Clinical Study Report	
Drug Substance	Exenatide
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A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes

Study Dates:
First subject enrolled: 12 May 2016
Last subject last visit: 06 May 2020
The analyses presented in this report are based on a final database lock date of 06 August 2020.

Phase of Development:
Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

2. SYNOPSIS

Study Center(s)

This study was performed at 36 study centers in 6 countries: Bulgaria (2), Hungary (5), Israel (3), Kuwait (1), Mexico (5), Ukraine (4), United States (16). Twenty-seven study centers randomized patients during the study.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the effect on glycemic control, as measured by HbA1c, of EQW following 24 weeks of treatment compared with placebo in children and adolescents with T2DM	Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
Primary	Safety	To evaluate the safety and tolerability of EQW compared with placebo following 24 weeks of treatment in children and adolescents with T2DM	Safety and tolerability endpoints including the incidence of treatment-emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 7 (Week 24), and to each intermediate visit as applicable [a]
Secondary	Efficacy/Safety	To compare the effects of EQW following 24 weeks of treatment to those achieved by placebo in children and adolescents with T2DM on the following: • Fasting plasma glucose concentration • Proportion of patients achieving HbA1c goals	• Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable • Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable • Proportions of patients achieving HbA1c goals of ≤ 6.5% and < 7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable[b]

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		• Body weight and Tanner pubertal stage • Blood pressure and lipids To assess the effects of long-term EQW therapy (~1 year) in children and adolescents with T2DM on the following: • Long-term safety and tolerability • Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of patients achieving HbA1c goals • Body weight and Tanner pubertal stage • Blood pressure and lipids	• Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable • Change in fasting insulin and C-peptide from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable[c] • Change in lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides) from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable • Change in blood pressure (systolic and diastolic) from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable • Proportions of patients discontinuing the study and the proportion of patients needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable • Proportions of patients reporting different injection site reactions[d] Safety Variables[a]: • Safety and tolerability endpoints including the incidence of treatment-emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
			• Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52) • Change in thyroid-stimulating hormone, thyroxine, prolactin, cortisol, insulin-like growth factor 1, and dehydroepiandrosterone from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52) • Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)
Secondary	Efficacy	To examine the effect of EQW on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the HOMA in children and adolescents with T2DM who were not taking insulin	Change in HOMA-B and insulin HOMA-S as measured by HOMA in EQW patients not taking insulin from baseline (Visit 2, Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
Secondary	PK	To assess the PK of EQW in children and adolescents with T2DM	Plasma exenatide concentrations at baseline (Visit 2, Week 0), Visit 7 (Week 24), Visit 10 (Week 52), and each intermediate visit as applicable
Exploratory[e]	Efficacy		Change from baseline (Visit 2, Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable, for the following parameters: • BMI • Body weight percentile and height percentile
Exploratory[e]	Safety		• Change in carcinoembryonic antigen from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52) • Change in bone specific alkaline phosphatase and N-telopeptide from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24) and Visit 10 (Week 52)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
			• Change in FSH, LH, FSH/LH[f], total testosterone, SHBG, and estradiol from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52) • Change in total testosterone and SHBG also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)
Exploratory Mixed Meal Substudy[g]			
Primary	PD	To evaluate the effect of EQW on postprandial beta-cell function as assessed by C-peptide secretion during a mixed meal test, following approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of drug therapy	• Change in incremental $AUC_{(0-240)}$ for C-peptide from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and Visit 11 (Week 62/Study Termination)[h]
Secondary	PD	To assess postprandial glucose and glucagon responses during a mixed meal test following approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of drug therapy	• Change in C_{max}, C_{ave}, T_{max}, and incremental $AUC_{(0-30)}$ for C-peptide from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination)[h] • Change in incremental $AUC_{(0-240)}$ and incremental $AUC_{(0-30)}$, C_{max}, C_{ave}, and T_{max}, for glucose and glucagon, from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination)[h] • Change in HOMA-B, HOMA-S and insulinogenic index from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination) in patients not taking insulin[h]
Safety[h]	Safety[i]		• AEs

[a] Note: the CSP and SAP do not separate out the safety endpoints into primary and secondary safety endpoints. This table considers the safety and tolerability endpoints to Week 24 the primary safety endpoints. No outputs were presented in the CSR for physical examination data as only categorical data ('Yes/No' response to 'was the physical examination performed') were collected.

[b] Additional goal of patients meeting HbA1c of < 6.5% introduced in the SAP.

[c] Change from baseline in C-peptide as a secondary endpoint was removed in the SAP as C-peptide values were collected at screening and at Weeks 52 and 62 only for patients in the mixed meal substudy.

[d] For reporting purposes, the SAP and CSR considers injection site reactions a safety endpoint.

[e] Exploratory endpoints introduced in the CSP and SAP with no associated exploratory objective.

[f] Change in FSH/LH may be reported as an addendum to the CSR.

[g] Exploratory mixed meal substudy to evaluate the change in postprandial beta-cell function after approximately 28 weeks of EQW therapy and at approximately 10 to 12 weeks following cessation of drug therapy.

[h] Due to an insufficient amount of data being collected for the substudy, C-peptide, glucose and glucagon data were presented using descriptive statistics and by AUC at each visit only for the Standardized Mixed Meal Test Evaluable Analysis Set. No outputs for HOMA-B, HOMA-S, or insulinogenic index were created for the mixed meal substudy due to data only being available for 6 patients.

[i] Safety endpoint introduced in the CSP with no associated objective.

AE Adverse event; CSP Clinical study protocol; CSR Clinical study report; EQW Exenatide once weekly; FSH Follicle-stimulating hormone; HbA1c Glycosylated hemoglobin; HOMA Homeostasis model assessment; HOMA-B Homeostasis model assessment-beta-cell function; HOMA-S Homeostasis model assessment-insulin sensitivity; LH Luteinizing hormone; PD Pharmacodynamic; PK Pharmacokinetic; SAP Statistical analysis plan; SHBG Sex hormone-binding globulin; T2DM Type 2 diabetes mellitus.

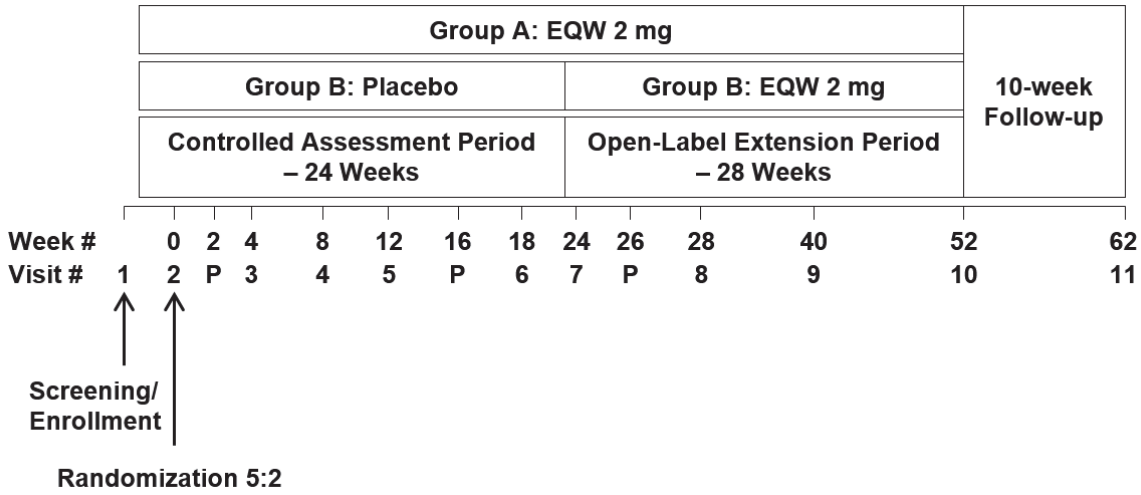
Study Design

This was a multicenter, randomized, parallel-group, Phase III study in adolescent patients with type 2 diabetes mellitus (T2DM) treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin. The study was divided in 4 periods:

- Screening period (5 weeks)
- Controlled assessment period (24 weeks): double-blind, placebo-controlled period to examine the efficacy and safety of exenatide once weekly (EQW) compared with placebo. Approximately 77 patients were to be randomly assigned in a 5:2 ratio to receive either EQW 2 mg (Group A) or placebo (Group B).
- Open-label extension period (28 weeks): open-label, uncontrolled period to examine the long-term safety and efficacy of EQW. Patients assigned to the EQW 2 mg treatment (Group A) were to continue to be treated with EQW 2 mg during the open-label extension period (through Week 52). Patients randomized to placebo (Group B) were to receive EQW 2 mg beginning at the start of the open-label extension period through Week 52.
- Post-treatment follow-up period (10 weeks).

In addition to receiving study medications, all patients were to participate in a lifestyle intervention program encompassing diet and physical activity modifications.

Figure S1 Flow Chart of Study Design



All visits scheduled during the controlled assessment period and during the open-label extension period were to occur within ± 2 days of the scheduled date, relative to Visit 2 (Week 0).

Visit 11 was to take place at least 10 weeks and no later than 12 weeks after the last dose of EQW.

The Investigator and/or qualified study-site personnel was to contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review AEs.

AE Adverse event; EQW Exenatide once weekly; P Phone call.

Patients participating in the study were also to be observed in an extended safety follow-up period following discontinuation of study medication administration. The extended follow-up period was designed to allow observation of ongoing development and growth on an individual patient basis and to describe the occurrence of selected adverse events (AEs) in the absence of EQW treatment following up to 52 weeks of EQW administration. The extended safety follow-up period will be reported as an addendum to the Clinical Study Report (CSR).

An exploratory mixed meal substudy was performed in approximately 20 patients to evaluate the effect of EQW on postprandial beta-cell function (as assessed by C-peptide secretion) and postprandial glucose and glucagon responses during a mixed meal test following approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of study medication treatment. The substudy design and planned procedures are detailed in Appendix F of the Clinical Study Protocol.

Target Subject Population and Sample Size

Male or female children and adolescents of 10 to < 18 years of age, diagnosed with T2DM, and treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (metformin and/or sulfonylurea [SU]) and/or insulin for at least 2 months prior to screening.

Target Sample Size

Approximately 77 patients who met all eligibility criteria were to be randomized into this study to yield 70 evaluable patients. This was estimated to provide an overall power of 74% to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for glycosylated hemoglobin (HbA1c) (%), with a common standard deviation of 1.0% and a 2-sided significance level of 0.05.

At least 40% and not more than 60% of the randomized patients were to be females. At least 40% of patients were to be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Caregivers were to administer study medication (2 mg EQW or matching placebo) subcutaneously to the patient (or the patient self-administered, if deemed appropriate) once weekly (± 2 days) relative to the date of the first dose of study medication (Visit 2 [Week 0]), for the duration of the study, as applicable.

Four batches of exenatide CCI [redacted] CCI and 4 batches of placebo were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of Treatment

The total study duration was to be approximately 67 weeks (5-week screening period, 24-week controlled assessment period, 28-week open-label extension period, and 10-week post-treatment follow-up period).

Statistical Methods

In general, primary and secondary continuous efficacy variables for which multiple postbaseline measurements were collected were to be analyzed using a mixed model with repeated measures (MMRM) approach. The statistical analysis of categorical variables was to be conducted using a stratified Cochran-Mantel-Haenszel test. If data has been collected at the Early Termination visit, it were to be included in the analyses.

Intercurrent events that may have occurred during the study were defined as receipt of rescue therapy, study medication discontinuation, and study withdrawal. Efficacy data collected after the initiation of rescue medication or following discontinuation of study medication were to be excluded from the analyses, except for select sensitivity analyses and plasma EQW concentration endpoints, where data after rescue were included.

The primary efficacy analysis was to compare treatment groups (EQW versus placebo) with respect to change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24) using MMRM. The model was to include change in HbA1c as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects.

A fixed-sequence procedure hierarchical testing strategy was to be followed for the primary endpoint and secondary endpoints in order to protect the family wise error rate. Endpoints were to be tested in order from HbA1c, fasting plasma glucose (FPG), body weight to fasting insulin.

All safety and tolerability variables (including examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide) were to be summarized descriptively by visit to Week 52, and where applicable also for the 10-week follow-up, by treatment groups. Observations post rescue were to be included for safety analyses.

Subject Population

A total of 159 patients enrolled in this study from 36 centers; 27 study centers randomized patients during the study.

A total of 83 patients were randomized and entered the double-blind controlled assessment period: 59 patients randomized to EQW and 24 patients randomized to placebo. Of the 83 randomized patients, 82 (98.8%) received EQW/placebo treatment, 73 (88.0%) completed the controlled assessment period, and 72 (86.7%) completed treatment during the controlled assessment period. Of the 73 patients who completed the controlled assessment period, all but 1 patient (randomized to EQW) entered the open-label extension period and received open-label EQW treatment. Of these patients, 64 (77.1% of all randomized patients) completed the open-label extension period and 62 (74.7% of all randomized patients) completed treatment during the open-label extension period. No patients discontinued treatment during the controlled assessment period or the open-label extension period due to an AE.

Key baseline characteristics of the patient population are summarized below.

Table S2 Summary of Demographic, Patient, and Disease Characteristics (Intent-To-Treat Analysis Set)

	EQW	Placebo	Total
	(N = 58)	(N = 24)	(N = 82)
Mean baseline age (SD); years[a]	14.9 (1.88)	15.6 (1.66)	15.1 (1.84)
Sex n (%)			
Male	27 (46.6)	7 (29.2)	34 (41.5)
Female	31 (53.4)	17 (70.8)	48 (58.5)
Race n %			
White	23 (39.7)	12 (50.0)	35 (42.7)
Black or African American	17 (29.3)	8 (33.3)	25 (30.5)
Asian	2 (3.4)	1 (4.2)	3 (3.7)
American Indian or Alaska Native	4 (6.9)	1 (4.2)	5 (6.1)
Other	12 (20.7)	2 (8.3)	14 (17.1)
Hispanic or Latino n (%)	25 (46.3)	8 (38.1)	33 (44.0)
Mean baseline weight (SD); kg	102.18 (30.108)	96.70 (22.684)	100.57 (28.112)
Mean body mass index (SD); kg/m^2	36.86 (9.278)	35.14 (6.575)	36.36 (8.572)
Mean baseline HbA1c (SD); %	8.13 (1.215)	8.28 (1.508)	8.17 (1.300)
Mean baseline diabetes duration (SD); years	2.2359 (2.17477)	2.5105 (1.96478)	2.3163 (2.10718)

[a] Age as collected on the demographics eCRF at study entry.

Baseline weight, height and BMI are displayed. BMI = weight (in kilograms)/(height [in meters^2]).

Duration of Diabetes (years) = (Date of screening – Date of diabetes diagnosis + 1) / 365.25.

Baseline is defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to first dose of randomized study medication.

Percentages are calculated from the number of patients in the analysis set with nonmissing data, by treatment group and total.

This table was derived from Table 14.1.6, Table 14.1.8, and Table 14.1.10. Please see source tables for full information.

BMI Body mass index; eCRF Electronic case report form; EQW Exenatide 2 mg once weekly; HbA1c Glycated hemoglobin A1c; N Number of patients in treatment group; n Number of patients included in analysis; SD Standard deviation.

Data Source: Table 14.1.6, Table 14.1.8, and Table 14.1.10.

The demographic, patient and baseline disease characteristics were generally representative of the intended adolescent population with T2DM. Demographic, patient, and baseline disease characteristics were broadly similar between the EQW and placebo groups, with the exception of minor imbalances in age, race, region, weight population percentile, and baseline diabetes duration; however, these imbalances would not be expected to affect the interpretation of the primary efficacy analysis. The pre-existing conditions and concomitant medications were as expected for the study population, and similar between treatment groups.

Summary of Efficacy Results

Results for the primary and secondary efficacy endpoints in the fixed-sequence procedure hierarchical testing strategy are summarized in the table below.

Table S3 Summary of Primary and Secondary Efficacy Endpoint Results in the Fixed-sequence Procedure Hierarchical Testing Strategy

	EQW	Placebo
	(N = 58)	(N = 24)
Primary Endpoint: Change in HbA1c from baseline to Week 24 (%) (Evaluable Analysis Set)[a,b]		
LS mean (SE) adjusted change from baseline to Week 24	-0.36 (0.184)	0.49 (0.273)
LS mean (SE) difference	-0.85 (0.330)	
95% 2-sided confidence interval for LS mean difference	(-1.51, -0.19)	
2-sided p-value	0.012	
Change from Baseline to Week 24 in Fasting Plasma Glucose (mg/dL) (Intent-to-Treat Analysis Set)[a,c]		
LS mean (SE) adjusted change from baseline to Week 24	-5.2 (7.65)	16.5 (11.32)
LS mean (SE) difference	-21.6 (13.70)	
95% 2-sided confidence interval for LS mean difference	(-49.0, 5.7)	
2-sided p-value	0.119	
Change from Baseline in Body Weight (kg) (Intent-to-Treat Analysis Set)[a,d]		
LS mean (SE) adjusted change from baseline to Week 24	-0.59 (0.665)	0.63 (0.982)
LS mean (SE) difference	-1.22 (1.189)	
95% 2-sided confidence interval for LS mean difference	(-3.59, 1.15)	
2-sided p-value	0.307	
Change from Baseline to Week 24 in Fasting Serum Insulin (pmol/L) (Intent-to-Treat Analysis Set)[a,e]		
LS mean (SE) adjusted change from baseline to Week 24	79.6 (52.28)	-15.3 (78.49)
LS mean (SE) difference	94.9 (95.26)	
95% 2-sided confidence interval for LS mean difference	(-95.6, 285.5)	
2-sided p-value	0.323	

[a] Excluding measurements after initiation of rescue therapy or discontinuation of study medication.

[b] Adjusted LS mean and treatment group difference in the change from baseline at Week 24 are modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline HbA1c value (continuous) and baseline HbA1c by visit interaction as fixed effects, using an unstructured covariance matrix.

[c] Adjusted LS mean and treatment group difference in the change from baseline values at each visit are modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline fasting plasma glucose value, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline fasting plasma glucose by visit interaction as fixed effects, using an unstructured covariance matrix.

[d] Adjusted LS mean and treatment group difference in the change from baseline values at each visit are modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction, baseline body weight, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline body weight by visit interaction as fixed effects, using an unstructured covariance matrix.

[e] Adjusted LS mean and treatment group difference in the change from baseline values at each visit are modeled using a MMRM including treatment group, region, visit, treatment group by visit interaction,

baseline fasting insulin, screening HbA1c (< 9.0% or ≥ 9.0%), and baseline fasting insulin by visit interaction as fixed effects, using an unstructured covariance matrix.

This table was derived from Table 14.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1. Please see source tables for full information.

EQW Exenatide 2 mg once weekly; HbA1c Glycated hemoglobin A1c; LS Least-squares; MMRM Mixed model with repeated measures; N Number of patients in the Intent-to-Treat Analysis Set within the treatment group; SE Standard error.

Data Source: Table 14.2.1.1, Table 14.2.2.2.1, Table 14.2.2.3.1, Table 14.2.2.4.1.

- EQW was statistically superior to placebo in reducing HbA1c at Week 24 (p = 0.012). Sensitivity analyses of the primary endpoint were consistent with the primary analysis.
- Secondary Endpoints:
  - The reduction in mean HbA1c observed within the first 24 weeks of EQW treatment gradually diminished over time, returning to approximate baseline levels by Week 52.
  - There were no significant differences between treatment groups in change from baseline at Week 24 in FPG, body weight, or fasting insulin. However, for patients in the EQW group numerical decreases in FPG and body weight, and numerical increases in fasting insulin were observed during the controlled assessment period.
  - At Week 24, numerically higher proportions of patients achieved HbA1c goals of < 6.5%, ≤ 6.5%, and < 7% in the EQW group compared with the placebo group.
  - At Week 24, there was a numerical decrease from baseline in mean triglycerides in the EQW group compared with a numerical increase in the placebo group. There were no notable differences between treatment groups in total cholesterol, low-density lipoprotein cholesterol, or high-density lipoprotein cholesterol.
  - There were no significant differences between treatment groups in change from baseline at Week 24 in systolic or diastolic blood pressure.
  - The cumulative proportion of patients needing rescue medication due to failure to maintain glycemic control at Week 24 was low (EQW: 1.7%, placebo: 0%).
  - Reductions in HbA1c were observed among patients who were switched from placebo to open-label EQW treatment, consistent with observations among patients treated with EQW during the controlled assessment period.

Summary of Pharmacokinetic Results

For the EQW group, exenatide plasma concentration reached steady state by Week 8 and was stable over time (Weeks 12 to 52). Data for the placebo → EQW group were not available for inclusion in the CSR and will be reported as a CSR addendum.

Summary of Pharmacodynamic Results

The numbers of patients in the EQW and placebo groups were too low to derive conclusions from the mixed meal substudy.

Summary of Safety Results

Treatment-emergent AEs are summarized in the table below.

Table S4 Overall Summary of Adverse Events - On-Treatment (Safety Analysis Set)

	Number (%) of Patients[a]			
	Controlled Assessment Period		Extension Period	
Patients with AE category	**EQW (N = 59)**	**Placebo (N = 23)**	**EQW (N = 50)**	**Placebo → EQW (N = 22)**
Any AE	36 (61.0)	17 (73.9)	27 (54.0)	11 (50.0)
Any AE with outcome of death	0	0	0	0
Any SAE including events with outcome of death	2 (3.4)	1 (4.3)	3 (6.0)	1 (4.5)
Any AE leading to discontinuation of treatment	0	0	0	0
Any SAE leading to discontinuation of treatment	0	0	0	0
Any AE leading to discontinuation from study	0	0	0	0
Any SAE leading to discontinuation from study	0	0	0	0
Any AE related to treatment[b]	15 (25.4)	5 (21.7)	5 (10.0)	2 (9.1)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

[b] Included causally related AEs as judged by the Investigator.

Controlled assessment period AE is defined as an AE starting on or after day of first dose of study medication up to but not including Week 24 for patients entering the extension period. For patients not entering extension period, the period is defined up to and including last dose of study medication + 7 days (+ 90 days for SAEs and other clinically significant or related AEs).

Extension period AE was defined as an AE starting on or after day of first dose of open-label EQW through Week 52 or last dose + 7 days for patients who discontinued open-label EQW prematurely (+ 90 days for SAEs and other clinically significant or related AEs).

Events are captured up to the later of period definition or Week 52, where patients completed treatment.

Percentages were calculated from the number of patients in the analysis set for the study period by treatment group.

Patients randomized to placebo during the controlled assessment period received EQW during the extension period.

AE Adverse event; EQW Exenatide 2 mg once weekly; N Number of patients in treatment group; SAE Serious AE.

Data source: Table 14.3.2.1.1.

- Exenatide was generally well-tolerated in adolescents with T2DM and safety findings in this study were consistent with the known safety profile of the drug.
- In the controlled assessment period, the mean duration of EQW/placebo exposure was similar between the EQW and placebo groups (157.3 and 165.6 days, respectively). In the treatment period, the mean duration of EQW exposure was longer in the EQW group (356.7 days) than the placebo → EQW group (161.1 days), as expected.

- The incidence of AEs overall was generally lower in the EQW group (61.0%) than the placebo group (73.9%) during the controlled assessment period; the most common AEs were upper respiratory tract infection and abdominal pain in the EQW and placebo groups, respectively. The incidence of AEs overall was generally lower in the open-label extension period than the controlled assessment period. Most AEs were mild or moderate in intensity.
- There were no deaths reported during the study. The incidence of serious AEs (SAEs) was low and comparable between the EQW and placebo groups during the controlled assessment period. No SAEs were reported by more than 1 patient in the EQW or placebo groups and none were considered related to study medication by the Investigator. Similar results were observed for patients with SAEs during the open-label extension period. No discontinuations of study treatment due to an AE were reported during the study.
- The incidence of gastrointestinal disorder-related AEs was low and comparable between the EQW and placebo groups during the controlled assessment period. The most frequent gastrointestinal disorder-related AEs were diarrhea, nausea, vomiting, and upper abdominal pain which occurred in a numerically higher proportion of patients in the EQW group than the placebo group. Fewer gastrointestinal disorder-related AEs were reported in the open-label extension period compared with the controlled assessment period. None of the gastrointestinal disorder-related AEs were considered serious, with the exception of a SAE of irritable bowel syndrome in the placebo group, and none led to study drug discontinuation.
- There were no major hypoglycemic events reported during the study. The occurrence of minor hypoglycemic events was low and comparable between the EQW and placebo groups during the controlled assessment period (1 patient [1.7%] and 1 patient [4.3%], respectively), and remained consistently low during the open-label extension period (1 patient [2.0%] in the EQW group). The majority of patients with hypoglycemia events reported insulin use at baseline, and most also received concomitant insulin throughout the study.
- The proportions of patients experiencing injection site reactions was low and comparable between the EQW and placebo groups during the controlled assessment period. Similar results were observed for patients who received open-label EQW during the treatment period. All injection-site reactions were reported among patients using the prefilled syringe device (none were reported among patients using the dual chamber pen device).
- In the EQW group, there was a trend towards a higher incidence of potentially immune-related AEs among patients who were positive for exenatide antibodies compared with patients who were negative; however, patient numbers were low. This trend is consistent with an immune mediated mechanism for some of these events. The most common potentially immune-related AEs were injection site erythema and injection site pruritus. None of the potentially immune-related AEs were considered serious or led to study drug discontinuation.
- There were no clinically meaningful trends in laboratory parameters over time and no notable differences between treatment groups in laboratory parameters. No patients met the criteria for a potential Hy's Law case.

- Treatment with EQW was associated with a small but notable reduction in systolic blood pressure and a small increase in heart rate. Of note, there were no AEs of hypotension or tachycardia reported during the study. No other clinically meaningful trends in vital signs over time or notable differences between treatment groups in vital sign parameters were observed. There were no new safety concerns related to vital signs.
- Development and growth assessed by Tanner staging resulted in comparable results for patients treated with EQW and placebo during the controlled assessment period.

Conclusion(s)

- EQW was statistically superior to placebo in improving HbA1c in adolescent patients with T2DM ($p = 0.012$).
- EQW 2 mg was generally well-tolerated in adolescents with T2DM and safety findings in this study were consistent with the known safety profile of the drug.