 to less than 18 years of age, a rat juvenile toxicity study was conducted in accordance with the agreed measures listed in the PIP. In addition to the juvenile toxicity study, a comparative analysis of dulaglutide versus liraglutide with respect to tumorigenic potential was performed as specified in the PIP. The juvenile toxicity study was performed in accordance with Good Laboratory Practice (GLP) regulations and conducted in a country (United States) that is a signatory to the Organisation for Economic Cooperation and Development (OECD) mutual acceptance of data (MAD) agreement and at a laboratory that is a member of the national GLP compliance program.

2.2.2. Pharmacology

N/A

2.2.3. Pharmacokinetics

N/A

2.2.4. Toxicology

Carcinogenicity

As specified in the PIP, a comparative analysis of the tumourigenic potential of dulaglutide and liraglutide was performed (Report Lira-Dula comparison).

Due to the fact that direct comparisons were not tested experimentally, this analysis reviewed publicly available data with respect to the effects of dulaglutide and liraglutide. Both dulaglutide and liraglutide have similar potency in terms of activating the human GLP-1 receptor. Both dulaglutide and liraglutide cause an increase in thyroid C-cell tumours in rats; however, when assessed in relation to relative therapeutic exposure, dulaglutide has a slightly reduced response in C-cell adenomas and carcinomas. Key findings from the comparative analysis included:

<u>*In-Vitro* Receptor Binding</u>

- Dulaglutide binds to the human GLP-1 receptor with a Ki of 4.2 nM, compared to the native GLP-1 (7-36)-NH2 with a Ki of 0.388 nM.

- Liraglutide binds to the GLP-1 receptor with an IC_{50} of 0.52 nM in the absence of serum albumin. In the presence of 2% human serum albumin, the IC_{50} of liraglutide is reduced to 18 nM. The native GLP-1 peptide was not described as control in these experiments.

- Based on the fact that native GLP-1 binding data were not available from the liraglutide evaluation, dulaglutide and liraglutide cannot be compared with respect to their ability to bind the human GLP-1 receptor.

In-Vitro Receptor Activation

- Dulaglutide has demonstrated full agonist activity with an EC_{50} of 12.5 pM and a standard error of mean of 2.5 pM in a recombinant reporter gene system.

- For liraglutide, the EC_{50} of cAMP accumulation in cell-based assays is described as 5 to 60 pM, versus 1 to 2 pM for the native GLP-1 peptide. In a similar assay, liraglutide displayed an EC_{50} of 61.0 ± 7.1 pM, versus 55 ± 19 pM for native GLP-1.

- Based on the evaluation of two independent series of experiments, both using native GLP-1 as control, dulaglutide and liraglutide seem to have similar potency of activating the human GLP-1 receptor.

Rodent Carcinogenicity Data

- Both liraglutide and dulaglutide produced preneoplastic and neoplastic lesions of the thyroid C-cells in rats.

- The dose-response curve in rats for thyroid C-cell neoplasms with dulaglutide appears to be right-shifted relative to liraglutide as indicated by an achievement of a NOAEL for tumourigenicity with dulaglutide (0.5-fold safety margin), whereas a NOAEL for neoplastic lesions with liraglutide was not established (< 0.5-fold safety margin). Furthermore, liraglutide produced C-cell carcinomas at clinically relevant exposures (< 0.5-fold the human plasma exposure) unlike dulaglutide (58-fold the human plasma exposure).

- Direct comparisons in mice are not available as liraglutide was tested in a 104-week traditional mouse carcinogenicity study and dulaglutide was tested in a 6-month rasH2 study. In these different mouse models, liraglutide produced injection site fibrosarcomas and thyroid C-cell lesions, whereas dulaglutide did not cause any increases in tumour incidence; however, mice in all dulaglutide groups were observed to have a minimal cytoplasmic hypertrophy based on the immunohistochemical staining for calcitonin. Therefore, it is important to note that although a biologic effect was detected in thyroid C-cells, the systemic exposures in this study decreased over time, potentially due to an anti-drug antibody response. These reductions in systemic exposure likely limited the utility of the mouse model to characterize the effects of dulaglutide and compare it to liraglutide.

Reproduction toxicity

In the Study WIL-353304, potential adverse effects of long-term subcutaneous administration of dulaglutide on neonatal growth and development in juvenile male and female rats when treated from Postnatal Day (PND) 7 through PND 91 were evaluated.

Dulaglutide was administered by subcutaneous injection every third day to juvenile male and female Crl:CD (SD) rats. Animals in the main study phase were dosed from PND 7 through 91 and animals in the sexual maturation phase were dosed from PND 7 through the day prior to euthanasia (PND 39 for females and PND 47 for males). Dose levels were 0.5, 2.0, and 7.0 mg/kg administered at a dose volume of 1 mL/kg. Additional animals were assigned to the toxicokinetic phase. Blood samples for toxicokinetic evaluation were collected at appropriate intervals on PND 7 and 91 and blood samples for possible immunogenicity evaluation were collected on PND 91.

The vehicle control, 0.5, and 2.0 mg/kg groups were pair-fed based on the mean food consumption of the 7.0 mg/kg group. The goal of pair feeding was to control for the anorexigenic effects of dulaglutide on food consumption and secondarily body weight and body weight gain and their influence on sexual maturation of the offspring.

Endpoints included developmental landmarks, sensory function, neurobehavioral testing, sexual maturity, reproductive performance, hormone evaluation (follicle stimulating hormone, luteinizing hormone, testosterone, oestradiol, growth hormone), and anatomic pathology.

Following the end of dosing, all surviving animals in the main study phase were mated for reproductive functional assessment.

Table 2: Subcutaneous Repeat-Dose Study in juvenile rats.

Study type/ Study ID/ GLP	Species; Number group	Route & dose (mg/kg)	Dosing period	Major findings	NOAEL (mg/kg/day)
Study WIL-353304 Juvenile rats GLP Adult rats for positive control	juvenile male and female Crl:CD(SD) Rat **main study phase:** 25/sex/ group **sexual maturation phase:** 20/sex/ group **toxico-kinetic phase:** 45 pups/sex/ group	s.c. injection: 0, 0.5, 2.0, and 7.0 maleate 1mg	every third day **main study phase:** PND 7 through 91 **sexual maturation phase:** PND 7 through the day prior to euthanasia (PND 39 for females and PND 47 for males)	**2 and 7 mg**: ↓ initial bw gains/ bw loss in both phases **7 mg:** ♀: lower mean ages of attainment of vaginal patency Lower mean ages of first estrus ♂ : higher levels of serum luteinizing hormone and growth hormone, higher levels of serum estrogen	NOAEL for developmental toxicity: 2 systemic toxicity, neurotoxicity, reproductive toxicity, and embryonic toxicity: 7

Pharmacologically mediated, transient reductions in body weight occurred following each dose administration. As a result of an initial mean body weight loss noted in the 7.0 mg/kg group for both phases, the mean body weights were lower than the vehicle control group generally during the pre-weaning period of dose administration (PND 7-19). Mean body weights were similar to or higher than the vehicle control group at 7.0 mg/kg thereafter. Mean body weights in the 0.5 and 2.0 mg/kg group males and females were generally similar to the vehicle control group throughout the entire treatment period. Because the transient and cyclic nature of the reductions in mean body weight gains had no sustained effect on mean body weights, these changes were not considered adverse.

There were no dulaglutide-related effects on survival at any dose level. There were unscheduled deaths in all groups including the vehicle control. Because there was no dose-response, all of the unscheduled deaths were considered incidental.

No dulaglutide-related clinical observations were noted for surviving males and females in the main study phase or sexual maturation phase at any dose level at the daily examinations or approximately 1 hour following dose administration.

Based on the lack of adverse dulaglutide-related effects on survival, clinical observations, body weights, food consumption, organ weights, and histopathology noted at any dose level in the main study phase or sexual maturation phase, the no-observed-adverse-effect level (NOAEL) for male and female systemic toxicity was considered to be 7.0 mg/kg, the highest dose level evaluated.

A dulaglutide-related decrease in mean age at attainment of vaginal patency was noted at 7.0 mg/kg for both phases; a corresponding decrease in the mean age at first estrus along with increased serum growth hormone levels were noted in the 7.0 mg/kg group females of the sexual maturation phase.

In addition, dulaglutide-related higher levels of serum luteinizing hormone and growth hormone were noted in sexually mature males and higher levels of serum estrogen were noted in sexually and non-sexually mature males at 7.0 mg/kg in the sexual maturation phase; however, there were no correlative effects on organ weights or microscopic changes observed.

Based on these results, the NOAEL for developmental toxicity was considered 2.0 mg/kg.

No dulaglutide-related effects were observed for motor activity on PND 21 and 61, auditory startle responsiveness on PND 22 and 62, or learning and memory assessments on PND 70.

Male and female mating, fertility, and copulation/conception indices were unaffected by dulaglutide administration at all dose levels in the main study phase. In addition, there were no dulaglutide-related effects on spermatogenic endpoints, estrous cyclicity, or pre-coital intervals at any dose level.

No adverse effects on neurobehavioral endpoints, reproductive performance, or intrauterine survival of the embryos were observed at any dose level for animals in the main study phase. Therefore, the NOAEL for developmental neurotoxicity, reproductive toxicity, and embryonic toxicity was considered 7.0 mg/kg.

Toxicokinetics

Subcutaneous administration of dulaglutide to juvenile male and female rats resulted in systemic exposure to dulaglutide. In terms of AUC_{last} and C_{max}, exposure to dulaglutide increased approximately dose-proportionally over the 0.5 to 7.0 mg/kg range on PND 7 and 91 (see Table 3).

Accumulation of dulaglutide was observed in plasma following dosing every 3 days for 12 weeks. No obvious gender differences in dulaglutide exposure between male and female animals were observed.

Table 3: Mean Toxicokinetic Parameters of dulaglutide determined in Juvenile Rats Following dosing every 3 days for 12 weeks.

Dose (mg/kg):	0.5	2.0	7.0	0.5	2.0	7.0
Gender		Males			Females	
PND 7						
AUC_{last} ($\mu g \cdot hr/mL$)	10.8	43.0	216	11.4	44.7	186
C_{max} ($\mu g/mL$)	0.632	2.12	12.3	0.518	1.65	8.20
T_{max} (hr)	4	4	12	12	12	4
PND 91						
AUC_{last} ($\mu g \cdot hr/mL$)	33.6	131	512	36.4	124	581
C_{max} ($\mu g/mL$)	1.11	3.81	14.60	1.20	3.39	15.8
T_{max} (hr)	12	12	12	12	12	12

Abbreviations: AUC_{last} = area under curve from 0 to T_{last} (72 hours postdosing), C_{max} = maximum plasma concentration, and T_{max} = time of maximum plasma concentration.

Table 4: Exposure Multiples for Twice-Weekly Subcutaneous Injection of dulaglutide in Pivotal Juvenile rat Toxicology Studies

Species Dose	$AUC_{0-\tau, ss}$ ($\mu g \cdot hr/mL$)	C_{ave} ($\mu g/mL$)	Exposure Multiple[a] Dose (mg/week)	
			1.5	3.0
Human Pediatric				
0.75 mg/week	4.17[b]	0.0248	–	–
1.5 mg/week	8.35[b]	0.0497	–	–
Juvenile Rat Toxicity (Study WIL-353304)[q]				
7.0 mg/kg/every 3 days[r]	547	7.60	306	153
2.0 mg/kg/every 3 days[s]	128	1.78	71.7	35.8
0.5 mg/kg/every 3 days	35.0	0.486	19.6	9.78

[a] AUC-based exposure multiple = ($AUC_{0-\tau}$ in animals ÷ τ in animals) ÷ ($AUC_{0-\tau}$ in humans ÷ τ in humans). τ is 96 hours in rats and monkeys; 72 hours in juvenile rats and adult rabbits; and 168 hours humans.
[r] NOAEL for systemic toxicity, developmental neurotoxicity, reproductive toxicity, and embryonic toxicity.
[s] NOAEL for sexual maturation.

2.2.5. Ecotoxicity/environmental risk assessment

The Applicant has justified that dulaglutide is exempt from an environmental risk assessment by its protein nature, which is agreed. As there is no expected environmental exposure and because there is no concern that dulaglutide (a recombinant protein) is persistent, bioaccumulative and toxic, a Phase II assessment is not necessary and environmental studies with dulaglutide are not required. The results of Phase I assessment yielded a PECsw of 0.003 µg/L, which is below the limit triggering Phase II. The use of dulaglutide in humans will not result in a risk to environmental organisms.

2.2.6. Discussion on non-clinical aspects

The comparative analysis of the tumourigenic potential of dulaglutide and liraglutide concluded that duaglutide and liraglutide have similar potency of activating the human GLP-1 receptor. In terms of a carcinogenic potential it was stated that based on available rat carcinogenicity studies dulaglutide might be less tumourigenic than liraglutide as no NOEL for neoplastic findings could be established for liraglutide while a NOAEL of 0.05 mg/kg/day was set for dulaglutide. The NOAEL for dulaglutide provides evidence of a threshold dose and a non-genotoxic mode of action. Overall, it can be agreed that dulaglutide does not have a higher potency in terms of receptor activation and carcinogenicity (thyroid) as compared to liraglutide. It also has to be noted that weight of evidence suggests the rodent tumours may not be predictive of an increased risk of thyroid C-cell disease in T2DM subjects on GLP-1 receptor agonist therapy. The clinical program for dulaglutide included thyroid safety and serial monitoring of serum calcitonin. So far, there was no evidence of an effect on thyroid C-cell disease (also refer to the section on Clinical Safety below).

Every third day subcutaneous administration of dulaglutide to juvenile male and female rats up to 7.0 mg/kg led to lower mean ages of attainment of vaginal patency, lower mean ages of first oestrus in the female rats and higher levels of serum luteinizing hormone and growth hormone and higher levels of serum oestrogen. Based on these sexual maturation findings for developmental toxicity, the NOAEL was set to 2.0-mg/kg.

Pharmacologically mediated, transient reductions in body weight occurred following each dose administration. However, no adverse effects on systemic toxicity, neurobehavioral endpoints, reproductive performance, or intrauterine survival of the embryos were observed.

When comparing exposure multipliers for twice-weekly subcutaneous injection at the NOAELs from the juvenile toxicity study to the proposed paediatric doses, a relatively high safety margin is noted (131-fold margin of safety for systemic toxicity and a 30.7-fold margin of safety for sexual maturation to the highest proposed paediatric dose of 1.5 mg/week).

Therefore, the non-clinical data do not identify any special safety concerns for the use of dulaglutide in paediatric patients aged 10 to less than 18 years.

2.2.7. Conclusion on the non-clinical aspects

Changes in reproductive endocrine hormones (luteinizing hormone, growth hormone, and estrogen) in male and female rats and earlier sexual maturation in female rats were observed in the rat juvenile toxicity study. Based on these findings the NOAEL for developmental toxicity is 2.0-mg/kg.

Pharmacologically mediated, transient reductions in body weight occurred following each dose administration. However, no adverse effects on systemic toxicity, neurobehavioral endpoints, reproductive performance, or intrauterine survival of the embryos were observed (NOAEL 7 mg/kg).

When comparing exposure multipliers for twice-weekly subcutaneous injection at the NOAELs from the juvenile toxicity study to the proposed paediatric doses, a relatively high safety margin is noted (131-fold margin of safety for systemic toxicity and a 30.7-fold margin of safety for sexual maturation to the highest proposed paediatric dose of 1.5 mg/week).

A Phase II environmental risk assessment is not required. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of dulaglutide.

In conclusion, the nonclinical data do not identify any special safety concerns for the use of dulaglutide in paediatric patients aged 10 to less than 18 years.

2.3. Clinical aspects

2.3.1. Introduction

Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA). In Phase 3 studies in adults, once weekly subcutaneous injection of dulaglutide (both 0.75 mg and 1.5 mg) was associated with clinically relevant long-term decreases in glucose concentration (as measured by HbA1c) and body weight, low risk of hypoglycemia, low risk of immunogenicity, and no new safety observations compared to the approved agents from the GLP-1 RA class (Edwards and Minze 2015).

Because of the pathophysiological similarities between type 2 diabetes mellitus (T2DM) in adults and children and adolescents aged 10 to less than 18 years, it is hypothesized that dulaglutide will also have efficacy in this paediatric population with a similar safety profile.

GCP

The Clinical trials provided as part of the application were performed in accordance with GCP as claimed by the MAH.

2.3.2. Pharmacokinetics

Pharmacokinetic results

Figure 1: Boxplot showing observed steady-state pharmacokinetic concentrations at Week 26 (Visit 9) and Week 52 (Visit 16) for subcutaneous dulaglutide doses of 0.75 and 1.5 mg given once weekly in paediatric patients with type 2 diabetes
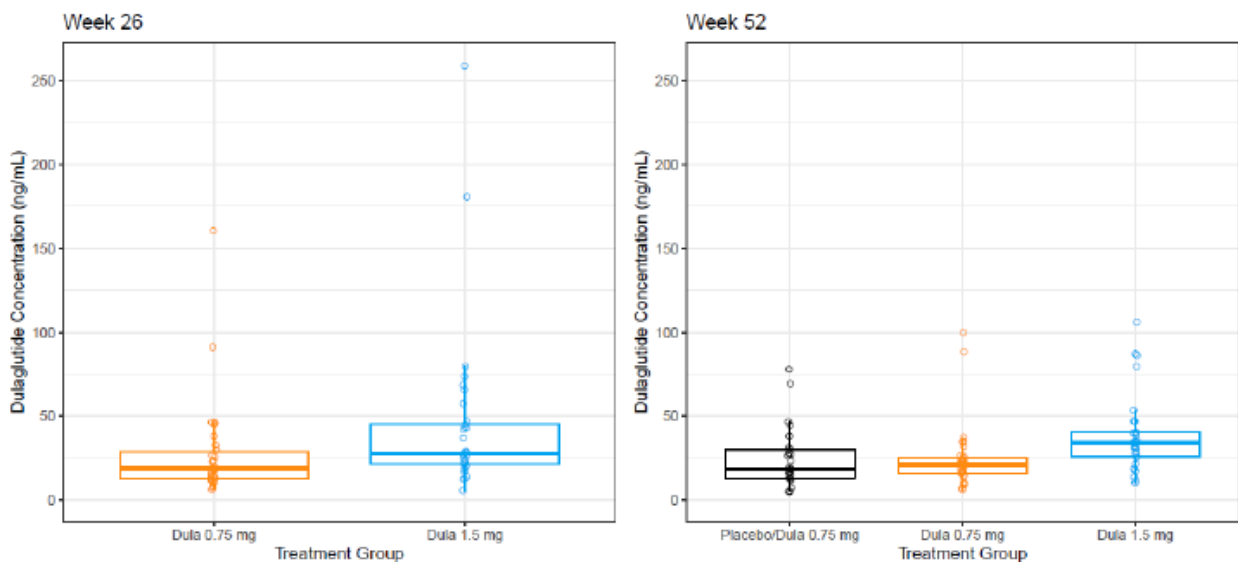
Abbreviation: Dula = dulaglutide
Note: Open colored circles denote observed dulaglutide concentrations. The middle line in each boxplot represents the median; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extent extends from the edges of the box to the largest and smallest values no further than 1.5× interquartile range.

Steady-state observed PK concentrations at Week 26 (Visit 9) and Week 52 (Visit 16) showed distinct

median observed exposure values for dulaglutide 0.75 and 1.5 mg with minimal overlaps of the 25th to 75th percentiles. The 95% confidence intervals in AUC over a weekly dosing interval at steady state [AUC (0-168)ss] and Cmax at steady state (Cmax,ss) showed adequate separation in exposure range between the dulaglutide doses of 0.75 and 1.5 mg.

Additional Analyses

PK concentrations for paediatric versus adult patients with T2DM

A comparison of the population mean PK exposures for dulaglutide in paediatric patients with T2DM from the Study GBGC versus adult patients with T2DM (from previous studies) is shown in the Table below.

Table 5: Mean (95% CI) steady-state pharmacokinetic exposures for paediatric and adult patients with type 2 diabetes receiving subcutaneous 0.75 and 1.5 mg of dulaglutide once weekly

	0.75 mg QW		1.5 mg QW	
	Pediatric	**Adult**	**Pediatric**	**Adult**
AUC (0-168)$_{ss}$ (ng·h/mL)	4170 (3770, 4510)	6650 (6220, 7080)	8350 (7640, 9070)	13100 (12300, 14000)
C$_{max,ss}$ (ng/mL)	31 (28.4, 33.5)	48.3 (45.0, 51.6)	62 (56.9, 67.2)	94.6 (88.8, 102.0)

Abbreviations: AUC (0-168)$_{ss}$ = steady-state area under concentration-time curve over a 1-week interval; CI = confidence interval; C$_{max,ss}$ = steady-state maximum concentration.
Note: Summarized from simulation of 200 trials with 150 patients per dose.

Figure 2:
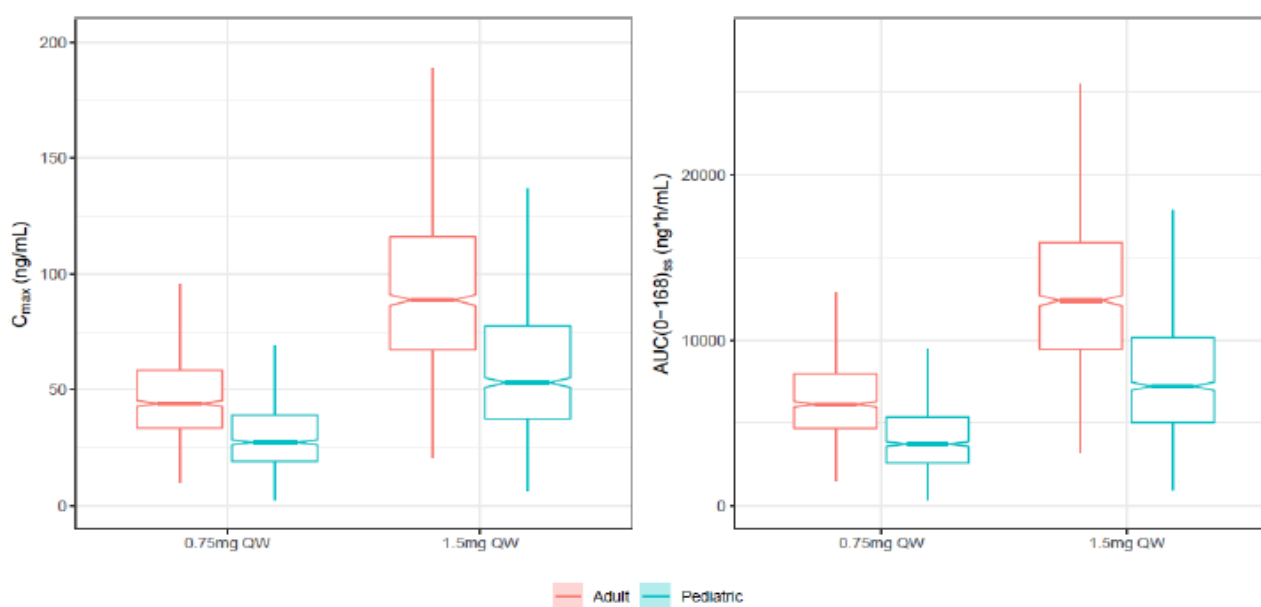
Abbreviations: AUC(0-168)$_{ss}$ = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; C$_{max,ss}$ = steady state maximum concentration; QW = once weekly.

Pharmacokinetic concentrations for paediatric patients with T2DM from Study GBGC were generally lower at each dose than PK concentrations for dulaglutide in adult patients with T2DM from previous studies. Since a clear improvement in efficacy endpoints of glycemic control (fasting glucose and HbA1c) in a dose-related manner was observed and PK concentrations versus safety endpoint correlations were generally consistent with trends observed in adult T2D patients, the adult doses of dulaglutide 0.75 mg and 1.5 mg sc QW were found to be appropriate and applicable to paediatric patients aged between 10 and less than 18 years and do not warrant the need for dose adjustment in this patient population.

Figure 3: Simulated dulaglutide Cmax,ss and AUC(0-168 hrs)ss at steady-state following once-weekly subcutaneous dosing in paediatric T2DM patients over a range of baseline body weights

Abbreviations: AUC(0-168)ss = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; Cmax,ss = steady state maximum concentration.

Figure 4: Simulated dulaglutide Cmax and AUC(0-168 hrs)ss at steady-state following once-weekly subcutaneous dosing in paediatric T2DM patients with different sex

Abbreviations: AUC(0-168)$_{ss}$ = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; C$_{max,ss}$ = steady state maximum concentration; QW = once weekly.

Figure 5: Simulated dulaglutide Cmax and AUC(0-168 hrs)ss at steady-state following once-weekly subcutaneous dosing in paediatric T2DM patients with different ages
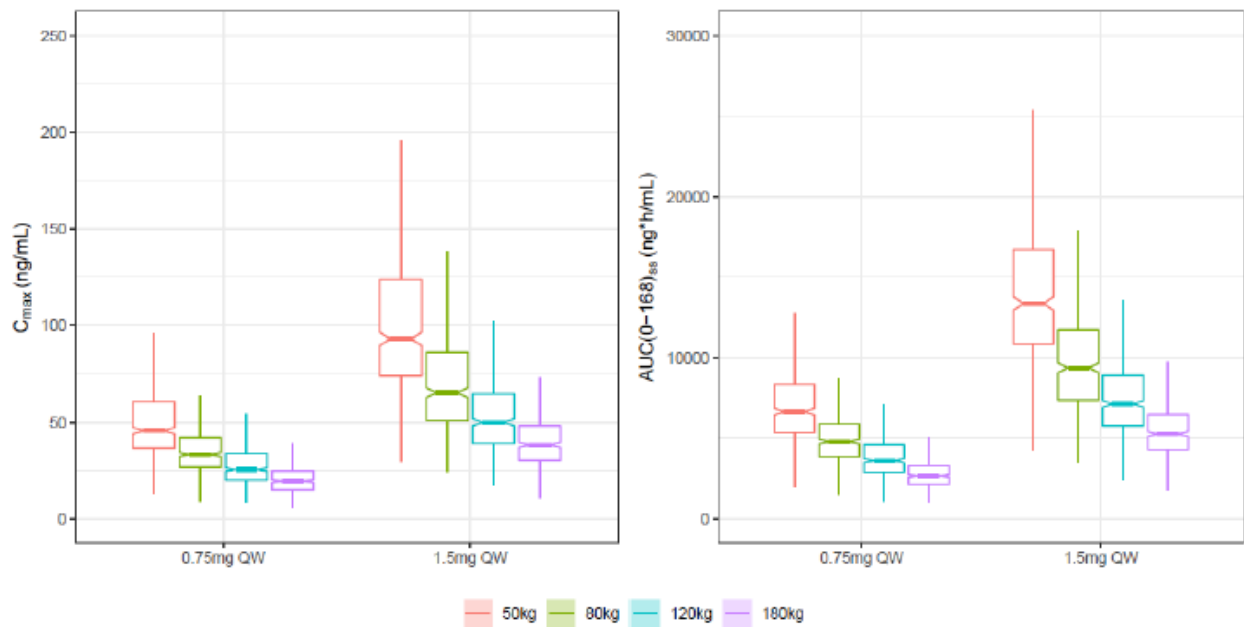

Abbreviations: AUC(0-168)ss = steady state area under the concentration-time curve over 1 dosing interval of 168 hours; Cmax,ss = steady state maximum concentration.

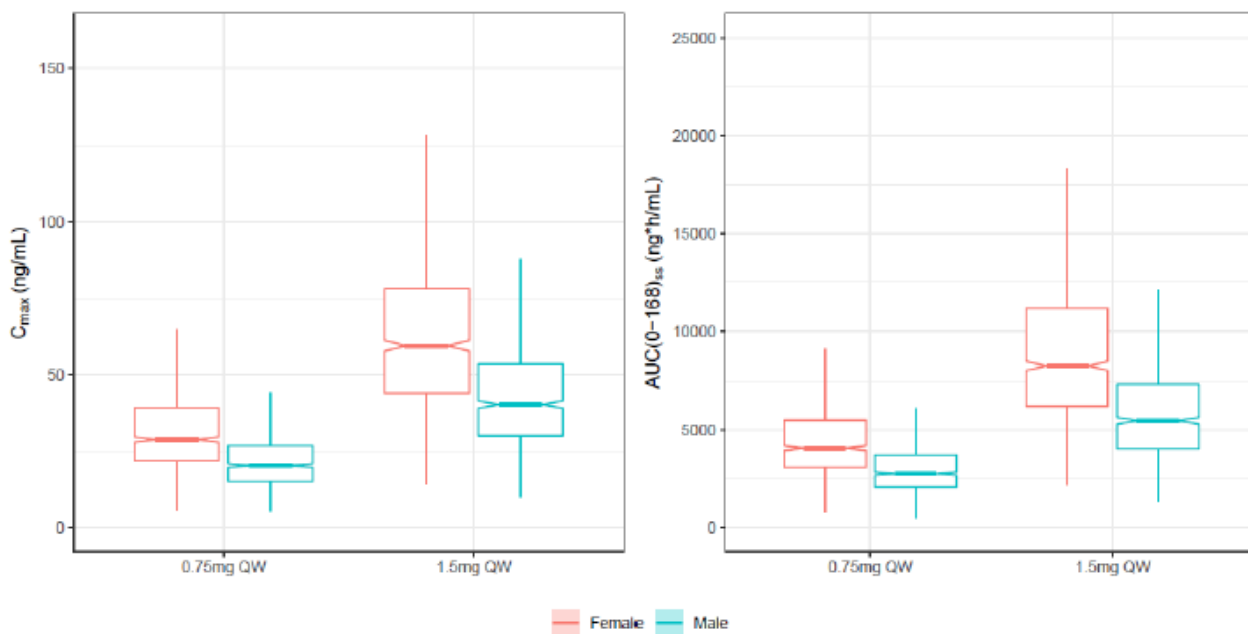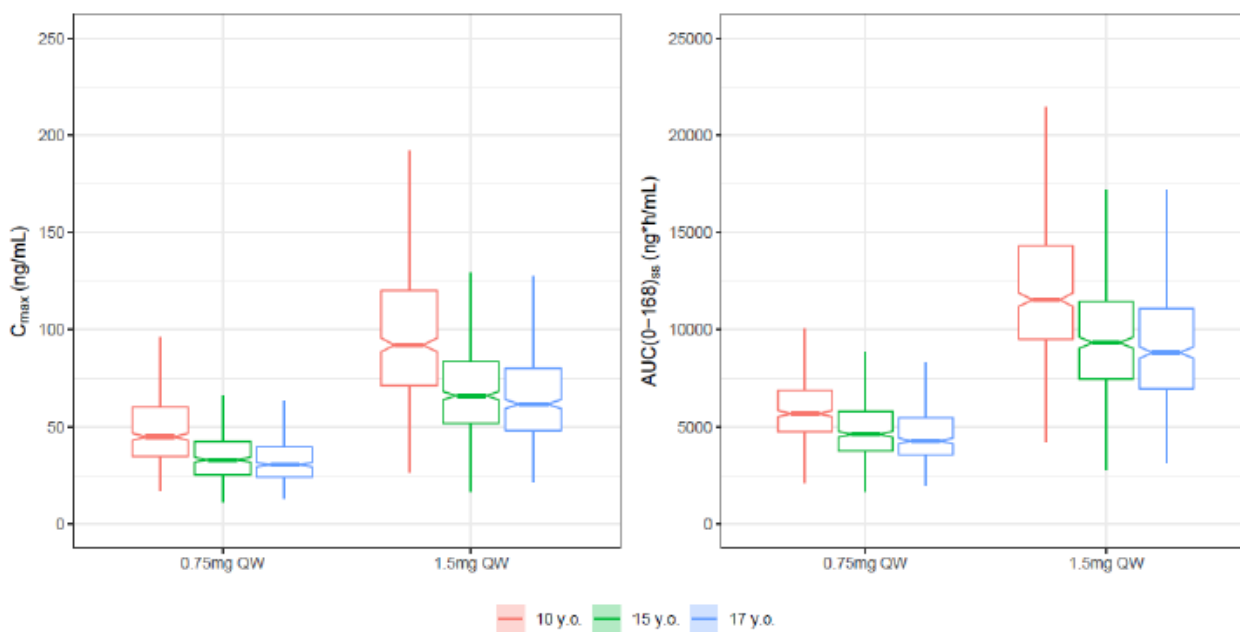Baseline body weight, gender and age were identified as covariates in the population PK model but not found to be clinically relevant consistent with findings from the subgroup analyses of baseline factors on the primary HbA1c efficacy endpoint where age, BMI, and body weight did not affect HbA1c differently. Male patients were found to have potentially larger placebo-adjusted change from baseline HbA1c, probably due to larger increases from baseline in HbA1c in the placebo group among male versus female patients, and consequently larger placebo-adjusted LS mean changes from baseline in HbA1c in the dulaglutide groups in male patients. The smaller number of males relative to females enrolled in Study GBGC and larger variability around the point estimates for LS mean treatment differences also may have contributed to the statistically significant treatment-by-sex interaction. Whether this interaction reflects a true difference between sexes in either treatment effect, is therefore considered unlikely.

Bioanalytical Method

Human plasma samples obtained during this study H9X-MC-GBGC were analyzed for dulaglutide using a validated radio immunoassay method.

Seven hundred eighty (780) original human plasma samples were received frozen and in good condition. The samples were stored at -80 °C without temperature excursions. Reported samples were analyzed within the 735 days demonstrated long-term storage stability at -80 °C. Samples that were outside of stability were not analyzed.

Calibration range was from 1.0 to 50.0 ng/mL. Each calibration curve was calculated using a four-parameter logistic (1/response² weighted) least-squares regression algorithm. Precision and accuracy were evaluated by replicate analyses of human plasma quality control pools prepared at three concentrations spanning the calibration range.

Table 6: Inter-assay precision and accuracy of back-calculated calibration standards and QC samples in H9X-MC-GBGC study

	Calibration standards	QC samples
Precision	≤ 13.8 %	≤ 20.3 %
Accuracy (bias)	-8.7 % to 3.9 %	-2.9 % to −2.5 %

To demonstrate reproducible quantitation of incurred subject samples, seventy-nine (79) samples were selected for incurred reanalysis. The results (80.8%) of the incurred sample repeats met the acceptance criteria (the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of $\leq \pm$ 30%.)

In summary, standard and critical reagent documentation was enclosed. Run acceptance criteria were in line with the Guideline on Bioanalytical Method Validation. Back-calculated concentrations of calibration standards and regression parameters were acceptable. At least 67% QC samples and 50% at each concentration level were within 20% of the nominal value. Data from failed analytical runs and re-assayed samples were presented in the bioanalytical report together with reason for re-assay, original and re-assay values. The ISR results were acceptable. The Method Validation Report and Validation Addendum Reports were submitted. The method was validated in 2010 (and revised later) and was used for LY2189265 estimation in K3EDTA human plasma samples in previous clinical trials having been already assessed.

2.3.3. Pharmacodynamics

Figure 6: Model-predicted and observed dulaglutide dose-response relationships for change from baseline fasting glucose (top) and HbA1c (bottom) at Week 26 (left) and Week 52 (right)
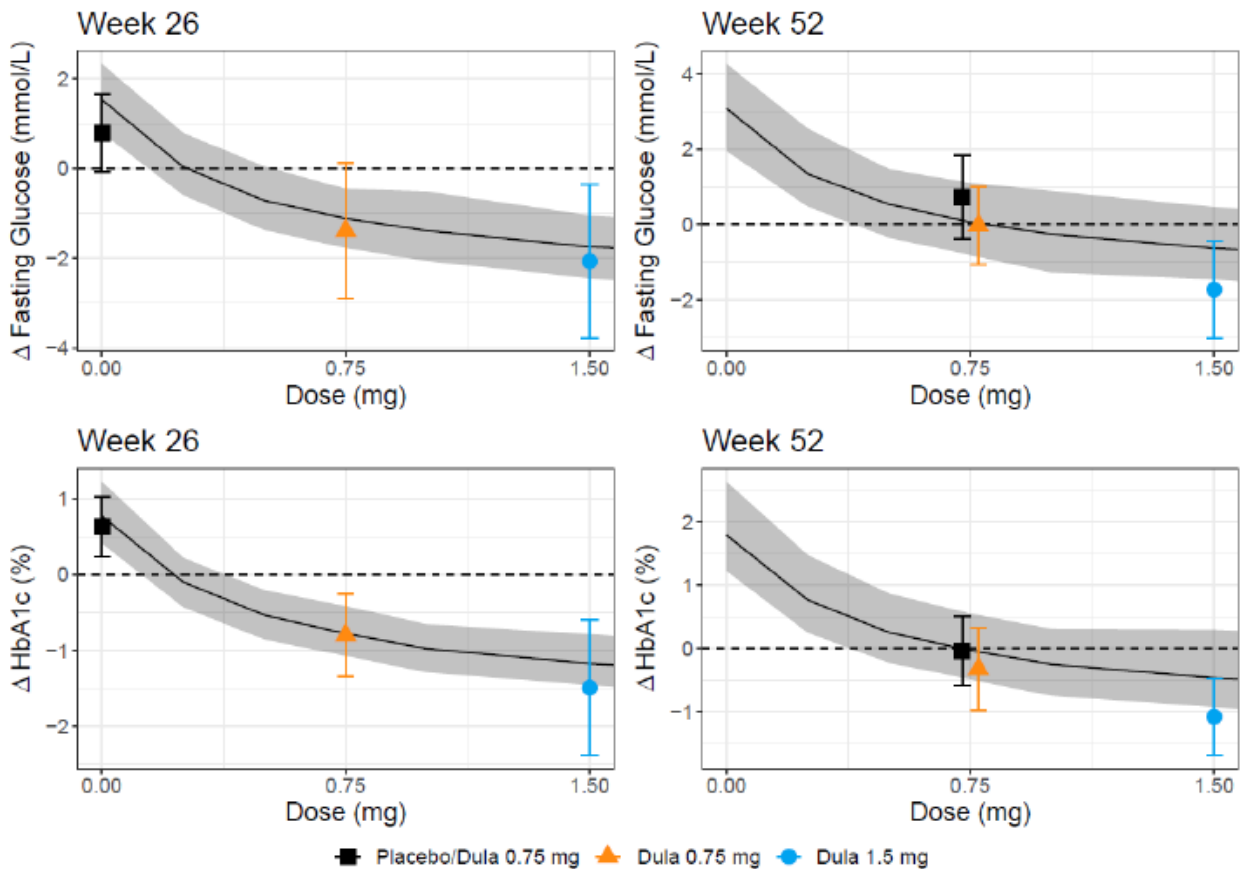
Abbreviations: Δ = change from baseline; CI = confidence interval;
HbA1c = hemoglobin A1c.
Note: Simulation was performed with 200 trials of 150 virtual patients for each treatment group at mean baseline HbA1c of 8.07% (95% CI: 7.84%, 8.26%). Solid black lines denote the mean of 200 trials, and the shaded areas denote the 95% CI of the mean. Colored symbols and error bars denote mean observed data and 95% CI.

Dulaglutide demonstrated clear exposure-response relationships for fasting glucose and HbA1c over the dose range of 0.75 to 1.5 mg sc QW at Week 26 and this dose-response relationship remained evident at Week 52. Paediatric patients initially assigned to placebo treatment up to Week 26, when switched to dulaglutide 0.75 mg, demonstrated HbA1c reduction by Week 52 which was close to HbA1c reduction of paediatric patients who received dulaglutide 0.75 mg throughout the entire study period.

Other PD biomarkers
Relative ratios of the PD biomarkers of insulin sensitivity (insulin sensitivity score [ISS]) and pancreatic beta-cell function (HOMA2-%B) showed statistically significant improvements for dulaglutide 0.75 and 1.5 mg compared with placebo by Week 13.

2.3.4. PK/PD modelling

Paediatric population PK model

The paediatric population pharmacokinetic model was built based on a total of 444 PK samples from 128 paediatric patients aged between 10 and less than 18 years with weekly dosing of 0.75 mg or 1.5 mg. A base model structurally similar to the previously built adult model, but without any pre-identified covariates was applied to fit Study GBGC data. In the final adult PK model, baseline body weight had been a covariate on F1. Covariate analyses for the paediatric model was conducted with forward inclusion (p-level 0.01) and backward elimination (p-level 0.001).

The selected base model had two compartments, with first-order absorption, first-order elimination and with interparticipant variability on absorption rate constant (ka), clearance and central volume of distribution. SC bioavailability (F1) was not specifically investigated and could not be reliably estimated. Therefore, F1 was fixed to 47% based on absolute SC bioavailability of 0.75-mg and 1.5-mg dose from population pharmacokinetic and pharmacodynamic analyses of adult studies: GBCF, GBDA, and GBDC. A proportional error model best described the residual error. Informative priors based on the PK model from Study GBGL were implemented on the PK parameters Q, and V3 to enable reliable estimation of these parameters.

In the final paediatric population PK model, clearance was allometrically scaled to baseline body weight (with fixed exponent 0.75). In addition, patient sex was a significant covariate on CL and age was a covariate on KA. Parameter estimates of the final model are given in the following table.

Table 7: Dulaglutide population pharmacokinetic parameter estimates in paediatric T2D patients from the base and final models

| | Mean (%SEE, 95% CI) | | | |
| | Base Model | | Final Model | |
Parameter Description	Population Estimates	IIV[a]	Population Estimates	IIV[a]
Absorption Rate Constant (1/h)				
First-order absorption rate, KA	0.00433 (15.2%, 0.00262 – 0.00602)	92.2 (25.9%, 57.1 - 146)	0.00379 (16.3%, 0.00211 – 0.00555)	74.1 (25.1%, 42.6 - 108)
Age effect on KA[b]			-2.98 (24.2%, -5.44 - -1.53)	
Clearance (L/h)				
Total clearance, CL	0.0979 (5.00%, 0.0880 – 0.108)	57.8 (18.5%, 45.5 – 68.9)	0.0738 (6.22%, 0.0655 – 0.0825)	47.2 (21.4%, 35.5 – 56.2)
Body weight effect on CL[c]	-	-	0.75 Fixed	-
Patient sex effect on CL[d]	-	-	0.484 (27. 9%, 0.258 – 0.752)	
Intercompartmental clearance, Q	0.011 (43%, 0.00392 – 0.0182)	-	0.00986 (76.9%, 0.00345 – 0.0178)	-
Volume (L)				
Central volume, V2	1.68 (19.6%, 0.997 – 2.64)	92.7 (53.2%, 28.0 - 164)	1.58 (21.0%, 0.918 – 2.47)	71.2 (123%, 13 - 140)
Peripheral volume, V3	3.55 (9.80%, 3.22 – 3.85)	-	3.51 (14.2%, 3.17 – 3.83)	-
Bioavailability (%)				
Absolute bioavailability, F1	0.47 Fixed	-	0.47 Fixed	-
Proportional Residual Error (%)[e]	0.342 (7.31%, 0.292 – 0.387)	-	0.344 (7.33%, 0.298 – 0.387)	-

Figure 8: Visual predictive check of the final pharmacokinetic model showing the overlaid plot of pharmacokinetic observations on pharmacokinetic model-simulated concentrations for dulaglutide doses of 0.75 mg and 1.5 mg in paediatric T2D patients

Notes:

- Blue circles denote observed dulaglutide concentrations.
- Solid red lines denote median of the observed concentrations.
- Dotted red lines denote 2.5th and 97.5th percentiles of the observed concentrations while the width of the colored bands corresponds to the model-simulated 95% CIs of the predicted 2.5th, 50th, and 97.5th percentiles.

Overall, model development was conducted according to standard methodology. The structure of the base model was the same as that previously used to describe the adult data for dulaglutide, which is considered acceptable. Observed data were mainly trough-samples and the VPCs do not allow to assess whether concentrations during one dosing interval were well captured by the model. Thus, uncertainty remains how well the paediatric model describes the PK behaviour in children. This should be kept in mind when evaluating model predicted exposures (e.g. AUC and especially Cmax).

Paediatric population PKPD model

The population PK/PD FG-HbA1c structural model developed for previous submissions of dulaglutide in adult T2D patients without any pre-identified covariates was applied to describe FG and HbA1c time course from study GBGC data. In this model, the time course of the HbA1c response was driven by FG concentration through a linked concentration-response model that fitted both FG and HbA1c data jointly. A disease progression model together with an offset compartment where dulaglutide and placebo effects were introduced was utilized to describe FG concentration over time. Dulaglutide effect was described via an Emax model based on individual post hoc PK parameter-derived dulaglutide concentrations. HbA1c time course was in turn described using a classical indirect response model driven by FG.

A small IIV value had to be included on the EC50 and HILL coefficient parameters to improve model stability. These values were fixed.

The following covariates were found to significantly influence the PKPD relations: The covariate for patients administered rescue therapy was found to be significant on HLIM (lower limit of HbA1c). Patients who required rescue therapy were estimated to have a 39.1% higher mean HLIM of 7.47% versus patients who did not require any rescue therapy 5.37% and was retained as a covariate in the model, although it reduced HLIM's IIV by just 2.2%.

Compared to similar FG-HbA1c models developed previously in adult T2D patients (population pharmacokinetic and pharmacodynamic analyses of studies: GBCF, GBDA, and GBDC; population pharmacokinetic and pharmacodynamic analyses of study H9X-MC-GBGL), the KDIS population mean value in paediatric T2D patients from study GBGC was estimated to be higher at 0.000163 h-1 versus 0.000104 h- 1 and 0.000134 h-1, previously estimated from adult T2D patients. This means that paediatric T2D patients were found to have a faster disease progression than adult T2D patients concurring with literature reports by Barrett et al. 2020 and The Rise Consortium 2021.

ADA titers and treatment-emergent-ADA were not found to be a covariate on the PD model.

In the adult PKPD model, baseline FPG and TZD coadministration had been found to influence maximum HbA1c effect.

The PKPD parameter estimates from the base and the final model are depicted in the following table.

Table 8: Dulaglutide Pharmacokinetic-fasting glucose-HbA1c Parameters from the Population Base and Final Models

	Mean (%SEE, 95% CI)			
	Final Base		**Final Model**	
Parameter Description	**Population Estimates**	**IIV[a]**	**Population Estimates**	**IIV[a]**
Baseline				
Fasting Glucose, E0G (mmol/L)	8.68 (3.02%, 8.27 – 9.12)	28.5 (17.4%, 25.2 – 31.7)	8.64 (2.94%, 8.25 – 9.04)	27.9 (17.4%, 24.8 – 30.4)
HbA1c, E0H (%)	7.95 (1.48%, 7.78 – 8.14)	14.1 (17.8%, 12.7 – 15.4)	8.00 (1.41%, 7.82 – 8.18)	13.7 (17.2%, 12.2 – 15.0)
Correlation between E0G and E0H[b]	0.843 (18.4%)	-	1.00 (17.0%)	-
Placebo Effect				
Placebo effect, PLAC (fraction)	0 Fix	22.6 (26.4%, 17.6 – 28.1)	0 Fix	23.2 (27.1%, 17.8 – 27.4)
Rate Constants				
Delay in drug effect on glucose reduction, KOFF (1/h)	0.00456 (9.02%, 0.00318 – 0.0103)	226 (51.7%, 159 - 390)	0.00654 (13.0%, 0.00347 – 0.0104)	254 (55.2%, 158 - 358)
First-order rate constant on HbA1c loss, KOUT (1/h)	0.000959 (2.25%, 0.000755 – 0.00134)	61.4 (71.3%, 47.5 - 107)	0.000912 (2.29%, 0.000671 – 0.00120)	69.0 (73.0%, 54.6 - 114)
Disease progression rate constant, KDIS (mmol/L/h)	0.000188 (2.20%, 0.000119 – 0.000243)	175 (26.0%, 143 - 269)	0.000168 (2.26%, 0.000121 – 0.000238)	189 (27.5%, 132 - 249)
Lower HbA1c Limit				
Lower limit on HbA1c, HLIM (%)	5.61 (4.67%, 5.34 – 5.96)	26.8 (22.2%, 20.4 – 31.1)	5.37 (4.84%, 5.06 – 5.66)	24.6 (22.2%, 17.0 – 29.0)
Rescue therapy effect on HLIM[c]	-	-	0.391 (24.3%, 0.159 – 0.648)	-
Drug Effect				
Hill coefficient, HILL (unitless)	1.11 (17.7%, 1.09 – 1.20)	15 Fixed	1.11 (18.7%, 1.09 – 1.16)	15 Fixed
Glucose Effect on HbA1c				
Glucose effect on HbA1c coefficient, GGAM (unitless)	0.691 (5.82%, 0.638 – 0.767)	26.2 (37.6%, 15.4 – 32.4)	0.685 (4.86%, 0.621 – 0.789)	34.7 (26.5%, 23.8 – 46.4)
Proportional residual error glucose (mmol/L)[d]	0.213 (2.43%, 0.194 – 0.228)	-	0.232 (2.83%, 0.217 – 0.252)	-
Proportional residual error HbA1c (%)[d]	0.0634 (3.19%, 0.0550 – 0.0697)	-	0.0664 (3.39%, 0.0588 – 0.0745)	-

Abbreviations: CI = bootstrap derived confidence interval; %CV = coefficient of variation; IIV = inter-individual variability; SEE = standard error of the estimate.

[a] Reported as %CV, calculated using the equation $= 100\% \cdot \sqrt{e^{OMEGA(N)} - 1}$, where OMEGA(N) is the NONMEM estimate of the variance for the interindividual variability.

[b] correlation coefficient, calculated using the equation $= \frac{COV(M,N)}{\sqrt{OMEGA(M) \cdot OMEGA(N)}}$, where COV(M,N) is the NONMEM estimate of the covariance between parameters M and N, OMEGA(M) and OMEGA(N) are the NONMEM estimate of the variance for the interindividual variabilities for parameters M and N.

[c] $HLIM_{inidividual} = HLIM_{typical} \cdot (1 + \theta)$ where $\theta = 0.391$ for patients who received rescue therapy and $\theta = 0$ otherwise

[d] Reported as standard deviation.

VPCs for HbA1c change after treatment with 0.75, 1.5 mg or placebo are shown in the figure below.

Figure 9: Visual predictive check of the final pharmacokinetic model showing the overlaid plot of pharmacokinetic observations on pharmacokinetic model-simulated concentrations for dulaglutide doses of 0.75 mg and 1.5 mg in paediatric T2D patients
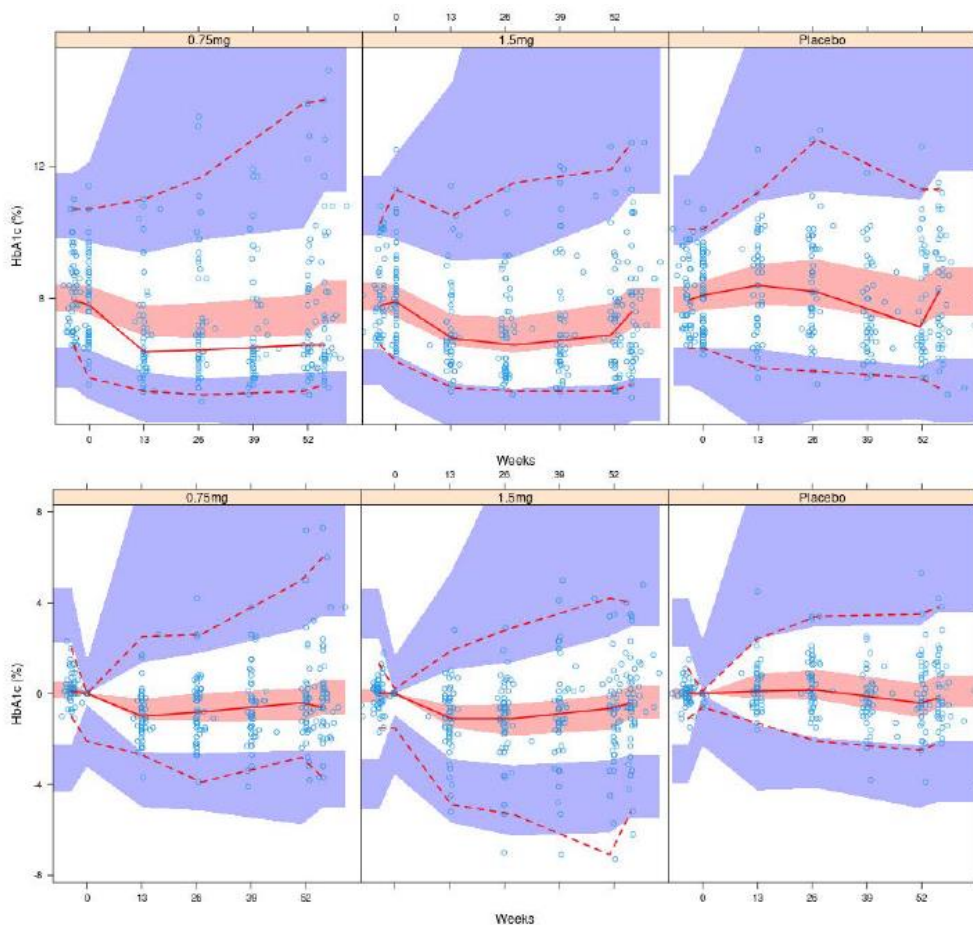
- Blue circles denote observed HbA1c values
- Solid red lines denote the median of the observed values
- Dotted red lines denote 2.5th and 97.5th percentiles of the observed values while the width of the colored bands corresponds to the model-simulated 95% CIs of the predicted 2.5th, 50th, and 97.5th percentiles.

The PKPD model depends on the population PK model since dulaglutide effect is based on *post hoc* PK parameters derived with the popPK model. Therefore, the above mentioned uncertainties with respect to the popPK model are also relevant for the PKPD model.

Evaluation of the PKPD model reveals that the effect of 0.75 mg dulaglutide on HbA1c was underpredicted by the model (see VPC above). Underprediction is less obvious with effects depicted as change from baseline.

Comparing PKPD parameters between children and adults revealed that EC50 in children was about half of the value in adults indicating that children were more sensitive to the drug.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

In Study GBGC, steady-state observed PK concentrations at Week 26 (Visit 9) and Week 52 (Visit 16) showws distinct median observed exposure values for dulaglutide 0.75 and 1.5 mg with minimal overlaps of the 25th to 75th percentiles. The 95% confidence intervals in AUC over a weekly dosing interval at steady state [AUC (0-168)ss] and Cmax at steady state (Cmax,ss) showed adequate separation in exposure range between the dulaglutide doses of 0.75 and 1.5 mg.

Pharmacokinetic concentrations for paediatric patients with T2DM from Study GBGC were generally lower at each dose than PK concentrations for dulaglutide 0.75 and 1.5 mg in adult patients with T2DM from previous studies. Since a clear improvement in efficacy endpoints of glycemic control (fasting glucose and HbA1c) in a dose-related manner was observed and PK concentrations versus safety endpoint correlations were generally consistent with trends observed in adult T2D patients, the adult doses of dulaglutide 0.75 mg and 1.5 mg sc QW were found to be appropriate and applicable to paediatric patients aged between 10 and less than 18 years and do not warrant the need for dose adjustment in this patient population.

Baseline body weight, gender and age were identified as covariates in the population PK model but not found to be clinically relevant consistent with findings from the subgroup analyses of baseline factors on the primary HbA1c efficacy endpoint where age, BMI, and body weight did not affect HbA1c differently. Male patients were found to have potentially larger placebo-adjusted change from baseline HbA1c, probably due to larger increases from baseline in HbA1c in the placebo group among male versus female patients, and consequently larger placebo-adjusted LS mean changes from baseline in HbA1c in the dulaglutide groups in male patients. The smaller number of males relative to females enrolled in Study GBGC and larger variability around the point estimates for LS mean treatment differences also may have contributed to the statistically significant treatment-by-sex interaction. Whether this interaction reflects a true difference between sexes in either treatment effect, is therefore considered unlikely.

In conclusion, pharmacokinetics of dulaglutide in paediatric patients aged between 10 and less than 18 years is considered sufficiently described by the MAH. Based on the popPK model, no dose adjustment is considered necessary for the intrinsic patient factors.

Pharmacodynamics

Exposure-response relationships
Dulaglutide 0.75 and 1.5 mg showed clear dose-related improvements in fasting glucose and HbA1c at both Weeks 26 and 52. Concentration-response findings on safety endpoints of heart rate, QTcF interval, PR interval, amylase, and lipase were consistent with data observed previously in adult patients with T2DM.

Dose selection
The evaluation of dulaglutide dose exposure-response relationships for efficacy and safety indicated incremental improvements in efficacy for glycemic control at the doses of 0.75 and 1.5 mg in paediatric patients with T2DM where PK exposures did not exceed that of adult patients with T2DM at the same dose level. The improvements from baseline in glycemic control with dulaglutide were generally sustained through 52 weeks. The overall safety profile of dulaglutide 0.75 and 1.5 mg once weekly in paediatric patients with T2DM was consistent with that established in adults with T2DM, with no new safety concerns. Hence, dulaglutide doses of 0.75 and 1.5 mg are appropriate and applicable to paediatric patients aged between 10 and less than 18 years and do not warrant the need for dose adjustment in this patient population.

2.3.6. Conclusions on clinical pharmacology

Overall, pharmacokinetic concentrations for paediatric patients with T2DM from Study GBGC were lower at each dose than PK concentrations for dulaglutide 0.75 and 1.5 mg in adult patients with T2DM from previous studies. Since a clear improvement in efficacy endpoints of glycemic control (fasting glucose and HbA1c) in a dose-related manner was observed and PK concentrations versus safety endpoint correlations were generally consistent with trends observed in adult T2D patients, the adult doses of dulaglutide 0.75 mg and 1.5 mg were found to be appropriate and applicable to paediatric patients aged between 10 and less than 18 years.

2.4. Clinical efficacy

2.4.1. Main study

Study H9X-MC-GBGC

Title of study
A randomized, double-blind study with an open-label extension comparing the effect of once weekly dulaglutide with placebo in paediatric patients with type 2 diabetes mellitus

Primary objective
To evaluate whether dulaglutide (0.75 and 1.5 mg sc QW, pooled) is superior to placebo in paediatric patients aged 10 to less than 18 years with T2DM as measured by change in HbA1c from baseline to Week 26.

Design for the paediatric phase 3 study GBGC
Study H9X-MC-GBGC (GBGC) is a Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter superiority trial with an open-label extension to investigate the efficacy, safety, PK, and PD in paediatric patients with T2DM receiving dulaglutide compared with placebo, who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin.

Figure 10:

Double-Blind Period | Open-Label Period[c]

Screening
Placebo → Dulaglutide 0.75 mg once weekly
Safety Follow-Up

Dulaglutide 0.75 mg once weekly → Dulaglutide 0.75 mg once weekly

Dulaglutide 0.75 mg once weekly[b,c] → Dulaglutide 1.5 mg once weekly[c] → Dulaglutide 1.5 mg once weekly

<4 weeks | 26 weeks | 26 weeks | 30 days

Visit 1   2   3[a]   4   5[a]   6   7[a]   8[a]   9   10[a]   11[a]   12[a]   13   14[a]   15[a]   16   801

Week -4   0   1   4   9   13   18   22   26   27   31   35   39   44   48   52   56

Randomization   Primary Endpoint   End of treatment

a   Phone visits.
b   Patients who tolerate the 0.75 mg/week dose in the opinion of the investigator will be changed to dulaglutide 1.5 mg/week at Week 4.
c   If patients do not tolerate the higher dose, they will be allowed to go back to the previous dose.

Patients received either dulaglutide (0.75 or 1.5 mg/week) or placebo weekly for 26 weeks during the double-blind period of the trial. Patients assigned to the dulaglutide 1.5 mg group were administered the 0.75 mg/week dose for the first 4 weeks and were then escalated to the 1.5 mg/week dose if they tolerated the 0.75 mg dose based on investigator assessment. During the 26-week open-label extension period, patients who received dulaglutide remained on the same dose they received in the double-blind period, while patients who had received placebo during the double-blind period were given dulaglutide 0.75 mg/week. After completion of the OL extension, patients returned 4 weeks later for safety follow-up.

Study drug, dose, and mode of administration

Double-Blind Treatment Period (26 weeks)
- Dulaglutide 0.75 mg sc QW
- Dulaglutide 1.5 mg sc QW
- Placebo injection sc QW

Open-Label Extension Period (from Week 26 – Week 52)
- Dulaglutide 0.75 mg sc QW
- Dulaglutide 1.5 mg sc QW
- Placebo switched to Dulaglutide 0.75 mg sc QW

Number of patients

Double-Blind Treatment Period (26 weeks)
- Randomized = 154
- Treated = 154
  - Dulaglutide 0.75 mg = 51
  - Dulaglutide 1.5 mg = 52
  - Placebo = 51
- Completed = 146

<u>Open-Label Extension Period (from Week 26 – Week 52)</u>
- − Treated = 146
  - • Dulaglutide 0.75 mg = 49
  - • Dulaglutide 1.5 mg = 50
  - • Placebo switched to Dulaglutide 0.75 mg = 47
- − Completed = 139

Main inclusion criteria

Patients were male or female children and adolescents aged 10 to less than 18 years at randomization who had T2DM as diagnosed by Global International Diabetes Foundation/International Society for Paediatric and Adolescent Diabetes (IDF-ISPAD 2011; IDF [WWW]) criteria.

Patients were required to have inadequate glycemic control on diet and exercise, metformin, and/or insulin. Doses of metformin and basal insulin must have been stable (±15%) for at least 8 weeks prior to screening visit. Lifestyle measures must have been in place for at least 8 weeks prior to the screening visit. For patients recruited in the EU, if patients were treated with lifestyle measures only, they could not be metformin naive.

Patients were required to have
- • an HbA1c greater than 6.5% and less than or equal to 11.0% at screening visit (unless newly diagnosed and only treated with lifestyle measures, in which case the HbA1c was to be greater than 6.5% and less than or equal to 9.0%),
- • BMI greater than the 85% percentile of the general age- and gender-matched population for that country or region, and
- • a body weight greater than or equal to 50 kg.

Main exclusion criteria

- • Known type 1 diabetes, positive GAD65 or IA2 antibodies, or history of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome.
- • A history of or at risk for pancreatitis, or a self or family history of multiple endocrine neoplasia type 2A or 2B, thyroid C-cell hyperplasia or medullary thyroid cancer, or a serum calcitonin result ≥20 pg/mL at screening.
- • Having an estimated glomerular filtration rate (eGFR) <60 mL/minute at screening.
- • A female of childbearing age, sexually active and not on birth control, pregnant or plan to be pregnant during the study, or breastfeeding.
- • Taking any diabetic medication other than metformin or basal insulin within 3 months prior to the screening visit (6 weeks for bolus or mealtime insulin).
- • Use of prescription weight loss medications in the last 30 days or plan to use during study.
- • Taking psychiatric medications if doses have not been stable (±10%) for at least 3 months prior to screening and/or if there is an intention to change or add new medications during the trial.

Table 9: Primary and key secondary efficacy objectives and endpoints

Objectives	Endpoints
Primary Objective	
To test the hypothesis that dulaglutide (0.75 and 1.5 mg, pooled) given subcutaneously once a week for 26 weeks to children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin is superior to placebo in the treatment of T2DM.	Change in hemoglobin A1c (HbA1c) between baseline and Week 26 (pooled dulaglutide doses)
Key Secondary Objectives	
To compare the dulaglutide 0.75- and 1.5-mg arms with placebo with respect to change in HbA1c between baseline and Week 26 (individual doses only)	Change in HbA1c between baseline and Week 26
To compare the dulaglutide 0.75- and 1.5-mg arms (pooled and individual doses) with placebo with respect to change in fasting blood glucose (FBG) between baseline and Week 26	Change in FBG between baseline and Week 26
To compare the dulaglutide 0.75- and 1.5-mg arms (pooled and individual doses) with placebo with respect to percentage of patients with HbA1c <7.0% at Week 26	Percentage of patients with HbA1c less than 7.0% at Week 26
To compare the dulaglutide 0.75- and 1.5-mg arms (pooled and individual doses) with placebo with respect to change in body mass index (BMI) between baseline and Week 26	Change in BMI between baseline and Week 26
Secondary PK/PD Objective	
Characterization of the PK of dulaglutide and the relationship between dulaglutide exposure and key safety and efficacy measures.	PK parameters (for example, C_{max}, AUC [area under the concentration versus time curve]) at steady state PD evaluations including changes from baseline in HbA1c, body weight, and heart rate at Weeks 26 and 52

Other secondary efficacy objectives

The effect of dulaglutide (individually and pooled dose arms) with respect to change in HbA1c, FBG, BMI between baseline and Week 52, and the percentage of patients with HbA1c <7% at Week 52 was

assessed as other secondary efficacy objectives. The ITT population without post-rescue therapy data (efficacy estimand) with all post-randomization visits up to Week 52 (Visit 16) was used for these other secondary efficacy analyses.

Statistical methods

Two primary estimands were pre-specified for analysis of primary and key secondary efficacy endpoints. One primary estimand was an efficacy estimand, which did not use post-rescue data; the other primary estimand was a treatment-regimen estimand, which used post-rescue data. The efficacy estimand measures the benefit of the assigned study treatment in the absence of the confounding effects of additional or alternative antihyperglycemic agents and regardless of compliance with study treatment. The treatment-regimen estimand measures the benefit of the assigned study treatment regardless of the use of any additional or alternative antihyperglycemic agents or compliance with study treatment. The primary analysis population for the FDA and other regulatory agencies (except for the EU) was the intent-to-treat (ITT) population including all randomized patients who took at least 1 dose of the assigned study medication. The primary analysis population for the EU was the ITT population excluding those patients treated with diet and exercise only who were metformin naïve. For the EU analyses, the efficacy estimand was of interest.

For the efficacy estimand, longitudinal continuous measures were analyzed using a mixed-model for repeated measures (MMRM) with stratification factors (insulin usage [yes, no], metformin usage [yes, no], HbA1c strata [HbA1c: <8.0%, ≥8.0%] (except for HbA1c analyses)), treatment, visit, and treatment-by-visit as fixed effects, and corresponding baseline measurement as a covariate. The Kenward-Roger method was used to estimate denominator degrees of freedom, and the restricted maximum likelihood (REML) approach to obtain model estimate. An unstructured covariance structure was used to model the within-patient errors. A longitudinal logistic regression model using the same terms as described for the MMRM was fitted to evaluate the proportion of patients achieving an HbA1c <7.0% at Week 26.

For the treatment-regimen estimand, continuous measures were analyzed using an analysis of covariance (ANCOVA) model with stratification factors and treatment as fixed effects, and corresponding baseline measurement as a covariate. Missing data from both treatment arms were imputed using the data from those patients in the placebo arm who had the measurement at Week 26. Missing data from the dulaglutide arms were imputed using only baseline and Week 26 data from the placebo arm and none of the intermediate data observed in the placebo or dulaglutide arms. Missing data from the placebo arm were imputed using both the baseline and all intermediate post-baseline and Week 26 data in the placebo arm. A logistic regression model using the same terms as described for the ANCOVA was fitted to evaluate the proportion of patients achieving an HbA1c <7.0% at Week 26. Missing data at Week 26 were imputed as not achieving the target. In addition, a sensitivity analysis was conducted where patients who had been rescued or had missing data at Week 26 were considered (imputed) as not having achieved the target.

A graphical approach for multiple comparisons (Bretz et al. 2009; Bretz et al. 2011), as presented in the following figure, was used to strongly control the overall type I error (2-sided alpha of 0.05) for testing the null hypothesis of no treatment effect with respect to the primary and key secondary efficacy endpoints. The numbers along the arrows represent the fraction of alpha from a null hypothesis, if it is rejected, to be passed to the next hypothesis. The graphical approach was conducted separately for each estimand at the full significance level of 0.05.

Figure 11:
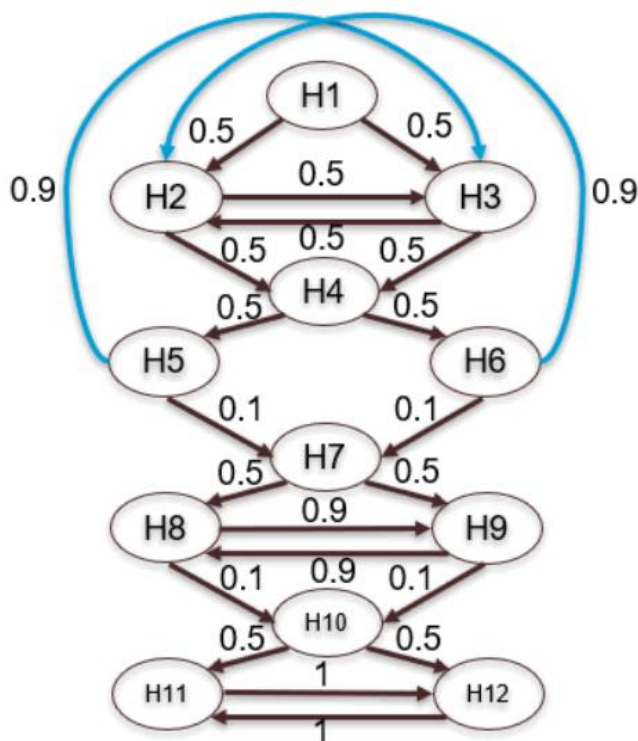
- H1: Superiority test of dulaglutide pooled arm (Pooled dulaglutide 1.5 mg and 0.75 mg) versus placebo in mean change from baseline in HbA1c at 26 weeks
- H2: Superiority test of dulaglutide 1.5 mg versus placebo in mean change from baseline in HbA1c at 26 weeks
- H3: Superiority test of dulaglutide 0.75 mg versus placebo in mean change from baseline in HbA1c at 26 weeks
- H4: Superiority test of dulaglutide pooled arm versus placebo in proportion of patients achieving an HbA1c <7.0% at 26 weeks
- H5: Superiority test of dulaglutide 1.5 mg versus placebo in proportion of patients achieving an HbA1c <7.0% at 26 weeks
- H6: Superiority test of dulaglutide 0.75 mg versus placebo in proportion of patients achieving an HbA1c <7.0% at 26 weeks
- H7: Superiority test of dulaglutide pooled arm versus placebo in mean change from baseline in FBG at 26 weeks
- H8: Superiority test of dulaglutide 1.5 mg versus placebo in mean change from baseline in FBG at 26 weeks
- H9: Superiority test of dulaglutide 0.75 mg versus placebo in mean change from baseline in FBG at 26 weeks
- H10: Superiority test of dulaglutide pooled arm versus placebo in mean change from baseline in BMI at 26 weeks
- H11: Superiority test of dulaglutide 1.5 mg versus placebo in mean change from baseline in BMI at 26 weeks
- H12: Superiority test of dulaglutide 0.75 mg versus placebo in mean change from baseline in BMI at 26 weeks

Efficacy analyses were based on the ITT population (or ITT population excluding metformin naïve patients for the EU). Still, patients without baseline assessment were excluded from analyses for the treatment-regimen estimand and patients without baseline or without post-baseline assessments were excluded

from analyses for the efficacy estimand. As requested, more details on the number of patients excluded in each treatment arm in the analyses of primary and key secondary endpoints have been provided. The impact on the results is limited due to generally low number of patients excluded and consistent conclusions based on different estimands.

As per the EMA Draft Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2), the actual adherence to study treatment (e.g. treatment discontinuation due to intolerance, lack of efficacy) should be reflected in the target of estimation and the evaluation of the effect of test product should not be confounded by rescue medication. Therefore, the estimand of primary interest would be the one targeting the effect regardless of adherence to study treatment (treatment policy strategy) and had rescue medication not been introduced (hypothetical strategy). For this estimand, data obtained after treatment discontinuation are of interest (patients are not expected to benefit once treatment is discontinued), but data obtained after initiation of rescue medication are not (they reflect the effect of the rescue medication itself) and should be imputed as lack of efficacy, e.g. using a placebo-based multiple imputation. Although the efficacy estimand did not use post-rescue data, the MAR assumption underlying the analysis models (i.e. MMRM and longitudinal logistic regression) is questionable to handle censored post-rescue data, as patients requiring rescue medication are simply due to this fact different from patients who had not required rescue medication. As requested, additional analyses in alignment to the estimand per guideline have been provided for all primary and key secondary efficacy endpoints, for both the ITT population and the ITT population excluding metformin naïve patients, using a placebo-based multiple imputation for censored data after initiation of rescue medication and other missing data. The effect estimates from these analyses are similar to or smaller than the effect estimates based on the treatment-regimen and efficacy estimands. Nevertheless, the conclusions generally remain unchanged.

Results

Recruitment

The paediatric study GBGC was conducted at 46 centers that randomized 154 patients in 9 countries (the US, Mexico, Brazil, Germany, France, United Kingdom, Turkey, India, Saudi Arabia). The first patient was enrolled on 29 December 2016 and the last patient completed the last visit on 12 January 2022.

Demographics and baseline disease characteristics

Demographic and baseline characteristics in the ITT Population reflected the enrolment criteria and were representative of the general population of children and adolescents with T2DM.

Overall, patients in the study GBGC:
- had a mean age of 14.5 years and were predominantly female (71.4%)
- had a mean duration of T2DM of 2.0 years
- had mean HbA1c at baseline of 8.08% with 54.5% of patients having a baseline HbA1c ≥ 8.0%, and
- had obesity (mean BMI, 34.1 kg/m2; mean BMI percentile, 98.0%)

Table 10: Summary and Analysis of Patient Demographics and Clinical Characteristics at Baseline, Intent-to-Treat Population

Parameter	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Total (N=154)
Age (years), mean ± SD	14.2 ± 2.1	14.7 ± 2.2	14.7 ± 1.8	14.5 ± 2.0
≤14 years, n (%)	25 (49.0)	16 (31.4)	19 (36.5)	60 (39.0)
>14 years, n (%)	26 (51.0)	35 (68.6)	33 (63.5)	94 (61.0)
Duration of diabetes (years), mean ± SD	2.0 ± 1.8	1.8 ± 1.8	2.1 ± 1.6	2.0 ± 1.7
Female, n (%)	41 (80.4)	35 (68.6)	34 (65.4)	110 (71.4)
Male, n (%)	10 (19.6)	16 (31.4)	18 (34.6)	44 (28.6)
Race, n (%)				
American Indian or Alaska Native	6 (11.8)	6 (11.8)	4 (7.7)	16 (10.4)
Asian	11 (21.6)	4 (7.8)	4 (7.7)	19 (12.3)
Black or African American	5 (9.8)	9 (17.6)	9 (17.3)	23 (14.9)
Native Hawaiian or other Pacific Islander	1 (2.0)	0	0	1 (0.6)
White	25 (49.0)	29 (56.9)	30 (57.7)	84 (54.5)
Multiple	3 (5.9)	1 (2.0)	3 (5.8)	7 (4.5)
Missing	0	2 (3.9)	2 (3.8)	4 (2.6)
Hispanic or Latino, n (%)	26 (51.0)	31 (60.8)	28 (53.8)	85 (55.2)
HbA1c (%), mean ± SD	8.14 ± 1.12	7.92 ± 1.27	8.16 ± 1.39	8.08 ± 1.26
Fasting serum glucose (mg/dL), mean ± SD	159.4 ± 59.4	149.3 ± 60.3	163.0 ± 61.4	157.2 ± 60.3
BMI (kg/m^2), mean ± SD	34.3 ± 10.2	33.6 ± 9.0	34.3 ± 7.0	34.1 ± 8.8
BMI percentile	97.8	98.0	98.3	98.0
BMI SDS	2.99	2.89	2.93	2.94
Weight (kg), mean ± SD	88.9 ± 29.4	90.0 ± 28.3	92.6 ± 21.6	90.5 ± 26.5
Height (cm), mean ± SD	160.2 ± 8.1	162.9 ± 9.9	164.1 ± 9.2	162.4 ± 9.2
eGFR (mL/min/1.73 m^2), mean ± SD	128.1 (29.2)	126.6 (34.1)	120.4 (31.1)	125.0 (31.5)

Abbreviations: BMI = body mass index; Dula = dulaglutide; eGFR = estimated glomerular filtration rate (bedside Schwartz equation); HbA1c = hemoglobin A1c; N = number of patients randomized and treated; n = number of patients in the specified category; SD = standard deviation; SDS = standard deviation score.

Overall, demographic and baseline characteristics were comparable across the treatment groups. The only statistically significant difference between dulaglutide and placebo groups was in height: patients assigned to dulaglutide 1.5 mg group were slightly taller (164.1 cm) compared with patients assigned to placebo (160.2 cm; p=0.031).

Patient disposition and sample size

Figure 12: Patient disposition for all screened and randomized patients through the primary Week 26 endpoint and final Week 52 endpoint
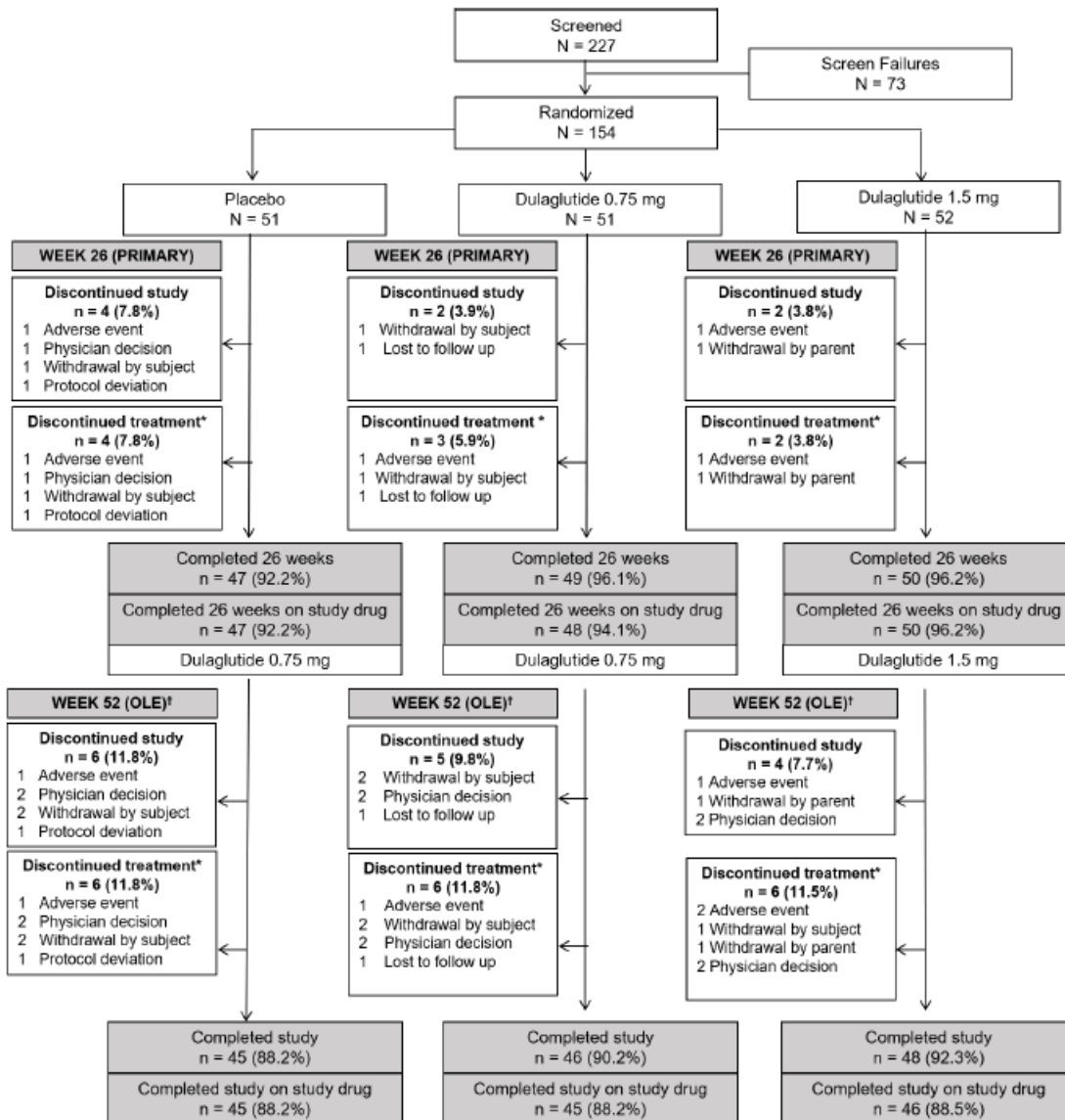
Abbreviations: N = number of patients in the analysis population; n = number of patients in the specified category; OLE = open-label extension.
*Includes patients who discontinued the study; †Week 52 disposition data include patients who discontinued up through Week 26.
Sources: Table GBGC.4.1, Table GBGC.8.13, and Table GBGC.8.14

Exposure

All randomized patients received at least 1 dose of study drug. The mean duration of exposure by assigned treatment group was follows:

- Placebo/dulaglutide 0.75 mg (N=51): 336.2 days
- Dulaglutide 0.75 mg (N=51): 338.8 days, and
- Dulaglutide 1.5 mg (N=52): 342.8 days.

Concomitant medication

Antihyperglycemic therapies at baseline
Overall, 90.9% of patients were taking at least 1 antihyperglycemic medication at baseline. The majority of paediatric patients were taking metformin at baseline:
- 63.0% on metformin alone, and
- 25.3% on metformin plus a basal insulin

Collectively, 27.9% of patients were taking basal insulin at baseline, most in combination with metformin.

Table 11: Antihyperglycemic interventions at baseline, Intent-to-Treat Population

Therapy, n (%)	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Total (N=154)
Patients with ≥1 antihyperglycemic medication	47 (92.2)	46 (90.2)	47 (90.4)	140 (90.9)
Metformin only	32 (62.7)	33 (64.7)	32 (61.5)	97 (63.0)
Metformin + basal insulin	14 (27.5)	11 (21.6)	14 (26.9)	39 (25.3)
Basal insulin only	1 (2.0)	2 (3.9)	1 (1.9)	4 (2.6)
Lifestyle intervention only	4 (7.8)	5 (9.8)	5 (9.6)	14 (9.1)
Metformin naive	2 (3.9)	5 (9.8)	3 (5.8)	10 (6.5)
Metformin intolerant	1 (2.0)	0	0	1 (0.6)
Other reasons	1 (2.0)	0	2 (3.8)	3 (1.9)

Abbreviations: Dula = dulaglutide; N = number of subjects in analysis population; n = number of subjects within category.

Change in antihyperglycemic medication during the study
Relative to baseline, there was little change in metformin use through the double-blind period and balanced across treatment groups. Use of insulin tended to increase during the double-blind period, primarily in the placebo group (baseline, 29.4%; double-blind period, 43.1%) due to initiation of rescue therapy. With the exception of 1 patient in the placebo group who inadvertently initiated a dipeptidyl peptidase-IV inhibitor and stopped after 3 days of treatment, no other category of antihyperglycemic medications was started during the double-blind period.

Table 12: Antihyperglycemic medication use by study period, Intent-to-Treat Population

	Placebo/Dula 0.75 mg N=51			Dula 0.75 mg N=51			Dula 1.5 mg N=52			Total N=154		
Study Period	BL	DB	OL	BL	DB	OL	BL	DB	OL	BL	DB	OL
Patients with ≥1 antihyperglycemic medication	47 (92.2)	47 (92.2)	45 (88.2)	46 (90.2)	46 (90.2)	45 (88.2)	47 (90.4)	47 (90.4)	42 (80.8)	140 (90.9)	140 (90.9)	132 (85.7)
Metformin	46 (90.2)	46 (90.2)	44 (86.3)	45 (88.2)	44 (86.3)	43 (84.3)	46 (88.5)	46 (88.5)	40 (76.9)	137 (89.0)	136 (88.3)	127 (82.5)
Insulin	15 (29.4)	22 (43.1)	24 (47.1)	13 (25.5)	15 (29.4)	15 (29.4)	15 (28.8)	15 (28.8)	14 (26.9)	43 (27.9)	52 (33.8)	53 (34.4)

Abbreviations: Dula = dulaglutide; BL = baseline; DB = double-blind period (Visit 3 to Visit 9); N = number of subjects in analysis population; OL = open-label period (Visit 10 to Visit 16).

Other concomitant medications

No patients were reported taking a weight loss medication at baseline. The use of antihypertensive and lipid-lowering medications at baseline was reported by 14.9% and 3.9% of patients, respectively.
No statistically significant or clinically relevant differences were observed between treatment groups using any other concomitant medications at baseline or postbaseline.

Efficacy results

Primary and key secondary objectives

The primary objective was met using both the treatment-regimen and efficacy estimands: dulaglutide (0.75 and 1.5 mg, pooled dose groups) was superior to placebo (p<0.001) in improving glycemic control as measured by baseline to Week 26 change in HbA1c in children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin. The primary objective was also met using the EMA analysis, excluding for patients who were treated with lifestyle measures only and were metformin naive at baseline.

Each dulaglutide dose group individually (0.75 mg or 1.5 mg) was superior to placebo with respect to baseline to Week 26 change in HbA1c using each estimand.

Superiority of dulaglutide to placebo in improving glycemic control was further supported by results of additional key secondary efficacy objectives (controlled for multiplicity), including the percentage of patients with an HbA1c <7% (<53 mmol/mol) at Week 26, and for the change in FBG from baseline to Week 26. Point estimates and inferences for the key secondary efficacy objectives were similar among the treatment-regimen estimand, efficacy estimand, and EU analysis.

Dulaglutide (pooled or individual doses) had no statistically significant effect on the key secondary efficacy outcome of change from baseline to Week 26 in BMI.

Table 13: Primary and key secondary efficacy results using each estimand

	Change in HbA1c (%) between baseline and Week 26: Primary Objective Pooled Dulaglutide Doses versus Placebo					
	Treatment-Regimen Estimand (Table GBGC.8.1)		**Efficacy Estimand** (Table GBGC.8.2)		**EMA analysis** (Table GBGC.8.3)	
	LSM (SE) % mmol/mol	**LSM Difference; p-value** % mmol/mol	**LSM (SE)** % mmol/mol	**LSM Difference; p-value** % mmol/mol	**LSM (SE)** % mmol/mol	**LSM Difference; p-value** % mmol/mol
Placebo	0.6 (0.2)		0.5 (0.2)		0.6 (0.2)	
	6.2 (2.4)		6.0 (2.6)		6.7 (2.6)	
Pooled dulaglutide (H1)	**-0.8 (0.2)**	**-1.4; p<0.001**	**-0.7 (0.2)**	**-1.3; p<0.001**	**-0.7 (0.2)**	**-1.3; p<0.001**
	-8.5 (1.6)	**-14.8; p<0.001**	**-8.2 (1.7)**	**-14.1; p<0.001**	**-7.5 (1.8)**	**-14.1; p<0.001**
Dulaglutide 1.5 mg (H2)	-0.9 (0.2)	-1.5; p<0.001	-1.0 (0.2)	-1.5; p<0.001	-1.0 (0.2)	-1.6; p<0.001
	-10.3 (2.3)	-16.5; p<0.001	-10.8 (2.4)	-16.8; p<0.001	-10.4 (2.5)	-17.2; p<0.001
Dulaglutide 0.75 mg (H3)	-0.6 (0.2)	-1.2; p<0.001	-0.5 (0.2)	-1.0; p=0.002	-0.4 (0.2)	-1.0; p=.0.003
	-6.8 (2.3)	-13.0; p<0.001	-5.5 (2.4)	-11.4; p=0.002	-4.3 (2.6)	-11.1; p=0.003

	Secondary Objective: Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 26					
	Treatment-Regimen Estimand (Table GBGC.8.4)		**Efficacy Estimand** (Table GBGC.8.5)		**EMA analysis** (Table GBGC.8.6)	
	%	**Odds Ratio; p-value**	%	**Odds Ratio; p-value**	%	**Odds Ratio; p-value**
Placebo	13.7		18.4		16.2	
Pooled dulaglutide (H4)	51.5	8.1; p<0.001	56.5	11.3; p<0.001	56.0	12.3; p<0.001
Dulaglutide 1.5 mg (H5)	48.1	7.4; p<0.001	53.2	11.7; p<0.001	52.3	13.2; p<0.001
Dulaglutide 0.75 mg (H6)	54.9	8.8; p<0.001	60.0	11.0; p<0.001	60.0	11.5; p<0.001

	Treatment-Regimen Estimand (Table GBGC.8.7)		Efficacy Estimand (Table GBGC.8.8)		EMA analysis (Table GBGC.8.9)	
Secondary Objective: Change in FBG between baseline and Week 26						
	LSM (SE) mg/dL mmol/L	LSM Difference; p-value mg/dL mmol/L	LSM (SE) mg/dL mmol/L	LSM Difference; p-value mg/dL mmol/L	LSM (SE) mg/dL mmol/L	LSM Difference; p-value mg/dL mmol/L
Placebo	17.1 (7.7)		17.3 (8.1)		19.4 (8.1)	
	1.0 (0.4)		1.0 (0.5)		1.1 (0.5)	
Pooled dulaglutide (H7)	-18.9 (5.2)	-35.9; p<0.001	-18.6 (5.2)	-35.5; p<0.001	-16.5 (5.3)	-35.4; p<0.001
	-1.1 (0.3)	-2.0; p<0.001	-1.0 (0.3)	-2.0; p<0.001	-0.9 (0.3)	-2.0; p<0.001
Dulaglutide 1.5 mg (H8)	-24.9 (7.5)	-42.0; p<0.001	-27.8 (7.4)	-45.1; p<0.001	-25.6 (7.5)	-45.0; p<0.001
	-1.4 (0.4)	-2.3; p<0.001	-1.5 (0.4)	-2.5; p<0.001	-1.4 (0.4)	-2.5; p<0.001
Dulaglutide 0.75 mg (H9)	-12.8 (7.3)	-29.9; p=0.005	-8.5 (7.4)	-25.9; p=0.021	-6.5 (7.6)	-25.9; p=0.022
	-0.7 (0.4)	-1.7; p=0.005	-0.5 (0.4)	-1.4; p=0.021	-0.4 (0.4)	-1.4; p=0.022

	Treatment-Regimen Estimand (Table GBGC.8.10)		Efficacy Estimand (Table GBGC.8.11)		EMA analysis (Table GBGC.8.12)	
Secondary Objective: Change in BMI (kg/m^2) between baseline and Week 26						
	LSM (SE)	LSM Difference; p-value	LSM (SE)	LSM Difference; p-value	LSM (SE)	LSM Difference; p-value
Placebo	0.0 (0.2)		-0.0 (0.2)		-0.0 (0.2)	
Pooled dulaglutide (H10)	-0.1 (0.1)	-0.1; p=0.553	-0.1 (0.1)	-0.1; p=0.776	-0.1 (0.1)	-0.1; p=0.771
Dulaglutide 1.5 mg (H11)	-0.1 (0.2)	-0.1; p=0.732	-0.1 (0.2)	-0.0; p=0.924	-0.0 (0.2)	-0.0; p=0.974
Dulaglutide 0.75 mg (H12)	-0.2 (0.2)	-0.2; p=0.492	-0.2 (0.2)	-0.1; p=0.689	-0.2 (0.2)	-0.1; p=0.638

Abbreviations: LSM = least squares mean; SE = standard error.
Notes: Results for the primary objective of the study are shown in bold.
H1 through H12 refers to hypotheses being tested in the graphical testing approach (Statistical Methods appendix [Figure 5.2]). Note: p-values highlighted in bold font represent the primary endpoint.

Other secondary efficacy objectives

Results for the secondary efficacy objectives of change in efficacy measures from baseline to 52 weeks were supportive of the primary and key secondary efficacy objectives:

- Improvements from baseline in HbA1c, fasting serum glucose, and percentage of patients with HbA1c <7% in patients assigned to dulaglutide were generally sustained through Week 52.
- Patients switching from placebo to dulaglutide 0.75 mg at Week 26 had improvements in HbA1c, FBG, and the percentage of these patients with HbA1c <7% at Week 52 that were similar to those observed between baseline and Week 26 in patients assigned to dulaglutide 0.75 mg.

Subgroup analyses on primary HbA1c efficacy endpoint

Subgroup analyses to assess treatment interaction with important baseline factors were conducted for the primary endpoint of HbA1c in the ITT population using the treatment-regimen estimand as summarized in the table below. For all subgroups examined, dulaglutide (individual and pooled dose groups) consistently reduced HbA1c from baseline to 26 weeks compared with placebo.

Table 14: Subgroup analyses for change from baseline in HbA1c at 26 weeks, by treatment and subgroup, Treatment-Regimen Estimand

Subgroup	n	Interaction p-Value
Sex		
Female	110	0.023
Male	44	
Baseline HbA1c		
<8.0%	70	0.055
≥8.0%	84	
Age group		
≤14 years	60	0.314
>14 years	94	
Race		
White	84	0.413
All Others	66	
Ethnicity		
Hispanic/Latino	85	0.494
Non-Hispanic/Latino	65	
Geographic region		
US	73	0.453
Non-US	81	
Geographic region		
EU[a]	15	0.305
Non-EU	139	
Duration of diabetes		
<Median (2 years)	71	0.389
≥Median (2 years)	83	
Baseline BMI		
<Median (32 kg/m^2)	77	0.487
≥Median (32 kg/m^2)	77	
Baseline weight		
< Median (85.85 kg)	77	0.407
≥ Median (85.85 kg)	77	
Baseline metformin use		
Yes	136	0.695
No	18	
Baseline insulin use		
Yes	43	0.319
No	111	
Baseline metformin and insulin use		
Yes	39	0.387
No	115	
Monotherapy only		
Yes	14	0.573
No	140	

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; n = number of subjects in the population with a nonmissing value at the specified time point; SD = standard deviation.

[a] The EU subgroup included patients enrolled in France, Germany, Turkey, and the United Kingdom.

Note: for continuous variables, data are presented as observed mean (SD).

The treatment-by-subgroup interactions for change in HbA1c was not statistically significant (evaluated at a 2-sided alpha of 0.1) based on age, race, ethnicity, BMI, weight, geographic region (US versus non-US; EU versus non-EU), duration of diabetes, or categories of baseline diabetes medication use.

The treatment-by-subgroup interaction for the primary endpoint of HbA1c was significant (p<0.10) for sex (female versus male) and baseline HbA1c (<8.0%, ≥8.0%).

Table 15: Change from baseline in HbA1c at 26 weeks, by treatment and sex or baseline HbA1c subgroup, treatment-regimen estimand

Change in HbA1c between baseline and Week 26:							
	Females (n=110)			Males (n=44)			
	LSM (SE) % mmol/mol	LSM Difference % mmol/mol	p-Value	LSM (SE) % mmol/mol	LSM Difference % mmol/mol	p-Value	p-Value for Interaction
Placebo	0.24 (0.41)			0.70 (0.87)			
	2.61 (4.53)			7.68 (9.46)			
Dulaglutide 0.75 mg	-0.95 (0.42)	-1.19	p<0.001	-0.72 (0.70)	-1.42	p=0.061	.023
	-10.41 (4.57)	-13.02		-7.89 (7.63)	-15.57		
Dulaglutide 1.5 mg	-1.21 (0.40)	-1.45	p<0.001	-1.16 (0.81)	-1.86	p=0.012	
	-13.26 (4.34)	-15.87		-12.67 (8.84)	-20.36		
Pooled dulaglutide	-1.08 (0.37)	-1.32	p<0.001	-0.94 (0.68)	-1.64	p=0.014	
	-11.83 (4.07)	-14.44		-10.28 (7.39)	-17.96		
Change from baseline by baseline HbA1c (<8%, ≥8%)							
	Baseline HbA1c <8% (n=70) Mean HbA1c_BL, 7.0%			Baseline HbA1c ≥8% (n=84) Mean HbA1c_BL, 9.0%			
	LSM (SE) % mmol/mol	LSM Difference % mmol/mol	p-Value	LSM (SE) % mmol/mol	LSM Difference % mmol/mol	p-Value	p-Value for Interaction
Placebo	0.19 (0.43)			0.61 (0.56)			
	2.03 (4.68)			6.66 (6.08)			
Dulaglutide 0.75 mg	-0.77 (0.41)	-0.95	p=0.004	-0.64 (0.54)	-1.25	p=0.007	.055
	-8.38 (4.48)	-10.41		-6.96 (5.89)	-13.62		
Dulaglutide 1.5 mg	-0.49 (0.42)	-0.67	p=0.045	-1.39 (0.54)	-2.00	p<0.001	
	-5.33 (4.61)	-7.36		-15.16 (5.85)	-21.82		
Pooled dulaglutide	-0.63 (0.38)	-0.81	p=0.005	-1.01 (0.48)	-1.62	p<0.001	
	-6.86 (4.19)	-8.88		-11.06 (5.27)	-17.72		

Abbreviations: HbA1c = hemoglobin A1c; HbA1c_BL = baseline HbA1c; LSM = least squares mean; n = number of patients analysed within subgroup; SE = standard error.

The treatment-by-subgroup interaction for the primary endpoint of HbA1c was significant (p<0.10) for sex (female versus male) and baseline HbA1c (<8.0%, ≥8.0%).

For the *subgroup analysis by sex*, the change from baseline in HbA1c favored dulaglutide at each dose compared with placebo in both female and male patients. The significant interaction appeared driven primarily by larger increases from baseline in HbA1c in the placebo group among male versus female patients, and consequently larger placebo-adjusted LS mean changes from baseline in HbA1c in the dulaglutide groups in male patients. The smaller number of males relative to females enrolled in the study and larger variability around the point estimates for LS mean treatment differences also may have contributed to the statistically significant treatment-by-sex interaction. Whether this interaction reflects a true difference between sexes in either treatment effect, is therefore considered unlikely.

For the *subgroup analysis by baseline HbA1c*, the change from baseline in HbA1c also favored dulaglutide compared with placebo in both patients with lower (<8%) or higher (≥8%) baseline HbA1c. The significant interaction was driven primarily by larger increases from baseline in HbA1c in the placebo

group among patients with higher baseline HbA1c, together with larger placebo-adjusted LS mean changes from baseline in HbA1c in each of the dulaglutide dose groups particularly in patients randomized to dulaglutide 1.5 mg. This interaction is consistent with prior studies of dulaglutide and other GLP-1 RAs, showing patients with higher HbA1c at baseline have treatment effects on HbA1c reduction that are greater and more dose dependent than among patients with lower HbA1c at baseline.

2.4.2. Discussion on clinical efficacy

Patient population

The patient population enrolled in Study GBGC was representative of the general population of children and adolescents with T2DM.

Patient retention and adherence to study drug during the primary, double-blind period of the study was high, with 95% of patients completing Week 26 on study drug. Overall compliance with study medication was nearly 99% and did not significantly differ across treatment groups. The proportion of patients discontinuing study drug prior to the Week 26 primary endpoint visit was low (5.8%) and not significantly different across treatment groups. These study characteristics provided for a valid and robust assessment of the study's primary and key secondary objectives.

Effects on glycemic control

Dulaglutide (0.75 and 1.5 mg sc QW, pooled dose groups) was superior to placebo (p<0.001) in improving glycemic control as measured by baseline to Week 26 change in HbA1c in children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin. The primary efficacy objective was met using either the treatment-regimen estimand or efficacy estimand, as well as the EU-requested analysis (efficacy estimand excluding patients who were metformin naive at baseline).

Each dulaglutide dose group individually (0.75 or 1.5 mg) was superior to placebo with respect to the primary efficacy measure of baseline to Week 26 change in HbA1c, with dose-related improvements in HbA1c from baseline to Week 26 of -1.2% in the 0.75 mg dose group and -1.5% in the 1.5 mg dose group (treatment-regimen estimand). Analyses using the efficacy estimand and EU-requested analysis supported the same conclusion. These improvements in HbA1c, adjusted for placebo, are in the range of those reported previously for dulaglutide 0.75 or 1.5 mg sc QW in adults with T2DM (Jendle et al. 2016).

Improvements in HbA1c from baseline to Week 26 favoured patients assigned to dulaglutide compared with placebo across patient subgroups based on age, sex, race, ethnicity, BMI, weight, geographic region (US versus outside the US; EU versus non-EU), duration of diabetes, or baseline diabetes medication use. Based on analysis of subgroup-by-treatment interaction effect, no heterogeneity of dulaglutide treatment effect on HbA1c was evident in subgroups relative to the overall study population, except for sex (female versus male) and baseline HbA1c (<8.0%, ≥8.0%). HbA1c improved in both male and female patients assigned to dulaglutide, but placebo-adjusted mean improvement was numerically greater in males versus females. The clinical relevance of this interaction is unclear and may have been related in part to the smaller sample of males randomized to the study versus females. HbA1c improved in patients assigned to dulaglutide regardless of baseline HbA1c, but placebo-adjusted mean improvement was numerically greater and more dose related among patients with higher HbA1c at baseline, consistent with dulaglutide studies in adults (Gallwitz et al. 2018; Frias et al. 2021).

Superiority of dulaglutide to placebo in improving glycemic control in children and adolescents with T2DM was further supported by results of additional key secondary efficacy objectives (controlled for multiplicity): regardless of estimand used, patients randomized to dulaglutide (pooled or individual dose

groups) compared with placebo had a statistically significantly higher odds of achieving an HbA1c <7% and significantly greater mean improvement in FBG.

Exploratory glycemic efficacy measures also supported the efficacy of dulaglutide, where dulaglutide had a significantly greater effect than placebo on

- improvement in HbA1c from baseline to Week 13 (the earliest time point tested)
- the percentage of patients with HbA1c ≤6.5% at Week 26
- the percentage of patients achieving the composite endpoints of HbA1c <7% or ≤6.5% without severe, documented symptomatic (PG <70 mg/dL), or probably hypoglycemia at Week 26, and
- dose-related improvements in markers of measures of insulin sensitivity and beta-cell function (HOMA2-%B) at Weeks 13 and 26.

Although not placebo-controlled beyond Week 26, results from the primary and secondary efficacy measures through 52 weeks further supported the glycemic efficacy of dulaglutide in these patients as evidenced by the following:

- patients switching from placebo to dulaglutide 0.75 mg at Week 26 had improvements in HbA1c, FBG, and percentage of these patients achieving glycemic control targets at Week 52 that were similar to those observed between baseline and Week 26 in patients assigned to dulaglutide 0.75 mg, and
- improvements from baseline in HbA1c, FBG, and percentage of patients achieving clinically relevant glycemic control targets (HbA1c <7% and ≤6.5%) in patients assigned to dulaglutide were generally sustained at Week 52.

Notably for the interpretation of these data, results from completed Phase 3 studies that maintained paediatric patients with T2DM beyond 26 weeks (Tamborlane et al. 2019; Jalaludin et al. 2022) show a more rapid increase in HbA1c over time, consistent with the more rapid disease progression established in youth with T2DM relative to adults (TODAY Study Group 2012; RISE Consortium 2019).

Effects on BMI and other body weight parameters
The key secondary efficacy objective of change in BMI was not met: dulaglutide (either pooled or individual dose groups) had no significant or clinically relevant effects on BMI compared with placebo through 26 weeks of treatment. Results for exploratory body weight parameters provided the same conclusion: 26-week changes in body weight, BMI SDS, and waist circumference were small in each treatment group with no clinically meaningful differences between dulaglutide groups and placebo, and no clinically relevant changes from baseline to 52 weeks were observed in BMI, BMI SDS, or body weight among patients assigned to either dose of dulaglutide.

The lack of effect of dulaglutide versus placebo on body weight parameters is consistent with other completed Phase 3 trials of the GLP-1 RAs in paediatric patients with T2DM: neither liraglutide nor exenatide once weekly had a statistically significant effect versus placebo on body weight parameters at the study primary endpoint (Tamborlane et al. 2019; Bensignor et al. 2021; Tamborlane et al. 2021).

Paediatric human factors studies
In December 2017, a human factors validation test completed to demonstrate that children or adolescents with T2DM can use the commercially available Trulicity pre-filled pen safely and effectively. The test showed that T2DM children can use the Trulicity pre-filled pen independently and successfully for self-injection and were able to acquire necessary knowledge from the Information For Use leaflet.

In February 2020, a Human Factors Engineering or Usability Engineering (HFE/UE) report completed. This report summarises the safety-related HFE/UE considerations, issues, processes, resolutions, and conclusions that support safe and successful use of Trulicity pre-filled pens by paediatric T2DM patients.

2.4.3. Conclusions on the clinical efficacy

In children and adolescents aged 10 to less than 18 years with inadequately controlled T2DM treated with or without metformin and/or basal insulin, treatment with dulaglutide 0.75 or 1.5 mg sc QW for 26 weeks was superior to placebo in improving glycemic control. The placebo-adjusted improvements in HbA1c were clinically relevant and comparable to those observed in adults with T2DM. The improvements from baseline in glycemic control with dulaglutide were generally sustained through 52 weeks, which is especially relevant given the more rapid underlying disease progression seen in the paediatric population compared with adults.

2.5. Clinical safety

Introduction

The submitted safety data were derived from the paediatric study GBGC. Since no other paediatric study was submitted, no pooling of data from several studies was possible. In Study GBGC, around 50 patients aged 10-17 years were treated for 26 weeks with placebo, 0.75 mg QW dulagluitide or 1.5 mg QW dulaglutide. These doses are also used in adults. Study GBGC also included an uncontrolled, open-label extension period of another 26 weeks, in which placebo patients were switched to 0.75 mg QW dulaglutide. For details, see the section on clinical efficacy above.

All randomized patients received at least 1 dose of study drug; thus, the Safety Population is equivalent to the ITT Population. Safety was assessed from first dose of the study drug until the end of safety follow-up (4 weeks after the end of the extension period).

The MAH provided the following table of key safety results, encompassing frequent spontaneously reported AEs as well as AEs of special interest, known from previous experience with dulaglutide in adults and from other GLP-1 receptor agonists.

Table 16: Key safety results, including AESIs (p12 of study report)

	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	All Dula (N=103)
Patients with ≥1 Adverse Event, n (%)[a]				
TEAEs	35 (68.6)	38 (74.5)	38 (73.1)	76 (73.8)
Nausea	4 (7.8)	7 (13.7)	8 (15.4)	15 (14.6)
Vomiting	2 (3.9)	9 (17.6)	7 (13.5)	16 (15.5)
Diarrhea	7 (13.7)	8 (15.7)	11 (21.2)	19 (18.4)
SAEs	3 (5.9)	1 (2.0)	1 (1.9)	2 (1.9)
Discontinuation from study drug due to AE	1 (2.0)	1 (2.0)	2 (3.8)	3 (2.9)
Allergic/Hypersensitivity Reaction TEAEs	2 (3.9)	3 (5.9)	2 (3.8)	5 (4.9)
Injection Site Reaction TEAEs	5 (9.8)	5 (9.8)	4 (7.7)	9 (8.7)
Hypoglycemia, n (%)				
Severe	0	0	0	0
Documented symptomatic PG <54 mg/dL (<3.0 mmol/L)	0	1 (2.0)	1 (1.9)	2 (1.9)
Total[b] with PG <54 mg/dL (<3.0 mmol/L)	1 (2.0)	4 (7.8)	5 (9.6)	9 (8.7)
Documented symptomatic PG <70 mg/dL (<3.9 mmol/L)	6 (11.8)	5 (9.8)	3 (5.8)	8 (7.8)
Total[b] with PG <70 mg/dL (3.9 mmol/L)	8 (15.7)	10 (19.6)	12 (23.1)	22 (21.4)
Patients requiring antihyperglycemic rescue, n (%)	9 (17.6)	2 (3.9)	1 (1.9)	3 (2.9)
Pancreatic enzymes (mean change from baseline)				
Total amylase (IU/L)	0.1	4.8	6.5	5.6
Pancreatic amylase (IU/L)	0.6	1.8	2.9	2.3
Lipase (IU/L)	2.2	4.4	3.9	4.1
Vital Signs Seated (LS mean change from baseline)				
Systolic blood pressure (mm Hg)	-1.0	2.8	1.5	2.1
Diastolic blood pressure (mm Hg)	2.1	1.3	-0.5	0.3
Heart rate (bpm)	0.8	1.2	2.1	1.5
ECG Parameters (LS mean change from baseline)				
Heart rate (bpm)	-0.5	0.3	2.6	1.5
QTcB (msec)	1.5	3.3	-1.5	0.9
PR interval (msec)	-2.1	3.3	1.1	2.2
Patients with treatment-emergent ADAs, n (%)[c]	1 (2.1)	2 (4.0)	2 (3.9)	4 (4.0)

Abbreviations: 'dula' for dulaglutide

Patient exposure

Treatment exposure was estimated from the date of first dose of study drug to the date of last dose of study drug plus 1 day. Mean exposure (days) and total patient-years of exposure to study intervention by randomization group were as follows:

- Placebo/dulaglutide 0.75-mg group: 336.2 days (46.9 patient-years)

- Dulaglutide 0.75-mg group: 338.8 days (47.3 patient-years), and
- Dulaglutide 1.5-mg group: 342.8 days (48.8 patient-years).

Adverse events

Overview of AEs

The following table provides an overview of the AE profile of dulaglutide in paediatric patients. The percentage of patients suffering a treatment-related AE was fairly balanced between the treatment groups. The incidence of serious AEs was low, which is reassuring. Incidence was numerically lower in the dulaglutide groups than in the placebo group, but firm conclusions are not possible because of the small number of events. In higher percentage of patients in the dulaglutide groups than in the placebo group, the AEs were considered treatment-related.

Table 17: Overview of All Adverse Events through Week 26 By Treatment Intent-to-Treat Population

	Placebo		Dula_0.75		Dula_1.5		All Dula		Total	
	(N=51)		(N=51)		(N=52)		(N=103)		(N=154)	
Number of Subjects*a	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Deaths*b	0		0		0		0		0	
Serious Adverse Events	3	(5.9)	1	(2.0)	1	(1.9)	2	(1.9)	5	(3.2)
Discontinuations from Study due to an Adverse Event*c	1	(2.0)	0		1	(1.9)	1	(1.0)	2	(1.3)
Discontinuations from Study Treatment due to an Adverse Event	1	(2.0)	1	(2.0)	2	(3.8)	3	(2.9)	4	(2.6)
Treatment-Emergent Adverse Events	35	(68.6)	38	(74.5)	38	(73.1)	76	(73.8)	111	(72.1)
Treatment-Emergent Adverse Events Related to Study Treatment*d	11	(21.6)	16	(31.4)	16	(30.8)	32	(31.1)	43	(27.9)

*a   Subjects may be counted in more than one category.
*b   Deaths are also included as serious adverse events and discontinuations due to an adverse event.
*c   Discontinuations from study are also included in discontinuations from study treatment due to an adverse event.
*d   Includes events that were considered related to study treatment as judged by the investigator.
Abbreviations: 'dula' for dulaglutide

AEs by Preferred Term

Most of the AEs that more frequently occurred with dulaglutide than with placebo were related to gastrointestinal (GI) function such as diarrhoea, nausea and vomiting. Furthermore, headache and dizziness were clearly more frequent with dulaglutide than with placebo. For details, see table below; the mentioned AE types are highlighted in blue. The overarching term "Gastrointestinal disorders" is also included.

Table 18: Summary of Treatment-Emergent Adverse Events by Treatment Group through Week 26 By Decreasing Frequency of Preferred Term; Intent-to-Treat Population

	Placebo		Dula 0.75 mg		Dula 1.5 mg		Pooled Dula	
	N=51		N=51		N=52		N=103	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with >= 1 TEAE	**35**	**(68.6)**	**38**	**(74.5)**	**38**	**(73.1)**	**76**	**(73.8)**
Gastrointestinal disorders	*14*	*(27.5)*	*21*	*(41.2)*	*22*	*(42.3)*	*43*	*(41.7)*
Diarrhoea	7	(13.7)	8	(15.7)	11	(21.2)	19	(18.4)
Headache	5	(9.8)	7	(13.7)	8	(15.4)	15	(14.6)
Nausea	4	(7.8)	7	(13.7)	8	(15.4)	15	(14.6)
Vomiting	2	(3.9)	9	(17.6)	7	(13.5)	16	(15.5)
Abdominal pain upper	4	(7.8)	3	(5.9)	5	(9.6)	8	(7.8)
Upper respiratory tract infection	4	(7.8)	2	(3.9)	6	(11.5)	8	(7.8)
Nasopharyngitis	3	(5.9)	5	(9.8)	2	(3.8)	7	(6.8)
Abdominal pain	3	(5.9)	4	(7.8)	1	(1.9)	5	(4.9)
Dizziness	1	(2.0)	4	(7.8)	2	(3.8)	6	(5.8)
Gastroenteritis	2	(3.9)	1	(2.0)	3	(5.8)	4	(3.9)
Pyrexia	2	(3.9)	2	(3.9)	2	(3.8)	4	(3.9)
Accidental overdose	0		3	(5.9)	2	(3.8)	5	(4.9)
Back pain	2	(3.9)	1	(2.0)	2	(3.8)	3	(2.9)
Urinary tract infection	3	(5.9)	2	(3.9)	0		2	(1.9)
Dysmenorrhoea*b	1	(2.4)	1	(2.9)	2	(5.9)	3	(4.3)
Influenza	0		2	(3.9)	2	(3.8)	4	(3.9)
Injection site pain	2	(3.9)	1	(2.0)	1	(1.9)	2	(1.9)
Rash	1	(2.0)	2	(3.9)	1	(1.9)	3	(2.9)
Sinusitis	2	(3.9)	1	(2.0)	1	(1.9)	2	(1.9)
Arthralgia	1	(2.0)	2	(3.9)	0		2	(1.9)
Ear infection	0		2	(3.9)	1	(1.9)	3	(2.9)
Fatigue	0		1	(2.0)	2	(3.8)	3	(2.9)
Injection site reaction	1	(2.0)	1	(2.0)	1	(1.9)	2	(1.9)
Nasal congestion	1	(2.0)	1	(2.0)	1	(1.9)	2	(1.9)
Pharyngotonsillitis	2	(3.9)	1	(2.0)	0		1	(1.0)
Somnolence	1	(2.0)	0		2	(3.8)	2	(1.9)
Abdominal discomfort	0		1	(2.0)	1	(1.9)	2	(1.9)
Abscess	1	(2.0)	1	(2.0)	0		1	(1.0)

Abbreviations: dula for dulaglutide

AEs of special interest

The MAH has defined the types of events listed below as AEs of special interest (AESIs):

- Gastrointestinal Events (Including Nausea and Vomiting)
- Hypoglycaemia
- Pancreatitis
- Thyroid C-Cell Hyperplasia and C-Cell Neoplasms
- Renal Impairment
- Supraventricular Arrhythmia
- Malignancy
- Allergic/Hypersensitivity Reactions and Injection site reactions

These are discussed in more detail in the following, except hypersensitivity and injection site reactions, which are discussed in the immunogenicity section below.

Gastrointestinal Events (Including Nausea and Vomiting)

The incidence of GI side effects is presented in the section on AEs per Preferred Term above. A more detailed analysis of the events, by severity and by time of occurrence is given below.

Severity of nausea, vomiting, and diarrhoea

As shown in the following table, most events of nausea, vomiting and diarrhoea were mild. Moderate events were mainly observed in the high-dose dulaglutide group. One patient suffered severe vomiting (in the low-dose dulaglutide group).

Table 19: Incidence of Treatment-Emergent Nausea, Vomiting, or Diarrhea by Treatment and Maximum Severity through Week 26, Intent-to-Treat Population

Event Severity	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
Nausea	4 (7.8)	7 (13.7)	8 (15.4)	15 (14.6)
Mild	3 (5.9)	6 (11.8)	6 (11.5)	12 (11.7)
Moderate	1 (2.0)	1 (2.0)	2 (3.8)	3 (2.9)
Severe	0	0	0	0
Vomiting	2 (3.9)	9 (17.6)	7 (13.5)	16 (15.5)
Mild	1 (2.0)	7 (13.7)	4 (7.7)	11 (10.7)
Moderate	1 (2.0)	1 (2.0)	3 (5.8)	4 (3.9)
Severe	0	1 (2.0)	0	1 (1.0)
Diarrhea	7 (13.7)	8 (15.7)	11 (21.2)	19 (18.4)
Mild	6 (11.8)	8 (15.7)	9 (17.3)	17 (16.5)
Moderate	1 (2.0)	0	2 (3.8)	2 (1.9)
Severe	0	0	0	0

Abbreviations: 'dula' for dulaglutide

Time course of nausea and vomiting

As expected from existing experience with GLP-1 receptor agonists, most events of nausea and vomiting occurred at the beginning of dulaglutide treatment, mainly in the first two weeks, see table below. The time-course of diarrhoea occurrence was similar.

Table 20: Summary of Incidence of Nausea and Vomiting through Week 52 by Treatment and Treatment Duration; Intent-to-Treat Population (p1010 of study report)

	Placebo/ Dula_0.75			Dula_0.75			Dula_1.5			All Dula		
	N=51			N=51			N=52			N=103		
	M	m	(%)	M	m	(%)	M	m	(%)	M	m	(%)
0 to <=2 Wk	51	1	(2.0)	51	9	(17.6)	52	8	(15.4)	103	17	(16.5)
>2 to <=4 Wk	50	1	(2.0)	51	1	(2.0)	52	4	(7.7)	103	5	(4.9)
>4 to <=6 Wk	50	1	(2.0)	51	1	(2.0)	52	2	(3.8)	103	3	(2.9)
>6 to <=8 Wk	50	0		51	0		52	1	(1.9)	103	1	(1.0)
>8 to <=10 Wk	50	0		51	1	(2.0)	52	2	(3.8)	103	3	(2.9)
>10 to <=12 Wk	49	0		51	1	(2.0)	51	0		102	1	(1.0)
>12 to <=14 Wk	49	0		51	1	(2.0)	51	0		102	1	(1.0)
>14 to <=16 Wk	47	1	(2.1)	51	0		51	0		102	0	
>16 to <=18 Wk	47	0		51	1	(2.0)	51	1	(2.0)	102	2	(2.0)
>18 to <=20 Wk	47	0		50	0		51	0		101	0	
>20 to <=22 Wk	47	0		50	1	(2.0)	51	0		101	1	(1.0)
>22 to <=24 Wk	47	0		50	0		51	0		101	0	
>24 to <=26 Wk	47	1	(2.1)	50	1	(2.0)	51	0		101	1	(1.0)
>26 to <=28 Wk	47	1	(2.1)	49	2	(4.1)	51	2	(3.9)	100	4	(4.0)
>28 to <=30 Wk	47	2	(4.3)	49	1	(2.0)	50	1	(2.0)	99	2	(2.0)
>30 to <=32 Wk	47	0		49	2	(4.1)	50	0		99	2	(2.0)
>32 to <=34 Wk	47	0		49	0		50	2	(4.0)	99	2	(2.0)
>34 to <=36 Wk	47	0		49	1	(2.0)	50	0		99	1	(1.0)
>36 to <=38 Wk	47	1	(2.1)	49	2	(4.1)	50	1	(2.0)	99	3	(3.0)
>38 to <=40 Wk	47	2	(4.3)	49	1	(2.0)	50	1	(2.0)	99	2	(2.0)
>40 to <=42 Wk	47	0		48	1	(2.1)	50	0		98	1	(1.0)
>42 to <=44 Wk	46	0		48	1	(2.1)	49	1	(2.0)	97	2	(2.1)
>44 to <=46 Wk	46	0		48	1	(2.1)	49	1	(2.0)	97	2	(2.1)
>46 to <=48 Wk	46	0		48	0		48	2	(4.2)	96	2	(2.1)
>48 to <=50 Wk	45	0		47	0		48	2	(4.2)	95	2	(2.1)
>50 to <=52 Wk	45	0		47	0		47	2	(4.3)	94	2	(2.1)
Total												
0 to <=52 Wk	51	9	(17.6)	51	15	(29.4)	52	17	(32.7)	103	32	(31.1)

M = number of subjects who had at least some time in interval; m = number of subjects with the onset of an event reported during the interval; N = number of subjects in analysis population.

Hypoglycaemia

The following table shows an analysis of hypoglycaemia per category. The percentage of patients having reported any hypoglycaemia event was slightly and dose-dependently increased with dulaglutide compared to placebo. The number of subjects suffering a documented hypoglycaemia <54 mg/dL was low. A numerical imbalance between placebo and dulaglutide can be seen in the category "Total with PG <54 mg/dL". Note that in this category also subjects are included which had no PG measurement, as a worst-case assumption.

No cases of severe hypoglycemia were reported at any time during the study.

Table 21: Summary and Analysis of Hypoglycaemia Incidence through Week 26

Hypoglycemia Category	Placebo N=51 n (%)	Dula 0.75 mg N=51 n (%)	Dula 1.5 mg N=52 n (%)	Pooled Dula N=103 n (%)
Severe	0	0	0	0
Total[a] with PG <70 mg/dL (<3.9 mmol/L)	8 (15.7)	10 (19.6) p=0.796	12 (23.1) p=0.456	22 (21.4) p=0.518
Documented symptomatic with PG <70 mg/dL (<3.9 mmol/L)	6 (11.8)	5 (9.8) p=1.000	3 (5.8) p=0.319	8 (7.8) p=0.552
Total[a] with PG <54 mg/dL (<3 mmol/L)	1 (2.0)	4 (7.8) p=0.362	5 (9.6) p=0.205	9 (8.7) p=0.166
Documented symptomatic with PG <54 mg/dL (<3 mmol/L)	0	1 (2.0) p=1.000	1 (1.9) p=1.000	2 (1.9) p=1.000
All[b] with PG <54 mg/dL (<3 mmol/L)	1 (2.0)	2 (3.9) p=0.000	2 (3.9) p=1.000	4 (3.9) p=1.000

Abbreviations: Dula = dulaglutide; PG = plasma glucose; N = number of patients randomized and treated; n = number of patients with hypoglycemia.
a   Total hypoglycemia category includes patients with documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia when PG measurement was missing. In cases of probable hypoglycemia, patients are counted in both the PG <70 mg/dL (<3.9 mmol/L) and <54 mg/dL (<3 mmol/L) categories.
b   Includes all patients with a measured PG <54 mg/dL (<3 mmol/L) at any time, including postrescue data.
        p-Values are for comparison between dulaglutide and placebo group incidence from Fisher's exact

In order to evaluate whether the observed events of hypoglycaemia were due to dulaglutide or due to accompanying insulin therapy, the MAH analysed the hypoglycaemia rate per baseline insulin use. In general, insulin used should not change from baseline during the study except for rescue medication.

Among patients not using insulin at baseline, the incidence of total hypoglycaemia at both PG thresholds (<70 mg/dL [<3.9 mmol/L] or <54 mg/dL [<3 mmol/L]) was numerically higher in patients in the dulaglutide groups compared with those receiving placebo; see table below. With insulin use, hypoglycaemia rate tended to be higher in the placebo group than in the dulaglutide groups.

Table 22: Summary and Analysis of Hypoglycaemia Incidence by Baseline Insulin Use through Week 26

Baseline insulin use Hypoglycemia Category	Placebo	Dula 0.75 mg	Dula 1.5 mg	Pooled Dula
Baseline insulin use = Yes	**N=15 n (%)**	**N=13 n (%)**	**N=15 n (%)**	**N=28 n (%)**
Total[a] with PG <70 mg/dL (<3.9 mmol/L)	6 (40.0)	4 (30.8) p=0.705	4 (26.7) p=0.700	8 (28.6) p=0.507
Documented symptomatic with PG <70 mg/dL (<3.9 mmol/L)	5 (33.3)	3 (23.1) p=0.686	2 (13.3) p=0.390	5 (17.9) p=0.281
Total[a] with PG <54 mg/dL (<3 mmol/L)	1 (6.7)	2 (15.4) p=0.583	1 (6.7) p=1.000	3 (10.7) p=1.000
Documented symptomatic with PG <54 mg/dL (<3 mmol/L)	0	1 (7.7) p=0.464	1 (6.7) p=1.000	2 (7.1) p=0.535
All with PG <54 mg/dL (<3 mmol/L)[b]	1 (6.7)	2 (15.4) p=0.583	1 (6.7) p=1.000	3 (10.7) p=1.000
Baseline insulin use = No	**N=36 n (%)**	**N=38 n (%)**	**N=37 n (%)**	**N=75 n (%)**
Total[a] with PG <70 mg/dL (<3.9 mmol/L)	2 (5.6)	6 (15.8) p=0.263	8 (21.6) p=0.085	14 (18.7) p=0.085
Documented symptomatic with PG <70 mg/dL (<3.9 mmol/L)	1 (2.8)	2 (5.3) p=1.000	1 (2.7) p=1.000	3 (4.0) p=1.000
Total[a] with PG <54 mg/dL (<3 mmol/L)	0	2 (5.3) p=0.494	4 (10.8) p=0.115	6 (8.0) p=0.174
Documented symptomatic with PG <54 mg/dL (<3 mmol/L)	0	0	0	0
All with PG <54 mg/dL (<3 mmol/L)[b]	0	0	1 (2.7) p=1.000	1 (1.3) p=1.000

Abbreviations: Dula = dulaglutide; PG = plasma glucose; N = number of patients randomized and treated; n = number of patients with hypoglycemia.

a   Total hypoglycemia category includes patients with documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia when PG measurement was missing. In cases of probable hypoglycemia, patients are counted in both the PG <70 mg/dL (<3.9 mmol/L) and <54 mg/dL (<3 mmol/L) categories.

b   Includes all patients with a measured PG <54 mg/dL (<3 mmol/L) at any time, including postrescue data.
     p-Values are for comparison between dulaglutide and placebo group incidence from Fisher's exact test.

Annualized rate of hypoglycemia

An analysis based on annualized rates, calculated as the number of individual hypoglycemic episodes divided by the total exposure in each treatment group, was also performed. There was an imbalance in the total number of hypoglycemic episodes <70 mg/dL (<3.9 mmol/L) reported across the 3 treatment groups through Week 26:

- placebo: 12 hypoglycemic episodes
- dulaglutide 0.75 mg: 60 hypoglycemic episodes,
- dulaglutide 1.5 mg: 18 hypoglycemic episodes.

A remarkable number of hypoglycaemic episodes occurred in the low-dose dulaglutide group. Reassuringly, the annualised hypoglycaemia rate in the high dose dulaglutide group was much closer to placebo level (refer also to the discussion on Clinical Safety below).

Pancreas-related events

AEs of pancreatitis

All suspected cases of acute or chronic pancreatitis were adjudicated by an independent clinical endpoint committee who was blinded to treatment allocation. In addition, AEs of severe or serious abdominal pain of unknown aetiology were submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease.

No TEAEs under the Acute Pancreatitis SMQ (narrow terms) or Chronic Pancreatitis LSC were reported during the study. One investigator-reported event was submitted for adjudication as possible pancreatitis: a TEAE of moderate abdominal pain upper in a patient assigned to and taking placebo at the time of the event. The event was adjudicated as no event.

Per the protocol, further diagnostic assessment for the assessment of asymptomatic elevated pancreatic enzymes was to be performed whenever lipase and/or amylase (pancreatic and/or total) are ≥3×ULN at any time during the study. No patients had a total or pancreatic amylase measurement ≥3× ULN at any time during the study. Four patients had a postbaseline lipase measurement ≥3× ULN through Week 52:

- placebo/dulaglutide 0.75-mg group: 2 patients (4.0%)
- dulaglutide 0.75-mg group: 0 patients
- dulaglutide 1.5-mg group: 2 patients (3.8%)

Mean serum levels of amylase and lipase

Serum amylase (pancreatic and total) was slightly but consistently and dose-dependently increased with dulaglutide treatment compared to placebo; see table below. A mean increase with dulaglutide was also observed for lipase.

Table 23: Baseline Means and Mean Change from Baseline to Week 26 in Pancreatic Enzymes, ITT Population

	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
Amylase, IU/L				
Baseline mean	56.7	53.6	50.6	52.1
Mean change at Week 26	0.09	4.8* p=0.006	6.5* p<0.001	5.6* p<0.001
Pancreatic amylase, IU/L				
Baseline mean	20.2	20.2	19.1	19.7
Mean change at Week 26	0.6	1.8* p=0.003	2.9* p<0.001	2.3* p<0.001
Lipase, IU/L				
Baseline mean	28.4	24.8	24.4	24.6
Mean change at Week 26	2.2	4.4* p<0.001	3.9* p<0.001	4.1* p<0.001

*p-Value <0.05 for within-treatment comparison to baseline from Wilcoxon signed-rank test.

Abbreviations: 'dula' for dulaglutide

Events of elevated pancreas enzymes in serum

A higher proportion of patients assigned to dulaglutide compared with placebo had TE abnormal elevations in serum **lipase** through Week 26 (p=0.010 for overall treatment group comparison):

- Placebo group: 1 (3.1%)
- dulaglutide 0.75-mg group: 13 (35.1%), p<0.001 versus placebo, and
- dulaglutide 1.5-mg group: 8 (20.0%), p=0.037 versus placebo.

Similar results were observed through Week 52.

No clinically relevant differences were observed across treatment groups in the proportion of patients with TE abnormal elevations in **amylase** (p=0.520) or **pancreatic amylase** (p=0.647) through Week 26.

Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Thyroid safety was evaluated on an ongoing basis by evaluation of thyroid-related TEAEs and by collection of calcitonin levels throughout the study and assessments based on the calcitonin-monitoring algorithm per pre-specified criteria.

No TEAEs under the Thyroid Neoplasms LSC were reported during the study.

The following mean changes from baseline through Week 26 in plasma calcitonin levels were obtained in the three treatment groups; the increases were small, and the largest increase was observed in the placebo group:

- placebo: 0.38 ng/L (0.11 pmol/L)
- dulaglutide 0.75 mg: 0.28 ng/L (0.08 pmol/L)
- dulaglutide 1.5 mg: 0.10 ng/L (0.03 pmol/L)

Renal Impairment

No TEAEs under the Acute Renal Failure SMQ were reported during the study. Four patients (2.6%) reported at least 1 TEAE under the Renal and Urinary Disorders system organ class through Week 52:

- 1 (2.0%) in placebo group
- 1 (2.0%) in dulaglutide 0.75-mg group (dysuria), and
- 2 (3.8%) in dulaglutide 1.5-mg group (1 patient with dysuria and 1 patient with haematuria).

A decreases in the mean eGFR was observed from baseline to Week 26 that was more pronounced in the dulaglutide groups than in the placebo group. This effect was still visible at Week 52. Correspondingly, cystatin C slightly increased over time in the dulaglutide groups.

Table 24: Baseline Means and Mean Change from Baseline to Weeks 26 and 52 in Renal Analytes (Conventional Units), ITT Population

Laboratory measure Time Point	Placebo/ Dula 0.75 mg (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
eGFR (bedside Schwartz), mL/min/1.73 m2				
Baseline mean	128.1	126.6	120.4	123.5
Mean change at Week 26	-1.67	-6.65*	-6.13*	-6.40*
Mean change at Week 52	-2.18	-7.31	-8.67	-8.01
Cystatin C, mg/L				
Baseline mean	0.81	0.79	0.79	0.79
Mean change at Week 26	-0.01	0.02	0.03*	0.02*
Mean change at Week 52	-0.01	0	0.01	0.01

*   Within-treatment p-value <0.05 through Week 26 from Wilcoxon signed-rank test.
Abbreviations: 'dula' for dulaglutide

Accordingly, five patients (3.2%) decreased in eGFR category from baseline to postbaseline:

- 1 patient (2.0%) assigned to placebo, and
- 4 patients (3.9%) assigned to dulaglutide.

There was a notable imbalance in mean UACR at baseline in the placebo group compared with the dulaglutide groups:

- Placebo group: 128.9 g/kg (14.6 g/mol)
- dulaglutide 0.75-mg group: 33.4 g/kg (3.8 g/mol)
- dulaglutide 1.5-mg group: 24.5 g/kg (2.8 g/mol)

Review of patient-level data suggests that this imbalance was driven primarily by 3 patients with UACR measurements >1000 g/kg (114 g/mol) at baseline, at least once postbaseline, or both, all assigned to the placebo group.

Supraventricular Arrhythmia

Overall, 3 patients with TEAEs were reported under the Arrhythmia related investigations, signs, and symptoms (SMQ) broad and narrow terms through Week 26 (0 patients on placebo, 1 patient receiving dulaglutide 0.75 mg and 2 patients receiving dulaglutide 1.5 mg).

Two additional patients reported this kind of AE between after 26 weeks, i.e. during the open-label extension.

Malignancy

No TEAEs under the Malignancy SMQ (narrow terms) were reported during the study

Serious adverse events/deaths/other significant events

Deaths

No deaths were reported during the study.

SAEs

Only few SAEs occurred during the study, most of them in the placebo group; see table below. The two SAEs in the dulaglutide groups were non-alcoholic fatty liver and stress fracture. The former could be

related to the underlying disease (T2D), but the number of events is far too low for meaningful conclusions.

Table 25: Summary of Serious Adverse Events by Treatment Group through Week 26 by Decreasing Frequency of Preferred Term; Intent-to-Treat Population

	Placebo (N=51)		Dula_0.75 (N=51)		Dula_1.5 (N=52)		All Dula (N=103)	
Subjects with >= 1 SAE	**3**	**(5.9)**	**1**	**(2.0)**	**1**	**(1.9)**	**2**	**(1.9)**
Diabetic ketoacidosis	1	(2.0)	0		0		0	
Genital herpes	1	(2.0)	0		0		0	
Nonalcoholic fatty liver disease	0		1	(2.0)	0		1	(1.0)
Pulmonary embolism	1	(2.0)	0		0		0	
Respiratory failure	1	(2.0)	0		0		0	
Right ventricular failure	1	(2.0)	0		0		0	
Stress fracture	0		0		1	(1.9)	1	(1.0)
Suicide attempt	1	(2.0)	0		0		0	

Abbreviations: 'dula' for dulaglutide

Other significant AEs specifically evaluated by the applicant

The following events were not pre-defined as AESI but were specifically evaluated by the applicant after a few of these had occurred:

- Hepatobiliary disorders
- Overdose

Further information given below.

Hepatobiliary disorders

Until Week 26, the following incidences were observed in total:

- placebo group: 2 patients (3.9%)
- dulaglutide 0.75-mg group: 3 patients (5.9%), and
- dulaglutide 1.5-mg group: 1 patient (1.9%).

The events were increase of transaminases and/or fatty liver.

One of these events was reported as SAE (non-alcoholic fatty liver disease in the dulaglutide 0.75 mg group), leading to discontinuation of study drug. This subject was 13-year old female with a baseline BMI of 38.2 kg/m^2.

After Week 26, two additional cases of increased ALT were reported.

Overdose

Accidental overdosing occurred in 5 patients, at a single occasion in each patient. Mostly, a dose was administered shortly (within 72 hours, but not at the same day) after the previous injection. No AEs related to this dousing errors were reported.

Laboratory findings

Haematology

No relevant findings were made.

Serum chemistry

Serum parameters for hepatic, renal pancreatic and C-cell disease are discussed along with the respective AESIs above.

Lipids:

Total cholesterol and LDL-C were slightly decreased from baseline to Week 26 in the dulaglutide 0.75 mg and 1.5-mg group, reaching statistical significance in the dulaglutide la 1.5 mg group (-8.36 mg/dL for total cholesterol; baseline, 166 mg/dL).

Electrolytes:

No relevant findings were made.

Urinalysis

Protein, glucose, ketones, leukocytes and blood were detected in the urine of some patients, but there was no obvious relationship to dulaglutide treatment.

Vital signs

GLP-1 receptor agonists are known to increase heart rate (HR). This was also the case in the paediatric study with dualglutide. However, the increase in HR vs. baseline was small, up to 1.3 bpm at Week 26, compared to placebo; see table below. Furthermore, there was a small increase in systolic blood pressure (SBP) vs. baseline, up to 3.8 mmHg at Week 26 compared to placebo. Diastolic blood pressure (DBP) was decreased (-2.6 mmHg vs. placebo).

Table 26: Summary and Analysis of Vital Signs Baseline Values and Change from Baseline at Week 26, Week 52, MMRM; Intent-to-Treat Population

Parameter/ Time Point	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
Heart Rate (bpm)				
Mean baseline	80.6	81.2	78.1	79.7
LS mean change at Week 26	0.8	1.2	2.1	1.5
LS mean change at Week 52	2.8	3.1	1.7	2.3
LS mean difference vs placebo at Week 26	N/A	0.4 p=0.848	1.3 p=0.509	0.9 p=0.624
Systolic Blood Pressure (mm Hg)				
Mean baseline	115.8	116.7	118.1	117.4
LS mean change at Week 26	-1.0	2.8*	1.5	2.1*
LS mean change at Week 52	0.9	2.8	2.5	2.5
LS mean difference vs placebo at Week 26	N/A	3.8 p=0.056	2.5 p=0.203	3.2 p=0.067
Diastolic Blood Pressure (mm Hg)				
Mean baseline	70.6	73.2	70.5	71.9
LS mean change at Week 26	2.1	1.3	-0.5	0.3
LS mean change at Week 52	0.9	2.5	0.1	1.3
LS mean difference vs placebo at Week 26	N/A	-0.8 p=0.626	-2.6 p=0.116	-1.7 p=0.236

Abbreviations: 'dula' for dulaglutide

ECG

Increased heart rate was also reflected in the ECG (up to 3.2 bpm vs. baseline and placebo, see table below). Accordingly, RR interval was shortened. Further changes were a slight prolongation of the PR interval (up to 5.4 ms) and shortening of the uncorrected and corrected QT interval. These are known effects of GLP-1 receptor agonists.

Table 27: Summary and Analysis of ECG Parameters Baseline Values and Change from Baseline at Week 26 (ANCOVA); Intent-to-Treat Population

| Parameter/ Time Point	Placebo (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
Heart Rate (bpm)	n=39	n=39	n=41	n=80
Mean baseline	73.9	77.1	72.9	74.9
LS mean change at Week 26	-0.5	0.3	2.6	1.5
LS mean difference vs placebo at Week 26	N/A	0.9 p=0.685	3.2 p=0.135	2.0 p=0.274
PR interval (msec)	n=39	n=38	n=41	n=79
Mean baseline	144.5	146.1	152.9	149.6
LS mean change at Week 26	-2.1	3.3	1.1	2.2
LS mean difference vs placebo	N/A	5.4 p=0.028	3.2 p=0.192	4.3 p=0.044
RR duration (msec)	n=39	n=39	n=41	n=80
Mean baseline	834.4	801.7	842.2	822.5
LS mean change at Week 26	6.3	-3.8	-31.8	-17.8
LS mean difference vs placebo	N/A	-10.1 p=0.669	-38.1 p=0.104	-24.1 p=0.237
QRS interval (msec)	n=39	n=38	n=41	n=79
Mean baseline	90.3	91.0	90.7	90.8
LS mean change at Week 26	0.4	1.5	-1.1	0.2
LS mean difference vs placebo	N/A	1.1 p=0.412	-1.5 p=0.231	-0.2 p=0.836
QT interval (msec)	n=38	n=38	n=41	n=79
Mean baseline	378.2	369.0	376.6	372.9
LS mean change at Week 26	3.6	1.5	-8.9*	-3.7
LS mean difference vs placebo	N/A	-2.1 p=0.598	-12.5 p=0.001	-7.3 p=0.032
QTcF interval (msec)	n=38	n=38	n=41	n=79
Mean baseline	402.8	398.3	399.7	399.0
LS mean change at Week 26	2.1	2.7	-4.0*	-0.7
LS mean difference vs placebo	N/A	0.7 p=0.803	-6.1 p=0.019	-2.7 p=0.230
QTcB interval (msec)	n=38	n=38	n=41	n=79
Mean baseline	416.2	414.4	412.2	413.2
LS mean change at Week 26	1.5	3.3	-1.5	0.9
LS mean difference vs placebo	N/A	1.8 p=0.623	-2.9 p=0.410	-0.6 p=0.853

Abbreviations: 'dula' for dulaglutide

Effects on development (Tanner staging, body height, hormones)

Tanner staging

The majority of patients had reached sexual maturity at baseline based on Tanner breast stage in females (70.0%) and Tanner genital stage in males (59.1%). The distribution of patients by Tanner stage was generally balanced across treatment groups, although there were some numerical differences particularly in the male patients, given the overall smaller sample size (44 male patients total) with only 10 male patients randomized to placebo.

Figure 13: Distribution of patients by Tanner stage at baseline, Week 26, and Week 52 (females)
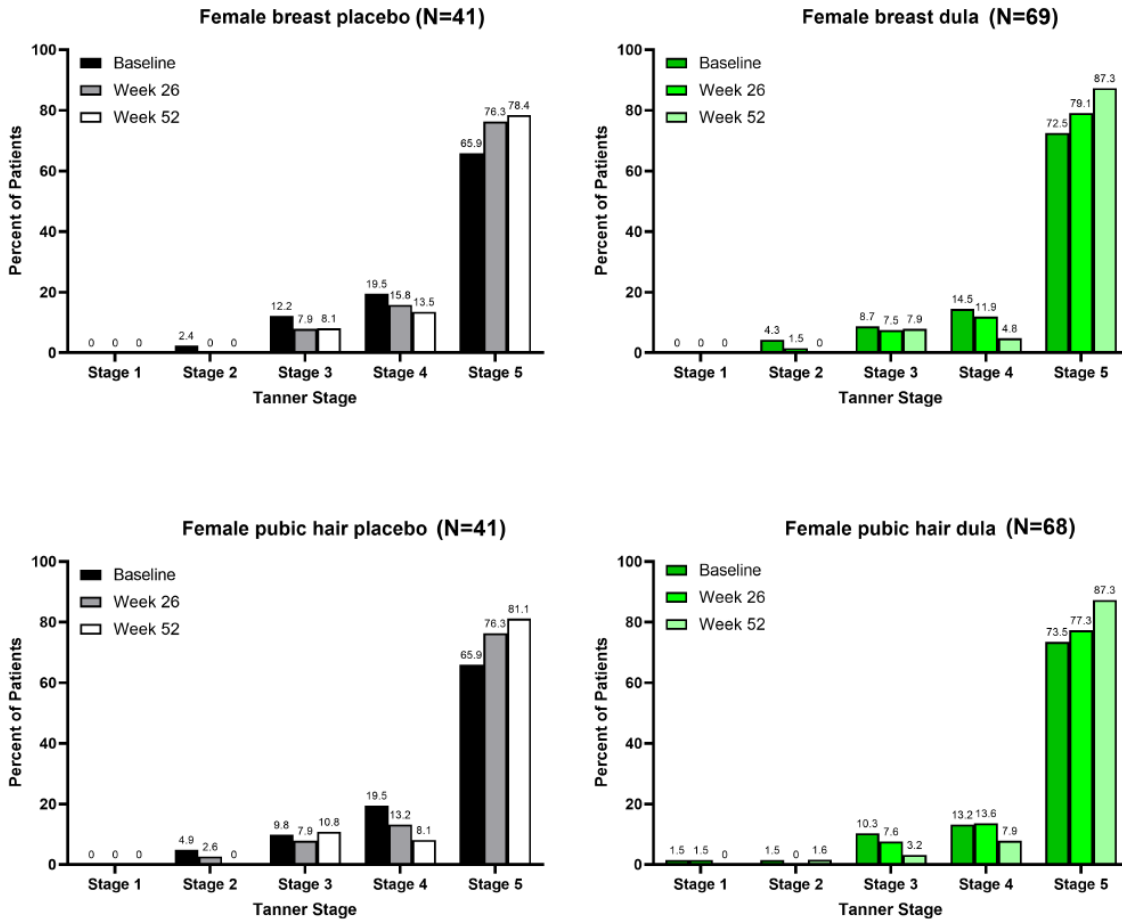
The above figures reveal a small tendency for dulaglutide to accelerate sexual development, Tanner stages 3 and 4 were generally slightly less frequent with dulaglutide whereas Tanner stage 5 was somewhat more frequent with dulaglutide than with placebo. This is not considered adverse but could be due to the improved glycaemic control.

Figure 14: Distribution of patients by Tanner stage at baseline, Week 26, and Week 52 (males)
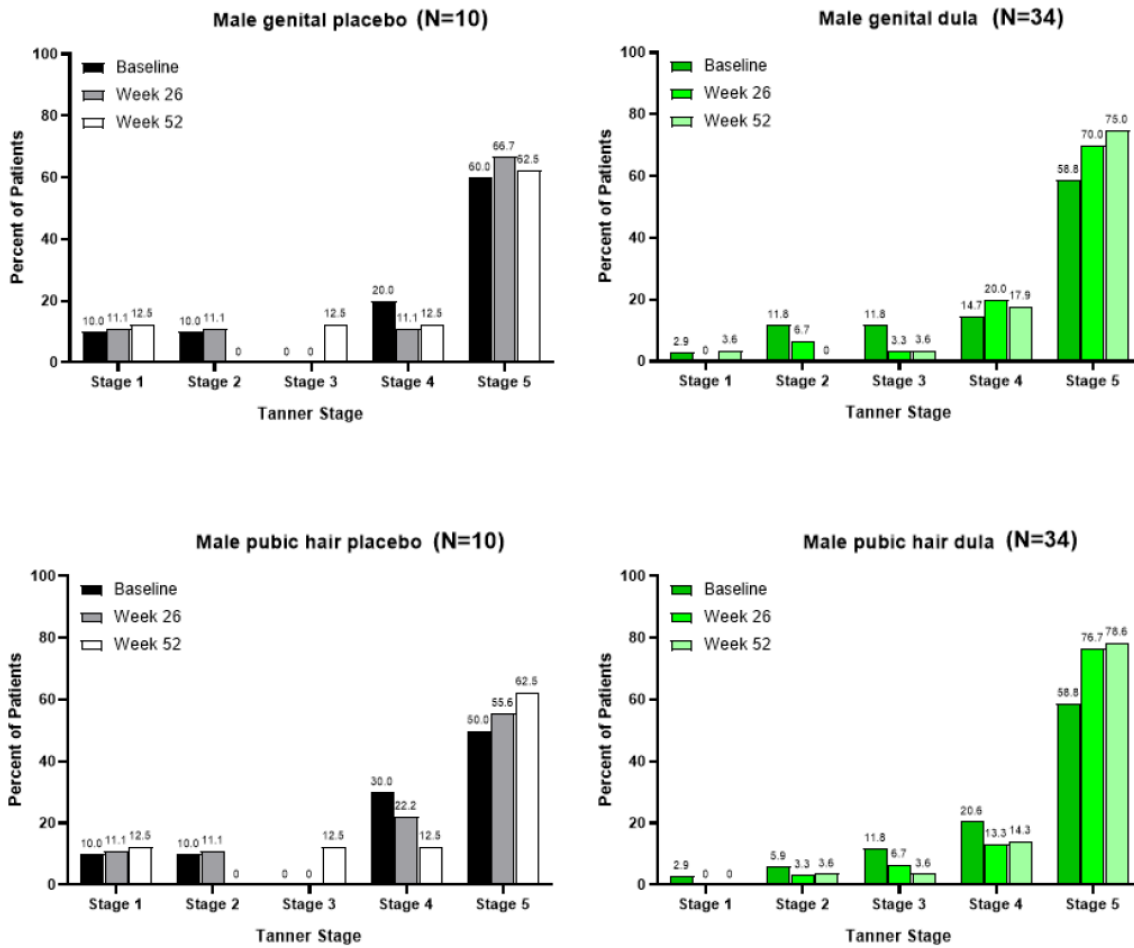
As with females, sexual development appeared to be slightly accelerated with dulaglutide compared to placebo.

Height

No relevant differences between dulaglutide and placebo in height at Weeks 26 and 52 relative to baseline (which essentially reflects growth rate) were observed. For details, see table below.

Table 28: Summary and Analysis of Height and Height SDS, Baseline Values and Change from Baseline at Weeks 26 and 52, MMRM, Intent-to-Treat Population

Assessment Time Point	Placebo/ Dula 0.75 mg (N=51)	Dula 0.75 mg (N=51)	Dula 1.5 mg (N=52)	Pooled Dula (N=103)
Height, cm				
Baseline mean	160.3	162.9	164.1	163.5
LS mean change at Week 26	0.4[a]	0.6[a]	0.3	0.5[a]
LS mean difference vs Placebo at Week 26		0.2 (-0.2, 0.6) p=0.362	-0.1 (-0.6, 0.3) p=0.531	0 (-0.3, 0.4) p=0.870
LS mean change at Week 52	1.1[a]	1.1[a]	0.7[a]	1.0[a]
Height SDS				
Baseline mean	0.09	0.20	0.14	0.17
LS mean change at Week 26	-0.12[a]	-0.07[a]	-0.12[a]	-0.10[a]
LS mean difference vs Placebo at Week 26		0.05 (-0.02, 0.12) p=0.186	0.01 (-0.07, 0.08) p=0.888	0.03 (-0.04, 0.09) p=0.399)
LS mean change at Week 52	-0.16[a]	-0.14[a]	-0.18[a]	-0.16[a]

a Within-treatment p-value <0.05

Abbreviations: 'dula' for dulaglutide

Hormones

Hormone-related safety was assessed by measurement of estradiol, testosterone (in males only), LH, IGF-1, cortisol, and prolactin in morning serum samples collected at baseline, Week 26, and Week 52 (or early study discontinuation).

No clinically meaningful differences were observed between dulaglutide and placebo groups in the mean change from baseline to Week 26 were detected except for cortisol. For the latter, an around 30% increase from baseline to Week 26 was observed in the placebo group (baseline 13.34 µg/dL, increase by 3.80 µg/dL). No such change was observed in the dulaglutide groups.

Safety in special populations

The safety profile of dulaglutide was evaluated for the most frequently reported TEAEs (occurring in ≥5% patients overall) based on the following intrinsic baseline factors:

- age (≤14, >14 years old)
- sex (male, female), and
- race (White versus all other race classifications).

No clinically meaningful findings were observed in TEAEs based on age, sex, or race.

The following table provides a more detailed overview of AE frequencies by age (≤14 vs. >14 years old); mainly GI effects were observed. There were some differences in AE frequency between older and younger children/adolescents in the placebo group. The AE pattern in the combined dulaglutide group was similar between subjects ≤14 and >14 years of age.

Table 29: Summary of Treatment-Emergent Adverse Events Occurring in ≥5% of Patients from Baseline to Week 26. By Decreasing Frequency of Preferred Term and Pooled Treatment Group. By Baseline Age Group (≤14, >14 Years). Intent-to-Treat Population

Preferred Term	Subgroup	Placebo n/N (%)	All_Dula n/N (%)	Odds Ratio*b
Diarrhoea	<=14 Y	5/25 (20.0)	6/35 (17.1)	0.83(0.22,3.09)
	>14 Y	2/26 (7.7)	13/68 (19.1)	2.84(0.59,13.55)
Headache	<=14 Y	3/25 (12.0)	4/35 (11.4)	0.95(0.19,4.66)
	>14 Y	2/26 (7.7)	11/68 (16.2)	2.32(0.48,11.25)
Nausea	<=14 Y	2/25 (8.0)	5/35 (14.3)	1.92(0.34,10.78)
	>14 Y	2/26 (7.7)	10/68 (14.7)	2.07(0.42,10.16)
Vomiting	<=14 Y	2/25 (8.0)	5/35 (14.3)	1.92(0.34,10.78)
	>14 Y	0/26	11/68 (16.2)	-
Abdominal pain upper	<=14 Y	4/25 (16.0)	4/35 (11.4)	0.68(0.15,3.01)
	>14 Y	0/26	4/68 (5.9)	-
Upper respiratory tract infection	<=14 Y	2/25 (8.0)	2/35 (5.7)	0.70(0.09,5.31)
	>14 Y	2/26 (7.7)	6/68 (8.8)	1.16(0.22,6.16)
Nasopharyngitis	<=14 Y	3/25 (12.0)	1/35 (2.9)	0.22(0.02,2.21)
	>14 Y	0/26	6/68 (8.8)	-
Abdominal pain	<=14 Y	2/25 (8.0)	1/35 (2.9)	0.34(0.03,3.95)
	>14 Y	1/26 (3.8)	4/68 (5.9)	1.56(0.17,14.67)

Y, Years

*b   odds ratio based on comparator Placebo as denominator

Abbreviations: 'dula' for dulaglutide

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Through Week 26, a total of 4 patients (2.6%) discontinued study treatment due to an AE:

- 1 in the placebo group;
- 1 in the dulaglutide 0.75-mg group, and
- 2 in the dulaglutide 1.5-mg group.

Two patients assigned to dulaglutide discontinued study treatment secondary to hepatic AEs:

- 1 (assigned to the 0.75-mg group) due to an AE of non-alcoholic fatty liver disease, and
- 1 (assigned to the 1.5-mg group) due to Alanine aminotransferase increased.

Both patients met protocol-specified criteria for study drug discontinuation related to transaminase increases. For details, see section on hepato-biliary events above.

One patient assigned to dulaglutide 1.5-mg group discontinued study treatment due to the AE of vomiting.

The placebo patient discontinued study treatment due to the AE of respiratory failure.

No additional patients discontinued study treatment due to an AE after Week 26 during the open-label period.

The number of subjects discontinuing due to AEs was low; this is reassuring. One subject discontinued due to vomiting, a known side effect of GLP-1 receptor agonists. Another discontinuation was due to fatty liver. This condition could be related to the underlying disease, i.e. diabetes and obesity.

Immunogenicity

Allergic/Hypersensitivity Reactions

TEAEs related to allergic/hypersensitivity reactions were identified using 4 SMQs (narrow terms):

- Hypersensitivity
- Anaphylactic reactions
- Angioedema
- Severe Cutaneous Adverse Reactions.

Seven patients (4.5%) reported at least 1 TEAE related to allergic/hypersensitivity reactions through Week 26, with no clinically meaningful difference across treatment groups:

- placebo: 2 (3.9%)
- dulaglutide 0.75 mg: 3 (5.9%)
- dulaglutide 1.5 mg: 2 (3.8%)

The most frequently reported TEAE related to allergic/hypersensitivity reactions was rash.

Injection site reactions

Fourteen patients (9.1%) reported at least 1 TEAE related to injection site reactions through Week 26, with no clinically meaningful difference across treatment groups:

- placebo: 5 (9.8%)
- dulaglutide 0.75 mg: 5 (9.8%)
- dulaglutide 1.5 mg: 4 (7.7%)

The most frequently reported TEAE related to injection site reactions was injection site pain.

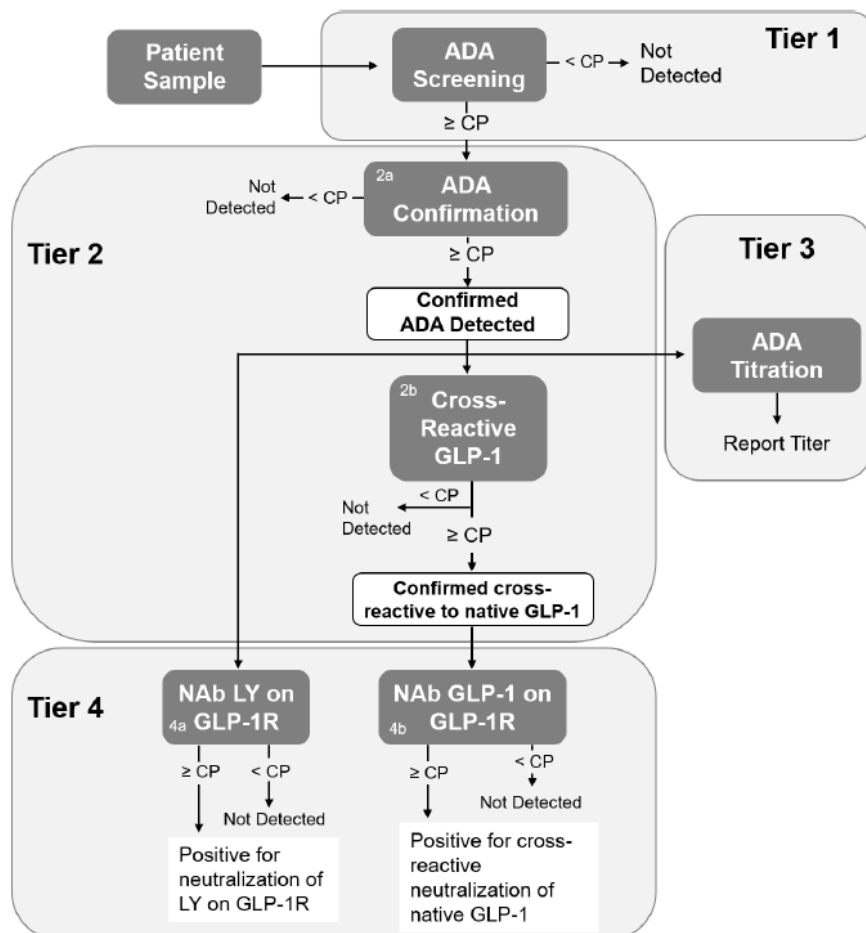### **Anti-Drug-Antibodies (ADA)**

Methods

The MAH has developed 3 separate immunogenicity assays to support the clinical development of dulaglutide:

- A solid-phase extraction with acid dissociation (SPEAD) enzyme-linked immunosorbent assay (ELISA) format to screen, confirm, and titre ADA against dulaglutide and assess ADA for cross-reactive binding to native GLP-1;
- A cell-based neutralizing assay to detect ADA capable of neutralizing the ability of dulaglutide to activate the GLP-1 receptor;
- A cell-based neutralizing assay to detect ADA capable of neutralizing the ability of native GLP-1 to activate the GLP-1 receptor.

A comprehensive validation package including all validation reports and accompanying method history summarizing the development of the assay, the validation strategy, an overview of validation studies performed, and a current assay description with a tabular summary of validation parameters is provided

in the Method History Report. Updated assay parameters were used for sample analysis in the paediatric Study GBGC. Samples were analysed using the 4-tier approach (see figure below).

Figure 15: Analytical results reporting flow chart

Abbreviations: ADA = antidrug antibody; CP = cut point; ELISA = enzyme-linked immunosorbent assay; GLP-1 = glucagon-like peptide-1; GLP-1R = glucagon-like peptide-1 receptor; LY = LY2189265; NAb = neutralizing antibody; SPEAD = solidphase extraction with acid dissociation.

Results

At the end of the placebo -controlled treatment period, i.e. after 26 weeks, treatment-emergent ADA (TE-ADA) were observed in one placebo -treated subject and in two subjects each of the dulaglutide 0.75 mg and the dulaglutide 1.5 mg group. For further details, see table below.

Table 30: Summary of Patients with Treatment-Emergent Dulaglutide Antidrug Antibodies Observations during the Double-Blind Treatment Period (through Week 26); Intent-to-Treat Population

	Placebo/ Dula 0.75 mg (N=51) n	Dula 0.75 mg (N=51) n	Dula 1.5 mg (N=52) n	Pooled Dula (N=103) n
Patients Evaluable for TE ADAs[a]	48	50	51	101
Evaluable Patients with ADAs Present at Baseline	5 (10.4)	8 (16.0)	3 (5.9)	11 (10.9)
Neutralizing LY for GLP-1R at Baseline	0	0	0	0
nGLP-1 Cross-Reactive at Baseline	1 (2.1)	1 (2.0)	2 (3.9)	3 (3.0)
Neutralizing nGLP-1 at Baseline	0	0	0	0
Patients Postbaseline TE ADA+[b]	1 (2.1)	2 (4.0)	2 (3.9)	4 (4.0)
Neutralizing LY for GLP-1R	1 (2.1)	1 (2.0)	0	1 (1.0)
nGLP-1 Cross-Reactive	1 (2.1)	2 (4.0)	1 (2.0)	3 (3.0)
Neutralizing nGLP-1	0	0	0	0
Patients Postbaseline TE ADA Inconclusive[b]	0	0	0	0
Patients Postbaseline TE ADAs-[b]	47 (97.9)	48 (96.0)	49 (96.1)	97 (96.0)

a   A subject is TE ADA evaluable if there is at least 1 nonmissing test result for LY ADA for each of the baseline period and postbaseline period. All percentages are relative to the total number of TE ADA-evaluable subjects in each treatment group.
b   A TE ADA-evaluable subject is considered to be TE ADA+ if the subject has at least 1 postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, then the subject is TE ADA+ if there is at least 1 postbaseline result of ADA Present with titer ≥1:4 (treatment induced). A TE ADA-evaluable subject is TE ADA Inconclusive if ≥20% of the subject's postbaseline samples are ADA Inconclusive and the subject is not otherwise TE ADA+. A TE ADA-evaluable subject is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.
Abbreviations: 'dula' for dulaglutide

At the end of the safety follow-up, 3 subjects were TE-ADA+ in each treatment group (placebo, dulaglutide 0.75 mg, dulaglutide 1.5 mg). It should be noted, however, that the placebo subjects have received dulaglutide 0.75 mg during the extension period so that an untreated control is missing.

Maximum TE ADA titres ranged from 1:4 to 1:32 (median 1:8).

The number of TE-ADA+ subjects was low. This is reassuring, but firm conclusions are not possible. Numerically, TE-ADA were more frequent with dulaglutide treatment than with placebo treatment (2 subjects vs. 1 subject). A weak immunogenicity of dulaglutide is known from adult studies. The presented results give no hint that immunogenicity is more pronounced in children/adolescents.

Further analyses were performed by the applicant, such as the effect of TE ADA on PK, efficacy and safety as well as changes in titre in relation to treatment. However, due to the low number of TE ADA positive subjects, further analysis is not meaningful. Any difference could be a chance finding.

Post-marketing experience

No post-marketing experience in paediatric patients exists.

2.5.1. Discussion on clinical safety

Safety information was derived from the phase 3 paediatric study GBGC. Overall, the safety profile for dulaglutide (0.75 mg QW and 1.5 mg QW) in children/adolescents (10 to 17y) was fully in line with the known profile from adult studies. The majority of side effects was related to the gastrointestinal (GI) tract, such as nausea, vomiting and diarrhoea. As expected, the frequency of these events was particularly high in the first week(s) after start of treatment. In one case, GI AEs led to discontinuation.

Further known effects of dulaglutide that were also observed in children/adolescents included small changes in vital signs and ECG such as increase of heart rate and systolic blood pressure, prolongation of the PR interval and shortening of the HR-corrected QT interval (QTc). Due to the small magnitude of the effects, they are not considered clinically relevant.

Mean increases in the level of serum pancreas markers (lipase, amylase, pancreatic amylase) were observed with dulaglutide compared to placebo; accordingly, the number of events of these values being above the upper normal limit was increased. This is also expected for GLP-1 receptor agonists and usually does not reflect pancreatitis.

No event of severe hypoglycaemia occurred during the paediatric study. Frequency of (non-serious) hypoglycaemias was higher with dulaglutide than with placebo in the subgroup of patients not taking basal insulin at baseline although the absolute number of events was low. As rescue therapy use was more frequent in the placebo group it cannot explain the increased dulaglutide-related hypoglycaemia rate in the subpopulation without insulin at baseline. 7 patients in the placebo group initiated insulin during the double-blind period, but only 2 in the dulaglutide 0.75 mg group and no one in the dulaglutide 1.5 mg group; see efficacy section above for details on rescue therapy. Thus, the increase in hypoglycaemia is most likely due to dulaglutide itself. Reassuringly, the number of more serious events (PG <54 mg/dL, symptomatic) was low, and no events of severe hypoglycaemia occurred.

In the subgroup taking insulin at baseline, the hypoglycaemia rate was markedly higher in all groups compared to the subgroup not taking insulin as expected. Notably in the insulin subgroup, hypoglycaemia rate was numerically slightly reduced with dulaglutide. This could be due to a reduced insulin need in the presence of dulaglutide since increase of basal insulin dose during the study was allowed as a rescue measure. In order not to confound the treatment effect of dulaglutide, adjusting the insulin dose was generally not allowed during the study. However, temporary increases in insulin dose were allowed to ensure that patients do not continue in the double-blind portion of the trial with poor glycemic control.

Further analyses showed that in the relevant subgroup (insulin use at baseline), the mean insulin dose was fairly constant throughout the study and there were no relevant differences in insulin dose with inclusion or exclusion of post-rescue data. The largest change in insulin dose from baseline to Week 26 was observed in the placebo group; it increased in mean by 0.62 U. Although this difference is quite small, it may have contributed to a higher hypoglycaemia rate in the placebo group and thereby to the observed difference in hypoglycaemia between placebo and dulaglutide.

A higher percentage of patients treated with dulaglutide than receiving placebo decreased in eGFR category from baseline to postbaseline. Accordingly, a decline in mean eGFR was observed in the dulaglutide groups compared to placebo.

Further analyses confirmed that dulaglutide caused a mean decrease in eGFR over time, most pronounced in the first 12 weeks after treatment initiation; after 26 weeks, the mean decrease was 5.8 mL/min/1.73m^2 in the combined dulaglutide groups (Zappitelli equation); virtually no change was observed in the placebo group. These analyses demonstrated that dehydration (due to GI side effects) most likely plays no role due to the fact that the dulaglutide effect on eGFR was similar between subjects

suffering at least one GI-related TEAE (nausea, vomiting or diarrhoea) and subjects not suffering such a TEAE.

On the other hand, it was demonstrated that baseline hyperfiltration is a more likely cause. In the 105 subjects who did not display hyperfiltration at study start, virtually no decrease in eGFR during dulaglutide treatment was observed. In contrast, the 49 subjects with hyperfiltration at baseline displayed a marked decrease in eGFR, by 15.4 mL/min/1.73m^2 in mean. Accordingly, the number of subjects displaying hyperfiltration decreased during treatment with dulaglutide. It was shown that subjects with hyperfiltration at baseline, albuminuria (measured as UACR) also became decreased with dulaglutide treatment.

Glomerular hyperfiltration is regarded as an early sign of glomerular damage, and is therefore preferentially found in young diabetics (Palatinin 2012, Nephrol Dial Transplant 27: 1708–1714). Thereafter, GFR progressively falls, along with a further increase in albuminuria, giving rise to typical diabetic kidney disease. The fact that glomerular hyperfiltration is less common in elderly subjects with a longer diabetes duration can explain why the decrease in eGFR with dual was pronounced in the paediatric study but did not become so obvious in prior adult studies.

Taken together, the explanation provided above is considered plausible and does not raise concerns

As in adults, immunogenicity of dulaglutide was low.

The MAH has measured specific parameters related to growth and development of the paediatric subject to exclude adverse effects in this respect. Increase in body height from baseline to Week 26 was not affected by dulaglutide compared to placebo. Sexual development appeared slightly accelerated by dulaglutide compared to placebo, with numerically more individuals revealing Tanner Stage 5 (and less Tanner Stages 3 and 4) with dulaglutide than with placebo. Plasma levels of hormones involved in sexual development were not noticeably changes with dulaglutide compared to placebo.

The Applicant provided a thorough discussion on the issue of safety in long-term use (more than 1 year) of dulaglutide in children and adolescents. A main focus was given to a pubertal development, height, growth and bone age as well as other AEs. Moreover, the long-term safety data of liraglutide as another GLP-1 RA were outlined, representing no findings which could alter the benefit-risk profile in the concerned population.
The long-term safety for children and adolescents using dulaglutide is expected to be consistent with that of adults. This aspect should be further monitored via routine pharmacovigilance activities.

2.5.2. Conclusions on clinical safety

In general, dulaglutide revealed a safety profile in the paediatric study, which is well in line with the safety experience from dulaglutide use in adults. Most prominent were (mainly transient) GI side effects, increase in pancreatic enzymes in the blood and minor changes on vital parameters (e.g. small increase in HR) and ECG (slight prolongation of PR and shortening of QTc intervals). No events of severe hypoglycaemia occurred, which is reassuring.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 7.2 with this application.

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

The PRAC considered that the risk management plan version 7.2 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Table 31: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	Thyroid C-cell tumours Pancreatic malignancy
Missing information	none

Pharmacovigilance plan

Table 32: On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Medullary Thyroid Carcinoma (MTC) Surveillance Study (H9X-MC-B001) Category 3	To determine the annual incidence of MTC in the US and to identify any possible increase related to the introduction of long-acting GLP-1 RAs, including dulaglutide, into the US market.	Potential risk of medullary thyroid carcinoma	Ongoing	Final Report: Estimated submission of study report: 31/03/2032
Dulaglutide Retrospective Study (H9X-MC-B013) Category 3	To estimate the incidence rates of events of interest among patients with T2DM treated with	Pancreatic and thyroid cancers	Ongoing	Estimated submission of study report: 31/12/2030

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	• dulaglutide compared to other second-line anti-diabetes medications, and • long-acting GLP-1 RAs compared to other second-line anti-diabetes medications.			

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 33: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Thyroid C-cell tumours	Routine risk communication: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: Not applicable.
Pancreatic malignancy	Routine risk communication: Not applicable. Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: Not applicable.

2.7. Update of the Product information

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the Package Leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The subject of this type II variation is to extend the use of Trulicity to paediatric patients 10 years and above with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.

The proposed text modifications to the Package Leaflet resulting from the addition of this new indication are considered minor and minimal and do not include text that is significantly different from that already user tested. The structure and design of the revised Trulicity Package Leaflet has not changed with the new information and the revisions do not significantly affect the overall readability. Therefore, it is not considered necessary to conduct additional consultation with target patient groups further to that performed for the initial MAA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Trulicity (dulaglutide) is currently approved for the treatment of type 2 diabetes mellitus in adults.

The modified indication wording will extend the use of dulaglutide to children and adolescents aged 10 to less than 18 years with T2DM and is proposed by the applicant as follows:

Type 2 Diabetes Mellitus
Trulicity is indicated for the treatment of ~~adults~~ **patients 10 years and above** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
• as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
• in addition to other medicinal products for the treatment of diabetes.
For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Proposed paediatric dosing
The starting dose for paediatric patients 10 years and above is 0.75 mg once weekly. If needed, the dose can be increased to 1.5 mg once weekly after at least 4 weeks. The maximum dose is 1.5 mg once weekly.

3.1.2. Available therapies and unmet medical need

The recommended treatment for paediatric type 2 diabetes is similar to that in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise, followed by the use

of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

For a long time, the only two approved treatment options for paediatric patients with type 2 diabetes in most countries were metformin and insulin. Recently, additional treatment options have become available in the EU for children and adolescents aged 10 to less than 18 years with type 2 diabetes, e.g. the GLP-1 receptor agonist Liraglutide (Victoza), Exenatide extended-release once-weekly injection (Bydureon) and the SGLT-2 inhibitor Dapagliflozin (Forxiga).

3.1.3. Main clinical studies

Primary efficacy data supporting this submission are based on the paediatric Study H9X-MC-GBGC (GBGC). Study GBGC was a Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter superiority trial with an open-label extension to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics in paediatric patients with T2DM aged 10 to less than 18 years receiving dulaglutide compared with placebo, who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin. The formulations used for Study GBGC were the same 0.75 and 1.5 mg doses that are commercially available for adults. For a detailed description of the paediatric Study GBGC, refer to the section on Clinical Efficacy above.

3.2. Favourable effects

In children and adolescents with inadequately controlled T2DM, once-weekly dulaglutide (pooled and individual 0.75 mg and 1.5 mg doses) was superior to placebo in:
- lowering HbA1c as measured by change from baseline to Week 26 in HbA1c, and
- bringing more patients to glycemic control as measured by the percentage of patients with HbA1c <7% at Week 26.

The primary efficacy endpoint in Study GBGC was powered to demonstrate superior reductions relative to the placebo group, and the primary endpoint measure (HbA1c) is an accepted endpoint in the T2DM population. Additionally, the study population was reflective of the target population with respect to the scope of potential background therapies, age (predominantly adolescent), sex (higher prevalence in females), racial and ethnic diversity, and geographic-specific prevalence.

The improvement in glycemic control was statistically significant versus placebo in both the pooled dulaglutide dose group and in the individual 0.75 mg and 1.5 mg dose groups, with a pattern of dose-related improvement in both HbA1c and FBG seen for dulaglutide.

There was consistency across the statistical analyses approaches used, as the primary endpoint was met with both the treatment-regimen and efficacy estimands, as well as with the requested analysis (efficacy estimand excluding metformin-naive patients).

There was also consistency of effect with other assessments related to glycemic control:
- for FBG, there was a statistically significant treatment group difference (mean change, treatment estimand, -35.9 mg/dL [-2.0 mmol/L]; efficacy estimand, -35.5 mg/dL [-2.0 mmol/L]), and
- reduced rescue therapy use (fewer patients with dulaglutide needed rescue therapy compared with placebo).

An additional advantage of dulaglutide relative to other treatment options relates to ease of use, as it is a ready-to-use weekly injection.

3.3. Uncertainties and limitations about favourable effects

Limitations
The indication is supported by a single study. While enrolment was open to a broad range of patients with respect to background diabetes therapy, only 14 patients total (9.1%) were enrolled on diet and exercise only, 10 of whom were metformin naive. Therefore, limited monotherapy data exist from Study GBGC.

Uncertainty
The longer-term effect of dulaglutide on glycemic control is still uncertain. During the open-label phase through 52 weeks, the reduction in HbA1c from baseline diminished compared with 26 weeks, but this was at least partially due to the faster progression of disease that characterizes T2DM in youth. While the time course of progressive dysglycemia as measured by HbA1c was clearly altered with dulaglutide treatment within the 52-week time period of the study, and the percent of patients with HbA1c below clinically relevant thresholds in the dulaglutide groups remained relatively constant between the Week 26 and Week 52 time points, the persistency of this effect over a longer-term remains unknown.

The efficacy (as well as safety and tolerability) of dulaglutide 0.75 and 1.5 mg in children and adolescents with T2DM was generally consistent with that previously established for adults. The efficacy and safety of the 3.0 and 4.5 mg doses were not assessed in Study GBGC, because these doses were not approved for use in adults at the time the study was designed and implemented. Further analysis of the PK/PD, safety, and efficacy results of Study GBGC, together with the results for the higher doses in adults (Study H9X-MC-GBGL), is required to help inform future study design or whether (and to what extent) it may be appropriate to extrapolate these results for the higher dulaglutide doses from adult to paediatric patients.

3.4. Unfavourable effects

Overall, the safety and tolerability profile of dulaglutide in children and adolescents aged 10 to less than 18 years was consistent with the well-established safety profile in adults with T2DM. Commonly reported TEAEs included nausea, vomiting, and diarrhoea. The incidence of nausea, vomiting, and diarrhoea were highest during the first 2 weeks after initiating dulaglutide and then waned over time. Nearly all TEAEs of nausea, vomiting, and diarrhoea were mild or moderate in severity. The proportion of patients discontinuing treatment overall or due to an AE was low (5.8% and 2.6%, respectively), was comparable between dulaglutide and placebo through Week 26, and remained low through the total 52 weeks of treatment. Although injection site reactions were more commonly observed in paediatric patients compared with adults, no new safety concerns were identified relative to the safety profile in adults.

Based on the mode of administration, mechanism, and safety risks associated with the T2DM population, several safety topics were considered in the determination of key risks, including, but not limited to, hypoglycemia, GI events, hypersensitivity, and acute pancreatitis.

Acute pancreatitis
In Study GBGC, no events of acute pancreatitis were reported. However, increases in pancreatic enzymes were observed in the dulaglutide groups versus placebo; these increases were consistent with the dulaglutide data in adults and the liraglutide data in paediatric patients with T2DM. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are considered not predictive of acute pancreatitis but may be related to increased expression of enzymes in the exocrine pancreatic cells in response to dulaglutide.

Hypoglycemia
The frequency of hypoglycemic events with dulaglutide in paediatric patients with T2DM was consistent with that established for adults. No cases of severe hypoglycemia were reported during the paediatric study GBGC, and there were no clinically meaningful differences in incidence of any hypoglycemia

category between dulaglutide and placebo groups through Week 26. Baseline use of insulin was associated with a higher incidence of hypoglycemia across treatment groups but not with an increase in the dulaglutide groups compared with placebo.

3.5. Uncertainties and limitations about unfavourable effects

The small sample size from the single study provides more limited safety data in this population relative to the safety database established in adults. However, paediatric studies in the indication T2DM are often rather small for various reasons so that this is not a specific concern for Study GBGC.

The trial enrolled a limited number of children younger than 14 years, and the majority of patients were female. This is consistent with the known epidemiology of T2DM in the paediatric population.

The majority of patients enrolled were adolescents who had already reached or were near peak growth and maturity, precluding a more complete assessment of effects on growth and sexual maturity.

3.6. Effects Table

Table 34: Effects Table for Dulaglutide (LY2189265) in Children and Adolescents Aged 10 to Less Than 18 Years with T2DM (Data Cut-Off Date of 07 February 2022) – EU Analysis (Efficacy Estimand Excluding Metformin Naïve Patients) Through 26 Weeks

Effect	Short description	Unit	Treatment Pooled Dula	Control placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c reduction	LS mean change (SE)	%	-0.7 (0.2)	0.6 (0.2)	**Strengths** Study population reflective of target population. Consistency of effect • across statistical analysis approaches • secondary glycaemic control endpoints • with currently approved treatments **Limitations/Uncertainties** • A single study • Limited monotherapy data in target population • Longer term effect (beyond 1 year) uncertain	GBGC
HbA1c <7.0%	% achieving HbA1c <7.0%	%	56.0	16.2		
FBG reduction	LS mean change (SE)	mg/dL	-16.5 (5.3)	19.4 (8.1)		
Unfavourable Effects						
Total AEs	subjects experiencing at least one event	n (%)	76 (73.8)	35 (68.6)	Overall safety profile in children/adolescents consistent with established safety profile in adults Limitations: • Small sample size from the single study • Limited number of children younger than 14 years of age	GBGC
Total SAEs		n (%)	2 (1.9)	3 (5.9)		
GI disorders		n (%)	43 (41.7)	14 (27.5)		

Abbreviations: 'GI' for gastrointestinal, 'dula' for dulaglutide

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Type 2 diabetes mellitus in children and adolescents is still relatively rare in Europe but is increasing due to increasing childhood obesity. Developing T2DM at a younger age is associated with a considerably higher risk of long-term complications compared with those who develop T2DM in the middle age.

Thus, there is an important need for additional approved agents to treat children and adolescents with T2DM that are safe, effective, and convenient to use (e.g. weekly versus daily administration).

3.7.2. Balance of benefits and risks

In children and adolescents aged 10 to less than 18 years with inadequately controlled T2DM treated with or without metformin and/or basal insulin, treatment with once-weekly dulaglutide 0.75 mg or 1.5 mg for 26 weeks was superior to placebo in improving glycemic control. The placebo-adjusted improvements in HbA1c were clinically relevant and comparable to those observed in adults with T2DM. Improvements from baseline in glycemic control with dulaglutide were observed through 52 weeks and were considered clinically relevant especially relative to the more rapid underlying disease progression in these patients in the absence of additional intervention. The overall safety profile of dulaglutide 0.75 mg and 1.5 mg once weekly in children and adolescents aged 10 to less than 18 years was consistent with that established in adults with T2DM, with no new safety concerns.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The benefit-risk of Trulicity (dulaglutide) 0.75 and 1.5 mg once weekly for the treatment of children and adolescents aged 10 to less than 18 years with insufficiently controlled type 2 diabetes mellitus is positive.

The updated RMP version 7.2 is acceptable.

The overall benefit-risk of Trulicity 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 type 2 diabetes mellitus (T2DM) in children and adolescents aged 10 to less than 18 years based on final results from study H9X-MC-GBGC; this is a phase 3, double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open label extension to evaluate safety. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.2 of the RMP 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).

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0409/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.