20 July 2017
EMA/538242/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bydureon

International non-proprietary name: exenatide

Procedure No. EMEA/H/C/002020/0041

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ALT	Alanine aminotransferase
BMI	Body mass index
BP	Blood pressure
CrCl	Creatinine clearance
CV	Cardiovascular
DBP	Diastolic blood pressure
eGFR	Estimated creatinine-based glomerular filtration rate
EQW	Exenatide once weekly
FPG	Fasting plasma glucose
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
LS	Least-squares
MTT	Meal Tolerance Test
MMRM	Mixed model for the repeated measures
od	Once daily
PPG	Postprandial glucose
SBP	Systolic blood pressure
SDT	Single dose tray
SGLT2	Sodium glucose cotransporter 2
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione
ULN	Upper limit of normal
UTI	Urinary tract infection

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 5 December 2016 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 for Bydureon to include the add-on use of exenatide in combination with dapagliflozin to patients whose diabetes is not adequately controlled with metformin based on the study D5553C00003 (Duration 8 study); section 4.1 of the SmPC is updated in order to align the indication wording with more recently approved glucose-lowering agents. Section 5.1 of the SmPC is also updated with the results of study D5553C00003 (Duration 8 study). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. Furthermore, the updated RMP version 24 has been submitted.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0130/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0130/2016) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

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: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	5 December 2016
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	17 February 2017
PRAC Rapporteur Assessment Report	17 February 2017
PRAC members comments	01 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017
Request for supplementary information (RSI)	23 March 2017
CHMP Rapporteur Assessment Report	26 June 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur Assessment Report	12 July 2017
Opinion	20 July 2017

2. Scientific discussion

2.1. Introduction

The purpose of this application is to provide information on the efficacy and safety of concomitant add-on treatment with exenatide and dapagliflozin as add-on to metformin, supporting addition of new study data to the Summary of Product Characteristics (SmPC), section 5.1.

As the combination with SGLT2 inhibitors is not covered by the current wording of the indication, an update of SmPC section 4.1 has been proposed, and the MAH proposed at the same time to simplify the wording to be in line with more recently approved glucose-lowering agents including other glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Exenatide once weekly

Exenatide, a GLP-1RA, exerts its glycaemic-lowering effect by enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying. In addition, it lowers weight by inducing satiety through central mechanisms.

Dapagliflozin

Dapagliflozin is a selective inhibitor of sodium glucose cotransporter 2 (SGLT2). SGLT2 inhibition leads to pharmacologically controlled glucosuria, which leads to subsequent glycaemic effects, including lowering of FPG and PPG, and reductions in HbA1c and weight. The glucosuria results in a mild osmotic diuresis which is associated with reductions in SBP.

Rationale for combination therapy with exenatide and dapagliflozin

Type 2 diabetes is a progressive disease that is characterised by defects in multiple organ systems and usually requires combination therapy with agents that target different pathways. Because physiological defects may be manifested differently in individual patients, and patients differ in their care needs due to differences in demographics, comorbidities, individual preferences and other factors, individualisation of diabetes management is emphasised in international guidelines as essential for successful diabetes care. The availability of various types and combinations of diabetes therapy is consistent with this emphasis on patient-centered care.

The combination of exenatide and dapagliflozin is expected to have greater glucose-, weight- and blood pressure (BP)-lowering effects compared to the individual agents due to complimentary mechanisms of action (MOAs). Dapagliflozin reduces plasma glucose in an insulin-independent fashion by causing excretion of urinary glucose, in contrast to the insulin-dependent mechanisms of glucose lowering with exenatide, including stimulation of insulin release and glucagon suppression. The urinary loss of calories that leads to weight loss with dapagliflozin may be associated with a compensatory increase in food intake; this effect may be counteracted by the increase in satiety that occurs with exenatide. In addition, the BP-lowering effects of dapagliflozin and exenatide are also likely due to at least partially differing mechanisms: dapagliflozin leads to osmotic diuresis and natriuresis, whereas the mechanism by which exenatide lowers SBP is unknown, potentially due to vasodilation and/or natriuresis. Both agents act via glucose-dependent mechanisms and do not intrinsically increase the risk of hypoglycaemia.

The clinical programme for this submission consists of a single Phase 3 study, Study D5553C00003. The efficacy and safety data from the 28-week treatment period of this study support concomitant add-on treatment with the combination of EQW 2 mg + dapagliflozin 10 mg od in patients with T2DM who have inadequate glycaemic control on metformin.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

No environmental risk assessment was performed because exenatide as a moderately sized naturally-occuring peptide is unlikely to result in significant risk to the environment, in line with the current ERA guideline (CPMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study ID	Objectives of the	Design and duration	Study drugs Background	Number of subjects	Gender (M/F)	Population

	study		therapy Route of administration	randomized/ treated	Mean age (range)	
D5553C00003 (DURATION 8)	Efficacy and safety	Randomized, double-blind, active-controlled, multi-center, Phase 3 Duration: 28 weeks (finalised), with 24- and 52- week extensions (ongoing)	EQW 2 mg (injection) + Dapa 10 mg (oral) versus EQW 2 mg (injection) + Dapa Placebo (oral) versus Dapa 10 mg (oral) + EQW Placebo (injection) Background: Met ≥1500mg/day	EQW/Dapa: 231/231 EQW/Placebo: 231/230 Dapa/Placebo: 233/233	48% M 52% F 54 yrs (26 to 80 yrs)	T2DM, ≥18 years, HbA1c ≥8% to ≤12% on Met, CrCl ≥60 mL/min

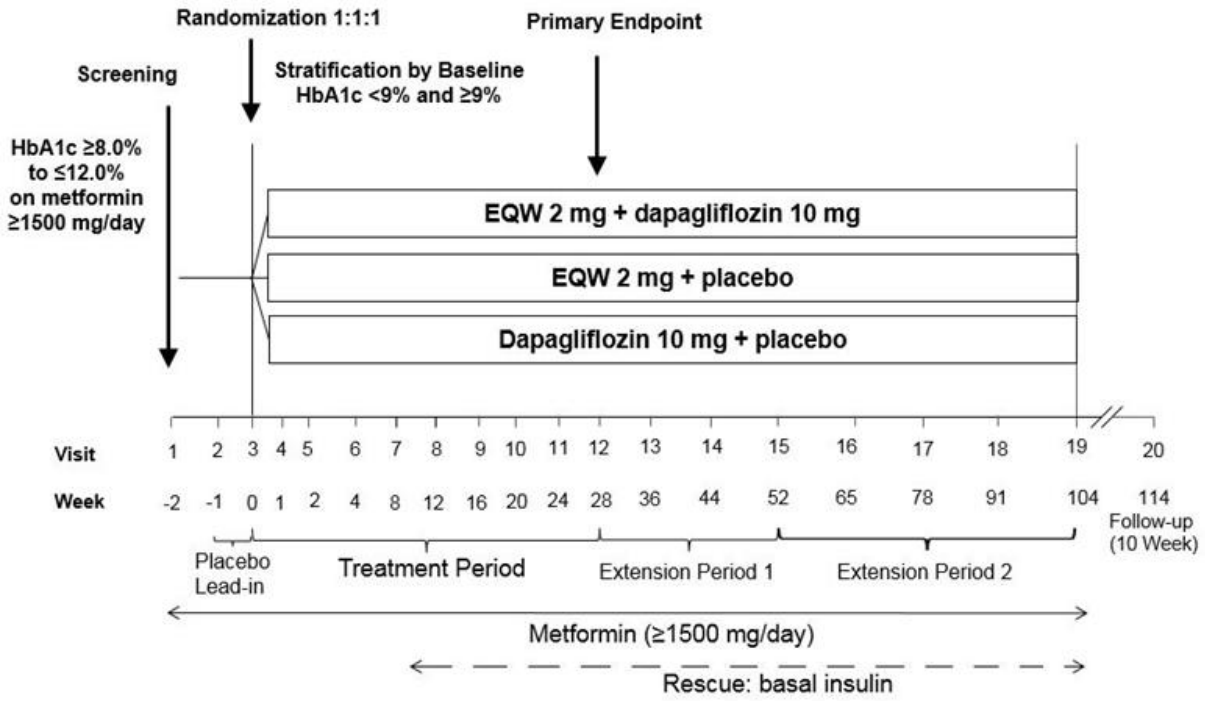
2.3.2. Main study

A 28-week, Multicentre, Randomised, Double-Blind, Active-Controlled, Phase 3 Study with a 24-week Extension Phase Followed by a 52-week Extension Phase to Evaluate the Efficacy and Safety of Simultaneous Administration of Exenatide Once Weekly 2 mg and Dapagliflozin Once Daily 10 mg Compared to Exenatide Once Weekly 2 mg Alone and Dapagliflozin Once Daily 10 mg Alone in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on Metformin

Methods

Study D5553C00003 was a 28-week, randomized, double-blind, active-controlled, multicentre, Phase III efficacy and safety study with a 24- and subsequent 52-week extension of simultaneous administration of EQW 2 mg and dapagliflozin 10 mg QD compared to EQW 2 mg alone and dapagliflozin 10 mg QD alone in T2DM patients with inadequate glycaemic control on metformin.

Figure 1 Flow chart of study design



EQW Exenatide once weekly; HbA1c Haemoglobin A1c

The study consisted of a Screening Visit (Visit 1), a 1-week placebo Lead-in period, a Randomization Visit (Visit 3), and 9 further visits at 1- to 4-week intervals during a treatment period of 28 weeks. At the end of treatment, patients were to enter a 24-week extension period (Extension Period 1), with 3 further visits at 8-week intervals and a subsequent 52-week extension period (Extension Period 2) with 4 further visits at 13-week intervals. A follow-up visit was conducted 10 weeks after the last dose of study medication in Extension Period 2.

Study participants

The population selected for this study were patients with T2DM and inadequate glycaemic control on metformin, with a stable dose of metformin ≥1500 mg/day for at least 2 months prior to screening. The HbA1c inclusion criterion at randomisation (ie, 8.0% to 12.0%, inclusive) was selected to include patients with poor glycaemic control.

The exclusion criterion at randomisation for creatinine clearance was <60 mL/min (1 mL/s) (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of ≥133 µmol/L for male patients and ≥124 µmol/L for female patients. These exclusion criteria are consistent with prescribing guidelines for metformin, dapagliflozin, and EQW.

The purpose of the majority of the inclusion and exclusion criteria was to limit confounding factors that may complicate the interpretation of the study results (e.g., corticosteroid-induced T2DM, haemoglobinopathies that would interfere with the HbA1c analyses), or to exclude patients whose safety could be compromised by participation in the study.

Treatments

This was a double-blind, active-controlled study. The comparison of the combination of dapagliflozin and exenatide with its individual components is consistent with regulatory guidance regarding the investigation of combination products (CHMP 2009).

Background therapy

Metformin is recommended as the initial pharmacological therapy in both the United States (US) and the European Union (EU).

Dapagliflozin

The 10 mg dose was chosen for this study as it has been extensively studied in Phase III trials and has demonstrated a favourable benefit-risk profile. In addition, it is the most effective approved dose and therefore the most appropriate option for patients with very poor glycaemic control.

Exenatide

The 2 mg dose was used for this study as it is the dose that was studied in the Phase III program, and is the only approved dose of exenatide once weekly. EQW was provided as a kit containing 1 vial of exenatide powder for injection, 1 syringe with diluents, 2 vial adaptors, and 2 23-Gauge x 5/16 inch needles. i.e. as SDT.

Rescue

During 28-Week randomised treatment period, patients with inadequate glycaemic control based on progressively stricter glycaemic criteria (Table 1) remained in the study and received open-label rescue therapy with basal insulin while they continued receiving study medication.

Table 1 Criteria for initiation of rescue therapy during the randomised 28-week treatment period

Period	Central laboratory FPG
From Visit 7/Week 8, inclusive, up to and including the day before Visit 8/Week 12	FPG >270 mg/dL (15 mmol/L)
From Visit 8/Week 12, inclusive, up to and including the day before Visit 10/Week 20	FPG >240 mg/dL (13.2 mmol/L)
From Visit 10/Week 20, inclusive, up to and including Visit 12/Week 28 and all unscheduled visits through the day prior to Visit 13/Week 36	FPG >200 mg/dL (11.1 mmol/L)

FPG fasting plasma glucose.
Note: Repeat FPG testing required for confirmation before rescue initiated.

Patients who meet the rescue criteria during the 28-Week treatment period had to complete Rescue visit procedures (equivalent to the Week 28 assessments) before receiving open-label rescue therapy. Rescued patients with central laboratory HbA1c values >8.0% despite a maximum tolerated dose of rescue therapy for 12 weeks were to be discontinued from the study and referred for additional anti-hyperglycaemic therapy.

Objectives

Primary objective

To compare the change from baseline in HbA1c at 28 weeks between exenatide once weekly (EQW) 2 mg and dapagliflozin 10 mg administered simultaneously compared to EQW 2 mg alone and dapagliflozin 10 mg alone.

Secondary objectives

To compare the effect of EQW+dapagliflozin to EQW+placebo and/or to dapagliflozin+placebo, on changes in glycaemic control and anthropometric measures.

Outcomes/endpoints

Primary endpoint

The primary endpoint was change in HbA1c from baseline to Week 28.

Secondary endpoints

Glycaemic

- Proportion of patients achieving HbA1c <7.0%.
- Change in FPG and 2-hour PPG after a standardised liquid meal tolerance test (MTT) from baseline to Week 28, and FPG from baseline to Week 2.

Body weight

- Change in total body weight from baseline to Week 28.
- Proportion of patients achieving weight loss ≥5.0%.

Blood pressure

- Change in SBP from baseline to Week 28.

Sample size

A total of 209 patients per treatment group were required assuming a mean difference of 0.35% in HbA1c change from baseline with EQW+dapagliflozin versus each monotherapy and a standard deviation of 1.1% and 90% power (based on a 2-sample t-test at a 0.05 significance level). Assuming a 5% drop-out rate prior to Week 4 (Visit 6), the first visit where HbA1c was to be tested, 220 patients per treatment arm (a total of approximately 660 patients) would have post-baseline measurements of HbA1c and thus be included in the primary endpoint analysis. Assuming 40% screen failure, a total of 1100 patients were to be screened.

Randomisation

Patients who met all study requirements based on inclusion and exclusion criteria were centrally randomised in a 1:1:1 ratio at Visit 3 (Day 0) by the IVRS/IWRS to receive 1 of 3 treatments: EQW+dapagliflozin, EQW+placebo or dapagliflozin+placebo. Randomisation was stratified by baseline HbA1c (<9.0% or ≥9.0%).

Blinding (masking)

This was a double-blind study. Patients, the investigator, study site personnel, and Sponsor personnel involved with data review and analysis were blinded starting at Visit 3/randomisation. Masking of treatment assignment was achieved through the use of matching placebo injections and placebo tablets. The trial was on-going at the time of the analyses on data collected from the 28 weeks of treatment. The Sponsor and applicable representative(s) were unblinded in Extension Periods 1 and 2 i.e. from Week 28 onwards. Sites and patients were to remain blinded during Extension Periods 1 and 2, until the study completion and final database lock.

Statistical methods

The Statistical Analysis Plan has not been amended and the current version (number 1.0) is dated 05 February 2016. No changes were made to the planned analyses.

The primary efficacy analysis assessed the benefit of the combination of EQW+dapagliflozin over the individual components for the change in HbA1c from baseline to Week 28. Superiority of the combination treatment group was to be concluded if and only if the comparisons of the combination treatment group

against both control groups (EQW+placebo and dapagliflozin+placebo) were statistically significant.

The primary efficacy analysis set was the Intent-to-Treat (ITT) based on all randomised patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment with patients analysed as randomised.

The primary endpoint was analysed using a mixed model with repeated measures (MMRM) that included treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week (Weeks 4, 8, 12 6, 20, 24, and 28), and treatment-by-week interaction as fixed effects. Baseline HbA1c was included as a continuous covariate. If a patient's last available measurement during the 28-week assessment period was from an unscheduled visit or Early Termination visit, it was mapped to the next closest scheduled visit and included in the MMRM analysis. No other missing data imputation was performed. Data collected after the initiation of the glycaemic rescue therapy or at the post-treatment follow-up visits after a premature treatment discontinuation, were excluded from the analysis.

Data collected post rescue therapy and post discontinuation of study medication were included in two sensitivity analyses using the same MMRM model as that for the primary efficacy analysis. For the primary endpoint, supportive analyses were further performed using the same MMRM model as in the primary analysis but based on the PP analysis set and the Randomised analysis set (all patients who signed informed consent and were randomised). The Per-protocol (PP) set was a subset of the ITT set excluding subjects with important protocol violation(s). In addition, an ANCOVA examining the last available observation prior to receiving rescue therapy in ITT analysis set was conducted.

Two additional methods of sensitivity analyses were performed to compare the results from a MAR-based (missing at random) analysis (MMRM) versus a MNAR–based analysis under several MNAR scenarios (missing not at random). The first using copy reference (CR) or Placebo-Based Multiple Imputation which assumes that values of patients from the experimental arm who discontinue treatment or initiate rescue therapy will subsequently follow a trajectory of outcomes in the control arm. The second was a Tipping Point Analysis to find a "tipping point" corresponding to a value of delta where the study conclusion of a significant treatment effect would no longer hold.

For the secondary endpoints, the same MMRM model (as in the primary analysis) was used for continuous variables and a stratified Cochran-Mantel-Haenszel (CMH) test was used for categorical variables. A sequential gatekeeping procedure (Dmitrienko et al 2009) was applied to the primary and secondary endpoints in order to control the family-wise type I error rate. If superiority of the combination treatment group was established for the primary endpoint at 5% level of significance the set of 7 secondary endpoints were to be tested sequentially based on a pre-defined hierarchical order.

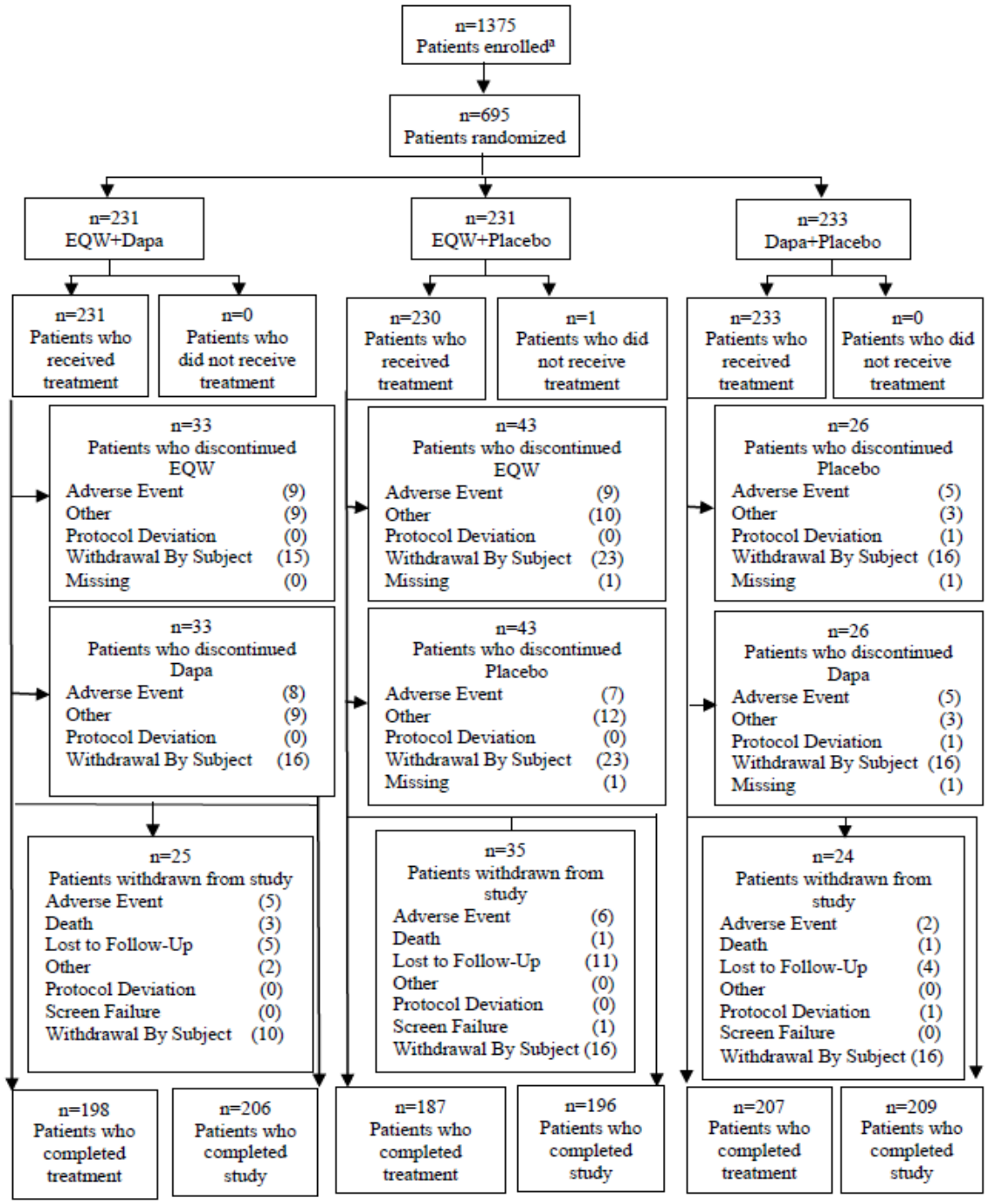
In the analysis of proportion of patients with weight loss ≥5% and HbA1c <7.0% at Week 28 patients with missing data were treated as non-responders. Additional analyses were performed were missing 28-week data was imputed using last observation carried forward (LOCF).

The trial was on-going at the time of the analyses conducted when all patients had completed 28 weeks of treatment. The analyses for the entire 52-week treatment period will be performed when all the patients completed the Extension Period 1. Similar analyses for the entire 104-week treatment period will be performed when all the patients completed the Extension Period 2.

Results

Participant flow

Table 2 Patient Disposition - 28 Week Treatment Period (All Patients)



[a] Informed consent received.
EQW=Exenatide 2 mg once weekly; Dapa=Dapagliflozin 10 mg QD; n=Number of patients.
Source: Figure 11.1.1.1.

Recruitment

A total of 1375 patients enrolled in this study from 137 centres in Hungary, Poland, Romania, Slovakia, South Africa and USA. The first subject was enrolled 04 September 2014 and the last subject last visit for 28-week Treatment Period was 26 April 2016.

Conduct of the study

Changes in the conduct of the study

There were three amendments to the protocol dated 3 Oct 2014, 20 Feb 2015 and 2 Sept 2015. All amendments concerned clarifications on study procedures and are not considered to affect the outcome or interpretation of data.

No changes were made to the planned analyses.

Protocol deviations

The number of patients with important protocol deviations in each treatment group is summarized in Table 3.

Table 3 Important protocol violations – leading to exclusion from per-protocol analysis set – 28-week treatment period (Intent-to-treat analysis set)

	Number (%) of patients			
Important Protocol Violations	EQW+Dapa (N=228)	EQW+Placebo (N=227)	Dapa+Placebo (N=230)	Total (N=685)
Total number of important violations[a]	27	30	24	81
Number of patients with at least 1 important violation	24 (10.5)	25 (11.0)	21 (9.1)	70 (10.2)
Systemic corticosteroids within 3 months prior to Screening (Visit 1)	8 (3.5)	2 (0.9)	1 (0.4)	11 (1.6)
Has HbA1c of [<7.8% or >12.2%] at Visit 2	0	0	1 (0.4)	1 (0.1)
Dispensed EQW used <70% or >130%	10 (4.4)	19 (8.4)	16 (7.0)	45 (6.6)
Dispensed Dapa used <70% or >130%	9 (3.9)	9 (4.0)	6 (2.6)	24 (3.5)

Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly; HbA1c=Hemoglobin A1c; N=Number of patients in treatment group.

[a] The same patient may have had more than 1 important protocol violation.

All percentages are calculated from the number of patients in the Intent-to-treat analysis set.

Baseline data

In general, baseline demographic characteristics were similar across the treatment groups. Overall, most patients randomized in this study were white (83.6%) and not Hispanic or Latino (60.4%). The majority of patients in the ITT analysis set were from the US (56.8%); approximately a third were from Europe (34.9%) and the remainder were from South Africa (8.3%).

Table 4 Demographic characteristics (Intent-to-treat analysis set)

Demographic characteristics		EQW+Dapa (N=228)	EQW+Placebo (N=227)	Dapa+Placebo (N=230)	Total (N=685)
Age (years)	n	228	227	230	685
	Mean	53.8	54.2	54.5	54.2
	SD	9.82	9.62	9.16	9.53
	Median	54.0	55.0	56.0	55.0
	Min	26	29	28	26
	Max	80	80	75	80
Age group (years) n (%)	< 65 Years	197 (86.4)	199 (87.7)	204 (88.7)	600 (87.6)
	≥ 65 Years	31 (13.6)	28 (12.3)	26 (11.3)	85 (12.4)
	≥ 75 Years	4 (1.8)	2 (0.9)	2 (0.9)	8 (1.2)
	Total	228 (100.0)	227 (100.0)	230 (100.0)	685 (100.0)
Sex n (%)	Male	102 (44.7)	116 (51.1)	110 (47.8)	328 (47.9)
	Female	126 (55.3)	111 (48.9)	120 (52.2)	357 (52.1)
	Total	228 (100.0)	227 (100.0)	230 (100.0)	685 (100.0)

Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly; Max=Maximum; Min=Minimum; SD=Standard deviation; n=Number of patients in analysis; N=Number of patients in treatment group.
Age (years) at informed consent.
All percentages are calculated based on the number of patients in the analysis set within each treatment group.

In general, baseline patient characteristics were similar across the treatment groups. The mean height of patients in the study was 166.3 cm, and the mean weight was 90.9 kg. The mean BMI was 32.7 kg/m2, and most patients were in the obese (≥30) BMI group (62.8%).

Table 5 Patient characteristics (ITT analysis set)

Patient characteristics		EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)	Total (N=685)
Weight (kg)	n	228	227	230	685
	Mean	91.79	89.77	91.06	90.88
	SD	22.235	20.222	19.711	20.735
	Median	88.55	86.00	88.95	87.70
	Min	43.4	52.1	47.8	43.4
	Max	181.4	164.2	171.5	181.4
BMI (kg/m^2)	n	228	227	230	685
	Mean	33.18	32.02	32.98	32.73
	SD	6.787	5.932	6.098	6.294
	Median	31.72	31.21	31.86	31.51
	Min	19.3	19.6	21.8	19.3
	Max	65.0	56.2	52.0	65.0
BMI group (kg/m^2) n (%)	<25	17 (7.5)	17 (7.5)	15 (6.5)	49 (7.2)
	≥25 and <30	71 (31.1)	78 (34.4)	57 (24.8)	206 (30.1)
	≥30	140 (61.4)	132 (58.1)	158 (68.7)	430 (62.8)

Weight and height collected at screening visit. BMI=weight (in kilograms)/(height (in meters)^2).
All percentages are calculated based on the number of patients in the analysis set within each treatment group.
BMI Body mass index; Dapa Dapagliflozin 10 mg od; EQW Exenatide 2 mg once weekly; ITT Intent to treat; Max Maximum; Min Minimum; SD Standard deviation; n Number of patients in analysis; N Number of patients in treatment group.

In general, baseline disease characteristics were similar across the treatment groups. The mean baseline HbA1c at the screening visit was 9.31%, and most patients were in the ≥9% HbA1c category (56.6%). The mean duration of diabetes was 7.4 years. The mean baseline eGFR was 98 mL/min/1.73 m^2.

Table 6 Disease characteristics (ITT analysis set)

Disease characteristics		EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)	Total (N=685)
Baseline HbA1c (%)	n	228	227	230	685
	Mean	9.34	9.30	9.30	9.31
	SD	1.067	1.064	1.031	1.053
	Median	9.10	9.10	9.20	9.10
	Min	6.6	6.7	6.7	6.6
	Max	12.6	12.0	12.4	12.6
Baseline HbA1c (%) n (%)	<8%	14 (6.1)	13 (5.7)	14 (6.1)	41 (6.0)
	≥8 to <9%	84 (36.8)	84 (37.0)	88 (38.3)	256(37.4)
	≥9%	130 (57.0)	130 (57.3)	128 (55.7)	388 (56.6)
Diabetes duration (years)	n	228	227	230	685
	Mean	7.569	7.432	7.057	7.352
	SD	6.0417	5.5011	5.5244	5.6901
	Median	6.000	6.000	6.000	6.000
	Min	0.17	0.17	0.17	0.17
	Max	35.00	26.00	39.00	39.00
Baseline eGFR (mL/min/1.73 m^2)	n	228	227	230	685
	Mean	97.657	99.375	97.546	98.189
	SD	23.7060	26.8281	23.9535	24.8417
	Median	97.634	96.717	96.142	96.719
	Min	43.15	42.46	40.26	40.26
	Max	183.83	216.91	180.76	216.91
Baseline eGFR (mL/min/1.73 m^2) n (%)	<30	0	0	0	0
	≥30 to <60	6 (2.6)	7 (3.1)	12 (5.2)	25 (3.6)
	≥60 to <90	89 (39.0)	85 (37.4)	79 (34.3)	253 (36.9)
	≥90	133 (58.3)	135 (59.5)	139 (60.4)	407 (59.4)

Duration of diabetes=(date of screening – date of diabetes diagnosis + 1)/365.25.
All percentages are calculated based on the number of patients in the ITT analysis set within each treatment group.
Dapa Dapagliflozin 10 mg od; eGFR Estimated creatinine based glomerular filtration rate (unit=mL/min/1.73 m^2); EQW Exenatide 2 mg once weekly; HbA1 Haemoglobin A1c; ITT Intent to treat; Max Maximum; Min Minimum; SD Standard deviation; n Number of patients included in analysis; N Number of patients in treatment group.

Medical history

In general, medical and surgical history was similar across the treatment groups.

The most commonly reported medical history terms were hypertension (63.4%), dyslipidaemia (21.6%), obesity (21.3%), and hyperlipidaemia (18.2%).

The most commonly reported surgical history terms were hysterectomy (8.5%), cholecystectomy (7.5%), female sterilization (6.9%), and appendectomy (6.1%).

Concomitant medication prior to study entry

The treatment groups were well balanced with regard to the use of prior concomitant medications. All patients in the Safety analysis set took at least 1 prior concomitant medication.

The most frequently used prior concomitant medications were metformin (82.3%), metformin hydrochloride (17.7%), acetylsalicylic acid (17.6%), and lisinopril (17.6%).

Concomitant medication added after study entry

The treatment groups were well balanced with regard to the use of new concomitant medications, reported for 98 patients (42.4%) in the EQW+dapagliflozin group, 99 patients (43.0%) in the EQW+placebo group, and 109 patients (46.8%) in the dapagliflozin+placebo group.

The most frequently used new concomitant medications were paracetamol (6.5%), insulin glargine (4.6%), amoxicillin (4.0%), and ciprofloxacin (4.0%). Insulin glargine was the rescue medication used in this study.

Use of rescue medication

A total of 36 (5.2%) patients used rescue medication: 9 patients (3.9%) in the EQW+dapagliflozin group, 10 patients (4.3%) in the EQW+placebo group, and 17 patients (7.3%) in the dapagliflozin+placebo group.

The most frequently used rescue medication was insulin glargine (29 patients; 4.2%). Open-label titrated basal insulin was the protocol-defined rescue medication.

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarized in Table 7.

Table 7 Analysis Sets – 28-week treatment period (Randomized analysis set)

	Number (%) of patients			
	EQW+Dapa (N=231)	EQW+Placebo (N=231)	Dapa+Placebo (N=233)	Total (N=695)
Patients included in Safety analysis set	231 (100.0)	230 (99.6)	233 (100.0)	694 (99.9)
Patients excluded from Safety analysis set	0	1 (0.4)	0	1 (0.1)
Did not receive treatment	0	1 (0.4)	0	1 (0.1)
Patients included in ITT analysis set	228 (98.7)	227 (98.3)	230 (98.7)	685 (98.6)
Patients excluded from ITT analysis set	3 (1.3)	4 (1.7)	3 (1.3)	10 (1.4)
Did not receive treatment	0	1 (0.4)	0	1 (0.1)
Missing required efficacy assessments	3 (1.3)	3 (1.3)	3 (1.3)	9 (1.3)
Patients included in Per-protocol analysis set	204 (88.3)	202 (87.4)	209 (89.7)	615 (88.5)
Patients excluded from Per-protocol analysis set	27 (11.7)	29 (12.6)	24 (10.3)	80 (11.5)
Did not receive treatment	0	1 (0.4)	0	1 (0.1)
Missing required efficacy assessments	3 (1.3)	3 (1.3)	3 (1.3)	9 (1.3)
Met important protocol violation criteria	24 (10.4)	25 (10.8)	21 (9.0)	70 (10.1)

Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly; HbA1c=hemoglobin A1c; ITT=intent-to-treat.
Randomized analysis set includes all patients who signed informed consent and who are randomized to a treatment group.
Safety analysis set includes all patients who receive at least 1 dose of randomized study medication.
ITT analysis set includes all randomized patients who received at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.
Per-protocol analysis set - a subset of the ITT without important protocol violations.
All denominators are based on the number of randomized patients within each treatment group.

Outcomes and estimation

Primary efficacy endpoint

Change in HbA1c from Baseline to Week 28

The combination of EQW+dapagliflozin was superior to EQW alone or dapagliflozin alone in reducing HbA1c over 28 weeks.

Mean HbA1c decreased from baseline to Week 28 for all treatment groups (Table 8). The LS mean change in HbA1c was -1.98% for the EQW+dapagliflozin group, -1.60% for the EQW+placebo group, and -1.39% for the dapagliflozin+placebo group. The difference in LS mean change between the EQW+dapagliflozin group and EQW+placebo group was -0.38% (p=0.004) and the difference in LS mean change between the EQW+dapagliflozin group and dapagliflozin+placebo group was -0.59% (p<0.001).

Table 8 MMRM analysis of change in HbA1c from baseline to Week 28 (ITT analysis set)

Measurement: HbA1c Unit: %	EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)
Summary statistics			
n	193	184	196
Baseline mean (SD)	9.29 (1.058)	9.26 (1.080)	9.25 (1.019)
Week 28 mean (SD)	7.24 (1.280)	7.58 (1.295)	7.74 (1.130)
Adjusted change from baseline to Week 28[a]			
LS mean (SE)	-1.98 (0.094)	-1.60 (0.095)	-1.39 (0.092)

Measurement: HbA1c Unit: %	EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)
95% two-sided CI	(-2.16, -1.79)	(-1.79, -1.41)	(-1.57, -1.21)
Difference from EQW + Dapa at Week 28[a]			
LS mean (SE)		-0.38 (0.129)	-0.59 (0.127)
95% two-sided CI		(-0.63, -0.13)	(-0.84, -0.34)
P-value[b]		0.003	<0.001

Baseline is defined as the last non-missing assessment prior to first dose.
This analysis excludes measurements post rescue therapy and post premature discontinuation of study medication.
[a] Adjusted least squares means (LS Means) and treatment group difference in the change from baseline values at Week 28 are modelled using an MMRM method including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.
[b] P-values are adjusted for multiplicity
CI Confidence interval; Dapa Dapagliflozin 10 mg QD; EQW Exenatide 2 mg once weekly; HbA1c Haemoglobin A1c; ITT Intent to treat; LS Least squares; MMRM Mixed model with repeated measures; n Number of patients with observed baseline and Week 28 values; N Number of patients in treatment group; SD Standard deviation; SE Standard error.

Sensitivity analyses of the primary endpoint

The results for each of the supportive and sensitivity analyses were consistent with those of the primary analysis. In comparing the analyses, the difference in estimated treatment differences was overall small, ranging from -0.34 to -0.38 for EQW+dapagliflozin vs EQW alone and from -0.51 to -0.59 for EQW+dapagliflozin vs dapagliflozin alone.

Subgroup analyses of the primary endpoint

As additional analyses, the primary efficacy variable, change in HbA1c from baseline to Week 28, was analysed by the following baseline subgroup categories: age, sex, region, ethnic group, baseline BMI, baseline HbA1c, diabetes duration, race, and eGFR.

At Week 28, a potential treatment by age subgroup interaction was observed (<65 vs ≥65, p=0.008). There were few patients in the ≥65 subgroup (21 to 29 per treatment group), which limits the interpretability of the interaction term for this subgroup analysis.

Table 9 MMRM analysis of HbA1c, observed and change from baseline to Week 28 by baseline age (Intent-to-treat analysis set)

Measurement: HbA1c Unit: % Subgroup	EQW+Dapa (N=228)	EQW+Placebo (N=227)	Dapa+Placebo (N=230)	Interaction p-value[a]
Age (years)				0.016
Age (years): <65				
n	164	160	175	
Baseline Mean (SD)	9.31 (1.095)	9.23 (1.061)	9.27 (1.008)	
Week 28 Mean (SD)	7.32 (1.304)	7.50 (1.213)	7.69 (1.122)	
Adjusted Change from Baseline to Week 28[a]				
LS Mean (SE)	-1.91 (0.100)	-1.65 (0.100)	-1.46 (0.097)	
95% two-sided confidence interval	(-2.11, -1.71)	(-1.85, -1.46)	(-1.65, -1.27)	
Difference from EQW+Dapa at Week 28[a]				
LS Mean (SE)		-0.26 (0.137)	-0.45 (0.135)	
95% two-sided confidence interval		(-0.53, 0.01)	(-0.72, -0.19)	
P-value		0.060	<0.001	
Age (years): ≥65				
n	29	24	21	
Baseline Mean (SD)	9.22 (0.832)	9.43 (1.211)	9.08 (1.118)	
Week 28 Mean (SD)	6.80 (1.039)	8.11 (1.680)	8.20 (1.118)	
Adjusted Change from Baseline to Week 28[a]				
LS Mean (SE)	-2.39 (0.240)	-1.25 (0.257)	-0.82 (0.266)	
95% two-sided confidence interval	(-2.86, -1.92)	(-1.76, -0.75)	(-1.34, -0.30)	
Difference from EQW+Dapa at Week 28[a]				
LS Mean (SE)		-1.14 (0.351)	-1.57 (0.357)	
95% two-sided confidence interval		(-1.82, -0.45)	(-2.27, -0.87)	
P-value		0.001	<0.001	

Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly; N=Number of patients in treatment group; n=Number of patients included in analysis; SD=Standard deviation; SE=Standard error.

a Adjusted least squares means (LS Means) and treatment group difference in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, subgroup, treatment by week, subgroup-by-week, subgroup-by-treatment, and subgroup-by-week-by-treatment interactions, as fixed factors, and baseline value as a covariate. The nominal p-value for the subgroup-by-treatment interaction is presented.

For age categories, interaction p-value is obtained for the age categories (<65 and ≥65) only.
Baseline is defined as the last non-missing assessment prior to first dose.
This analysis excludes measurements post rescue therapy and post study medication discontinuation.

No other potential subgroup-by-treatment interactions were observed.

In the table below is the analysis by baseline HbA1c.

Table 10 MMRM Analysis of HbA1c, Observed and Change from Baseline to Week 28 by Baseline Subgroup Categories (Intent-to-treat Analysis Set)

Measurement: HbA1c Unit: % Subgroup	Number (%) of patients EQW+Dapa (N=228)	EQW+Placebo (N=227)	Dapa+Placebo (N=230)	Interaction P-Value [a]
HbA1c (%): <8%				0.977
n	11	13	14	
Baseline Mean (SD)	7.56 (0.434)	7.62 (0.361)	7.66 (0.301)	
Week 28 Mean (SD)	6.44 (0.573)	7.24 (1.162)	6.97 (0.675)	
Adjusted Change from Baseline to Week 28 [a]				
LSmean (SE)	-1.60 (0.374)	-0.74 (0.360)	-1.04 (0.347)	
95% two-sided confidence interval	(-2.33, -0.87)	(-1.44, -0.03)	(-1.72, -0.36)	
Difference from EQW+Dapa at Week 28 [a]				
LSmean (SE)		-0.86 (0.507)	-0.56 (0.498)	
95% two-sided confidence interval		(-1.86, 0.13)	(-1.54, 0.42)	
P-value		0.089	0.263	
HbA1c (%): >=8 - <9%				
n	75	75	76	
Baseline Mean (SD)	8.47 (0.263)	8.45 (0.277)	8.49 (0.263)	
Week 28 Mean (SD)	6.92 (1.055)	7.41 (1.047)	7.64 (1.038)	
Adjusted Change from Baseline to Week 28 [a]				
LSmean (SE)	-1.68 (0.150)	-1.28 (0.149)	-1.02 (0.146)	
95% two-sided confidence interval	(-1.98, -1.39)	(-1.58, -0.99)	(-1.31, -0.74)	
Difference from EQW+Dapa at Week 28 [a]				
LSmean (SE)		-0.40 (0.200)	-0.66 (0.198)	
95% two-sided confidence interval		(-0.79, -0.01)	(-1.05, -0.27)	
P-value		0.047	<0.001	
HbA1c (%): >=9%				
n	111	104	108	
Baseline Mean (SD)	10.07 (0.806)	10.04 (0.792)	9.99 (0.734)	
Week 28 Mean (SD)	7.60 (1.400)	7.80 (1.463)	7.92 (1.188)	
Adjusted Change from Baseline to Week 28 [a]				
LSmean (SE)	-2.16 (0.126)	-1.87 (0.127)	-1.64 (0.126)	
95% two-sided confidence interval	(-2.40, -1.91)	(-2.12, -1.62)	(-1.89, -1.39)	
Difference from EQW+Dapa at Week 28 [a]				
LSmean (SE)		-0.28 (0.163)	-0.52 (0.162)	
95% two-sided confidence interval		(-0.60, 0.04)	(-0.84, -0.20)	
P-value		0.085	0.002	

EQW=Exenatide 2 mg once weekly; Dapa=Dapagliflozin 10 mg QD.

SD=Standard deviation; SE=Standard error; N=Number of patients in treatment group; n=Number of patients included in analysis; Adjusted least squares means (LSMeans) and treatment group difference in the change from baseline values at week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (<9.0% or >=9.0%), week, subgroup, treatment by week, subgroup-by-week, subgroup-by-treatment, and subgroup-by-week-by-treatment interactions, as fixed factors, and baseline value as a covariate. The nominal p-value for the subgroup-by-treatment interaction is presented. Baseline is defined as the last non-missing assessment prior to first dose. This analysis excludes measurements post rescue therapy and post study medication discontinuation.

Secondary efficacy endpoints

Glycaemic endpoints

The EQW+dapagliflozin group had between 1.6 and 2.3 times as many patients who achieved HbA1c <7.0% at Week 28 compared with the EQW+placebo and dapagliflozin+placebo groups, respectively (Table 11). The combination of EQW+dapagliflozin was also superior to EQW+placebo and dapagliflozin+placebo in reducing FPG at Weeks 2 and 28, and 2-hour PPG at Week 28 (Table 11).

Body weight endpoints

The combination of EQW+dapagliflozin was superior to EQW+placebo and dapagliflozin+placebo in reducing mean body weight and the proportion achieving weight loss ≥5% at Week 28 (Table 11). The effect on weight loss was additive in the EQW+dapagliflozin group compared to the individual therapies.

Blood pressure

The combination of EQW+dapagliflozin was superior to EQW alone and dapagliflozin alone in reducing systolic blood pressure over 28 weeks (Table 11). The BP-lowering effect was at least additive for EQW+dapagliflozin compared to the individual therapies.

Table 11 Change from baseline to Week 28 in secondary efficacy endpoints (ITT analysis set)

Parameter Statistic	EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)
Body weight (kg)[a]			
LS mean (SE)	-3.55 (0.289)	-1.56 (0.293)	-2.22 (0.284)
LS mean differences (SE)		-2.00 (0.406)	-1.33 (0.400)
95% CI for LS mean differences		(-2.79, -1.20)	(-2.12, -0.55)
P-value[b]		<0.001	<0.001
FPG at Week 28 (mmol/L)[a]			
LS mean (SE)	-3.66 (0.163)	-2.54 (0.168)	-2.73 (0.162)
LS mean differences (SE)		-1.12 (0.223)	-0.92 (0.219)
95% CI for LS mean differences		(-1.55, -0.68)	(-1.36, -0.49)
P-value[b]		<0.001	<0.001
2-hour PPG (mmol/L)[a]			
LS mean (SE)	-4.88 (0.226)	-3.34 (0.237)	-3.39 (0.228)
LS mean differences (SE)		-1.54 (0.287)	-1.49 (0.283)
95% CI for LS mean differences		(-2.10, -0.98)	(-2.04, -0.93)
P-value[b]		<0.001	<0.001
Body weight loss (kg) ≥5.0%[c]			
Week 28, n (%)	76 (33.3)	31 (13.7)	46 (20.0)
P-value[b]		<0.001	0.001
FPG at Week 2 (mmol/L) [a]			
LS mean (SE)	-2.30 (0.145)	-1.17 (0.148)	-1.46 (0.145)
LS mean differences (SE)		-1.13 (0.194)	-0.83 (0.193)
95% CI for LS mean differences		(-1.51, -0.74)	(-1.21, -0.46)
P-value[b]		<0.001	<0.001[d]
HbA1c <7%[c]			
Week 28, n (%)	102 (44.7)	61 (26.9)	44 (19.1)
P-value[b]		<0.001	<0.001

Parameter Statistic	EQW + Dapa (N=228)	EQW + Placebo (N=227)	Dapa + Placebo (N=230)
SBP (mmHg) [a]			
LS mean (SE)	-4.3 (0.80)	-1.2 (0.82)	-1.8 (0.79)
LS mean differences (SE)		-3.0 (1.08)	-2.4 (1.06)
95% CI for LS mean differences		(-5.2, -0.9)	(-4.5, -0.4)
P-value[b]		0.005	0.022

This analysis excludes measurements post rescue therapy and post of premature discontinuation study medication. Only SBP analysis includes measurements post rescue therapy and post study medication discontinuation

[a] Adjusted LS means and treatment group difference in the change from baseline values at Week 28 are modelled using an MMRM including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[b] Between group comparison is significant at alpha = 0.05 using the gatekeeping procedure.

[c] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on the CMH test stratified by baseline HbA1c (<9.0% or ≥9.0%). P values are from the general association statistics

[d] Nominal p-value.

BP Blood pressure; CI Confidence interval; CMH Cochran-Mantel-Haenszel; Dapa Dapagliflozin 10 mg od; EQW Exenatide 2 mg once weekly; FPG Fasting plasma glucose; HbA1c Haemoglobin; ITT Intent-to-treat; LS Least squares; MMRM Mixed model with repeated measures; n Number of patients with observed baseline and Week 28 values; N Number of patients in treatment group; od Once daily; PPG Postprandial glucose; SBP Systolic blood pressure; SD Standard deviation; SE Standard error

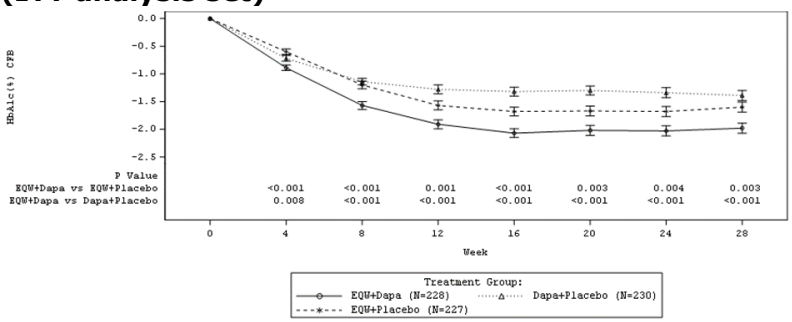
Exploratory efficacy endpoints

Glycaemic and weight-related exploratory endpoints were generally consistent with the results of the primary and secondary endpoints. The p-values reported for all exploratory variables are nominal.

Changes in HbA1c over time from baseline to Week 28

The change in HbA1c over time from baseline to Week 28, is presented in (Figure 2). Mean HbA1c continued to decrease from baseline through Weeks 12 to 16 of the study, and then remained stable for all treatment groups through Week 28.

Figure 2 LS mean changes (SE) in HbA1c (%) over time from baseline to Week 28 (ITT analysis set)

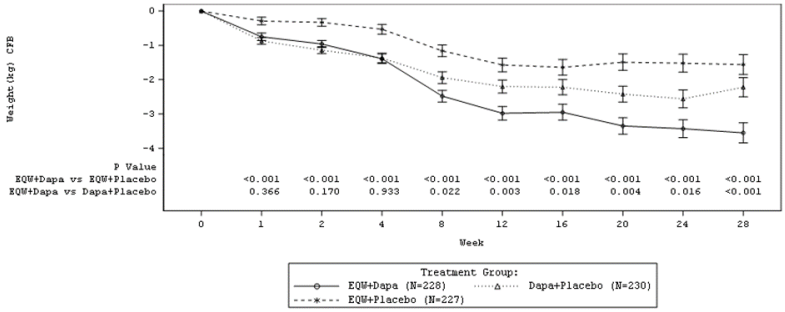


Baseline is defined as Week 0.
CFB change from baseline; Dapa Dapagliflozin 10 mg QD; EQW Exenatide 2 mg once weekly; HbA1c Haemoglobin A1c; ITT Intent-to-treat; LS Least squares; N Number of patients; SE Standard error; vs Versus.

Change in weight over time from baseline to Week 28

The change in weight over time from baseline to Week 28, is presented graphically in Figure 3. Mean weight continued to decrease from baseline through Week 12 of the study, and then remained relatively stable in the groups administered the single agents, while in the combination treatment group weight continued to decrease through Week 28.

Figure 3 LS mean changes (SE) in weight (kg) over time from baseline to Week 28 (ITT analysis set)



Baseline is defined as Week 0.
CFB Change from baseline; Dapa Dapagliflozin 10 mg od; EQW Exenatide 2 mg once weekly; ITT Intent-to-treat; LS Least squares; N Number of patients; SE Standard error; vs Versus.

Proportion of patients achieving HbA1c ≤6.5% from baseline at Week 28

The proportion of patients achieving HbA1c ≤6.5% at Week 28 was 30.3% in the EQW+dapagliflozin group, 18.5% in the EQW+placebo group, and 10.4% in the dapagliflozin+placebo group at Week 28 . A greater proportion of patients achieved HbA1c ≤6.5% at Week 28 in the EQW+dapagliflozin group compared to the EQW+placebo group (p=0.003), and the dapagliflozin+placebo group (p<0.001). All patients with missing data were treated as non-responders.

Change in diastolic blood pressure from baseline at Week 28

There were no clinically relevant changes from baseline in the 3 treatment groups or statistical differences between treatment groups for DBP change from baseline to Week 28.

Change in lipid profiles from baseline to Week 28

There were no clinically relevant changes in cholesterol parameters (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], or non-HDL cholesterol) in the EQW+dapagliflozin group or in the EQW+placebo group. There were small increases in total cholesterol, LDL, and non-HDL cholesterol in the dapagliflozin+placebo group. There was a clinically meaningful decrease in mean triglycerides in each of the 3 treatment groups EQW+dapagliflozin group (-0.31 mmol/L) compared to the EQW+placebo (-0.18 mmol/L) and dapagliflozin+placebo (-0.11 mmol/L) groups from baseline to Week 28. The nominal p-values for the differences between the EQW + dapagliflozin group and the dapagliflozin + placebo and EQW + placebo groups were 0.036 and 0.181, respectively.

Exploratory pharmacokinetic endpoint

Exenatide and dapagliflozin pharmacokinetic profiles

The exenatide and dapagliflozin pharmacokinetics (PK) in the EQW + dapagliflozin, dapagliflozin + placebo, and EQW + placebo treatment groups were evaluated. No difference in exenatide exposure or dapagliflozin exposure across the EQW+dapagliflozin, EQW+placebo or dapagliflozin+placebo groups were seen. High inter-individual variability in data was observed.

Long-term efficacy

Study D5553C00003 efficacy data from the extension up to 52 weeks are summarised in the following.

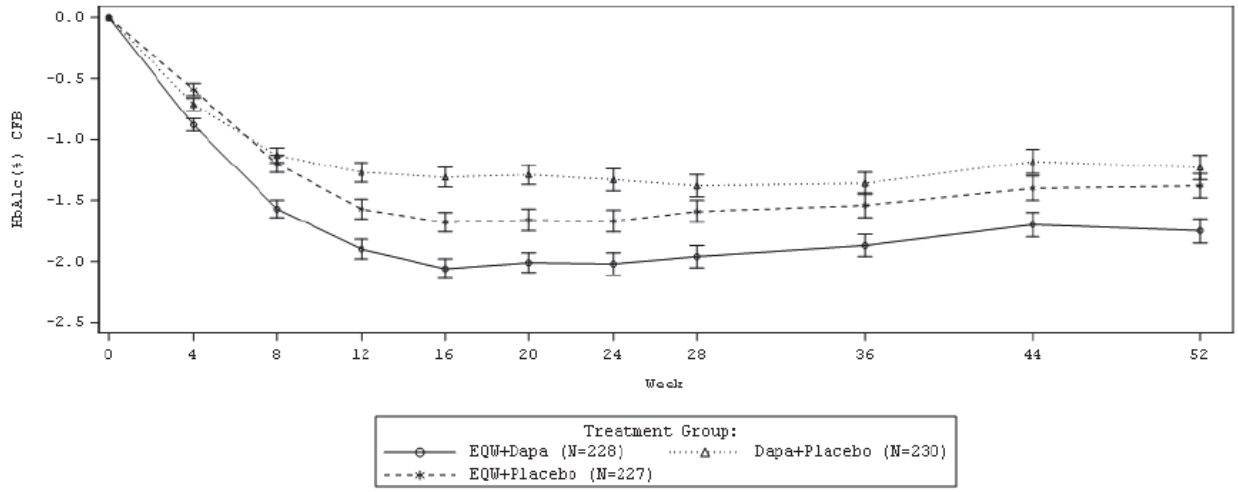
In total, 81% of the 695 randomised patients completed the 52-week treatment period and 75% of randomised patients completed treatment. The drop-out rate was highest in the EQW+placebo group (23%) and lower in the two other groups (16% in the EQW+dapa group and 17% in the dapa+placebo group).

Change in HbA1c from baseline to Week 52

The differences between treatment groups observed at week 28 were maintained at 52 weeks.

Mean HbA1c decreased from baseline to Week 52 for all treatment groups. The LS mean change in HbA1c was -1.75% for the EQW + dapagliflozin group, -1.38% for the EQW + placebo group, and -1.23% for the dapagliflozin + placebo group at Week 52. The difference in LS mean change between the EQW + dapagliflozin group and EQW + placebo group was -0.37% (p=0.006) and the difference in LS mean change between the EQW + dapagliflozin group and dapagliflozin + placebo group was -0.52% (p<0.001).

Figure 4 Change in HbA1c over time, LS mean (SE) – 52-Week Treatment Period (Intent-to-treat analysis set)

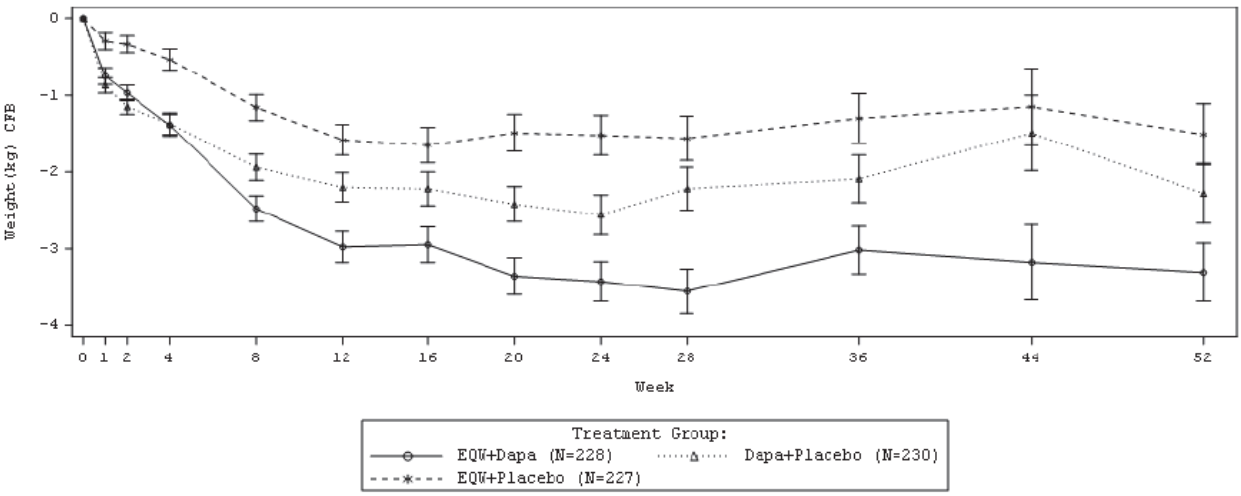


CFB=change from baseline; Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly; HbA1c=hemoglobin A1c; SE=standard error.
Baseline is defined as Week 0.
Adjusted 95% confidence intervals for change from baseline values over time for each treatment group are included.

Change from baseline to Week 52 in total body weight

The differences between treatment groups observed at week 28 were maintained at 52 weeks.

Figure 5 Change in weight over time, LS Mean (SE) – 52-Week Treatment Period (Intent-to-treat analysis set)



CFB = change from baseline; Dapa=Dapagliflozin 10 mg QD; EQW=Exenatide 2 mg once weekly.
Baseline is defined as Week 0.
Adjusted 95% confidence intervals for change from baseline values overs time for each treatment group are included.

Proportion of patients achieving HbA1c <7.0% at Week 52

Larger proportions of patients achieved HbA1c <7.0% in the EQW + dapagliflozin group compared to the EQW alone and dapagliflozin alone groups at Week 28 and Week 52.

The proportion of patients achieving HbA1c <7% at Week 52 was 33.8% in the EQW + dapagliflozin group, 24.2% in the EQW + placebo group (p=0.024 for the treatment comparison against EQW + dapagliflozin group), and 15.2% in the dapagliflozin + placebo group (p<0.001 for the treatment comparison against EQW + dapagliflozin group). The difference in proportion of patients who achieved HbA1c <7% between the EQW + dapagliflozin group and EQW + placebo group was 9.5% and between the EQW + dapagliflozin group and dapagliflozin + placebo group was 18.6%.

All patients with missing endpoint data were treated as non-responders.

Long-term efficacy up to 104 weeks will be available 2Q 2018.

Summary of main study

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

Table 12 Summary of Efficacy for trial D5553C00003

Title: A 28-week, Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Study with a 24-week Extension Phase Followed by a 52-week Extension Phase to Evaluate the Efficacy and Safety of Simultaneous Administration of Exenatide Once Weekly 2 mg and Dapagliflozin Once Daily 10 mg Compared to Exenatide Once Weekly 2 mg Alone and Dapagliflozin Once Daily 10 mg Alone in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin.			
Study identifier	Study D5553C00003		
Design	Randomised, double-blind, active-controlled, multicentre, Phase 3b efficacy and safety study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 weeks not applicable/a 1-week placebo lead-in period a 24- and subsequent 52-week extension
Hypothesis	Superiority		
Treatments groups	EQW+dapagliflozin		Exenatide QW 2mg/Dapagliflozin 10 mg OD Randomised 231
	EQW+placebo		Exenatide QW 2mg/Placebo. Randomised 231
	Dapagliflozin+placebo		Dapagliflozin 10 mg OD/Placebo. Randomised 233
Endpoints and definitions	Primary endpoint	HbA1c	Change in HbA1c from Baseline to Week 28
	Secondary endpoint	HbA1c<7%	Patients achieving HbA1c<7% at Week 28
	Secondary endpoint	Body weight	Change in body weight from Baseline to Week 28
Database lock			
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat Week 28			
Descriptive statistics and estimate variability	Treatment group	EQW+ dapagliflozin	EQW+placebo	Dapagliflozin+ placebo
	Number of subject	228	227	230
	HbA1c (LS Mean)	-1.98	-1.60	-1.39
	(SE)	0.094	0.095	0.092
	HbA1c<7% (n)	102	61	44
	%	44.7	26.9	19.1
	Body weight (LS Mean)	-3.55	-1.56	-2.22
	(SE)	0.289	0.293	0.284

Effect estimate per comparison	Primary endpoint HbA1c	Comparison groups	EQW+dapagliflozin vs EQW+placebo
		LS Mean Differences (SE)	-0.38 (0.129)
		95% CI	(-0.63, -0.13)
		P-value	0.003
		Comparison groups	EQW+dapagliflozin vs Dapagliflozin+placebo
		LS Mean Differences (SE)	-0.59 (0.127)
		95% CI	(-0.84, -0.34)
		P-value	<0.001
	Secondary endpoint HbA1c<7%	Comparison groups	EQW+dapagliflozin vs EQW+placebo
		%	17.4%
		P-value	<0.001
		Comparison groups	EQW+dapagliflozin vs Dapagliflozin+placebo
		%	25.6%
		P-value	<0.001
		Comparison groups	EQW+dapagliflozin vs EQW+placebo
	Secondary endpoint Body weight	LS Mean Differences (SE)	-2.00 (0.406)
		95% CI	(-2.79, -1.20)
		P-value	<0.001
		Comparison groups	EQW+dapagliflozin vs Dapagliflozin+placebo
		LS Mean Differences (SE)	-1.33 (0.400)
		95% CI	(-2.12, -0.55)
		P-value	<0.001
Notes			
Analysis description			

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study D5553C00003 was a 28-week, randomised, double-blind, active-controlled, multicentre, Phase 3b efficacy and safety study with a 24- and subsequent 52-week extension of simultaneous administration of EQW 2 mg + dapagliflozin 10 mg od compared to EQW 2 mg + placebo and dapagliflozin 10 mg od + placebo in patients with T2DM who had inadequate glycaemic control on metformin. The total study duration will be 2 years; this submission presents data from the 28-week treatment period and the first extension period up to 52 weeks.

The three-armed study designs allows for assessment of the contribution of each of the components in the combined therapy.

The study included patients with T2DM treated with metformin only and with poor metabolic control as reflected by a HbA1c between 8% and 12%. This is adequate considering that two glucose lowering drugs were initiated at once. No restrictions regarding BMI were included in the criteria. The study duration is sufficient to allow assessment of the short-term effect on HbA1c. Long-term data up to 104 weeks will be available once the second extension period of the study have been finalised.

The rationale for choosing the combination of a GLP1-RA (exenatide) and a SGLT2-inhibitor is based on the complementary MOAs of the two different drugs. The doses selected were based on the respective product information. The use of metformin as the background medication is supported by current guidelines. Criteria for starting rescue therapy (i.e. basal insulin) were in place.

The statistical considerations regarding the study design are overall acceptable. The trial was on-going at the time of the analyses of the 28-week data; however, sites and patients were to remain blinded until study completion and final database lock (after extension period 2). Randomisation was 1:1:1 and stratified by baseline HbA1c (<9.0% or ≥9.0%). Efficacy data were to be continuously collected also during rescue therapy and post-treatment follow-up. The study was seemingly sufficiently powered and took into account the proportion of patients (assumed to be 5%) expected to be excluded from the primary Intent-to-Treat (ITT) analysis. The sample size calculation was based on a mean difference of 0.35% in HbA1c change from baseline, EQW+dapagliflozin versus each monotherapy.

Considering planned analyses no changes were made and the Statistical Analysis plan had not been amended. For the primary and the set of 7 secondary efficacy endpoints multiplicity was sufficiently handled through the use of a gatekeeping testing strategy. In addition (considering two pairwise comparisons) superiority of the combination treatment group was to be concluded if and only if the comparisons of the combination treatment group against both control groups (EQW+placebo and dapagliflozin+placebo) were statistically significant; hence no further multiplicity correction was needed.

To be included in the ITT set a patient had to have been randomised, should have received at least one dose of study medication, and have at least one HbA1c post-baseline assessment. The first visit where HbA1c was to be evaluated was at Week 4 (Visit 6). The primary endpoint and continuous secondary endpoints were analysed using a mixed model with repeated measures (MMRM) based on the assumption of data missing at random (MAR) i.e. that treatment response can be estimated without bias using exclusively observed data. In the analyses, data collected after initiation of rescue therapy and after treatment discontinuation were excluded. Several sensitivity and supportive analyses were planned and have been presented. Among them the primary analysis repeated based on the Randomised set and analyses using the primary MMRM model but taking data collected post rescue therapy and post discontinuation of study medication into account. Two sensitivity analyses were performed to address violations of the missing at random (MAR) assumption, one analysis using a Placebo-Based Multiple Imputation and a Tipping Point Analysis.

In general the study appears well conducted. Important protocol violations were relatively few (10 % of patients), evenly distributed between treatment groups and mainly related to compliance with treatment.

In the EQW+dapagliflozin arm a total of 206/231 (89.2%) completed the 28 week treatment period. In the EQW monotherapy arm and in the dapagliflozin monotherapy arm it was 196/231 (84.8%) and 209/233 (89.7%) respectively. Of those who discontinued the study, the most common reasons were withdrawal by subject, lost to follow-up and adverse event.

Overall, 14.7% (102/695) discontinued study treatment; 14.3% (33/231) of patients in the EQW+dapagliflozin group, 18.6% (43/231) of patients in the EQW+placebo group, and 11.2% (26/233) of patients in the dapagliflozin+placebo group.

It was few patients who used rescue, more in the in the dapagliflozin+placebo group however than in the other two arms. In the whole study population it was 36/695 (5.2%) whereof 9/231 (3.9%) in the EQW+dapagliflozin group, 10/231 (4.3%) in the EQW+placebo group, and 17/233 (7.3%) in the dapagliflozin+placebo group.

A similar proportion of patients in each treatment arm was excluded from the ITT analysis set; 3/231 (1.3%) in the EQW+dapagliflozin arm, 4/231 (1.7%) in the EQW+placebo arm and 3/233 (1.3%) in the dapagliflozin+placebo arm. All patients but one in the EQW+placebo treatment group who did not receive treatment was excluded due to missing required efficacy assessment. In the primary ITT analysis it was however 14.3% (98/685) of the patients who did not contribute with data and overall, this implied that 15.5% (108/695) of those who had been randomised were excluded in the primary analysis.

Efficacy data and additional analyses

The primary ITT analysis included 197/228 (86.4%), 192/227 (84.6%) and 198/230 (86.1%) patients in the EQW+dapagliflozin, EQW+placebo and dapagliflozin+placebo arm respectively.

The study included subjects in general representative of poorly controlled T2DM patients. The population was, however, rather heterogeneous with e.g. BMI ranging from 19 to 65, HbA1c ranging from 6.6% to 12.6%. The duration of diabetes was also very variable from 2 months up to 39 years.

Inclusion was based on screening values. The MAH has clarified that only 5 of the 41 patients with baseline HbA1c <8.0% had an HbA1c below the lower limit for inclusion at screening. With regards to renal function, different methods to assess renal function were applied at screening compared to the remaining part of the study. The difference between these methods explains the discrepancies observed in all but one of the 25 cases with eGFR below <60 mL/min/1.73m^2 at baseline. Thus the number of patients actually violating inclusion criteria was low.

At baseline, all patients but two were on a metformin dose of 1500 mg or more and the maximum dose used was 3000 mg. No patients were using basal insulin at baseline.

The difference in HbA1c mean change from baseline week 28 in the primary analysis was -0.38 (-0.63, -0.13; p=0.003) for EQW+dapagliflozin vs EQW+placebo and -0.59 (-0.84, -0.34; p<0.001) for EQW+dapagliflozin vs dapagliflozin+placebo.

Thus the contribution of exenatide to the effect of the combination was larger than that of dapagliflozin. However, both monotherapies contributed with a clinically relevant effect although the dapagliflozin effect is of somewhat borderline character.

Results of sensitivity analyses were consistent with those of the primary analysis supporting a conclusion of superiority in favour of the combined treatment of EQW and dapagliflozin over each monotherapy. In comparing the analyses, the difference in estimated treatment differences was overall small (the exception being the analysis based on the PP set; not presented here), ranging from -0.34 to -0.38 for

EQW+dapagliflozin vs EQW alone and from -0.51 to -0.59 for EQW+dapagliflozin vs dapagliflozin alone implying that e.g. the exclusion of post rescue and post treatment discontinuation data had minor impact.

However, most of the sensitivity analyses were based on the same MMRM model as used in the primary analysis and several was seemingly based on data from the same number of patients as in the primary analysis including the analysis on all randomised patients in which estimated outcomes was identical to the outcomes in the primary analysis. Although the number of patients excluded in the analyses was fairly well balanced between the treatment arms, this concerned approximately 15% of randomised patients. While both the analysis using a placebo-based multiple imputation and the Tipping Point analysis are appreciated as such, again MMRM was used and the same proportion of patients as in the primary analysis were excluded. None of the sensitivity analyses of the primary endpoint included all randomised patients and it may be that none was sufficiently conservative to challenge the primary analysis. In addition, the analyses of 4 (out of 5) continuous secondary endpoints were based on the same MMRM model as was used in the primary analysis resulting in the exclusion of data from similar proportions of patients as in the primary analysis. The MAH was asked to repeat analyses of the primary and continuous secondary endpoints based on a data set with better adherence to the ITT-principle (e.g. the currently defined (modified) ITT for which the exclusion of approximately 1.4% of randomised patients can be accepted). The MAH clarified that analyses involved all randomised patients who received at least 1 dose of study medication and had at least 1 on-treatment measurement and that no patient from this study population was excluded from any of the efficacy analysis. The only new analyses provided in response to this request were analyses of secondary endpoints including post-rescue/post study medication discontinuation data. The results taking these data into account were consistent with the results of analyses excluding these data. For SBP this was the primary analysis approach (and hence, the "new" analysis provided was the same as the one already presented in e.g. the CSR). Sensitivity analyses of the primary endpoint were requested to be performed based on all randomised patients using a conservative imputation approach in case data was missing. In at least one analysis patients with missing endpoint data, patients in need of rescue therapy and patients who discontinued the study and/or study treatment should be handled as treatment failures (using baseline observation carried forward). Additional sensitivity analyses for the primary endpoint (Change in HbA1c from baseline to Week 28) using ANCOVA (BOCF) have now been provided. Although not based on all randomised but ITT; this is not further pursued considering the minor difference and the statistically convincing outcomes. Irrespective of analysis, differences between the treatments were (still) statistically convincing with outcomes appearing to be robust; for the comparison of EQW+Dapa versus EWQ+placebo; estimates were very similar compared to the outcome in the primary analysis. For EQW+Dapa versus Dapa+Placebo the difference between the treatments was slightly smaller (point estimate of e.g. -0.45) compared to the outcome in the primary analysis (point estimate -0.59). For the above sensitivity analyses it was (as requested) clarified in how many cases endpoint data were available at week 28, and in how many cases endpoint data were missing and imputation used.

Subgroup analyses were performed for the primary endpoint. There was a statistically significant interaction with age. Older subjects (≥65 years) showed an overall greater effect of the combination than younger patients (<65 years) (-2.39% vs -1.91%). The treatment effect of both monotherapies was numerically lower in the older age group, the difference between age groups being most pronounced for dapagliflozin. The responder analysis by age group was in line with the analysis for change from baseline HbA1c. The lower effect of dapagliflozin in the older age group is in line with the data from previous studies with dapagliflozin, whereas no difference in effect by age has been observed with EQW. There is currently no apparent explanation to the higher than expected effect of the combination in the older patients. However, due to the low number of subjects, the data has to be interpreted with caution.

The subgroup analysis by HbA1c showed that the effect of both the combination and the monotherapies was, as expected, most pronounced in patients with HbA1c ≥9%. The outcome of the primary analysis

was only preserved in patients with HbA1c 8-9%, thus the combination was superior to both monotherapies in this group.

In the largest subgroup, i.e. patients with HbA1c ≥9%, the combination was only superior to monotherapy with dapagliflozin.

In the subgroup with HbA1c <8%, which was the smallest subgroup, the combined treatment and monotherapy with dapagliflozin showed a comparable effect to that observed in patients with HbA1c 8-9%, whereas a lower effect was observed in the EQW monotherapy group. Superiority of the combination was not shown for any of the monotherapies, the number of patients with HbA1c <8 was however low, thus the data should be interpreted with caution.

In order to better understand the impact of baseline HbA1c on the outcome, a table with data on responders (HbA1c <7%) by baseline HbA1c (HbA1c <8%, HbA1c 8-9% and HbA1c ≥9%) was provided. Although the change in HbA1c is most pronounced in the subgroup with HbA1c > 9% at baseline, the responder rate in this subgroup is lower than in the subgroups with lower baseline HbA1c as may be expected. A similar pattern, with more responders with combination therapy and less for the single components, was observed for all three subgroups.

The combination of EQW+dapagliflozin was superior to EQW alone and dapagliflozin alone for all secondary endpoints.

The proportion of patients achieving HbA1c <7% at Week 28 was 44.7% in the EQW+dapagliflozin group, 26.9% in the EQW+placebo group, and 19.1% in the dapagliflozin+placebo group. The difference between the EQW+dapagliflozin group and EQW+placebo group was 17.4% ($p<0.001$) and between the EQW+dapagliflozin group and dapagliflozin+placebo group was 25.6% ($p<0.001$). This analysis, based on the ITT set excluding only 1.4% of randomised patients treating all patients with missing endpoint data as non-responders, is considered to support a superior efficacy of EQW+dapagliflozin in reducing HbA1c.

Body weight decreased by -3.6 kg in the EQW+dapagliflozin group, -1.6 kg in the EQW+placebo group, and -2.2 kg in the dapagliflozin+placebo group. Thus there was an additive effect on body weight by the combination. This was also reflected by a significantly higher proportion of patients achieving a body weight reduction of ≥5% in the EQW+dapagliflozin group (33%) compared to the EQW+placebo group (14%), and the dapagliflozin+placebo group (20%).

An additive effect was also observed on SBP at Week 28. SBP decreased by -4.3 mmHg in the EQW+dapagliflozin group, -1.2 mmHg in the EQW+placebo group, and -1.8 mmHg in the dapagliflozin+placebo group.

Efficacy data up to 52 weeks has been provided. There was a slight increase in HbA1c of about 0.2% in all treatment groups between week 28 and week 52 but an adequate effect was maintained and the differences observed between treatment arms at week 28 were essentially maintained. The body weight remained essentially stable in all treatment groups between week 28 and 52 with only a slight increase. The proportion of patients achieving HbA1c < 7% decreased with about 10 % in the EQW+dapa group and about 5% in the monotherapy groups between week 28 and 52.

2.3.4. Conclusions on the clinical efficacy

The combination of exenatide QW and dapagliflozin was superior to monotherapy with either exenatide or dapagliflozin on top of metformin in lowering HbA1c after 28 weeks. The effect was maintained up to 52 weeks.

2.4. Clinical safety

Introduction

The safety and tolerability of exenatide and dapagliflozin as both single agent therapies and in combination with other therapies for T2DM, including metformin, were thoroughly documented and evaluated in the clinical development programmes for BYDUREON and FORXIGA.

The most frequent adverse reactions reported with EQW were mainly gastrointestinal related (nausea which was the most frequent reaction and associated with the initiation of treatment and decreased over time, and diarrhoea). In addition, injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache occurred. Most adverse reactions associated with prolonged-release exenatide were mild to moderate in intensity. The risk of hypoglycaemia is low and dependent on the background therapy used.

Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly.

The most frequently reported adverse reaction with dapagliflozin treatment was hypoglycaemia, which depended on the type of background therapy used in each study. In general the rate of minor hypoglycaemias was low (<5%). Other adverse reactions reported are related to the glucosuric effect of dapagliflozin such as events related to volume depletion and uro-genital infections.

Patient exposure

The mean duration of exenatide exposure was similar across the treatment groups in Study D5553C00003. The mean duration of dapagliflozin exposure was similar across the treatment groups.

The mean duration of exenatide/placebo exposure was 174.6 days in the EQW+dapagliflozin group, 175.0 days in the EQW+placebo group, and 183.0 days in the dapagliflozin+placebo group.

The mean duration of dapagliflozin/placebo exposure was 180.2 days in the EQW+dapagliflozin group, 179.8 days in the EQW+placebo group, and 188.5 days in the dapagliflozin+placebo group.

Adverse events

AEs and serious adverse events (SAEs) were reported by similar numbers of patients across the treatment groups (Table 13). Adverse events related to study drug and AEs leading to discontinuation were higher in the EQW+dapagliflozin and EQW+placebo groups than in the dapagliflozin+placebo group. During the study, 5 subjects died.

Table 13 Overall summary of adverse events for the 28-week treatment period (Safety analysis set)

Adverse event category	Number (%) of patients[a]			
	EQW + Dapa (N=231)	EQW + Placebo (N=230)	Dapa + Placebo (N=233)	Total (N=694)
Any AE	131 (56.7)	124 (53.9)	121 (51.9)	376 (54.2)
Any AE with outcome of death	3 (1.3)	1 (0.4)	1 (0.4)	5 (0.7)
Any SAE (including events with outcome = death)	10 (4.3)	8 (3.5)	10 (4.3)	28 (4.0)
Any AE leading to discontinuation of treatment	9 (3.9)	11 (4.8)	5 (2.1)	25 (3.6)

Table 13 Overall summary of adverse events for the 28-week treatment period (Safety analysis set)

Adverse event category	Number (%) of patients[a]			
	EQW + Dapa (N=231)	EQW + Placebo (N=230)	Dapa + Placebo (N=233)	Total (N=694)
Any SAE leading to discontinuation of treatment	0	2 (0.9)	1 (0.4)	3 (0.4)
Any AE related to treatment[b]	60 (26.0)	53 (23.0)	37 (15.9)	150 (21.6)

A 28-week treatment period AE is defined as an AE occurring or an existing event worsening during or after the time of the first dose of randomised study drug through EOT. EOT refers to Week 28. For patients early discontinued, the EOT refers to the period after the last dose + 7 days for all treatment groups.
Includes patient , who prematurely discontinued study drug prior to Week 28 and died 22 days after last dose.
All percentages are calculated based on the number of patients in the Safety analysis set within each treatment group.
Due to the ongoing nature of the study, when the database extraction was performed post unlock for 1 SAE case on date 08 July 2016 it was found that additional AEs had been added by sites 7803, 7824, 7833, 7836, and 7852.
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Includes causally related AEs as judged by the investigator.
AE Adverse event; Dapa Dapagliflozin 10 mg QD; EOT End of the treatment; EQW Exenatide 2 mg once weekly; N Number of patients in treatment group; SAE Serious adverse event.
Source: Module 2.7.4, Table 3

Common adverse events

The most commonly reported AEs (frequency ≥5.0% in any treatment group) by preferred term (PT) were diarrhoea, injection site nodule, nausea, and urinary tract infection (UTI) (Table 14).

Adverse events of nausea and diarrhoea were more common in the EQW+dapagliflozin and EQW+placebo groups compared to the dapagliflozin+placebo group. There were no relevant differences in UTI across the 3 treatment groups.

Table 14 Most common (frequency ≥5.0%) adverse events by preferred term –28-week treatment period (Safety analysis set)

Preferred term	Number (%) of patients[a]		
	EQW + Dapa (N=231)	EQW + Placebo (N=230)	Dapa + Placebo (N=233)
Patients with any AE	131 (56.7)	124 (53.9)	121 (51.9)
Injection site nodule	18 (7.8)	14 (6.1)	12 (5.2)
Nausea	12 (5.2)	17 (7.4)	7 (3.0)
Diarrhoea	10 (4.3)	13 (5.7)	7 (3.0)
Urinary tract infection	10 (4.3)	12 (5.2)	13 (5.6)

A 28-week treatment period AE is defined as an AE occurring or an existing event worsening during or after the time of the first dose of randomized study drug through EOT. EOT refers to Week 28. For patients early discontinued, the EOT refers to the period after the last dose + 7 days for all treatment groups.
All percentages are calculated based on the number of patients in the analysis set within each treatment group.
MedDRA version 19.0.
Due to the ongoing nature of the study, when the database extraction was performed post unlock for 1 SAE case on date 08 July 2016 it was found that additional adverse events had been added by sites 7803, 7824, 7833, 7836, and 7852.
Most common is defined as an AE with at least 5% incidence in any treatment.
Patients with multiple events in the same category (ie, same preferred term) are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[a] Number (%) of patients with an AE, sorted by alphabetic order for PT.

AE Adverse event; Dapa Dapagliflozin 10 mg QD; EOT End of treatment; EQW Exenatide 2 mg once weekly; N Number of patients in treatment group; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; SAE Serious adverse event

Source: Module 2.7.4, Table 4

All adverse events

The SOCs with the greatest frequency of AEs (>5% in any treatment group) included: infections and infestations (EQW+dapagliflozin, 24.2%; EQW+placebo, 26.5%; dapagliflozin+placebo, 26.2%); GI disorders (15.6%; 15.2%; 11.6%; respectively); general disorders and administration site conditions (13.9%; 13.5%; 9.0%;); nervous system disorders (13.0%; 5.7%; 8.2%); skin and subcutaneous tissue disorders (5.6%; 3.0%; 3.0%); investigations (4.8%; 9.6%; 7.7%); musculoskeletal and connective tissue disorders (4.3%; 7.4%; 7.3%); and metabolism and nutrition disorders (3.5%; 5.2%; 4.3%).

Headache, dizziness, dermatitis, and rash were more common in the EQW+dapagliflozin group (4.8%, 3.5%, 1.3%, and 0.9%, respectively) compared to the EQW+placebo (3.5%, 0.4%, 0%, and 0.4%, respectively) and dapagliflozin+placebo groups (3.0%, 1.7%, 0%, and 0%, respectively).

One patient in the EQW+placebo group had an AE of diabetic ketoacidosis. The event was moderate in severity and considered unrelated to study drug.

No malignancies were reported during the study other than skin neoplasms.

Adverse events reported as related to study drug

Adverse events reported as related to study drug as judged by the investigator were higher in the EQW+dapagliflozin (26%) and EQW+placebo (23%) groups than in the dapagliflozin+placebo (15.9%) group.

The most common AEs related to study drug were injection site nodule (EQW+dapagliflozin, 7.8%; EQW+placebo, 5.7%; dapagliflozin+placebo, 4.7%), nausea (3.9%, 7.0%, and 1.3%, respectively), vomiting (0.4%, 3.5%, and 1.7%, respectively), diarrhoea (1.7%, 3.0%, and 0.4%, respectively), and injection site induration (1.7%; 2.6%; 0.9%, respectively).

Serious adverse event/deaths/other significant events

Deaths

A total of 5 patients died during the study: 3 patients (1.3%) in the EQW+dapagliflozin group (PTs: multiple injuries, arteriosclerosis coronary artery, and toxicity to various agents), 1 patient (0.4%) in the EQW+placebo group (myocardial infarction), and 1 patient (0.4%) in the dapagliflozin+placebo group (ischaemic stroke). None of the deaths were considered by the investigator to be related to study drug.

Other serious adverse events

The frequency and types of SAEs during the 28-week treatment period were low and similar across treatment groups: SAEs were reported by 10 patients (4.3%) in the EQW+dapagliflozin group, 8 patients (3.5%) in the EQW+placebo group, and 10 patients (4.3%) in the dapagliflozin+placebo group.

More SAEs were reported in the following SOCs for the EQW+dapagliflozin group compared to the dapagliflozin+placebo and EQW+placebo groups (>1% difference): GI disorders and hepatobiliary disorders.

Anaphylactic reaction SAEs were reported for a total of 2 patients. The event in the EQW+placebo group was severe in intensity, required hospitalisation, and was considered related to study drug. The event in the dapagliflozin+placebo group was severe in intensity, required hospitalisation, and was considered not related to study drug.

At the PT level, no SAE was reported by more than 1 patient per treatment group.

Adverse events of special interest

Incidence of hypoglycaemia

Major hypoglycaemia was an event that resulted in loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia), which resolved after administration of glucagon or glucose. In addition, any event that required third party assistance to resolve because of severe impairment in consciousness or behaviour and was associated with a plasma or capillary glucose concentration of <3 mmol/L (54 mg/dL) was classified as major hypoglycaemia.

Minor hypoglycaemia was a non-major hypoglycaemia event that had symptoms consistent with hypoglycaemia and had plasma or capillary glucose value of <3 mmol/L (54 mg/dL) prior to treating the episode.

There were no events of major or minor hypoglycaemia in the study.

A total of 8 patients (3.5%) in the EQW+dapagliflozin group, 3 patients (1.3%) in the EQW+placebo group, and 3 patients (1.3%) in the dapagliflozin+placebo group had hypoglycaemia events which were classified as other (defined as not meeting criteria for major or minor hypoglycaemia). Glucose values for these events ranged from 3.0 mmol/L to 4.2 mmol/L. Most events were associated with symptoms, most events were considered mild, and there were no severe events.

Other adverse events of special interest

Adjudicated CV events

There were few confirmed adjudicated CV events in the study, with no relevant differences in event numbers across treatment groups: a total of 1 patient in the EQW+dapagliflozin group and 2 patients each in the EQW+placebo and dapagliflozin+placebo groups had confirmed adjudicated CV events.

Adjudicated hepatic events

During the study, 2 events met criteria for hepatic adjudication. One event was an SAE of hepatic enzyme increased in the EQW+placebo group that met biochemical Hy's Law criteria. The other event was elevated alanine aminotransferase (ALT) in the dapagliflozin+placebo group. Both events were adjudicated by a blinded hepatic adjudication committee and considered unlikely to be causally related to study drug.

Volume depletion

There were few potentially volume depletion-related events reported in this study: 2 patients (0.9%) in the EQW+dapagliflozin group (3 events in total, all of dehydration), no patients in the EQW+placebo group, and 3 patients (1.3%) in the dapagliflozin+placebo group (2 events were of hypotension and one of syncope). None of these events were SAEs or led to discontinuation, and all of these events resolved.

Pancreatitis-related events

During the study, 2 pancreatitis-related events were reported: 1 patient (0.4%) in the EQW+dapagliflozin group, 1 patient (0.4%) in the EQW+placebo group. Neither of the events was an SAE. Both events led to discontinuation and 1 event was considered related to study drug.

Acute renal failure-related events

Few acute renal failure-related events were reported in this study: no patients in the EQW+dapagliflozin group, 2 patients (0.9%) in the EQW+placebo group, and 1 patient (0.4%) in the dapagliflozin+placebo group. None were SAEs, none led to study discontinuation, none of the events were considered related to study drug, and all events resolved.

Pancreatic carcinoma related- or thyroid neoplasm-related events

No pancreatic carcinoma-related events or thyroid neoplasm-related events were reported during the study.

Injection site-related events

There were greater numbers of injection site-related AEs in the EQW+dapagliflozin (12.1%) and EQW+placebo (11.7%) groups than in the dapagliflozin+placebo (6.9%) group. Most of these events were mild in intensity and considered related to study drug.

Gastrointestinal-related events

Gastrointestinal-related events were reported more commonly in the EQW+dapagliflozin (36 patients, 15.6%) and EQW+placebo (35 patients, 15.2%) groups than in the dapagliflozin+placebo (27 patients, 11.6%) group. Most GI-related events were mild or moderate in intensity. The most commonly reported AEs were nausea and diarrhoea. Four of GI-related events were reported as SAEs in the EQW+dapagliflozin group; all 4 events had different PTs (abdominal pain lower, anal haemorrhage, gastrooesophageal reflux disease, and umbilical hernia).

Laboratory findings

Haematology

Patients in the EQW+dapagliflozin and dapagliflozin+placebo groups showed an increase in mean haemoglobin and haematocrit from baseline to Week 28 (mean change from baseline to Week 28 in haemoglobin: EQW+dapagliflozin, 3.6 g/L; and dapagliflozin+placebo, 4.6 g/L; haematocrit: EQW+dapagliflozin 0.01, dapagliflozin+placebo 0.01). In the EQW+placebo group, changes in mean haemoglobin and haematocrit during the 28-week treatment period were -1.5 g/L and -0.01, respectively.

Clinical chemistry

The mean eGFR was slightly decreased in all treatment groups, and to the smallest extent in the EQW+dapagliflozin group. At Week 28, the mean change from baseline was -0.59 mL/min/1.73 m^2 in the EQW+dapagliflozin group, -0.39 mL/min/1.73 m^2 in the EQW+placebo group, and -2.04 mL/min/1.73 m^2 in the dapagliflozin+placebo group.

Individual marked laboratory abnormalities

Creatinine elevations >1.5x higher than pre-treatment creatinine were reported for more patients in the EQW+dapagliflozin group (14 patients; 6.1%) compared to the EQW+placebo (9 patients; 3.9%) and dapagliflozin+placebo groups (9 patients; 3.9%). One patient in the EQW+dapagliflozin group had a creatinine elevation (≥221 µmol/L). In the EQW+dapagliflozin group, all but 2 of the cases were one-time elevations, and in 6 of 14 patients, the creatinine value remained within the normal range. One of the creatinine elevations in the EQW+dapagliflozin group was reported as an AE and none were reported as SAEs.

Haematocrit elevations (>0.55) were reported for 2 patients (0.9%) in the EQW+dapagliflozin group, no patients in the EQW+placebo group, and 4 patients (1.7%) in the dapagliflozin+placebo group. None of these events were associated with AEs.

Elevations in alanine aminotransferase or aspartate aminotransferase accompanied by elevations in total bilirubin

One patient (E7886303) in the EQW+placebo group met biochemical Hy's Law Criteria (ALT ≥3x upper limit of normal (ULN) or aspartate aminotransferase (AST) ≥3x ULN and total bilirubin ≥2x ULN). The

event was initially reported as an AE of elevated liver enzymes on Day 57 that was moderate in intensity and did not require additional treatment. The investigator did not consider this event an SAE; however, the investigator was asked to upgrade the event to an SAE based on protocol specifications. This event was adjudicated by a blinded adjudication committee as unlikely to be causally related to study drug.

Urinalysis

Mean urine glucose/creatinine ratio increased from baseline in the EQW+dapagliflozin group, did not increase in the EQW+placebo group, and showed the greatest increase from baseline in the dapagliflozin+placebo group over time. These findings are consistent with the MOA of dapagliflozin.

Vital signs

Pulse rate increased from baseline in the EQW+dapagliflozin group (mean change from baseline at Week 28 was 2.1 bpm). In the EQW+placebo group, mean change from baseline was 0.7 bpm. Pulse rate remained stable during the study in the dapagliflozin+placebo group (mean change from baseline was -0.1 bpm).

Few patients had a documented BP value <90/55 mmHg at any time in the study (Table 15). Between 19% and 32% of patients had decreases in SBP of >20 mmHg or DBP of >10 mmHg; the incidence of these findings was similar in the EQW+dapagliflozin and dapagliflozin+placebo groups, and slightly higher than in the EQW+placebo group.

Table 15 Number (%) of patients with marked blood pressure abnormalities at any time during the 28-week treatment period (Safety analysis set)

Vital signs	SI Units	Criterion[a]	EQW + Dapa (N=231)	EQW + Placebo (N=230)	Dapa + Placebo (N=233)
SBP	mmHg	<90	0	0	1 (0.4)
		>20 Decrease	65 (28.1)	44 (19.1)	60 (25.8)
DBP	mmHg	<55	2 (0.9)	0	4 (1.7)
		>10 Decrease	70 (30.3)	61 (26.5)	75 (32.2)

All percentages are calculated based on the number of patients within that treatment group.
[a] Prespecified vital signs marked abnormality criteria that is considered clinically important.
Dapa Dapagliflozin 10 mg QD; DBP Diastolic blood pressure; EQW Exenatide 2 mg once weekly; SBP Systolic blood pressure.
Source: Derived from CSR Table 47.

Anti-exenatide antibodies

A majority of patients in the EQW+dapagliflozin and EQW+placebo groups developed anti-exenatide antibodies at some point over the 28-week treatment period. Patients with positive antibodies had a higher rate of injection-site-related AEs.

Anti-exenatide antibodies were observed in 74.4% of patients in the EQW+dapagliflozin group and 76.1% of patients in the EQW+placebo group at any time during the study. The EQW+dapagliflozin group showed a greater percentage of patients (41.7%) with high positive antibody titres as compared to the EQW+placebo group (28.0%). The proportion of patients positive for anti-exenatide antibodies plateaued at Week 8 and remained stable through the end of the 28-week treatment period.

The mean change from baseline in HbA1c was similar across anti-exenatide antibody status and titre at Week 28 in both the EQW+dapagliflozin and EQW+placebo groups. Injection site-related AEs were more common among patients who were positive for exenatide anti-exenatide antibodies (10.8% in the EQW+dapagliflozin group and 10.4% in the EQW+placebo group) compared to patients who were negative (1.3% for both subgroups).

Safety in special populations
No data provided.

Safety related to drug-drug interactions and other interactions
No data provided.

Discontinuation due to adverse events
The rate of discontinuations due to AEs was low in all groups. More patients discontinued due to AEs in the EQW+dapagliflozin (3.9%) and EQW+placebo (4.8%) groups than in the dapagliflozin+placebo group (2.1%).

The most commonly reported AE leading to discontinuation of EQW/placebo or dapagliflozin/placebo was nausea (1.0% overall), reported by 1 patient (0.4%) in the EQW+dapagliflozin group, 5 patients (2.2%) in the EQW+placebo group, and 1 patient (0.4%) in the dapagliflozin+placebo group. At the PT level, no other AE leading to discontinuation was reported by more than 1 patient per treatment group.

Post marketing experience
Limited data are available from post-marketing reports of concomitant use of EQW+dapagliflozin.

2.4.1. Discussion on clinical safety

With study D5553C00003, 28 week data on the concomitant treatment with exenatide and dapagliflozin has been provided. A total of 694 patients were included in the study out of which 231 received the combined treatment. The mean duration of exposure to both exenatide and dapagliflozin was about 180 days with a slightly shorter exposure for active EQW than for active dapagliflozin.

The overall reporting of AEs was somewhat higher in the EQW+dapagliflozin group (57%) compared to the EQW group (54%) and the dapagliflozin group (52%).

Treatment related AEs were more common in the EQW treated groups (EQW+dapagliflozin, 26%; EQW 23%) than in the dapagliflozin treated group (16%).

Common adverse events constituted about 40% of all AEs in the EQW+dapagliflozin group, 45% in the EQW group and 32% in the dapagliflozin group. GI events were more common with EQW than with dapagliflozin. Injection site nodules were observed in all treatment groups, most common with EQW+dapagliflozin (7.8%) but common also with placebo (5.2%). UTIs were fairly balanced but most common with dapagliflozin (5.6% vs 4.3% with EQW+dapagliflozin and 5.2% with EQW).

For the SOCs with the greatest frequency of AEs, the reporting was rather well balanced between groups. Headache, dizziness, dermatitis, and rash were more common in the EQW+dapagliflozin group (4.8%, 3.5%, 1.3%, and 0.9%, respectively) compared to the EQW+placebo (3.5%, 0.4%, 0%, and 0.4%, respectively) and dapagliflozin+placebo groups (3.0%, 1.7%, 0%, and 0%, respectively). One patient in the EQW+placebo group had an AE of diabetic ketoacidosis. No malignancies were reported during the study other than skin neoplasms.

AEs judged as drug related were mainly GI events and injection site reactions, in line with the known safety profile for exenatide.

Five deaths occurred during the study, 3 of which were in the EQW+dapagliflozin groups. Two of these deaths were due to trauma/suicide. The three remaining deaths were all CV deaths, one in each treatment group.

The overall reporting of SAEs was balanced between groups. There were more SAEs in the SOC GI disorders and hepatobiliary disorders for EQW+dapagliflozin (4 and 3) than with EQW (0 and 1) whereas no such events were reported for dapagliflozin. Two anaphylactic reactions were reported, one in the EQW group and one in the dapagliflozin group. At the PT level, no SAE was reported by more than 1 patient per treatment group and no specific patterns could be observed.

Hypoglycaemia was an AE of special interest in the study. As expected, the incidence of hypoglycaemia was low and no events met the criteria of minor or major hypoglycaemia. A total of 8 patients (3.5%) in the EQW+dapagliflozin group, 3 patients (1.3%) in the EQW+placebo group, and 3 patients (1.3%) in the dapagliflozin+placebo group had hypoglycaemia events with glucose values ranging from 3.0 mmol/L to 4.2 mmol/L.

With regards to other AEs of special interest, CV events were few and balanced between groups. Two patients in the EQW+dapagliflozin group and 3 patients in the dapagliflozin group reported events potentially volume depletion-related. One pancreatitis related event was reported each in the EQW+dapagliflozin and EQW group. Two patients in the EQW group and one in the dapagliflozin group had events related to acute renal failure. There were no cases of pancreatic or thyroid cancer. Comparable rates of injection site reactions were observed in the two EQW groups (12%) and 7% of patients in the dapagliflozin+placebo group reported such events.

Gastrointestinal-related events were equally common in the two EQW groups (15.6 and 15.2%), but rather common also in the dapagliflozin group (12%). The findings in the EQW groups were expected based on the increased rate of GI events observed with EQW in previous studies.

Increases in haemoglobin and haematocrit were observed in both dapagliflozin groups, consistent with changes observed in the dapagliflozin programme. Decreases in haemoglobin and haematocrit were observed in the EQW group. A slight decrease in eGFR was observed in all three groups, most pronounced in the dapagliflozin group. Creatinine elevations >1.5 ULN were most common in the EQW+dapagliflozin group (6.1%) and less common in the monotherapy groups (3.9% in both groups). Many events were one-time elevations. Haematocrit elevations (>0.55) were most common in the dapagliflozin group (1.7%) and in the EQW+dapagliflozin group (0.9).

One patient in the EQW group met biochemical Hy´s law criteria. This was not related to treatment but to underlying hepatobiliary disease.

An increase in heart rate was observed in the EQW treated groups with the most pronounced increase (2.1 bpm) in the EQW+dapagliflozin group. These findings are consistent with results observed in other EQW studies. No increase was observed in the dapagliflozin group.

Only one patient in the dapagliflozin group had a SBP <90 mmHg. Two patients in the EQW+dapagliflozin group and 4 in the dapagliflozin group had DBP <55 at any time of the study. Between 20-30% of patients had a >20 mmHg decrease in SBP (lowest in the EQW group) and 26-32% had a >10 mmHg decrease in DBP (lowest rate in the EQW group).

About 75% of patients in both groups treated with EQW developed anti-exenatide antibodies at any time-point during the study. Although a larger proportion of patients in the EQW+dapagliflozin treated group (42%) had high positive titres at any time point compared to patients on EQW monotherapy (28%) there was no apparent difference between treatment arms at the time-points when antibodies were measures (week 4, 8, 12, 20 and 28). The rate of high antibody titres at study endpoint was consistent with the rate observed in a previous comparable study with EQW.

The occurrence of antibodies did not affect the effect on HbA1c but injection site-related events were more common in patients with ADA. Increased injection site related AEs in patients with positive antibodies have also been observed in previous EQW studies.

Safety data was also presented by age groups < 65 years and ≥ 65 years. Due to the imbalance in the number of patients in each group (607 patients < 65 years and 87 patients ≥ 65 years) the interpretation of data has to be made with caution. There was no apparent difference in the overall reporting of AEs between age groups and the reporting was numerically lower in the older age. Nor was there any apparent difference in the pattern of AEs reported. The only finding of some significance was the observation that the decrease in eGFR observed at week 1 was more pronounced in the older age group. The recovery was also smaller in this age group at week 28.

Apart from this finding, the data presented give no indication on a difference in the safety profile for the combination therapy or the single components across the two age groups.

The safety data reported with the 52 week CSR did not reveal any new safety concerns. The overall reporting of AEs was slightly higher in the EQW+dapa group and comparable in the two monotherapy arms. The reporting of AEs was lower during the extension phase of the study and there was change in the pattern of reported AEs. Seven SAEs were reported during the extension phase (1 in the EQW+dapa group, 4 in the EQW+placebo group and 2 in the dapa+placebo group). Among these events, 1 event of renal neoplasm was reported in the EQW+placebo group. There were no deaths during extension phase of the study. There were no events of major hypoglycaemia during the extension phase. In total 24 patients reported hypoglycaemias and the reporting was slightly higher with the combination treatment. There was a decrease in the proportion of patients with positive antibody titers from week 28 to week 52.

2.4.2. Conclusions on clinical safety

The safety data provided with study D5553C00003 is in line with the known safety profile for exenatide and dapagliflozin. There was no indication of added toxicity in the group on combination therapy although the overall reporting of AEs was slightly higher in this group compared to monotherapy. No new safety concerns that arise from the data presented (up to 52 weeks of treatment).

2.4.3. PSUR cycle

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

2.5. Risk management plan

The updated RMP version 24 was initially submitted as part of this application. A consolidated updated version of the RMP, version 27, was subsequently submitted and assessed within the procedure.

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

The PRAC considered that the risk management plan version 27 is acceptable.

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

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 27 with the following content:

Safety concerns

Important identified risks	• Pancreatitis • Acute renal failure • Rapid weight loss • Injection site reactions (exenatide QW)
Important potential risks	• Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions) • Cardiac events • Pancreatic cancer • Thyroid neoplasms • Administration error (exenatide QW) • Malignant neoplasm following combination treatment with insulin
Missing information	• Adolescents • Pregnant women • Very elderly (≥75 years old) • Patients using exenatide in combination with other agents (TZDs and insulins) • Severe gastrointestinal disease (exenatide QW) • Various degrees of impaired renal function (exenatide QW) • Hepatic impairment (exenatide QW)

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
H8O-MC-GWDQ/ D5551C00003 (BCB109; EXSCEL) (CV) Category 3	The primary objective of EXSCEL will be to evaluate the effect of exenatide QW, used in conjunction with the current usual care for glycaemic control, on major macrovascular events when administered to patients with T2DM	Cardiac events Pancreatitis Acute renal failure Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions) Pancreatic cancer Thyroid neoplasms	Ongoing	Final report (CSR) Q4 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
H8O-JE-EX01/D5550C00001:Byetta post-marketing surveillance study/Prospective patient cohort Category 3	To assess primarily the occurrence of acute pancreatitis and major adverse CV events in relation to the exposure to exenatide BID	Pancreatitis, CV events	Ongoing	Final report Q3 2020
H8O-MC-B016/ D5551N00006: An Observational Post-Authorisation Modified Prescription-Event Monitoring Safety Study to Monitor the Safety and Utilization of Exenatide Once Weekly (Bydureon®) in the Primary Care Setting In England Category 3	To study the utilisation and safety of exenatide QW to treat T2DM in new user patients (exenatide naïve) and switchers (past exenatide BID users) under normal conditions of use in primary care in England. The objective is to quantify the incidence rate of the important identified risk of acute pancreatitis in the first 12 months after starting treatment	Pancreatitis	Ongoing	Interim report was conducted in Q4 2015 with 2538 exenatide QW users Final report when 5000 patients are available: Dependent upon enrolment
H8O-MC-B017: Incidence of Thyroid Neoplasm and Pancreatic Cancer in T2DM Patients who Initiate Bydureon® Compared to Other Antihyperglycaemic Drugs (UK study) Category 3	The objective of this study is to estimate and compare the incidence of thyroid neoplasm and pancreatic cancer among initiators of exenatide QW compared to other antidiabetes agents. Primary Objectives are: (1) to estimate the absolute and relative incidence of newly diagnosed thyroid cancer among initiators of exenatide QW compared to matched initiators of other antidiabetes drugs – assessing events 1-year post drug initiation by duration of follow-up and drug exposure; (2) to estimate the absolute and relative incidence of newly diagnosed pancreas cancer among initiators of exenatide QW compared to matched initiators of other antidiabetes drugs – assessing events 1-year post drug initiation by duration of follow-up and drug exposure.	Pancreatic cancer Thyroid neoplasms	Ongoing	Risk assessment: Every two years until study ends Interim report (when 20000 exenatide QW users are available): years (dependent upon enrolment) Final analysis will be performed after 55000 exenatide QW users: years depending on enrolment

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
BCB402/ D5551R00001: MTC Surveillance Study: A Case Series Registry/Registry Category 3	The objectives of this prospective active surveillance program are: (1)To establish a multicentre registry of incident cases of MTC in adults in the US in order to characterize their medical histories and possible risk factors, including history of treatment with EQW and other long-acting GLP-1RAs; (2) To systematically monitor the annual incidence of MTC in the US through the NAACCR to identify any possible increase related to the introduction of EQW and other long-acting GLP-1RAs into the US market	Medullary thyroid carcinoma	Ongoing	Annual assessment report each Q1 until the end of the study; final report : Q3 2028
H8O-MC-GWBQ (Adolescent) (Byetta®) Category 3	The primary objective of this study is to test the hypothesis that glycaemic control, as measured by change in HbA1c from baseline to endpoint, with exenatide BID daily is superior (in at least 1 of the exenatide treatment arms) to that of placebo after 28 weeks of treatment in adolescent patients with T2DM who are naïve to antidiabetes agents, or patients who are being treated with metformin, an SU, or a combination of metformin and an SU.	Adolescents	Ongoing	Final report: Q2 2019
BCB114/D5551C00002 (Adolescent) Category 3	Primary objectives: To assess the effect on glycaemic control, as measured by HbA1c, of exenatide QW following 14 weeks of treatment compared to placebo in adolescents with T2DM; to evaluate the safety and tolerability of exenatide QW compared to placebo following 14 weeks of treatment in adolescents with T2DM	Adolescents	Ongoing	Final report: Q1 2019

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
H8O-MC-B015 extension (D5550R00003) Category 3	To estimate the absolute and relative incidence of pancreatic cancer and thyroid neoplasm among exenatide initiators relative to initiators of OADs.	Pancreatic cancer Thyroid neoplasms	Ongoing	Final Report: 2018

BID twice daily; CSR clinical study report; CV cardiovascular; EQW exenatide once weekly; GLP-1RA glucagon-like peptide 1 receptor agonist; HbA1c haemoglobin A1c; MTC medullary thyroid carcinoma; NAACCR North American Association of Central Cancer Registries; OAD oral antidiabetes drug; PhV pharmacovigilance; Q1 first quarter; Q3 third quarter; Q4 fourth quarter; QW once weekly; SU sulphonylurea; T2DM type 2 diabetes mellitus; UK United Kingdom; US United States.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Pancreatitis	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Acute renal failure	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Rapid weight loss	Statements within Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Injection site reactions (exenatide QW)	Product information such as product labelling and medication guide	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks		
Risks associated with anti-exenatide antibodies (focus on anaphylactic-type reactions)	Statements within Sections 4.3 (Contraindications), and 4.8 (Undesirable effects) of the SmPC.	None
Cardiac events	No association identified between exenatide and cardiac events to date.	None
Pancreatic cancer	No association identified between exenatide and pancreatic cancer to date.	None
Thyroid neoplasms	None. Section 5.3 Preclinical safety data of the SmPC describes the thyroid cancer incidence observed in rats. No reasonable causal association between exenatide and thyroid neoplasm in humans has been identified to date.	None
Administration error (exenatide QW)	Product information such as product labelling and user manual	None
Malignant neoplasm following combination treatment with insulin	No association identified between exenatide and combination insulin use to date.	None
Missing information		
Adolescents	Statements within Sections 4.4 (Special warnings and precautions for use) and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Pregnant women	Statements within Section 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Very elderly (≥75 years of age)	Statements within Sections 5.2 (PK properties) of the SmPC.	None
Use of Exenatide in Combination with Other Agents (TZDs and insulins)	No differential adverse event profile has been found for patients taking exenatide in combination with other agents (TZDs and insulins).	None
Severe Gastrointestinal Disease (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration) and 5.2 (PK properties) of the SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Various Degrees of Impaired Renal Function (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration), 4.4 (Special warnings and precautions for use) and 5.2 (PK properties) of the SmPC.	None
Hepatic Impairment (exenatide QW)	Statements within Sections 4.2 (Posology and Method of administration) and 5.2 (PK properties) of the SmPC.	None

QW once weekly; PK Pharmacokinetic; SmPC Summary of Product Characteristics; TZD thiazolidinedione.

2.6. Update of the Product information

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

4.1 Therapeutic indications

~~Bydureon is indicated for treatment of type 2 diabetes mellitus in combination with~~

- ~~Metformin~~
- ~~Sulphonylurea~~
- ~~Thiazolidinedione~~
- ~~Metformin and sulphonylurea~~
- ~~Metformin and thiazolidinedione~~

~~in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.~~

Bydureon is indicated in adults 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose-lowering medicinal products when the therapy in use, together with diet and exercise, does not provide adequate glycaemic control (see section 4.4, 4.5 and 5.1 for available data on different combinations).

For changes in the SmPC section **5.1 Pharmacodynamic properties** see full PI in attachment.

Minor editorial changes were also made to the PI and accepted by the CHMP.

2.6.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study D5553C00003 was a 28-week, randomised, double-blind, active-controlled, multicentre, Phase 3b efficacy and safety study of simultaneous administration of exenatide (EQW) 2 mg + dapagliflozin 10 mg od compared to EQW 2 mg + placebo and dapagliflozin 10 mg od + placebo in patients with T2DM. The patients were to have inadequate glycaemic control on metformin as reflected by HbA1c between 8% and 12%. The total study duration will be 2 years; this submission presents data from the 28-week main treatment period. The rationale for choosing the combination of a GLP1-RA (exenatide) and a SGLT2-inhibitor (dapagliflozin) is based on the complementary MOAs of the two different drugs. The three-armed study designs allows for assessment of the contribution of each of the components to the effect of the combined therapy.

The primary objective of the study was met since the difference in HbA1c mean change from baseline week 28 in the primary analysis was -0.38 (-0.63, -0.13; p=0.003) for EQW+dapagliflozin vs EQW+placebo and -0.59 (-0.84, -0.34; p<0.001) for EQW+dapagliflozin vs dapagliflozin+placebo. Thus superiority of the combined treatment over each of the monotherapies was shown. The contribution of exenatide (-0.59%) to the effect of the combination was larger than that of dapagliflozin (-0.38%).

The proportion of patients achieving HbA1c <7% at Week 28 was 44.7% in the EQW+dapagliflozin group, 26.9% in the EQW+placebo group, and 19.1% in the dapagliflozin+placebo group. The difference between the EQW+dapagliflozin group and EQW+placebo group was 17.4% (p<0.001) and between the EQW+dapagliflozin group and dapagliflozin+placebo group was 25.6% (p<0.001).

Subgroup analyses were performed for the primary endpoint. There was a statistically significant interaction with age. Older patients (≥65 years) showed an overall greater effect of the combination than younger patients (<65 years) (-2.39% vs -1.91%). The effect of both monotherapies was lower in older patients compared to younger patients, with the largest difference between age groups observed with dapagliflozin.

The subgroup analysis by HbA1c showed that the effect of both the combination and the monotherapies was, as expected, most pronounced in patients with HbA1c ≥9%. The outcome of the primary analysis was only preserved in patients with HbA1c 8-9%, thus the combination was superior to both monotherapies in this group. In the subgroup of patients with HbA1c ≥9%, which constitutes the largest subgroup, the combination was only superior to monotherapy with dapagliflozin and in the smallest subgroup with HbA1c <8%, superiority of the combination was not shown over any of the monotherapies. A similar pattern, with more responders with combination therapy and less for the single components, was observed for all three subgroups. Although the change in HbA1c is most pronounced in the subgroup with HbA1c > 9% at baseline, the responder rate in this subgroup is lower than in the subgroups with lower baseline HbA1c as may be expected.

Body weight decreased with -3.6 kg in the EQW+dapagliflozin group, with -1.6 kg in the EQW+placebo group, and with -2.2 kg in the dapagliflozin+placebo group. Thus there was an additive effect on body weight by the combination.

An additive effect was also observed on SBP at Week 28. SBP decreased by -4.3 mmHg in the EQW+dapagliflozin group, -1.2 mmHg in the EQW+placebo group, and -1.8 mmHg in the dapagliflozin+placebo group.

Efficacy data up to 52 weeks has been provided. There was a slight increase in HbA1c of about 0.2% in all treatment groups between week 28 and week 52 but an adequate effect was maintained and the

differences observed between treatment arms at week 28 were essentially maintained. The body weight remained essentially stable in all treatment groups between week 28 and 52 with only a slight increase. The proportion of patients achieving HbA1c < 7% decreased with about 10 % in the EQW+dapa group and about 5% in the monotherapy groups between week 28 and 52.

Uncertainty in the knowledge about the beneficial effects

The duration of the favourable effects has only been studied up to 52 weeks. However, at 52 weeks, only a slight attenuation of the effect was observed.

Risks

Unfavourable effects

With study D5553C00003, 28 week data on the concomitant treatment with exenatide and dapagliflozin has been provided. A total of 694 patients were included in the study out of which 231 received the combined treatment. The mean duration of exposure to both exenatide and dapagliflozin was about 180 days with a slightly shorter exposure for active EQW than for active dapagliflozin.

The overall reporting of AEs was somewhat higher in the EQW+dapagliflozin group (57%) compared to the EQW group (54%) and the dapagliflozin group (52%).

Treatment related AEs were more common in the EQW treated groups (EQW+dapagliflozin, 26%; EQW 23%) than in the dapagliflozin treated group (16%).

Common adverse events constituted about 40% of all AEs in the EQW+dapagliflozin group, 45% in the EQW group and 32% in the dapagliflozin group. GI events were more common with EQW than with dapagliflozin. Injection site nodules were observed in all treatment groups, most common with EQW+dapagliflozin (7.8%) but common also with placebo (5.2%). UTIs were fairly balanced but most common with dapagliflozin (5.6% vs 4.3% with EQW+dapagliflozin and 5.2% with EQW).

For the SOCs with the highest frequency of AEs, the reporting appeared balanced between groups. Headache, dizziness, dermatitis, and rash were more common in the EQW+dapagliflozin group (4.8%, 3.5%, 1.3%, and 0.9%, respectively) compared to the EQW+placebo (3.5%, 0.4%, 0%, and 0.4%, respectively) and dapagliflozin+placebo groups (3.0%, 1.7%, 0%, and 0%, respectively). One patient in the EQW+placebo group had an AE of diabetic ketoacidosis. No malignancies were reported during the study other than skin neoplasms.

AEs judged as drug related were mainly GI events and injection site reactions, in line with the known safety profile for exenatide.

The overall reporting of SAEs was balanced between groups. There were more SAEs in the SOC GI disorders and hepatobiliary disorders for EQW+dapagliflozin (4 and 3) than with EQW (0 and 1) whereas no such events were reported for dapagliflozin. Two anaphylactic reactions were reported, one in the EQW group and one in the dapagliflozin group.

Hypoglycaemia was an AE of special interest in the study. As expected, the incidence of hypoglycaemia was low and no events met the criteria of minor or major hypoglycaemia. A total of 8 patients (3.5%) in the EQW+dapagliflozin group, 3 patients (1.3%) in the EQW+placebo group, and 3 patients (1.3%) in the dapagliflozin+placebo group had hypoglycaemia events with glucose values ranging from 3.0 mmol/L to 4.2 mmol/L.

A comparable proportion of patients in both groups treated with EQW developed anti-exenatide antibodies (about 75%), however, a larger proportion of patients in the EQW+dapagliflozin treated group (42%) had

high positive titres compared to patients on EQW monotherapy (28%). The MAH is asked to discuss if there is any biological rationale for this observed difference.

The occurrence of antibodies did not affect the effect on HbA1c but injection site-related events were more common in patients with ADA.

Safety data was also presented by age groups < 65 years and ≥ 65 years. Due to the imbalance in the number of patients in each group (607 patients < 65 years and 87 patients ≥ 65 years) the interpretation of data has to be made with caution. There was no apparent difference in the overall reporting of AEs between age groups and the reporting was numerically lower in the older age. Nor was there any apparent difference in the pattern of AEs reported. The only finding of some significance was the observation that the decrease in eGFR observed at week 1 was more pronounced in the older age group. The recovery was also smaller in this age group at week 28. Apart from this finding, the data presented give no indication on a difference in the safety profile for the combination therapy or the single components across the two age groups.

The safety data reported for the extension of the study, with 52 week of exposure to the combination treatment, did not reveal any new safety concerns.

Uncertainty in the knowledge about the unfavourable effects

The safety data available only covers 52 weeks of exposure, however, the reporting of AEs decreased over time and no new safety concerns arose during the extension of the study.

Effects Table

Table 1. Effects Table for exenatide for treatment of adults with T2DM

Effect	Description	Unit	EQW+ dapa	EQW+ placebo	Dapa+ placebo	Un-certainties/ Strength of evidence	Refe-rences
	Favourable Effects						
HbA1c	Mean change in HbA1c from baseline	%	-1.98	-1.60	-1.39		
	Treatment difference (95% CI)			-0.38 (-0.63, -0.13)	-0.59 (-0.84, -0.34)		
Body weight	Mean change in body weight from baseline	kg	-3.55	-1.56	-2.22		
	Treatment difference (95% CI)			-2.00 (-2.79, -1.20)	-1.33 (-2.12, -0.55)		
Fasting plasma glucose	Mean change in FPG from baseline	mmol/ L	-3.66	-2.54	-2.73		
	Treatment difference (95% CI)			-1.12 (-1.55, -0.68)	-0.92 (-1.36, -0.49)		

Effect	Description	Unit	EQW+ dapa	EQW+ placebo	Dapa+ placebo	Un-certainties/ Strength of evidence	Refe-rences
SBP	Change from baseline	mmHg	-4.3	-1.2	-1.8		
	Treatment difference (95% CI)			-3.0 (-5.2, -0.9)	-2.4 (-4.5, -0.4)		
		Unfavourable Effects					
Diarrhoea	Incidence of Diarrhoea	%	4.3	5.7	3.0		
Nausea	Incidence of Nausea	%	5.2	7.4	3.0		
Injection site nodule	Incidence of Injection site nodule	%	7.8	6.1	5.2		
UTI	Incidence of UTI	%	4.3	5.2	5.6		
ADA	Incidence of Positive ADA	%	75	76	-		
	Incidence of High titers	%	42	28	-		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Study D5553C00003 provides short-term (28 weeks) data on combined treatment with a GLP1-RA (exenatide) and a SGLT2-inhibitor (dapagliflozin). The population of T2DM patients included were in rather poor metabolic control with a mean HbA1c in baseline of 9.3%. The combination therapy resulted in a clinically relevant HbA1c reduction of almost 2%. The largest contribution appears to be from exenatide, whereas the contribution from dapagliflozin was less prominent. However, when taking the rate of responders into account, there was a clinically relevant increase in the rate of responders both in comparison to EQW and dapagliflozin monotherapy.

In addition to the effects on metabolic control, additive effects on both body weight and SBP were observed. The magnitude of these effects is considered clinically relevant, especially as longer term data (52 week) show that this effect is maintained over time.

The safety data provided does not indicate that there is any additive toxicity or change in the safety profile when exenatide is used concomitantly with dapagliflozin. There was a somewhat higher reporting of AEs in the EQW+dapagliflozin treated group but the pattern of reported events did not differ compared to the known safety profile for each of the monotherapies. A somewhat higher occurrence of high titers of anti-exenatide antibodies was observed with combined treatment which possibly explains the higher reporting of injection site reactions in this group.

Benefit-risk balance

The benefit risk balance for the combined use of exenatide and dapagliflozin is considered positive.

Discussion on the Benefit-Risk Balance

T2DM is a progressive disease where metabolic control is often difficult to achieve. Once life style changes are insufficient to maintain metabolic control, metformin remains the first step in pharmaceutical

treatment. Upon failure on metformin, current treatment guidelines recommend individualised treatment, combining existing treatment options based on the patient's needs. A majority of T2DM patients is overweight and hypertensive, thus there is a need for treatment options which at least not aggravate these conditions.

Concomitant treatment with exenatide and dapagliflozin resulted in a significantly greater reduction of HbA1c when compared to exenatide or dapagliflozin alone. Both agents have weight and blood pressure reducing properties and an additive effect was observed in the study.

The beneficial effects were achieved without any substantial change in the safety profile known for the two agents.

The combination of exenatide with dapagliflozin could therefore be an important treatment option in patients where further weight increase or increase in blood pressure needs to be avoided and when there is a need for improvement of the metabolic control.

Since the initial authorisation of exenatide once weekly, the wording of the indication for medicinal products for the treatment of diabetes has evolved, and in addition more data, including from study D5553C00003 (Duration 8 study), has been accumulated regarding the combined use of exenatide once weekly with other products for the treatment of diabetes representing the standard of care. Therefore, the wording of the indication in section 4.1 of the SmPC refers now in more general terms to the combined use of exenatide once weekly with other products for the treatment of diabetes. Although the wording of the indication is relatively broad, the combinations studied are clearly described in section 5.1 of the SmPC.

Conclusions

The overall B/R of Bydureon 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 for Bydureon to include the add-on use of exenatide in combination with dapagliflozin to patients whose diabetes is not adequately controlled with metformin based on the study D5553C00003 (Duration 8 study); section 4.1 of the SmPC is updated in order to align the indication wording with more recently approved glucose-lowering agents. Section 5.1 of the SmPC is also updated with the results of study D5553C00003 (Duration 8 study). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to update the Irish local representative information in the Package Leaflet. Furthermore, the consolidated RMP version 27 has been agreed.

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

5. EPAR changes

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

Scope

Extension of indication for Bydureon to include the add-on use of exenatide in combination with dapagliflozin to patients whose diabetes is not adequately controlled with metformin based on the study D5553C00003 (Duration 8 study); section 4.1 of the SmPC is updated in order to align the indication wording with more recently approved glucose-lowering agents. Section 5.1 of the SmPC is also updated with the results of study D5553C00003 (Duration 8 study). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to update the Irish local representative information in the Package Leaflet. Furthermore, the consolidated RMP version 27 has been agreed.

Summary

Please refer to the scientific discussion Bydureon EMEA/H/C/002020/II/41.