PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DUFORZIG 5: 5 mg film-coated tablets

DUFORZIG 10: 10 mg film-coated tablets

DUFORZIG IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES MELLITUS. DUFORZIG IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS, HEART FAILURE AND CHRONIC KIDNEY DISEASE.

There have been reports of metabolic acidosis, including ketoacidosis, which were life-threatening or fatal, in patients taking DUFORZIG.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 14 mmol/L. DUFORZIG should be discontinued and the patient should be promptly evaluated and managed accordingly.
Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with DUFORZIG.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting

from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. DUFORZIG is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DUFORZIG 5:

Each tablet contains the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol.

Contains sugar: 25 mg lactose anhydrous per 5 mg tablet.

DUFORZIG 10:

Each tablet contains the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol.

Contains sugar: 50 mg lactose anhydrous per 10 mg tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

DUFORZIG 5:

Yellow, biconvex, 0,7 cm diameter round, film-coated tablet with "5” debossed on one side and "1427" debossed on the other side.

DUFORZIG 10:

Yellow, biconvex, approximately 1,1 x 0,8 cm diamond shaped, film-coated tablet with "10” debossed on one side and "1428" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

DUFORZIG is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- as monotherapy as an adjunct to diet and exercise to improve glycaemic control.
- as add-on combination therapy, with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a dipeptidyl peptidase 4 (DPP4) inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- to reduce the risk of developing new or worsening existing heart failure or cardiovascular death in patients with established cardiovascular (CV) disease or multiple CV risk factors.

Heart failure

DUFORZIG is indicated in adults to reduce the risk of worsening heart failure or cardiovascular death, in patients with heart failure (NYHA class II-IV).

Chronic kidney disease

DUFORZIG is indicated for the treatment of chronic kidney disease.

4.2 Posology and method of administration

Posology

Type 2 diabetes mellitus

Monotherapy and add-on combination therapy

The recommended dose is 10 mg DUFORZIG once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a DPP4 inhibitor or insulin.

The recommended starting doses of DUFORZIG and metformin when used as initial combination therapy are 10 mg DUFORZIG plus 500 mg metformin once daily. Patients with inadequate glycaemic control on this starting dose should have their metformin dose increased according to the approved metformin professional information leaflet.

Use with medicines known to cause hypoglycaemia

When DUFORZIG is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

Heart failure

The recommended dose of DUFORZIG is 10 mg taken orally once daily at any time of the day regardless of meals. DUFORZIG can be used in conjunction with other heart failure therapies.

Chronic kidney disease

The recommended dose of DUFORZIG is 10 mg taken orally once daily at any time of the day regardless of meals. In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease related therapies (see section 5.1).

Special populations

Patients with renal impairment

No dosage adjustment is required based on renal function.

In patients with diabetes mellitus, the glucose lowering efficacy of DUFORZIG is reduced in patients with eGFR < 45 mL/min/1,73 m^2 (see section 4.4). Therefore, if eGFR falls below 45 mL/min/1,73 m^2, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus if further glycaemic control is needed. Treatment with dapagliflozin should be continued for

the management of renal and cardiovascular comorbidities.

Hepatic impairment

No dosage adjustment for DUFORZIG is necessary for patients with mild Child-Pugh class A or moderate Child-Pugh class B hepatic impairment. DUFORZIG is not recommended for patients with severe hepatic Child-Pugh class C impairment as efficacy has not been established (see section 5.2).

Elderly

No dosage adjustment for DUFORZIG is required based on age (see section 4.4).

Paediatric population

Safety and effectiveness of DUFORZIG in paediatric and adolescent patients have not been established. No data are available.

4.3 Contraindications

- Hypersensitivity to dapagliflozin or to any of the excipients of DUFORZIG.
- Diabetes mellitus type 1.
- Pregnant women or women who are breastfeeding their infants (see section 4.6).
- Patients with history of pancreatitis or pancreatic surgery (see section 4.4).

4.4 Special warnings and precautions for use

General

DUFORZIG may cause a decrease in systolic blood pressure and diastolic blood pressure.

DUFORZIG should not be used for the treatment of diabetic ketoacidosis.

Metabolic acidosis including ketoacidosis in patients with diabetes mellitus

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 2 diabetes mellitus taking DUFORZIG. DUFORZIG is contraindicated for the treatment of patients with type 1 diabetes mellitus (see section 4.3).

Patients treated with DUFORZIG who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, DUFORZIG should be discontinued, and the patient should be promptly evaluated.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. DUFORZIG is not indicated in these patients.

Impairment of renal function

There is limited experience with initiating treatment with DUFORZIG in patients with eGFR < 25 mL/min/1,73 m^2.

DUFORZIG is not recommended for the treatment of type 2 diabetes mellitus to improve glycaemic control when eGFR is persistently below 45 mL/min/1,73 m^2 as the glycaemic efficacy of dapagliflozin is dependent on renal function (see section 4.2). However, treatment with DUFORZIG should be continued for the management of renal and cardiovascular comorbidities and additional glucose lowering treatment should be considered if further glycaemic control is needed.

Urinary tract and genital infections

SGLT2 inhibitors such as DUFORZIG have been associated with an increased risk of urinary tract infection and/or genital infection in both males and females caused by bacteria and/or fungi.

Genital and fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Temporary interruption of DUFORZIG should be considered when treating pyelonephritis or urosepsis.

Discontinuation of DUFORZIG may be considered in cases of recurrent urinary tract infections, see section 4.8.

The renal function should be monitored as follows:

- prior to initiation of DUFORZIG and at least yearly thereafter.
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- for renal function approaching eGFR 45 mL/min/1,73 m^2, at least 2 to 4 times per year.

If the renal function falls persistently below eGFR < 45 mL/min/1,73 m^2, treatment with DUFORZIG should be discontinued (see section 4.3).

Use with medicines known to cause hypoglycaemia

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with DUFORZIG (see section 4.8).

Paediatric population

Safety and efficacy of DUFORZIG in paediatric patients has not been established.

Other populations

Patients with severe renal impairment (eGFR < 20 mL/min/1,73m^2) or end stage renal disease or with recent (< 2 months) cardiovascular event or who are breastfeeding or are pregnant, have been excluded from clinical studies.

Lactose

DUFORZIG contains lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DUFORZIG.

4.5 Interaction with other medicines and other forms of interaction

The metabolism of dapagliflozin is primarily mediated by UGT1A9- dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in-vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O- glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitor of dapagliflozin 3-O-glucuronide formation by UGT1A9 (IC50 = 32 µM).

Effects of other medicines on DUFORZIG

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of DUFORZIG were not altered by metformin (a human OCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1,

hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other alpha-glucosidase inhibitor would not be expected.

A 22 % decrease in dapagliflozin systemic exposure following co-administration with rifampicin was considered not to be large enough to warrant a dose adjustment.

Co-administration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Effect of DUFORZIG on other medicines

Dapagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after dapagliflozin initiation and dose changes. The dose of lithium may need to be adjusted.

In interaction studies conducted in healthy subjects, using mainly single dose design, DUFORZIG did not alter the pharmacokinetics of metformin (a hOCT 1 and hOCT 2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a hOAT 3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C19 substrate, R-warfarin or the anticoagulatory effects of warfarin as measured by the prothrombin time [international normalised ratio (INR)]). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (international normalised ratio [INR]).

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of DUFORZIG have not been studied.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay should not be used, as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors, including DUFORZIG. Use alternative methods to monitor glycaemic control.

4.6 Fertility, pregnancy and lactation

Pregnancy

DUFORZIG is contraindicated in pregnancy.

Maternal exposure to DUFORZIG in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

When pregnancy is detected, DUFORZIG should be discontinued (see section 4.3).

Breastfeeding

Mothers on DUFORZIG should not breastfeed their infants.

Alternatively, mothers breastfeeding their infants must not use DUFORZIG. Studies in rats have shown excretion of DUFORZIG in milk. Exposure to DUFORZIG must be avoided during the first 2 years of life (see section 4.3).

Fertility

The effect of dapagliflozin on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Patients must bear in mind the possibility of hypoglycaemia and its effects on their motor skills.

4.8 Undesirable effects

a. Summary of the safety profile

More than 30 000 patients with type 2 diabetes mellitus, heart failure and chronic kidney disease were randomised, including 15 000 patients treated for type 2 diabetes mellitus, more than 5 000 subjects treated for heart failure and more than 2 000 subjects treated for chronic kidney disease with DUFORZIG in 24 double-blind, controlled, clinical safety and efficacy studies conducted to evaluate the effects of DUFORZIG. DUFORZIG 10 mg was evaluated in 13 of these studies.

The incidence of adverse reactions was determined using a pre-specified pool of patients from 13 short-term (mean duration 22 weeks), placebo- controlled studies in type 2 diabetes mellitus. Across these 13 studies, 2 360 patients were treated once daily with DUFORZIG 10 mg and 2 295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

Additionally, DUFORZIG 5 mg was evaluated in a 12-study, short- term, placebo-controlled pool of type 2 diabetes mellitus patients that included 1 145 patients treated with DUFORZIG 5 mg (mean exposure = 22 weeks) and 1 393 patients treated with placebo (mean exposure = 21 weeks), either as monotherapy or in combination with other antidiabetic therapies. In the dedicated cardiovascular (CV) outcomes study in patients with type 2 diabetes mellitus (DECLARE), 8 574 patients received DUFORZIG 10 mg and 8 569 received placebo for a median exposure time of 48 months. In total, there were 30 623 patient-years of exposure to DUFORZIG.

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF), 2 368 patients were treated with dapagliflozin 10 mg and 2 368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1,73 m^2. In the dapagliflozin cardiovascular outcome study in patients with heart failure with left ventricular ejection fraction (LVEF) > 40 % (DELIVER), 3 126 patients were treated with dapagliflozin 10 mg and 3 127 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR
≥ 25 mL/min/1,73 m^2.

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2 149 patients were treated with dapagliflozin 10 mg and 2 149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes mellitus, with eGFR ≥ 25 to ≤ 75 mL/min/1,73 m^2, and albuminuria (urine albumin eGFR creatinine ratio [UACR] ≥ 200 and ≤ 5 000 mg/g. Treatment was continued if eGFR fell to levels below 25 mL/min/1,73 m^2.

The safety profile of dapagliflozin was overall consistent across the studied indications. DKA was observed only in patients with diabetes mellitus.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100) and rare (≥ 1/10 000,
< 1/1 000).

b. Tabulated list of adverse reactions

Table 1 Adverse reactions (Regardless of investigator assessment of causality) in placebo-controlled studies[a] reported in ≥ 2 % of patients treated with DUFORZIG 10 mg and ≥ 1 % more frequently than in patients treated with placebo.

System organ class	**Very common**	**Common***	**Uncommon****	**Rare**
Infections and infestations		Vulvo-vaginitis, balanitis and related genital infections[b,c], urinary tract infection[b,e], including pyelo-nephritis, cystitis		
Metabolism and nutrition disorders	Hypo-glycaemia (when used with SU or insulin)[b]		Volume depletion, dehydration, hypovolaemia, hypotension, thirst**	Diabetic ketoacidosis [b]
Gastrointestinal disorders			Constipation	
Skin and subcutaneous tissue disorders		Rash[h]	Hyperhidrosis	
Musculoskeletal and connective tissue disorders		Back pain		

Renal and urinary disorders	Glucosuria	Dysuria, polyuria[d]	Nocturia	
Reproductive system and breast disorders			Vulvovaginal pruritus	
Investigations		Dyslipidaemia[f], haematocrit increased[g]	Blood urea increased	

[a] The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b] See corresponding subsection below for additional information.

[c] Genital infection includes the preferred terms: Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess, balanoposthitis, genitourinary tract infection, penile abscess and posthitis.

[d] Polyuria includes the preferred terms: pollakiuria, polyuria, increased urine output and osmotic diuresis.

[e] Urinary tract infection includes the preferred terms: Escherichia urinary tract infection, genitourinary tract infection, trigonitis, urethritis, kidney infection and prostatitis.

[f] Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2,5 % versus 0,0 %; HDL cholesterol 6,0 % versus 2,7 %; LDL cholesterol 2,9 % versus -1,0 %; triglycerides -2,7 % versus -0,7 %.

[g] Mean changes from baseline in haematocrit were 2,3 % for dapagliflozin 10 mg versus -0,33 % for placebo. Haematocrit values > 55 % were reported in 1,3 % of the subjects treated with dapagliflozin 10 mg versus 0,4 % of placebo subjects.

[h] Adverse reaction was identified through post-marketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N = 5 936, all control, N = 3 403), the frequency of rash was similar for dapagliflozin (1,4 %) and all control (1,4 %), respectively (see “Post-marketing adverse events”).

* Reported in ≥ 2 % of subjects and ≥ 1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo/comparator.

[**] Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0,2 % of subjects and ≥ 0,1 % more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

c. Description of selected adverse reactions

Genital infections

Events of genital infections were reported in 5,5 % and 0,6 % of patients who received DUFORZIG 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Infections were more frequently reported in females (8,4 % DUFORZIG 10 mg vs 1,2 % placebo) than in males (3,4 % DUFORZIG 10 mg vs 0,2 % placebo).

In the DECLARE study, the number of patients with Serious Adverse Events (SAEs) of genital infections were few and balanced: 2 (< 0,1 %) patients in each of the DUFORZIG and placebo groups.

In the DAPA-HF study, no patient reported a Serious Adverse Events (SAE) of genital infections in the DUFORZIG group and one in the placebo group. There were 7 (0,3 %) patients with adverse events leading to discontinuations (DAE) due to genital infections in the DUFORZIG group and

none in the placebo group. In the DELIVER study, one (< 0,1 %) patient in each treatment group reported a SAE of genital infections. There were 3 (0,1 %) patients with DAEs due to genital infection in the DUFORZIG group and none in the placebo group.

In the DAPA-CKD study, there were 3 (0,1 %) patients with serious adverse events of genital infections in the DUFORZIG group and none in the placebo group. There were 3 (0,1 %) patients with adverse events leading to discontinuation due to genital infections in the DUFORZIG group and none in the placebo group.

Urinary tract infections

Events of urinary tract infections (UIT) were reported in 4,7 % and 3,5 % of patients who received DUFORZIG 10 mg and placebo, respectively, in the short term, placebo-controlled pool. Infections were more frequently reported in females (8,5 % DUFORZIG 10 mg vs 6,7 % placebo) than in males (1,8 % DUFORZIG 10 mg vs 1,3 % placebo).

In the DECLARE study there were fewer patients with Serious Adverse Events (SAEs) of urinary tract infections in the DUFORZIG group compared with the placebo group: 79 (0,9 %) and 109 (1,3 %), respectively.

The number of patients with Serious Adverse Events (SAEs) of UTI were low and balanced in the DAPA-HF and DELIVER studies: in DAPA-HF there were 14 (0,6 %) patients in the DUFORZIG group and 17 (0,7 %) in the placebo group and in DELIVER there were 41 (1,3 %) patients in the DUFORZIG group and 37 (1,2 %) in the placebo group. In the DAPA-HF study, there were 5 (0,2 %) patients with Discontinuation due to Adverse Events (DAEs) due to UTI in each of the DUFORZIG and placebo groups. In the DELIVER study, there were 13 (0,4 %) patients with DAEs due to UTI in the DUFORZIG group and 9 (0,3 %) in the placebo group.

In the DAPA-CKD study, there were 29 (1,3 %) patients with Serious Adverse Events (SAEs) of UTI in the DUFORZIG group and 18 (0,8 %) patients in the placebo group. There were 8 (0,4 %) patients with DAE's due to UTI in the DUFORZIG group and 3 (0,1 %) in the placebo group.

Diabetic ketoacidosis (DKA)

In the DECLARE CV outcomes study with a median exposure time of 48 months, events of DKA were reported in 27 patients in the DUFORZIG 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the DUFORZIG group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

In the DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the DUFORZIG group and none in the placebo group. In the DELIVER study, events of DKA were reported in 2 patients with type 2 diabetes mellitus in the DUFORZIG group and none in the placebo group.

In the DAPA-CKD study, events of DKA were not reported in any patients in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see section 4.4). In an add-on to glimepiride study up to 24 weeks, episodes of hypoglycaemia were reported in 10 (6,6 %) patients in the DUFORZIG 10 mg plus glimepiride group and 3 (2,1 %) patients in the placebo plus glimepiride group.

In an add-on to insulin study up to 24 weeks, episodes of hypoglycaemia were reported in 79 (40,3 %) patients in the DUFORZIG 10 mg plus insulin group and in 67 (34 %) patients in placebo plus insulin group. Patients in this study could also be treated with a maximum of 2 oral anti-diabetes medicines (OADs) including metformin.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0,7 %) patients treated with dapagliflozin and 83 (1,0 %) patients treated with placebo.

In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0,2 %) patients in both the dapagliflozin therapy and placebo treatment groups and observed only in patients with type 2 diabetes mellitus.

Laboratory findings

Haematocrit

A moderate increase in haematocrit occurs and may be an indication of volume depletion.

Serum inorganic phosphorous

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at week 24 in DUFORZIG 10 mg treated patients compared with placebo (mean increases of 0,0419 mmol/L vs 0,0129 mmol/L, respectively). Similar results were seen at week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥ 1,81 mmol/L if age 17 – 65 or ≥ 1,65 mmol/L if ≥ age 66) were reported in DUFORZIG 10 mg group vs placebo at week 24 (1,7 % vs 0,9 %, respectively) and during the short-term plus long-term phase (3,0 % vs 1,6 %, respectively). The clinical relevance of these findings is unknown.

Lipids

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at week 24 in DUFORZIG 10 mg treated patients compared with placebo. Mean percent change from baseline at week 24 for DUFORZIG 10 mg vs placebo, respectively was as follows: total cholesterol 2,5 % vs 0,0 %; HDL cholesterol 6,0 % vs 2,7 %; LDL cholesterol 2,9 % vs -1,0 %; triglycerides -2,7 % vs -0,7 %. Mean percent change from baseline at week 102 for DUFORZIG 10 mg vs placebo, respectively was as follows: total cholesterol 2,1 % vs -1,5 %; HDL cholesterol 6,6 % vs 2,1 %; LDL cholesterol 2,9 % vs -2,2 %; triglycerides -1,8 % vs -1,8 %. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at week 24.

In the CV outcomes study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

Post-marketing adverse events

Spontaneous reports:

Skin and sub-cutaneous tissue disorders: Rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, rash erythematous.

Phimosis have been reported with the use of SGLT2 inhibitors such as DUFORZIG.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects may be elicited or exacerbated. Appropriate symptomatic and supportive treatment should be initiated as dictated by the patient's clinical status. The removal of DUFORZIG by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglycaemics.

Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01.

Mechanism of action

Dapagliflozin is a reversible inhibitor of sodium glucose co-transporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardio-renal benefits.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubulo-glomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight.

The cardio-renal benefits of dapagliflozin go beyond the blood glucose lowering effect and are not limited to patients with diabetes mellitus as demonstrated in the DAPA-HF and DAPA-CKD studies. In addition to the osmotic diuretic and related haemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may

be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin.

Dapagliflozin reduces both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Thus, in subject with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtered glucose is small and can be reabsorbed SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in homeostasis model assessment for pancreatic beta cell function (HOMA beta cell) has been observed in clinical studies with dapagliflozin.

The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is more than 1 400 times more selective for SGLT2 vs SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects

The urinary glucose excretion with dapagliflozin results in osmotic diuresis and increases in urinary volume. The increase in urinary volume may be associated with a transient increase in urinary sodium excretion that which may not be associated with changes in serum sodium concentrations.

Dapagliflozin may cause a decrease in systolic blood pressure and diastolic blood pressure.

Urinary uric acid excretion was also increased and accompanied by a reduction in serum uric acid concentration. At 24 weeks, changes in serum uric acid concentrations from baseline ranged from -0,0183 mmol/L to -0,0483 mmol/L.

Clinical efficacy and safety

Clinical trial information – type 2 diabetes mellitus

More than 28 000 patients have been included in 23 double-blind, controlled type 2 diabetes mellitus clinical studies conducted to evaluate the safety and efficacy of DUFORZIG; more than 15 000 patients in these studies were treated with DUFORZIG.

DUFORZIG has been studied as monotherapy and in combination with metformin (with or without a sulphonylurea), sulphonylurea (glimepiride), thiazolidinedione (pioglitazone), sitagliptin (with or without metformin), saxagliptin and metformin, prolonged-release exenatide when initiated concomitantly with DUFORZIG (on a background of metformin) or insulin (with or without other oral antidiabetic therapy).

Dedicated studies of the glycaemic efficacy and safety of DUFORZIG were performed in patients with type 2 diabetes and cardiovascular disease (CVD), with type 2 diabetes and hypertension, with type 2 diabetes and moderate renal impairment.

A large CV outcomes trial (DECLARE) assessed the effect of dapagliflozin on CV and renal outcomes in type 2 diabetes mellitus patients with or without established CV disease.

Clinical efficacy

Glycaemic efficacy

Treatment of adult patients with DUFORZIG as monotherapy, as add-on combination therapy with metformin (with or without a sulphonylurea), sulphonylurea (glimepiride), thiazolidinedione (pioglitazone), sitagliptin (with or without metformin), saxagliptin and metformin, insulin (with or without other oral antidiabetic therapy), or prolonged release exenatide when initiated concomitantly with DUFORZIG (on a background of metformin), produced clinically relevant and statistically significant improvements in mean change from baseline at week 24 or week 28 (combination with exenatide study) in HbA1c, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) (where measured) compared to control. Treatment with DUFORZIG in concomitant initiation with saxagliptin as add-on to metformin produced clinically relevant and statistically significant improvements in mean change from baseline at week 24 in HbA1c compared to control.

These clinically relevant glycaemic effects were sustained in all long-term extensions up to 208 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease and baseline body mass index (BMI).

Additionally, at week 24, clinically relevant and statistically significant reductions in mean changes from baseline in body weight were seen with DUFORZIG combination treatments compared to control. Body-weight reductions were sustained in long-term extensions up to 208 weeks. In a dedicated clinical study, decrease in weight was mainly attributable to a reduction in body-fat mass as measured by DXA.

In two studies of DUFORZIG 10 mg in type 2 diabetes patients with CVD, statistically significant improvements in HbA1c and significant reductions in body weight and seated systolic blood pressure were seen at week 24 in patients treated with DUFORZIG 10 mg compared to those treated with placebo and were sustained through week 104.

In two studies of DUFORZIG 10 mg in type 2 diabetes patients with hypertension, statistically significant reductions in mean seated systolic blood pressure were also seen in patients treated with DUFORZIG 10 mg combined with other oral antidiabetic and antihypertensive treatments (an angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB] in one study and an ACE inhibitor or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at week 12.

DUFORZIG was evaluated at 10 mg once daily in 19 of the 21 double-blind glycaemic efficacy studies. Doses of dapagliflozin 2,5 mg and DUFORZIG 5 mg were also evaluated in some of these studies; 2,5 mg was not consistently effective for glycaemic control and 10 mg had numerically better efficacy and comparable safety to DUFORZIG 5 mg.

Monotherapy

A total of 840 treatment-naive patients with inadequately controlled type 2 diabetes participated in two placebo-controlled studies to evaluate the efficacy and safety of monotherapy with DUFORZIG.

In one monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24-week study with a 78-week controlled, blinded, extension period. Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c ≥ 7 % and ≤ 10 % were randomised to dapagliflozin 2,5 mg, DUFORZIG 5 mg, or 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo in the morning only.

At week 24, treatment with DUFORZIG 10 mg QAM provided significant improvements in HbA1c and FPG compared with placebo (Table 2, Figure 1). Overall, the PM administration of DUFORZIG had a comparable safety and efficacy profile to DUFORZIG administered in the AM. Adjusted mean change from baseline in HbA1c and FPG was −0,61 % and −27,0 mg/dL, respectively, at

week 102 in the QAM group for patients treated with DUFORZIG 10 mg, and −0,17 % and −6,9 mg/dL, respectively, for patients treated with placebo based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients in the main cohort who were rescued or discontinued for lack of glycaemic control at week 24 (adjusted for baseline HbA1c) was higher for placebo (12,0 %) than for DUFORZIG 10 mg (0,0 %). By week 102 (adjusted for baseline HbA1c), more patients treated with placebo (44,0 %) required rescue therapy than patients treated with DUFORZIG 10 mg (35,0 %).

Table 2 Results at week 24 (LOCF*) in a placebo-controlled study of DUFORZIG monotherapy in patients with type 2 diabetes (Main cohort AM doses)

Efficacy parameter	**DUFORZIG 10 mg N=70†**	**Placebo N=75†**
HbA1c (%)		
Baseline (mean)	8,01	7,79
Change from baseline (adjusted mean‡)	−0,89	−0,23
Difference from placebo (adjusted mean‡) (95 % CI)	−0,66§ (−0,96; −0,36)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	50,8%¶	31,6%
Change from baseline in HbA1c in patients with baseline HbA1c ≥ 9 % (adjusted mean‡)	−2,04¶ (N=14)	0,19 (N=5)
FPG (mg/dL)		

Efficacy parameter	DUFORZIG 10 mg N=70†	Placebo N=75†
Baseline (mean)	166,6	159,9
Change from baseline (adjusted mean‡)	−28,8	−4,1
Difference from placebo (adjusted mean‡) (95 % CI)	−24,7§ (−35,7; −13,6)	
Body weight (kg)		
Baseline (mean)	94,13	88,77
Change from baseline (adjusted mean‡)	−3,16	−2,19
Difference from placebo (adjusted mean‡) (95 % CI)	−0,97 (−2,20; 0,25)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

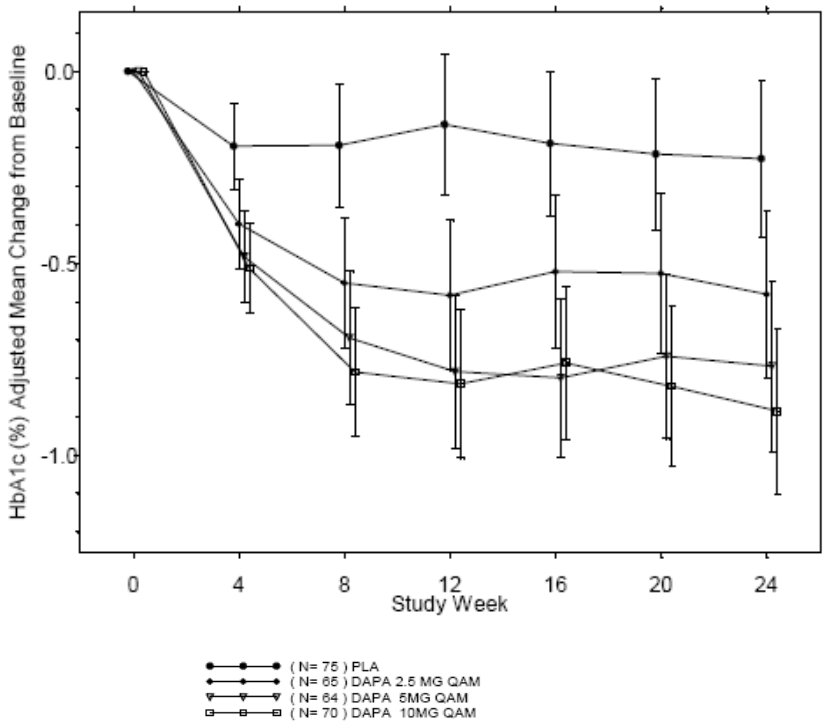
† All randomised patients who took at least one dose of double-blind study medicine during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value < 0,0001 *versus* placebo.

¶ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.

Figure 1 Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24 week placebo-controlled study of DUFORZIG monotherapy in patients with type 2 diabetes (Group 1 AM doses)



Error bars represent 95 % confidence intervals for the adjusted mean change from baseline

Another 24-week study conducted evaluating dapagliflozin 1 mg, 2,5 mg, and DUFORZIG 5 mg monotherapy *versus* placebo also showed clinically relevant and statistically significant improvements in glycaemic parameters and body weight.

Combination therapy

DUFORZIG was studied as initial combination with metformin, and as add-on to metformin, sulphonylurea (glimepiride), metformin plus a sulphonylurea, thiazolidinedione (pioglitazone), insulin (with or without other oral antidiabetic therapy), sitagliptin (with or without metformin), or saxagliptin plus metformin, as concomitant initiation therapy with saxagliptin added to metformin, and as concomitant initiation therapy with exenatide added to metformin.

Combination therapy with metformin

Four studies were conducted in combination with metformin therapy. Two studies evaluated

DUFORZIG added to metformin as initial combination therapy, one study evaluated the effect of DUFORZIG added to metformin in patients already on metformin, and one study evaluated the effect of DUFORZIG added to metformin *versus* sulphonylurea added to metformin.

Initial combination therapy with metformin

A total of 1 236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥ 7,5 % and ≤ 12 %) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of initial therapy with DUFORZIG 5 mg or 10 mg in combination with metformin extended-release formulation (XR).

In one study, 638 patients randomised to one of three treatment arms following a 1-week lead-in period received DUFORZIG 10 mg plus metformin XR (up to 2 000 mg per day), DUFORZIG 10 mg plus placebo, or metformin XR (up to 2 000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2 000 mg.

The combination treatment of DUFORZIG 10 mg plus metformin XR provided significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and significant reductions in body weight compared with metformin XR alone (Table 3, Figure 2 and Figure 3). DUFORZIG 10 mg as monotherapy also provided significant improvements in FPG and significant reduction in body weight compared with metformin XR alone and was noninferior to metformin XR monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycaemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher for treatment with metformin XR plus placebo (13,5 %) than for DUFORZIG 10 mg plus placebo and DUFORZIG 10 mg plus metformin XR (7,8 % and 1,4 %, respectively).

Table 3 Results at week 24 (LOCF*) in an active-controlled study of DUFORZIG initial

combination therapy with metformin XR

Efficacy parameter	**DUFORZIG 10 mg + metformin XR**	**DUFORZIG 10 mg**	**metformin XR**
	N = 211†	**N = 219†**	**N = 208†**
HbA1c (%)			
Baseline (mean)	9,10	9,03	9,03
Change from baseline (adjusted mean‡)	−1,98	−1,45	−1,44
Difference from DUFORZIG (adjusted mean‡) (95 % CI)	−0,53§ (−0,74; −0,32)		
Difference from metformin XR (adjusted mean‡) (95 % CI)	−0,54§ (−0,75; −0,33)	−0,01¶ (−0,22; 0,20)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	46,6 %#	31,7 %	35,2 %
Change from baseline in HbA1c in patients with baseline HbA1c ≥ 9 % (adjusted mean‡)	−2,59#	−2,14	−2,05
FPG (mg/dL)			
Baseline (mean)	189,6	197,5	189,9
Change from baseline (adjusted mean‡)	−60,4	−46,4	−34,8
Difference from DUFORZIG (adjusted mean‡) (95 % CI)	−13,9§ (−20,9; −7,0)		
Difference from metformin XR (adjusted mean‡) (95 % CI)	−25,5§ (−32,6; −18,5)	−11,6¶ (−18,6; −4,6)	
Body weight (kg)			

Baseline (mean)	88,56	88,53	87,24
Change from baseline (adjusted mean‡)	−3,33	−2,73	−1,36
Difference from metformin XR (adjusted mean‡) (95 % CI)	−1,97§ (−2,64; −1,30)	−1,37§ (−2,03; −0,71)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.

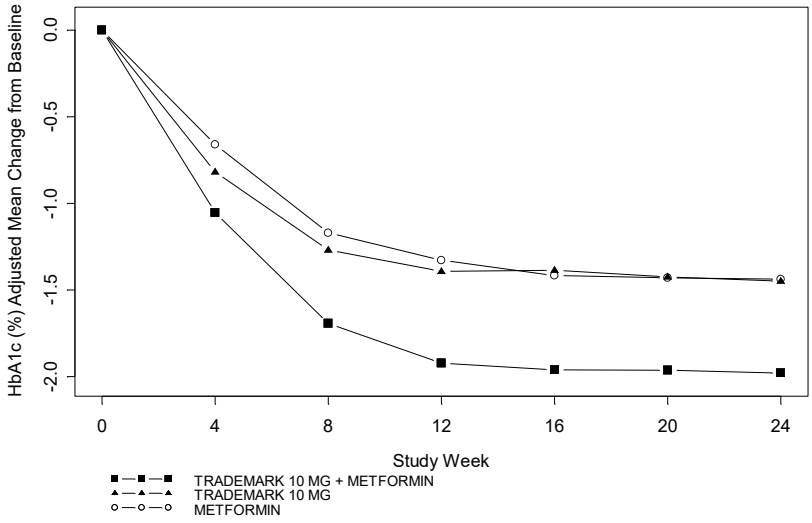
‡ Least squares mean adjusted for baseline value.

§ p-value < 0,0001.

¶ Noninferior *versus* metformin XR.

p-value < 0,05.

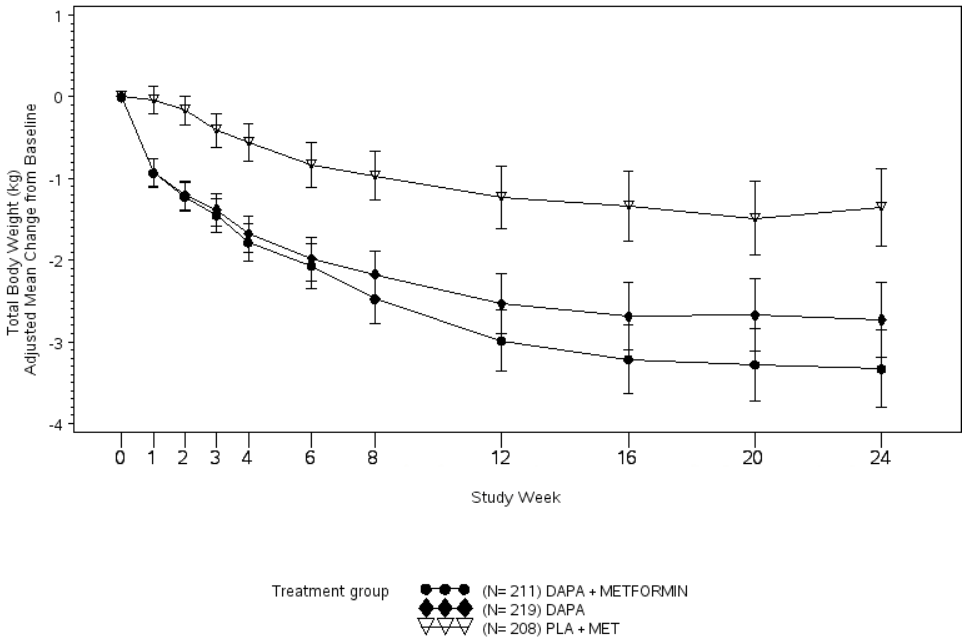
Figure 2 Adjusted mean change from baseline over time (LOCF[a]) in HbA1c (%) in a 24-week active-controlled study of DUFORZIG initial combination therapy with metformin



Values in the plot represent adjusted mean and 95% confidence intervals (for week 24 only) based on the ANCOVA model using LOCF (Last observation (prior to rescue for rescued subjects) carried forward) data

Figure 3 Adjusted mean change from baseline over time (LOCF[a]) in total body weight (kg) in

a 24-week active-controlled study of dapagliflozin initial combination therapy with metformin XR



Another 24-week study evaluating DUFORZIG 5 mg plus metformin XR showed clinically relevant and statistically significant improvements in glycaemic parameters *versus* DUFORZIG 5 mg monotherapy and metformin XR monotherapy.

Add-on to metformin

A total of 546 patients with type 2 diabetes with inadequate glycaemic control (HbA1c ≥ 7 % and ≤ 10 %) participated in a 24-week, placebo-controlled study with a 78-week controlled, blinded extension period to evaluate DUFORZIG in combination with metformin. Patients on metformin at a dose of at least 1 500 mg per day were randomised after completing a 2-week, single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomised to dapagliflozin 2,5 mg, DUFORZIG 5 mg, or 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, DUFORZIG 10 mg provided significant improvements in HbA1c

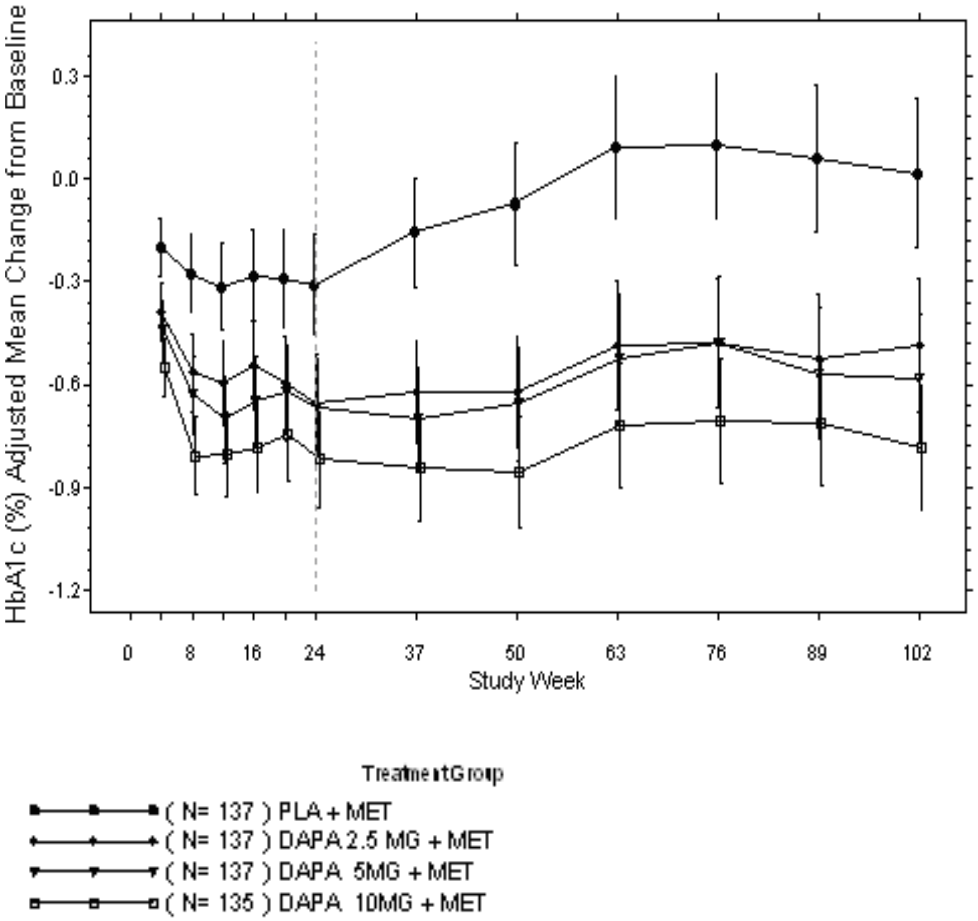
and FPG, and significant reduction in body weight compared with placebo at week 24 (Table 4). At week 102, adjusted mean change from baseline in HbA1c (Figure 4), FPG, and body weight was −0,78 %, −24,5 mg/dL, and −2,81 kg, respectively, for patients treated with DUFORZIG 10 mg plus metformin and 0,02 %, −10,4 mg/dL, and −0,67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue (Figure 4). The proportion of patients who were rescued or discontinued for lack of glycaemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo plus metformin group (15,0 %) than in the DUFORZIG 10 mg plus metformin group (4,4 %). By week 102 (adjusted for baseline HbA1c), more patients treated with placebo plus metformin (60,1 %) required rescue therapy than patients treated with DUFORZIG 10 mg plus metformin (44,0 %).

Table 4 Results of a 24-week (LOCF*) placebo-controlled study of DUFORZIG in add-on combination with metformin

Efficacy parameter	**DUFORZIG 10 mg + metformin N = 135†**	**Placebo + metformin N = 137†**
HbA1c (%)		
Baseline mean	7,92	8,11
Change from baseline (adjusted mean‡)	−0,84	−0,30
Difference from placebo (adjusted mean‡) (95 % CI)	−0,54§ (−0,74; −0,34)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	40,6 %¶	25,9 %
Change from baseline in HbA1c in patients with baseline HbA1c ≥ 9 % (adjusted mean‡)	−1,32¶ (N= 18)	−0,53 (N= 22)
FPG (mg/dL)		

Baseline mean	156,0	165,6
Change from baseline at week 24 (adjusted mean‡)	−23,5	−6,0
Difference from placebo (adjusted mean‡) (95 % CI)	−17,5§ (−25,0; −10,0)	
Change from baseline at week 1 (adjusted mean‡)	−16,5§ (N=115)	1,2 (N=126)
Body weight (kg)		
Baseline mean	86,28	87,74
Change from baseline (adjusted mean‡)	−2,86	−0,89
Difference from placebo (adjusted mean‡) (95 % CI)	−1,97§ (−2,63; −1,31)	

Figure 4 Adjusted mean change from baseline over time in HbA1c (%) in a 102-week placebo-controlled study of DUFORZIG in combination with metformin (Longitudinal repeated measures analysis, excluding data after rescue)



Error bars represent 95 % confidence intervals for the adjusted mean change from baseline.

Active glipizide-controlled study add-on to metformin

A total of 816 patients with type 2 diabetes with inadequate glycaemic control (HbA1c > 6,5 % and ≤ 10 %) were randomised in a 52-week, glipizide-controlled, noninferiority study with a 156-week extension period to evaluate DUFORZIG as add-on therapy to metformin. Patients on metformin at a dose of at least 1 500 mg per day were randomised following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2,5 mg, respectively) and were up-titrated over 18 weeks to optimal glycaemic effect (FPG < 110 mg/dL, < 6,1 mmol/L) or to the highest dose level (up to glipizide 20 mg and DUFORZIG 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycaemia. Rescue for lack of glycaemic control was not available in this study through week 104, but was available between weeks 105 and 208.

At the end of the titration period, 87 % of patients treated with DUFORZIG had been titrated to the maximum study dose (10 mg) *versus* 73 % treated with glipizide (20 mg). DUFORZIG led to a similar mean reduction in HbA1c from baseline at week 52, compared with glipizide, thus demonstrating noninferiority (Table 5). DUFORZIG treatment led to a significant mean reduction in body weight from baseline at week 52 compared with a mean increase in body weight in the glipizide group.

At weeks 104 and 208, adjusted mean changes from baseline in HbA1c were −0,32 % and −0,10 %, and changes in body weight were −3,70 kg and −3,95 kg, respectively, for patients treated with DUFORZIG; adjusted mean changes from baseline in HbA1c were −0,14 % and 0,20 %, respectively, and changes in body weight were 1,36 kg and 1,12 kg, respectively, for patients treated with glipizide based on the longitudinal repeated measures analysis (Figure 5 and Figure 6). The percent of patients achieving weight loss of ≥ 5 % (adjusted) at weeks 104 and 208 were 23,8 % and 51,0 %, respectively, for patients treated with DUFORZIG and 2,8 % and 9,9 %, respectively, for patients treated with glipizide.

By weeks 52, 104, and 208, the proportion of patients who discontinued or were rescued for lack of glycaemic control (adjusted for baseline HbA1c) were higher for glipizide plus metformin (3,6 %, 21,6 %, and 44,9 %, respectively) than for DUFORZIG plus metformin (0,2 %, 14,5 % and 39,4 %, respectively). At 52, 104, and 208 weeks, respectively, a significantly lower proportion of patients treated with DUFORZIG (3,5 %, 4,3 %, and 5,0 %) experienced at least one event of hypoglycaemia, compared to glipizide (40,8 %, 47,0 % and 50,0 %).

Table 5 Results at week 52 (LOCF*) in an active-controlled study comparing DUFORZIG to glipizide as add-on to metformin

Efficacy parameter	DUFORZIG + metformin N = 400†	Glipizide + metformin N = 401†
HbA1c (%)		
Baseline (mean)	7,69	7,74
Change from baseline (adjusted mean‡)	−0,52	−0,52
Difference from Glipizide + Metformin (adjusted mean‡)	0,00§	
(95 % CI)	(−0,11; 0,11)	
Body weight (kg)		
Baseline (mean)	88,44	87,60
Change from baseline (adjusted mean‡)	−3,22	1,44
Difference from Glipizide + Metformin (adjusted mean‡)	−4,65¶	
(95 % CI)	(−5,14, −4,17)	
Percent of patients achieving weight loss > 5 % (adjusted) (95 % CI)	33,3 %¶ (28,7; 37,9)	2,5 % (1,0; 4,0)

* LOCF: last observation carried forward.

† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

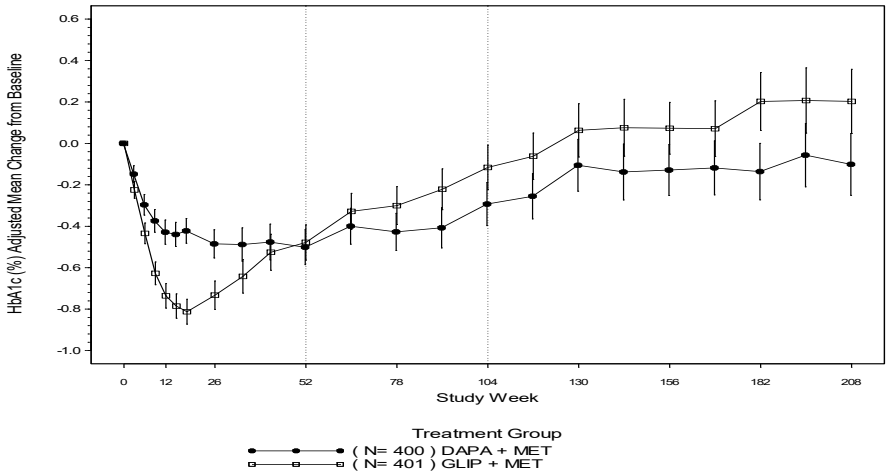
‡ Least squares mean adjusted for baseline value.

§ Noninferior to glipizide + metformin.

¶ p-value < 0,0001.

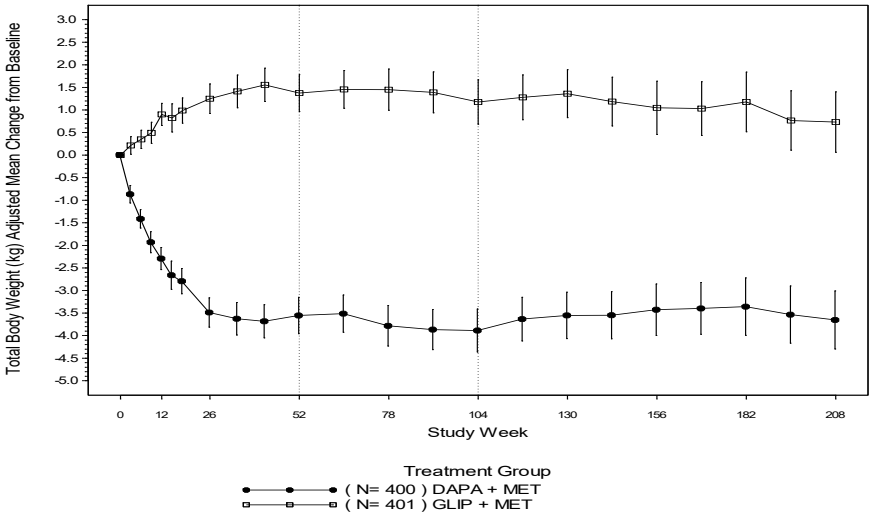
Figure 5 Adjusted mean change from baseline over time in HbA1c (%) in a 208-week active-

controlled study comparing DUFORZIG to glipizide as add-on to metformin (Longitudinal repeated measures analysis, excluding data after rescue)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Figure 6 Adjusted mean change from baseline over time in body weight (kg) in a 208-week active-controlled study comparing DUFORZIG to glipizide as add-on to metformin (Longitudinal repeated measures analysis, excluding data after rescue)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

*Add-on combination with other antidiabetic **[~~agents~~]**medicines*

Add-on combination therapy with a sulphonylurea

A total of 597 patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥ 7 % and ≤ 10 %) were randomised in this 24-week, placebo-controlled study with a 24-week extension period to evaluate DUFORZIG in combination with glimepiride (a sulphonylurea).

Patients on at least half the maximum recommended dose of a glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomised to dapagliflozin 2,5 mg, DUFORZIG 5 mg, or 10 mg, or placebo in addition to glimepiride 4 mg per day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycaemia during the treatment period; no up-titration of glimepiride was allowed.

In combination with glimepiride, treatment with DUFORZIG 10 mg provided significant improvement in HbA1c, FPG, 2-hour PPG, and significant reduction in body weight compared with placebo plus glimepiride at week 24 (Table 6, Figure 7). At week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were −0,73 %, −28,8 mg/dL, and −2,41 kg, respectively, for patients treated with DUFORZIG 10 mg plus glimepiride, and −0,04 %, 2,6 mg/dL, and −0,77 kg for patients treated with placebo plus glimepiride at week 48 based on the longitudinal repeated measures analysis excluding data after rescue.

At week 24, the proportion of patients who were rescued or discontinued for lack of glycaemic control (adjusted for baseline HbA1c) was higher for placebo plus glimepiride (16,2 %) than for DUFORZIG 10 mg plus glimepiride (2,0 %). By week 48 (adjusted for baseline HbA1c), more patients on placebo plus glimepiride (52,1 %) required rescue therapy than patients on DUFORZIG 10 mg plus glimepiride (18,4 %).

Add-on combination therapy with metformin and a sulphonylurea

A total of 218 patients with type 2 diabetes and inadequate glycaemic control (HbA1c ≥ 7 % and ≤ 10,5 %) participated in a 24-week, placebo-controlled study with a 28-week extension period to evaluate DUFORZIG in combination with metformin and a sulphonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1 500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment were randomised after an 8-week placebo lead-in period to DUFORZIG 10 mg or placebo. Dose-titration of DUFORZIG or metformin was not permitted during the 24-week treatment period. Down-titration of sulphonylurea was permitted to prevent hypoglycaemia, but no up-titration was permitted.

As add-on treatment to combined metformin and a sulphonylurea, treatment with DUFORZIG 10 mg provided significant improvements in HbA1c and FPG and significant reductions in body weight compared with placebo at week 24 (Table 6). Significant reduction in seated systolic blood pressure at week 8 was also observed in patients treated with DUFORZIG 10 mg compared to placebo. The effects in HbA1c, FPG and body weight observed at week 24 were sustained at week 52.

At week 24, no patients treated with DUFORZIG 10 mg combined with metformin and a sulphonylurea and 10 patients (9,3 %) treated with placebo combined with metformin and a sulphonylurea were rescued or discontinued for lack of glycaemic control (adjusted for baseline HbA1c). By week 52 (adjusted for baseline HbA1c) more patients on placebo combined with metformin and a sulphonylurea (42,7 %) were rescued for lack of glycaemic control than patients on DUFORZIG (10,1 %). No patient was discontinued from study medicine due to inadequate glycaemic control.

Add-on combination therapy with a thiazolidinedione

A total of 420 patients with type 2 diabetes with inadequate glycaemic control (HbA1c ≥ 7 % and ≤

10,5 %) participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate DUFORZIG in combination with pioglitazone (a thiazolidinedione) alone. Patients on a stable dose of pioglitazone of 45 mg/day (or 30 mg/day, if 45 mg/day was not tolerated) for 12 weeks were randomised after a 2-week lead-in period to 5 mg or 10 mg of DUFORZIG or placebo in addition to their current dose of pioglitazone. Dose titration of DUFORZIG or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with DUFORZIG 10 mg provided significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c < 7 %, and a significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (Table 6, Figure 8) at week 24. Treatment with DUFORZIG 10 mg plus pioglitazone also led to a significant reduction in waist circumference compared with the placebo plus pioglitazone group. At week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were −1,21 %, −33,1 mg/dL, and 0,69 kg, respectively, for patients treated with DUFORZIG 10 mg plus pioglitazone, and −0,54 %, −13,1 mg/dL, and 2,99 kg for patients treated with placebo based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients who were rescued or discontinued for lack of glycaemic control (adjusted for baseline HbA1c) was higher in the placebo plus pioglitazone group (11,6 %) than in the DUFORZIG 10 mg plus pioglitazone group (3,7 %) at week 24. By week 48 (adjusted for baseline), more patients treated with placebo plus pioglitazone (33,8 %) required rescue therapy than patients treated with DUFORZIG 10 mg plus pioglitazone (11,8 %).

Add-on combination therapy with insulin

A total of 808 patients with type 2 diabetes who had inadequate glycaemic control (HbA1c ≥ 7,5 % and ≤ 10,5 %) were randomised in a 24-week, placebo-controlled study with an 80-week extension period to evaluate DUFORZIG as add-on therapy to insulin. Patients on a stable insulin regimen,

with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior and on a maximum of two OADs including metformin, were randomised after completing a 2-week enrolment period to receive dapagliflozin 2,5 mg, DUFORZIG 5 mg, or 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycaemic goals. Dose modifications of blinded study medicine or OADs were not allowed during the treatment phase, with the exception of decreasing OADs where there were concerns over hypoglycaemia after cessation of insulin therapy.

In this study, 50 % of patients were on insulin monotherapy at baseline, while 50 % were on 1 or 2 OADs in addition to insulin. At week 24, DUFORZIG 10 mg dose provided significant improvement in HbA1c and mean insulin dose, and a significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (Table 6); the effect of DUFORZIG on HbA1c was similar in patients on insulin alone and patients on insulin plus OADs.

At weeks 48 and 104, adjusted mean changes from baseline in HbA1c were −0,93 % and −0,71 %, changes in FPG were −21,5 mg/dL and −18,2 mg/dL, and changes in body weight were −1,79 kg and −1,97 kg, respectively, for patients treated with DUFORZIG 10 mg plus insulin; adjusted mean changes from baseline in HbA1c were −0,43 % and −0,06 %, changes in FPG were −4,4 mg/dL and −11,2 mg/dL, and changes in body weight were −0,18 kg and 0,91 kg, respectively, for patients treated with placebo plus insulin (see Figure 9).

At week 24, a significantly higher proportion of patients on DUFORZIG 10 mg reduced their insulin dose by at least 10 % compared to placebo. The proportion of patients who required up-titration of their insulin dose or discontinued due to lack of glycaemic control (adjusted for baseline HbA1c) was higher for placebo plus insulin (29,2 %) than for DUFORZIG 10 mg plus insulin (9,7 %). By

weeks 48 and 104, the insulin dose remained stable in patients treated with DUFORZIG 10 mg at an average dose of 76 IU/day, but continued to increase (mean increase 10,5 IU and 18,3 IU, respectively, from baseline) in placebo-treated patients. By weeks 48 and 104 (adjusted for baseline HbA1c), more patients treated with placebo required up-titration with insulin to maintain glycaemic levels or discontinued due to lack of glycaemic control (42,8 % and 50,4 %, respectively) compared with patients treated with DUFORZIG 10 mg (15,3 % and 25,5 %, respectively).

Table 6 Results of 24-week placebo-controlled studies of DUFORZIG in combination with antidiabetic medicines

Efficacy parameter	**DUFORZIG 10 mg**	**Placebo**
In combination with sulphonylurea (glimepiride)		
Intent-to-treat population	**N = 151†**	**N = 145†**
HbA1c (%)*		
Baseline (mean)	8,07	8,15
Change from baseline (adjusted mean‡)	−0,82	−0,13
Difference from placebo (adjusted mean‡) (95 % CI)	−0,68§ (−0,86; −0,51)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	31,7 %§	13,0 %
FPG (mg/dL)*		
Baseline (mean)	172,4	172,7
Change from baseline (adjusted mean‡)	−28,5	−2,0
Difference from placebo (adjusted mean‡) (95 % CI)	−26,5§ (−33,5; −19,5)	
2-hour PPG¶ (mg/dL)*		
Baseline (mean)	329,6	324,1

Change from baseline (adjusted mean‡)	−60,6	−11,5
Difference from placebo (adjusted mean‡) (95 % CI)	−49,1§ (−64,1; −34,1)	
Body weight (kg)*		
Baseline (mean)	80,56	80,94
Change from baseline (adjusted mean‡)	−2,26	−0,72
Difference from placebo (adjusted mean‡) (95 % CI)	−1,54§ (−2,17; −0,92)	
In combination with metformin and sulphonylurea		
Intent-to treat population	**N=108†**	**N=108†**
HbA1c (%)‡‡		
Baseline mean	8,08	8,24
Change from baseline (adjusted mean‡)	−0,86	−0,17
Difference from placebo (adjusted mean‡) (95 % CI)	−0,69§ (−0,89, −0,49)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	31,8 %§	11,1 %
FPG (mg/dL)*		
Baseline mean	167,4	180,3
Change from baseline at week 24 (adjusted mean‡)	−34,2	−0,8
Difference from placebo (adjusted mean‡) (95 % CI)	−33,5§ (−43,1; −23,8)	
Body weight (kg)*		
Baseline mean	88,57	90,07
Change from baseline (adjusted mean‡)	−2,65	−0,58
Difference from placebo (adjusted mean‡)	−2,07§	

(95 % CI)	(−2,79; −1,35)	
Seated systolic blood pressure at week 8 (mmHg)*		
Baseline mean	134,7	136,3
Change from baseline at week 8 (adjusted mean‡)	−4,0	−0,3
Difference from placebo (adjusted mean‡) (95 % CI)	−3,8** (−7,1; −0,5)	
In combination with thiazolidinedione (Pioglitazone)		
Intent-to-treat population	**N = 140#**	**N = 139#**
HbA1c (%)*		
Baseline (mean)	8,37	8,34
Change from baseline (adjusted mean‡)	−0,97	−0,42
Difference from placebo (adjusted mean‡) (95 % CI)	−0,55§ (−0,78; −0,31)	
Percent of patients achieving HbA1c < 7 % adjusted for baseline	38,8 %**	22,4 %
FPG (mg/dL)*		
Baseline (mean)	164,9	160,7
Change from baseline (adjusted mean‡)	−29,6	−5,5
Difference from placebo (adjusted mean‡) (95 % CI)	−24,1§ (−32,2; −16,1)	
2-hour PPG¶ (mg/dL)*		
Baseline (mean)	308,0	293,6
Change from baseline (adjusted mean‡)	−67,5	−14,1
Difference from placebo (adjusted mean‡) (95 % CI)	−53,3§ (−71,1; −35,6)	

Body weight (kg)*		
Baseline (mean)	84,82	86,40
Change from baseline (adjusted mean‡)	−0,14	1,64
Difference from placebo (adjusted mean‡) (95 % CI)	−1,78§ (−2,55; −1,02)	
Change from baseline in waist circumference (cm) (adjusted mean‡)	−0,17**	1,38
In combination with insulin with or without up to 2 oral antidiabetic therapies		
Intent-to-treat population	**N = 194†**	**N = 193†**
HbA1c (%)*		
Baseline (mean)	8,58	8,46
Change from baseline (adjusted mean‡)	−0,90	−0,30
Difference from placebo (adjusted mean‡) (95 % CI)	−0,60§ (−0,74; −0,45)	
Mean daily insulin dose (IU)††		
Baseline (mean)	77,96	73,96
Change from baseline (adjusted mean‡)	−1,16	5,08
Difference from placebo (95 % CI)	−6,23§ (−8,84; −3,63)	
Percent of patients with mean daily insulin dose reduction of at least 10 % adjusted for baseline	19,6 %**	11,0 %
FPG (mg/dL)*		
Baseline (mean)	173,7	170,0
Change from baseline (adjusted mean‡)	−21,7	3,3
Difference from placebo (adjusted mean‡) (95 % CI)	−25,0§ (−34,3; −15,8)	

Body weight (kg)*		
Baseline (mean)	94,63	94,21
Change from baseline (adjusted mean‡)	−1,67	0,02
Difference from placebo (adjusted mean‡) (95 % CI)	−1,68§ (−2,19; −1,18)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

†Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value < 0,0001 *versus* placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

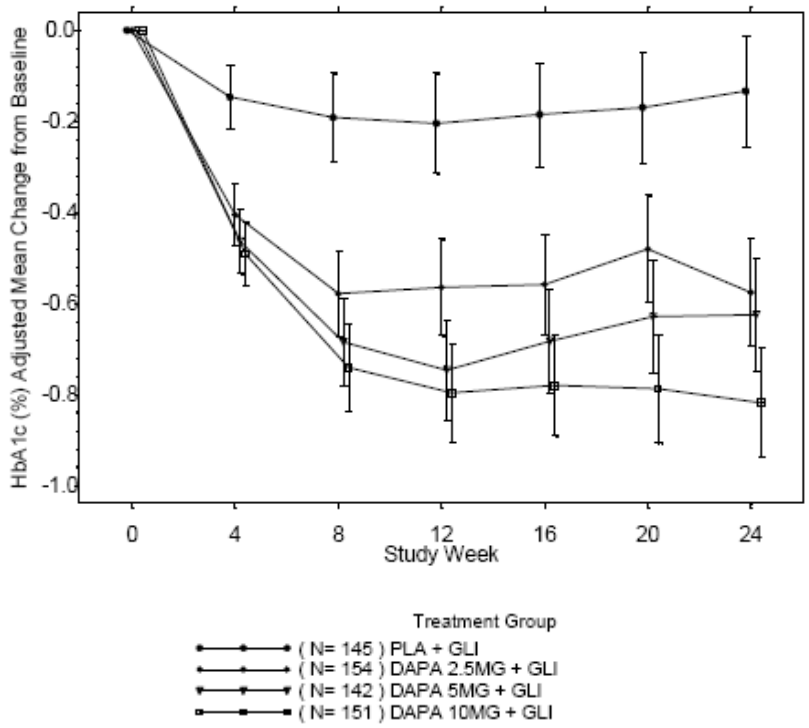
All randomised patients who took at least one dose of double-blind study medicine during the short-term, double-blind period.

** p-value < 0,05 *versus* placebo.

†† LOCF: last observation (after rescue) carried forward.

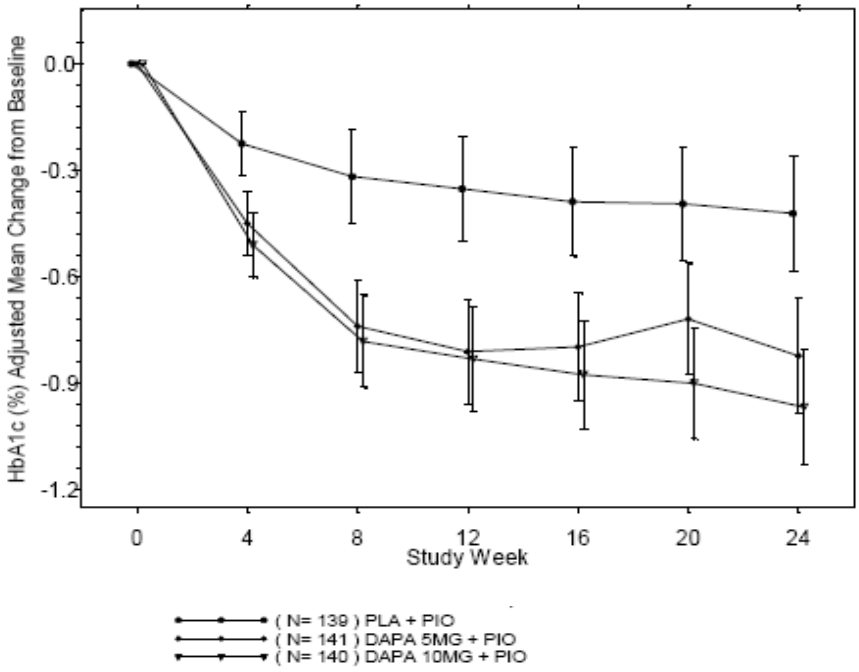
‡‡ LRM: longitudinal repeated measures analysis.

Figure 7 Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24-week, placebo-controlled study of DUFORZIG in combination with sulphonylurea (glimepiride)



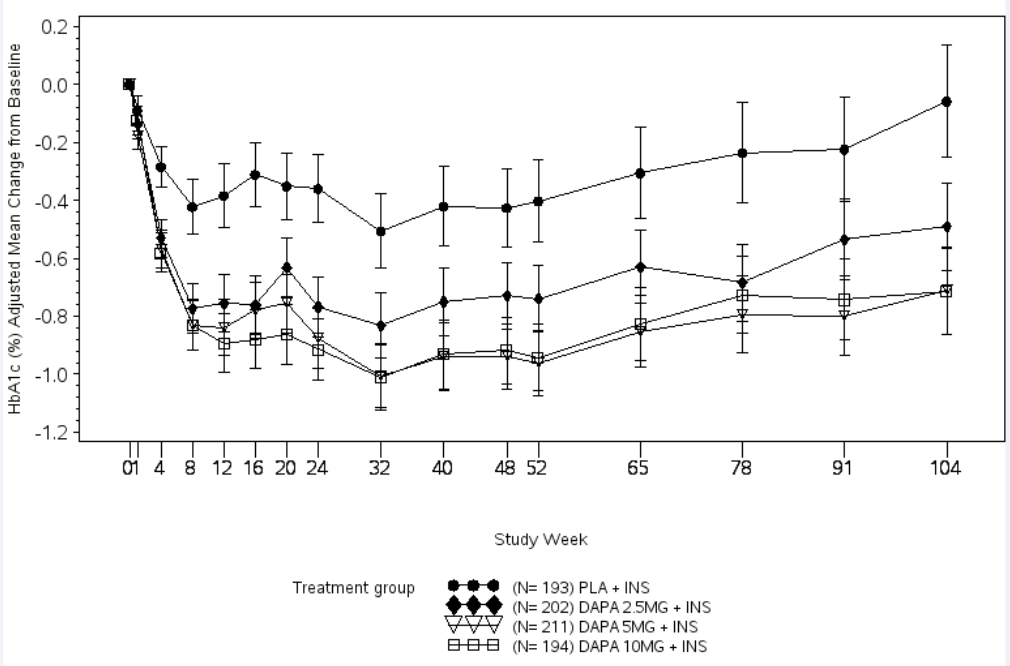
Error bars represent 95 % confidence intervals for the adjusted mean change from baseline.

Figure 8 Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24-week placebo-controlled study of DUFORZIG in combination with a thiazolidinedione (Pioglitazone)



Error bars represent 95 % confidence intervals for the adjusted mean change from baseline.

Figure 9 Adjusted mean change from baseline over time in HbA1c (%) in a 104-week placebo-controlled study of DUFORZIG in combination with insulin with or without up to 2 oral anti-diabetic therapies excluding data after insulin up-titration



Add-on to sitagliptin alone or in combination with metformin

A total of 452 patients with type 2 diabetes who were medicine naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycaemic control (HbA1c ≥ 7,0 % and ≤ 10,0 % at randomisation), participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate DUFORZIG in combination with sitagliptin (a DPP4 inhibitor) with or without metformin.

Eligible patients were stratified based on the presence or absence of background metformin (≥ 1 500 mg/day) and within each stratum were randomised to either DUFORZIG 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for

DUFORZIG 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37 %) of patients were medicine naive, 32 % were on metformin alone, 13 % were on a DPP4 inhibitor alone, and 18 % were on a DPP4 inhibitor plus metformin. Dose titration of DUFORZIG, sitagliptin or metformin was not permitted during the study.

In combination with sitagliptin (with and without metformin), DUFORZIG 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥ 8 %, and FPG, and significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at week 24 (Table 7). These improvements were also seen in the stratum of patients who received DUFORZIG 10 mg plus sitagliptin alone (n = 110) compared with placebo plus sitagliptin alone (n = 111), and the stratum of patients who received DUFORZIG 10 mg plus sitagliptin and metformin (n = 113) compared with placebo plus sitagliptin with metformin (n = 113) (Table 7).

At week 48, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥ 8 % at baseline, FPG, PPG, and body weight were −0,30 %, −0,72 %, −19,7 mg/dL, −43,0 mg/dL, and −2,03 kg, respectively, for patients treated with DUFORZIG 10 mg plus sitagliptin with or without metformin, and 0,38 %, 0,26 %, 13,5 mg/dL,−12,1 mg/dL, and 0,18 kg for patients treated with placebo plus sitagliptin with or without metformin based on the longitudinal repeated measures analysis excluding data after rescue. At week 48, for the stratum of patients without metformin, adjusted mean change from baseline in HbA1c for patients treated with DUFORZIG 10 mg plus sitagliptin was 0,00 % and placebo plus sitagliptin was 0,85 %; and for the stratum of patients with metformin, adjusted mean change from baseline in HbA1c for patients treated with DUFORZIG 10 mg plus sitagliptin was −0,44 % and placebo plus sitagliptin was 0,15 % based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients at week 24 and week 48 who were rescued or discontinued for lack of

glycaemic control (adjusted for baseline HbA1c) was higher for sitagliptin with or without metformin (40,5 % and 56,5 %, respectively) than for DUFORZIG plus sitagliptin with or without metformin (19,5 % and 32,6 %, respectively).

Table 7 Results of a 24-week (LOCF*) placebo-controlled study of DUFORZIG in add-on combination with sitagliptin with or without metformin (Full analysis set and strata without or with metformin)

Efficacy parameter	**DUFORZIG 10 mg + Sitagliptin + or – Met**	**Placebo + Sitaglipti n + or −Met**	**DUFORZI G 10 mg + Sitagliptin**	**Placebo + Sitaglipti n**	**DUFORZI G 10 mg + Sitagliptin +Met**	**Placebo + Sitagliptin + Met**
	N = 223†	N = 224†	N = 110†	N = 111†	N = 113†	N = 113†
HbA1c (%)						
Baseline (mean)	7,90	7,97	7,99	8,07	7,80	7,87
Change from baseline (adjusted mean‡)	−0,45	0,04	−0,47	0,10	−0,43	−0,02
Difference from placebo	−0,48§ (−0,62;		−0,56§ (−0,79;		−0,40§ (−0,58;	

(adjusted mean‡) (95 % CI)	−0,34)		−0,34)		−0,23)	
Change from baseline in HbA1c in patients with baseline HbA1c ≥ 8 % (adjusted mean‡)	−0,80§ (N= 94)	0,03 (N= 99)	−0,81§	0,06	−0,79§	0,0
FPG (mg/dL)						
Baseline (mean)	161,7	163,1	157,3	161,5	165,9	164,7
Change from baseline at Week 24 (adjusted mean‡)	−24,1	3,8	−22,0	4,6	−26,2	3,0
Difference	−27,9§		−26,6§		−29,2§	

from placebo (adjusted mean‡) (95 % CI)	(−34,5; −21,4)		(−36,3; −16,85)		(−38,0; −20,4)	
Body weight (kg)						
Baseline (mean)	91,02	89,23	88,01	84,20	93,95	94,17
Change from baseline (adjusted mean‡)	−2,14	−0,26	−1,91	−0,06	−2,35	−0,47
Difference from placebo (adjusted mean‡) (95 % CI)	−1,89§ (−2,37; −1,40)		−1,85§ (−2,47; −1,23)		−1,87§ (−2,61; −1,13)	
Seated SBP at week 8 in patients with						

baseline seated SBP ≥130 mmHg (mmHg)						
Baseline (mean)	140,5 (N=101)	139,3 (N=111)	138,5	137,9	141,9	140,3
Change from baseline (adjusted mean‡)	−6,0	−5,1	−6,6	−4,2	−5,3	−5,5
Difference from placebo (adjusted mean‡) (95 % CI)	−0,86 (−3,8; 2,0)		−2,4 (−6,4; 1,7)		0,2 (–3,85; 4,32)	
2-hour PPG¶ (mg/dL)						
Baseline (mean)	227,8	226,3	225,3	231,2	230,2	221,0
Change from baseline	−47,7	−4,8	−46,3	−2,6	−48,9	−7,2

(adjusted mean‡)						
Difference from placebo (adjusted mean‡) (95% CI)	−42,9 (−52,1; −33,8)		−43,7 (−55,9; −31,5)		−41,6 (−55,4; −27,8)	
Patients with HbA1c decrease ≥ 0,7 % (adjusted %)	35,3	16,6	42,8	17,2	28,0	16,0

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0,0001 *versus* placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Concomitant initiation of saxagliptin and DUFORZIG in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c ≥ 8 % and ≤ 12 %), participated in this 24-week randomised, double blind,

active comparator-controlled superiority trial to compare the combination of saxagliptin and DUFORZIG added concurrently to metformin, versus saxagliptin (DPP4 inhibitor) or DUFORZIG added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and DUFORZIG 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or DUFORZIG 10 mg and placebo added to metformin XR.

The saxagliptin and DUFORZIG combination group achieved significantly greater reductions in HbA1c versus either saxagliptin group or DUFORZIG group at 24 weeks. Forty-one percent (41 %) of patients in the saxagliptin and DUFORZIG combination group achieved HbA1c levels of less than 7 % compared to 18 % patients in the saxagliptin group and 22 % patients in the DUFORZIG group.

Table 8 HbA1c at week 24 (LRM*) in active-controlled study comparing the combination of saxagliptin and DUFORZIG added concurrently to metformin with saxagliptin or DUFORZIG added concurrently to metformin

Efficacy parameter	**Saxagliptin 5 mg + DUFORZIG 10 mg + Metformin XR N = 179†**	**Saxagliptin 5 mg + Metformin XR N = 176†**	**DUFORZIG 10 mg + Metformin XR N = 179†**
HbA1c (%) at week 24 (LRM)*			
Baseline (mean)	8,93	9,03	8,87
Change from baseline (adjusted mean‡) (95 % CI) for adjusted mean change	−1,47 (−1,62; −1,31)	−0,88 (−1,03; −0,72)	−1,20 (−1,35; −1,04)

from baseline			
Difference from saxagliptin + metformin (adjusted mean‡) (95 % CI)	−0,59§ (−0,81; −0,37)	-	-
Difference from DUFORZIG + metformin (adjusted mean‡) (95 % CI)	−0,27¶ (−0,48; −0,05)	-	-
* LRM = Longitudinal repeated measures (*using values prior to rescue)*. † Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement. ‡ Least squares mean adjusted for baseline value. § p-value < 0,0001. ¶ p-value = 0,0166.			

The adjusted mean change in body weight at 24 weeks was −2,05 kg (95 % CI [-2,52, -1,58]) in the saxagliptin and DUFORZIG plus metformin group and −2,39 kg (95 % CI [-2,87, -1,91]) in the DUFORZIG plus metformin group. The adjusted mean change for body weight in the saxagliptin plus metformin group had no change 0,00 kg (95 % CI [-0,48, 0,49]).

Add-on therapy with DUFORZIG in patients inadequately controlled on saxagliptin plus metformin:
A 24-week randomised, double-blind, placebo-controlled study compared the sequential addition of 10 mg DUFORZIG to 5 mg saxagliptin and metformin to the addition of placebo to 5 mg saxagliptin (DPP4 inhibitor) and metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 7 % and ≤ 10,5 %). 320 subjects were randomised equally into either the DUFORZIG added to saxagliptin plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group.

The group with DUFORZIG sequentially added to saxagliptin and metformin achieved statistically significant (p-value < 0,0001) greater reductions in HbA1c *versus* the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see Table 9).

Table 9 Results of a week 24 (LRM*) placebo-controlled study of DUFORZIG in add-on combination with saxagliptin and metformin

Efficacy parameter	**DUFORZIG 10 mg + Saxagliptin 5 mg + Metformin (N = 160)†**	**Placebo + Saxagliptin 5 mg + Metformin (N = 160)†**
HbA1c (%) at week 24*		
Baseline (mean)	8,24	8,16
Change from baseline (adjusted mean‡)	−0,82	−0,10
(95 % CI)	(−0,96; −0,69)	(−0,24; 0,04)
Comparison of DUFORZIG added to saxa + met *vs* placebo + saxa + met: Adjusted mean*		−0,72
(95 % CI)		(−0,91; −0,53)§
FPG (mg/dL)		
Baseline (mean)	178,5	176,6
Change from baseline (adjusted mean‡)	−32,7	−5,3
(95 % CI)	(−38,3; −27,2)	(−11,1; 0,6)
Comparison of DUFORZIG added to saxa + met *vs* placebo + saxa + met: Adjusted mean *		−27,5
(95 % CI)		(−35,4; −19,6)§

2-hour PPG¶ (mg/dL)		
Baseline (mean)	239,8	241,3
Change from baseline (adjusted mean‡)	−73,5	−38,0
(95 % CI)	(−81,5; −65,5)	(−46,1; −29,9)
Comparison of DUFORZIG added to saxa + met *vs* placebo + saxa + met: Adjusted mean¶		−35,5§
(95 % CI)		(−46,3; −24,7)

* LRM = Longitudinal repeated measures (using values prior to rescue).

† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

¶ LOCF: last observation (prior to rescue for rescued patients) carried forward.

§ p-value < 0,0001 *versus* placebo.

saxa=saxagliptin; met=metformin

The proportion of patients achieving HbA1c < 7,0 % at week 24 was higher in the DUFORZIG plus saxagliptin plus metformin group 38,0 % (95 % CI [30,9; 45,1]) compared to the placebo plus saxagliptin plus metformin group 12,4 % (95 % CI [7,0; 17,9]).

The adjusted changes from baseline at week 24 in body weight were −1,91 kg (95 % CI [−2,34; −1,48]), in the DUFORZIG plus saxagliptin plus metformin group and -0,41 kg (95 % CI [−0,86; −0,04]), in the placebo plus saxagliptin plus metformin group.

The effects in HbA1c, FPG and body weight observed at week 24 were sustained at week 52. Adjusted mean change from baseline in HbA1c, FPG, and body weight were −0,74 % (95 % CI

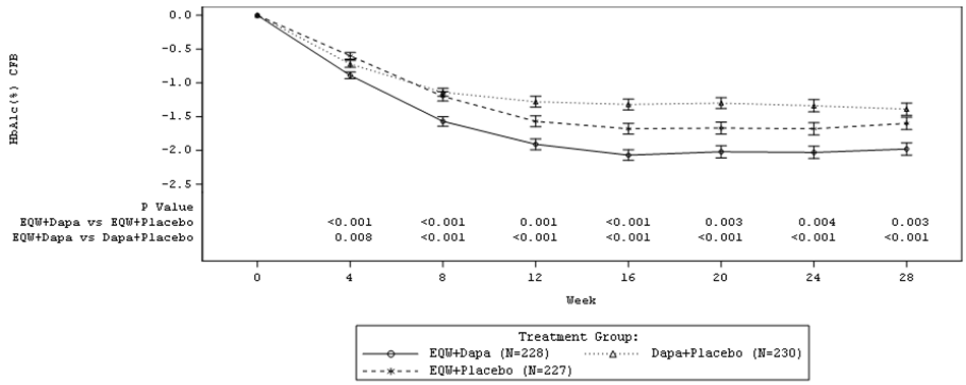
[−0,90; −0,57]), -26,8 mg/dL (95 % CI [-34,2; -19,4]) and –2,13 kg (95 % CI [-2,70; -1,56]), respectively, for patients treated with DUFORZIG 10 mg plus saxagliptin with metformin, and 0,07 % (95 % CI [−0,13; 0,27]), 10,2 mg/dL (95 % CI[1,6; 18,8]) and –0,37 kg (95 % CI [-1,01; 0,26]) for patients treated with placebo plus saxagliptin with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

Concomitant initiation of DUFORZIG and prolonged-release exenatide in patients inadequately controlled on metformin

A total of 694 adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥ 8,0 and ≤ 12,0 %) on metformin alone (≥ 1,500 mg/day) participated in this 28-week randomised, double blind, active- controlled trial to compare the concomitant initiation of DUFORZIG 10 mg QD and prolonged-release exenatide 2 mg QW (GLP-1 receptor agonist) on a background of metformin versus prolonged-release exenatide 2 mg QW alone and DUFORZIG 10 mg QD alone, when added to metformin. Following a 1-week placebo lead-in period, patients were randomised equally to one of three double-blind treatment groups to receive either DUFORZIG 10 mg and prolonged-release exenatide, DUFORZIG 10 mg and placebo or prolonged-release exenatide and placebo. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study. Randomisation was stratified by glycated haemoglobin A1c (HbA1c) at baseline (< 9,0 % or ≥ 9,0 %).

The primary endpoint was the change in HbA1c from baseline to week 28 (Figure 10). Compared to DUFORZIG 10 mg alone and to prolonged-release exenatide alone, concomitant initiation of DUFORZIG 10 mg and prolonged-release exenatide resulted in statistically significant reductions in HbA1c from baseline at week 28 (Table 10).

Figure 10 Change in HbA1c over time, LS mean (SE) – 28-week treatment period (Intent-to-treat analysis set)



CFB=change from baseline; EQW=exenatide 2 mg once weekly; Dapa=dapagliflozin 10 mg QD. Baseline is defined as week 0.

Table 10 Results of a 28-week active-controlled trial of DUFORZIG 10 mg and prolonged-release exenatide concomitant add-on to metformin

Efficacy parameter	**DUFORZIG 10 mg QD + Prolonged-release exenatide 2 mg QW**	**DUFORZIG 10 mg QD + Placebo QW**	**Prolonged-release exenatide 2 mg QW + Placebo QD**
Intent-to-treat population (N)[c]	**228**	**230**	**227**
HbA1c (%)			
Baseline (mean)	9,29	9,25	9,26
Change from baseline[a]	-1,98	-1,39	-1,60
Mean difference in change from baseline vs DUFORZIG	-0,59*		
(95 % CI)	(-0,84; -0,34)		
Mean difference in change from baseline vs Prolonged-release exenatide QW	-0,38**		

(95 % CI)	(-0,63; -0,13)		
Percent of patients achieving HbA1c < 7,0 %[b]	44,7 %	19,1 %	26,9 %
Body weight (kg)			
Baseline (mean)	92,13	90,87	89,12
Change from baseline[a]	-3,55	-2,22	-1,56
Mean difference in change from baseline vs DUFORZIG	-1,33*		
(95 % CI)	(-2,12; -0,55)		
Mean difference in change from baseline vs Prolonged-release exenatide (95 % CI)	-2,00* (-2,79; -1,20)		
Proportion of patients achieving weight loss ≥ 5,0 %[b]	33,3 %	20,0 %	13,7 %
Difference in proportion of patients vs DUFORZIG (%)	13,3**		
Difference in proportion of patients vs Prolonged-release exenatide (%)	19,7*		
FPG (mg/dL)			
Baseline (mean)	195,0	188,5	189,3
Change from baseline[a]	-65,8	-49,2	-45,8
Mean difference in change from baseline vs DUFORZIG	-16,64*		
(95 % CI)	(-24,39; -8,89)		
Mean difference in change from baseline vs Prolonged-release exenatide	-20,08*		

(95 % CI)	(-27,95; -12,20)		
2-hour PPG (mg/dL)			
Standard meal test population (n)	198	199	188
Baseline (mean)	268,5	261,5	266,1
Change from baseline[a]	-87,8	-61,1	-60,1
Mean difference in change from baseline vs DUFORZIG	-26,78*		
(95 % CI)	(-36,78; -16,78)		
Mean difference in change from baseline vs Prolonged-release exenatide	-27,74*		
(95 % CI)	(-37,89; -17,59)		
Seated systolic blood pressure (mmHg)			
Baseline (mean)	130,7	129,5	129,3
Change from baseline[a]	-4,3	-1,8	-1,2
Mean difference in change from baseline vs DUFORZIG	-2,4[#]		
(95 % CI)	(-4,5; -0,4)		
Mean difference in change from baseline vs Prolonged-release exenatide (95 % CI)	-3,0** (-5,2; -0,9)		

QD=once daily, QW=once weekly, N=number of patients in treatment group, CI=confidence interval.

[a] Adjusted least squares means (LS Means) and treatment group difference(s) 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, and

treatment by week interaction as fixed factors, and baseline value as a covariate.

[b] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c (< 9,0 % or ≥ 9,0 %). P-values are from the general association statistics.

[c] Patients who received at least 1 dose of study medicine and had at least 1 post-baseline HbA1c assessment.

*p < 0,001.

**p < 0,01.

#p < 0,05.

P values are all adjusted p-values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medicine, except for systolic blood pressure analysis, which includes measurements post rescue therapy but excludes data post premature discontinuation of study medicine discontinuation.

Concomitant initiation therapy of DUFORZIG 10 mg and prolonged-release exenatide resulted in a greater proportion of patients achieving HbA1c ≤ 6,5 % at week 28 (30,3 %) compared to DUFORZIG alone (10,4 %) and prolonged-release exenatide alone (18,5 %). The mean baseline HbA1c was 9,3 %.

Cardiovascular and renal outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of DUFORZIG compared with placebo on CV and renal outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional CV risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or

current tobacco use) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention). DECLARE was designed to ensure inclusion of a broad population.

Of 17 160 randomised patients, 6 974 (40,6 %) had established CV disease and 10 186 (59,4 %) did not have established CV disease. 8 582 patients were randomised to DUFORZIG 10 mg and 8 578 to placebo and were followed for a median of 4,2 years.

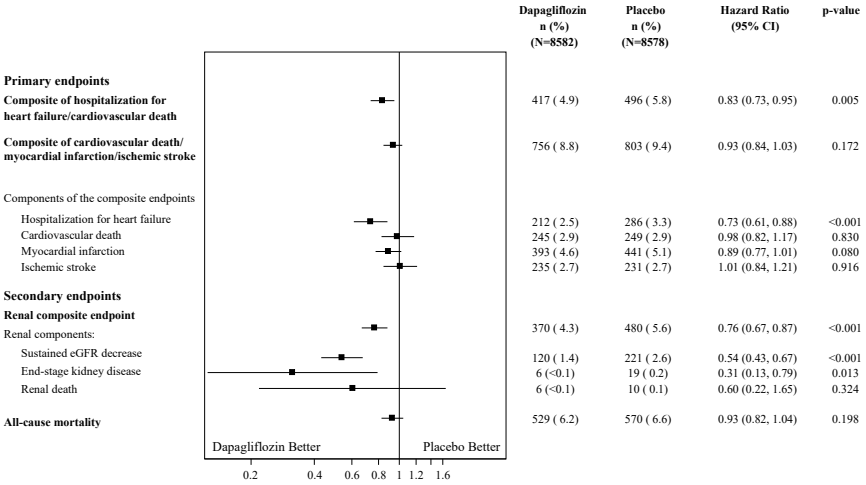
The mean age of the study population was 63,9 years, 37,4 % were female, 79,6 % were white, 3,5 % black or African American and 13,4 % Asian. In total, 22,4 % had had diabetes for ≤ 5 years, mean duration of diabetes was 11,9 years. Mean HbA1c was 8,3 % and mean BMI was 32,1 kg/m^2.
At baseline, 10,0 % of patients had a history of heart failure. Mean eGFR was 85,2 mL/min/1,73 m^2, 7,4 % of patients had eGFR <60mL/min/1,73 m^2 and 30,3 % of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥ 30 to ≤ 300 mg/g or >300 mg/g, respectively).

Most patients (98,1 %) used one or more diabetic medicines at baseline, 82,0 % of the patients were being treated with metformin, 40,9 % with insulin, 42,7 % with a sulphonylurea, 16,8 % with a DPP4 inhibitor, and 4,4 % with a GLP-1 agonist.

Approximately 81,3 % of patients were treated with ACE inhibitor or ARB, 75,0 % with statins, 61,1 % with antiplatelet therapy, 55,5 % with acetylsalicylic acid, 52,6 % with beta-blockers, 34,9 % with calcium channel blockers, 22,0 % with thiazide diuretics and 10,5 % with loop diuretics.

Results on primary and secondary endpoints are displayed in Figures 11 and 12.

Figure 11 Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components

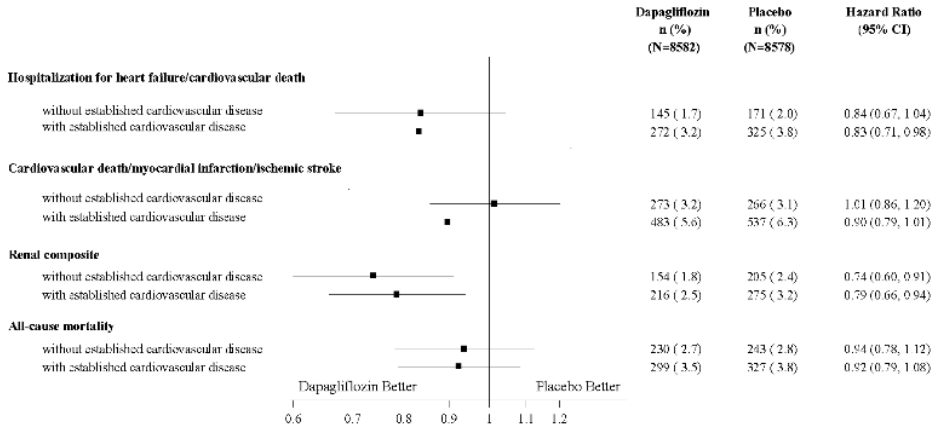


P-values are two-sided p-values for primary endpoints and nominal p-values for secondary endpoints and single components. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

Renal composite endpoint is defined as sustained confirmed ≥ 40 % decrease in eGFR to eGFR < 60 mL/min/1,73 m^2 and/or ESKD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1,73 m^2) and/or renal or CV death.

CI=confidence interval.

Figure 12 Treatment effects for the primary and secondary endpoints in patients with and without established CV disease



Renal composite defined as: sustained confirmed ≥ 40 % decrease in eGFR to eGFR < 60 mL/min/1,73 m^2 and/or ESKD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1,73 m^2) and/or renal or CV death. Time to first event was analysed in a Cox proportional hazards model.

CI=confidence interval

Heart failure or cardiovascular death

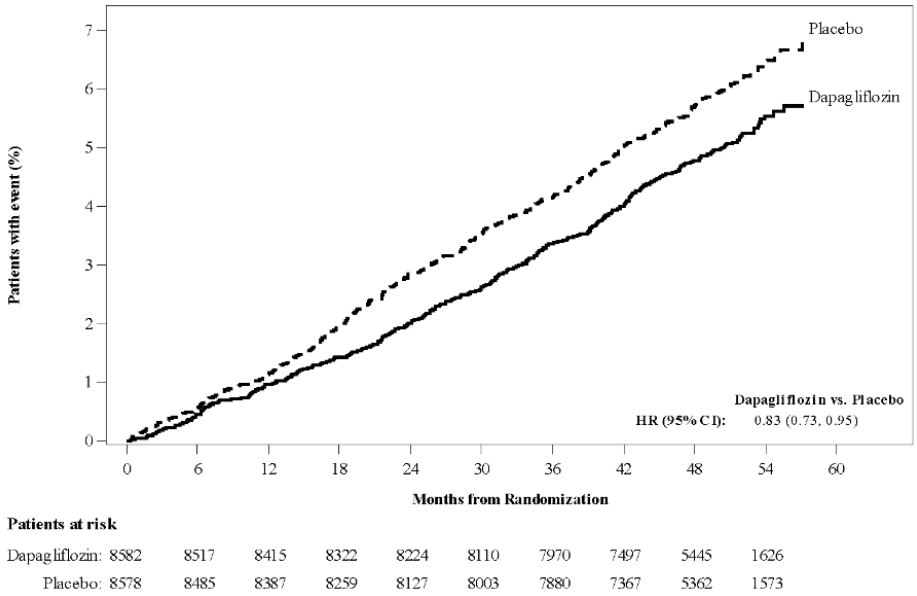
DUFORZIG 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalisation for heart failure or CV death (Hazard Ratio [HR] 0,83 [95 % CI 0,73; 0,95]; p = 0,005) (Figure 13).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalisation for heart failure (HR 0,73 [95 % CI 0,61; 0,88]) (Figure 11), with no clear difference in CV death (HR 0,98 [95 % CI 0,82 to 1,17]).

The treatment benefit of DUFORZIG over placebo was observed both in patients with and without established CV disease (Figure 12), with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

Figure 13 Time to first occurrence of hospitalisation for heart failure or cardiovascular

death



Patients at risk is the number of patients at risk at the beginning of the period.

CI Confidence interval, HR Hazard ratio.

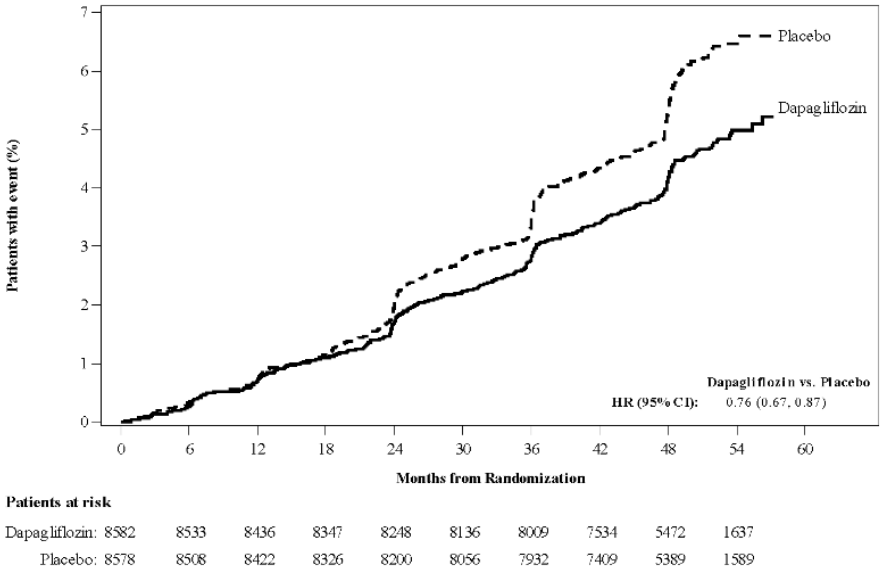
Major adverse cardiovascular events

DUFORZIG demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p < 0,001). There were numerically fewer MACE events in the DUFORZIG group compared with the placebo group (HR 0,93 [95 % CI 0,84; 1,03]; p = 0,172) (Figures 11 and 12).

Nephropathy

DUFORZIG reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESKD, renal or CV death (HR 0,76 [95 % CI 0,67; 0,87]; nominal p < 0,001, Figure 14). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESKD and renal death (Figure 11), and was observed both in patients with and without CV disease (Figure 12).

Figure 14 Time to first occurrence of sustained eGFR decrease, ESKD, renal or CV death



Patients at risk is the number of patients at risk at the beginning of the period.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥ 40 % to eGFR < 60 mL/min/1,73 m^2 and/or ESKD and/or renal or CV death.

CI Confidence interval; HR Hazard ratio.

When evaluating the renal components, there were 127 and 238 events of new or worsening nephropathy (sustained eGFR decrease, ESKD or renal death) in patients in the DUFORZIG and placebo groups, respectively. The HR for time to nephropathy was 0,53 (95 % CI 0,43; 0,66) for DUFORZIG versus placebo.

Beneficial effects of DUFORZIG on renal outcomes were also observed for albuminuria, e.g.

- In patients without pre-existing albuminuria, DUFORZIG reduced the incidence of sustained albuminuria (UACR > 30 mg/g) compared with placebo (HR 0,79 [95 % CI 0,72; 0,87], nominal p < 0,001).
- In patients without pre-existing macroalbuminuria, new onset of macroalbuminuria (UACR > 300 mg/g) was reduced in the [DUFORZIG group compared with the placebo group (HR 0,54 [95 % CI 0,45; 0,65], nominal p < 0,001).

- In patients with pre-existing macroalbuminuria, regression of macroalbuminuria was greater in the DUFORZIG group compared with the placebo group (HR 1,82 [95 % CI 1,51; 2,20], nominal p < 0,001).

The treatment benefit of DUFORZIG over placebo was observed both in patients with and without existing renal impairment.

Supportive studies

Dual energy X-ray absorptiometry in type 2 diabetic patients

Due to the mechanism of action of DUFORZIG, a study was done to evaluate body composition and bone mineral density in 182 patients with type 2 diabetes. Treatment with DUFORZIG 10 mg added on to metformin over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2,96 kg versus −0,88 kg); waist circumference (mean change from baseline: −2,51 cm versus −0,99 cm), and body-fat mass as measured by DXA (mean change from baseline: −2,22 kg versus −0,74 kg) rather than lean tissue or fluid loss. DUFORZIG plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (change from baseline: −322,6 cm^3 versus −8,7 cm^3) in an MRI sub-study. Week 24 was analysed using last observation carried forward (LOCF) analysis including data after rescue.

At week 24, 2 patients (2,2 %) in the placebo plus metformin group and no patients in the DUFORZIG 10 mg plus metformin group were rescued for lack of glycaemic control.

At week 50 and week 102, improvements were sustained in the DUFORZIG 10 mg added on to metformin group compared with the placebo plus metformin group for body weight (adjusted mean change from baseline at week 50: −4,39 kg versus −2,03 kg; adjusted mean change from baseline at week 102: −4,54 kg versus −2,12 kg), waist circumference (adjusted mean change from

baseline at week 50: −5,0 cm versus −3,0 cm; adjusted mean change from baseline at week 102: −5,0 cm versus −2,9 cm), and body-fat mass as measured by DXA at week 102 (mean change from baseline: −2,80 kg versus −1,46 kg) based on the longitudinal repeated measures analysis including data after rescue. In an MRI sub-study at weeks 50 and 102, DUFORZIG plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (adjusted mean change from baseline at week 50: −120,0 cm3 versus 61,5 cm^3; adjusted mean change from baseline at week 102: −214,9 cm^3 versus −22,3 cm^3).

The proportion of patients at week 50 (unadjusted for baseline HbA1c) and week 102 (adjusted for baseline HbA1c) who were rescued or discontinued for lack of glycaemic control was higher in the placebo plus metformin group (6,6 % and 33,2 %, respectively) than in the DUFORZIG 10 mg plus metformin group (2,2 % and 13,5 %, respectively).

In an extension of this study to week 50, there was no change in bone mineral density (BMD) for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean decrease from baseline for all anatomical regions < 0,5 %). There was also no change in BMD in either treatment group up to week 102 (mean decrease from baseline for all anatomical regions < 1,0 %). There were no clinically meaningful changes in markers of bone resorption or bone formation.

Clinical safety

Events related to decreased renal function:

In the 13 study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at week 1 (mean change from baseline: 0,041 mg/dL DUFORZIG 10 mg versus 0,008 mg/dL placebo) and decreased toward baseline by week 24 (mean change from baseline: 0,019 mg/dL DUFORZIG 10 mg versus 0,008 mg/dL placebo). There were no further changes through week 102.

In the CV outcomes study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and UACR in the DUFORZIG group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the DUFORZIG group compared with the placebo group: 422 (4,9 %) and 526 (6,1 %), respectively. There were fewer patients with events reported as acute kidney injury in the DUFORZIG group compared with the placebo group: 125 (1,5 %) and 175 (2,0 %), respectively. There were fewer patients with SAEs of renal events in the DUFORZIG group compared with the placebo group: 80 (0,9 %) and 136 (1,6 %), respectively.

Glycaemic control in special populations

Use in patients with type 2 diabetes and hypertension

In two 12-week, placebo-controlled studies, a total of 1 062 patients with inadequately controlled type 2 diabetes and hypertension were treated with DUFORZIG 10 mg or placebo. Patients with inadequately controlled hypertension (seated systolic blood pressure ≥ 140 and < 165 mmHg, seated diastolic blood pressure ≥ 85 and < 105 mmHg, and a 24-hour mean blood pressure of ≥ 130/80 mmHg) despite pre-existing stable treatment with an ACE inhibitor or ARB (alone [Study 1] or in combination with an additional antihypertensive [Study 2]) as well as inadequate glycaemic control (HbA1c ≥ 7,0 % and ≤ 10,5 %) despite pre-existing stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies. During the studies, no adjustments in antidiabetic and antihypertensive medicines were allowed. Across the 2 studies, 527 patients were treated with DUFORZIG 10 mg and 535 with placebo. Patients treated with DUFORZIG 10 mg or placebo also received the following medicines for blood pressure control, which were balanced between treatment groups: ACE inhibitors (64 %), ARBs (36 %), thiazide diuretics (16 %), calcium channel blockers (9 %), and beta-blockers (6 %).

At week 12 for both studies, DUFORZIG 10 mg plus usual treatment provided significant

improvement in HbA1c and significant reduction in seated systolic blood pressure compared with placebo plus usual treatment (see Table 11). Consistent reductions were seen in mean 24-hour ambulatory systolic blood pressure in patients treated with DUFORZIG 10 mg treatment compared with placebo. There was a small reduction in mean seated diastolic blood pressure in patients treated with DUFORZIG 10 mg that was not statistically significant compared with placebo.

Table 11 Results at week 12 in 2 placebo-controlled studies of DUFORZIG in patients with type 2 diabetes and hypertension

Efficacy parameter	**DUFORZIG 10 mg + usual treatment**	**Placebo + usual treatment**	**DUFORZIG 10 mg + usual treatment**	**Placebo + usual treatment**
	N = 302†	**N = 311†**	**N = 225†**	**N = 224†**
HbA1c (%) (LRM)*				
Baseline (mean)	8,1	8,0	8,1	8,0
Change from baseline (adjusted mean‡)	−0,6	−0,1	−0,6	0,0
Difference from placebo (adjusted mean‡)	−0,5§		−0,6§	
(95 % CI)	(−0,6; −0,3)		(−0,8; −0,5)	
Seated systolic blood pressure (mmHg) (LRM)*				
Baseline (mean)	149,8	149,5	151,0	151,3
Change from baseline (adjusted mean‡)	−10,4	−7,3	−11,9	−7,6
Difference from placebo	−3,1¶		−4,3¶	

(adjusted mean‡)				
(95 % CI)	(−4,9; −1,2)		(−6,5; −2,0)	

* LRM: longitudinal repeated measures analysis.

† All randomised patients who took at least one dose of double-blind study medicines during the short-term, double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value < 0,0001.

¶ p-value < 0,05.

Use in patients with type 2 diabetes and cardiovascular disease

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1 887 patients with type 2 diabetes and CVD were treated with DUFORZIG 10 mg or placebo.

Patients with established CVD and inadequate glycaemic control (HbA1c ≥ 7,0 % and ≤ 10,0 %), despite pre-existing, stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (< 65 years or ≥ 65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (> 1 year or < 1 year prior to enrolment). Across the 2 studies, 942 patients were treated with DUFORZIG 10 mg and 945 with placebo. Ninety-six percent (96 %) of patients treated with DUFORZIG 10 mg across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying cardiovascular events were coronary heart disease (75 %) or stroke (22 %). Approximately 19 % of patients received loop diuretics at entry and 15 % had congestive heart failure (2 % had NYHA Class III). Approximately 37 % of patients treated with DUFORZIG 10 mg also received metformin plus one additional OAD (sulphonylurea, thiazolidinedione, DPP4[-] inhibitor, or other OAD with or without insulin at entry), 38 % received insulin plus at least one OAD, and 18 % received insulin alone.

At week 24 for both studies, when added to pre-existing antidiabetic treatments, treatment with DUFORZIG 10 mg provided significant improvement to coprimary endpoints of HbA1c and composite clinical benefit compared with placebo. Composite clinical benefit was defined as the proportion of patients with an absolute drop from baseline of 0,5 % in HbA1c, and a relative drop from baseline of at least 3 % in total body weight, and an absolute drop from baseline of at least 3 mmHg in seated SBP (Table 12). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with DUFORZIG 10 mg compared with placebo.

At week 52 and week 104 for study 1, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0,44 % and −0,41 %, −3,40 mmHg and −2,64 mmHg, and −2,89 % and −3,53 %, respectively, for patients treated with DUFORZIG 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0,22 % and 0,50 %, 0,18 mmHg and 1,54 mmHg, and −0,29 % and −0,02 %. At week 52 and week 104, percent composite clinical benefit was still higher in the DUFORZIG 10 mg group (6,6 % and 3,8 %) than in the placebo group (0,7 % and 0,5 %).

At week 24, week 52, and week 104 for study 1, the proportion of patients who were rescued for lack of glycaemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (24,0 %, 51,8 %, and 57,3 %, respectively) than in the DUFORZIG 10 mg plus usual treatment group (7,9 %; 24,6 %, and 31,8 %, respectively).

At week 52 and week 104 for study 2, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0,47 % and −0,37 %, −3,56 mmHg and −1,96 mmHg, and −3,20 % and −3,51 %, respectively, for patients treated with DUFORZIG 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0,03

% and −0,18 %, −0,91 mmHg and −0,37 mmHg, and −1,12 % and −0,65 %. At week 52 and week 104, percent composite clinical benefit was still higher in the DUFORZIG 10 mg group (10,6 % and 4,2 %) than in the placebo group (3,1 % and 1,1 %).

At week 24, week 52, and week 104 for Study 2, the proportion of patients who were rescued for lack of glycaemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (22,3 %, 43,6 %, and 50,5 %, respectively) than in the DUFORZIG 10 mg plus usual treatment group (7,6 %, 18,7 % and 27,5 %, respectively).

Table 12 Results at week 24 (LOCF*) in two placebo-controlled studies comparing DUFORZIG to placebo in patients with type 2 diabetes and cardiovascular disease

	Study 1		**Study 2**	
Efficacy parameter	**DUFORZIG 10 mg + usual treatment**	**PLACEBO + usual treatment**	**DUFORZIG 10 mg + usual treatment**	**PLACEBO + usual treatment**
	N = 455†	**N = 459†**	**N = 480†**	**N = 482†**
HbA1c (%)				
Baseline mean	8,18	8,08	8,04	8,07
Change from baseline (adjusted mean‡)	−0,38	0,08	−0,33	0,07
Difference from placebo (adjusted mean‡) (95 % CI)	−0,46§ (−0,56; −0,37)		−0,40§ (−0,50; −0,30)	
Responders of Composite Clinical Benefit (%)	11,7	0,9	10,0	1,9
Difference from placebo	9,9§		7,0§	

(adjusted %)				
Components of composite endpoint (%)				
Patients with absolute reduction HbA1c ³ 0,5 % (adjusted %)	45,3	20,6	42,4	21,1
Patients with body weight decrease of at least 3 % from baseline (adjusted %)	40,0	13,9	41,3	15,4
Patients with absolute reduction in SBP ³ 3 mmHg (adjusted %)	49,1	41,6	46,1	40,9
Body weight (kg)				
Baseline mean	92,63	93,59	94,53	93,22
Change from baseline (adjusted percent‡)	−2,56	−0,30	−2,53	−0,61
Difference from placebo (adjusted percent‡) (95 % CI)	−2,27§ (−2,64; −1,89)		−1,93§ (−2,31; −1,54)	
Body weight decrease of at least 5 % in patients with baseline BMI ³ 27 kg/m^2 (%)	16,5§	4,0	18,4§	4,8
Seated systolic blood pressure (mmHg)				
Change from baseline at week 24 (adjusted mean‡)	−2,99	−1,03	−2,70	0,32

Difference from placebo (adjusted mean‡) (95 % CI)	−1,95¶ (−3,56; −0,34)		−3,02¶ (−4,59; −1,46)	
Change from baseline seated SBP (mmHg) at week 8 in patients with baseline SBP ³ 130 mmHg (adjusted mean‡)			−5,33¶	−1,89
* LOCF: last observation carried forward. † Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement. ‡ Least squares mean adjusted for baseline value. § p-value < 0,0001. ¶ p-value < 0,05.				

At week 24, patients treated with DUFORZIG 10 mg in the predefined age groups (< 65 and ≥ 65 years of age) also showed significant improvements in the coprimary endpoints of HbA1c and composite clinical benefit compared with placebo in both studies. A significant reduction in total body weight was also seen in both age groups and a significant reduction of seated SBP in patients < 65 years treated with DUFORZIG 10 mg compared with placebo at week 24. These effects were maintained at week 52 and week 104.

The safety profile of DUFORZIG in these studies was consistent with that of DUFORZIG in the general clinical study population through 104 weeks of treatment.

Use in patients with type 2 diabetes and renal impairment

Patients with mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1,73 m^2).

In the clinical trial programme more than 3 000 patients with mild renal impairment were treated

with dapagliflozin. Efficacy was assessed in a pooled analysis across 9 clinical studies consisting of 2 226 patients with mild renal impairment. The mean change from baseline in haemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was −1,03 % and −0,54 %, respectively, for DUFORZIG 10 mg (n = 562). The safety profile in patients with mild renal impairment is similar to that in the overall population.

Patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1,73 m^2)
The glycaemic efficacy and safety of DUFORZIG was evaluated in two dedicated studies of patients with moderate renal impairment and in two subgroup analyses of pooled clinical studies.

In a randomised, double blind, placebo-controlled trial a total of 321 adult patients with type 2 diabetes mellitus and eGFR ≥ 45 to < 60 mL/min/1,73 m^2 (moderate renal impairment subgroup CKD 3A), with inadequate glycaemic control on current treatment regimen, were treated with DUFORZIG 10 mg or placebo. At week 24, DUFORZIG 10 mg (n = 159) provided significant improvements in HbA1c, FPG, body weight and SBP compared with placebo (n = 161) (Table 13). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0,37 % and −0,34 %, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -21,46 mg/dL and -16,59 mg/dL, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3,42 % and -1,43 %, respectively. The mean reduction in seated systolic blood pressure (SBP) and the placebo-corrected mean reduction in SBP was -4,8 mmHg and -3,1 mmHg, respectively.

Table 13 Results at week 24 in a placebo-controlled study of DUFORZIG treatment in diabetic patients with moderate renal impairment (Class 3A, eGFR ≥ 45 to < 60 mL/min/1,73 m^2)

Efficacy parameter	DUFORZIG	Placebo

	10 mg N = 159	N = 161
HbA1c (%)		
Baseline (mean)	8,35	8,03
Change from baseline (adjusted mean*)	-0,37	-0,03
Difference from placebo (adjusted mean*) (95 % CI)	-0,34§ (-0,53; -0,15)	
FPG (mg/dL)		
Baseline (mean)	183,04	173,28
Change from baseline (adjusted mean*)	-21,46	-4,87
Difference from placebo (adjusted mean*) (95 % CI)	-16,59§ (-26,73; -6,45)	
Body weight (percentage)		
Baseline (mean)	92,51	88,30
% Change from baseline (adjusted mean*)	-3,42	-2,02
Difference from placebo (adjusted mean*) (95 % CI)	-1,43§ (-2,15; -0,69)	
Seated systolic blood pressure (mmHg)		
Baseline (mean)	135,7	135,0
Change from baseline (adjusted mean*)	-4,8	-1,7
Difference from placebo (adjusted mean*) (95 % CI)	-3,1¶ (-6,3; 0,0)	
* Least squares mean adjusted for baseline value. § p-value ≤ 0,001. ¶ p-value < 0,05.		

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes. Mean eGFR decreased initially during the treatment period in the dapagliflozin group and subsequently remained stable during the 24-week treatment period (DUFORZIG: -3,39 mL/min/1,73 m^2 and placebo: 0,90 mL/min/1,73 m^2). At 3 weeks after termination of DUFORZIG, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (DUFORZIG: 0,57 mL/min/1,73 m^2 and placebo: -0,04 mL/min/1,73 m^2).

Efficacy in patients with moderate renal impairment was assessed in a pooled analysis across 9 clinical studies (366 patients, 87 % with eGFR ≥ 45 to < 60 mL/min/1,73 m^2); this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was −0,87 % and −0,39 %, respectively, for DUFORZIG 10 mg (n = 85).

Safety in patients with moderate renal impairment was assessed in a pooled analysis of 12 clinical studies (384 patients, 88 % with eGFR ≥ 45 to < 60 mL/min/1,73 m^2); this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. At week 24, safety was similar to that seen in the overall program of clinical studies except for a higher proportion of patients reporting at least one event related to renal impairment or failure (7,9 % DUFORZIG 10 mg versus 5,6 % placebo). Of these events, increased serum creatinine was the most frequently reported (6,7 % DUFORZIG 10 mg versus 2,8 % placebo). Increases in mean parathyroid hormone (PTH) and serum phosphorus observed with DUFORZIG in the overall program of clinical studies were also seen in the pooled analysis. In the short-term plus long-term safety pool up to 102 weeks, the safety profile remained similar.

The efficacy and safety of [DUFORZIG was also assessed in a study of 252 diabetic patients with eGFR ≥ 30 to < 60 mL/min/1,73 m^2 (moderate renal impairment subgroup CKD 3A and CKD 3B).

DUFORZIG treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. In an additional analysis of the subgroup CKD 3A, DUFORZIG 10 mg (n=32) provided a placebo-corrected mean HbA1c change at 24 weeks of −0,33 %. At week 52, DUFORZIG was associated with changes from baseline in mean eGFR (DUFORZIG 10 mg −4,46 mL/min/1,73 m^2 and placebo −2,58 mL/min/1,73 m^2). At week 104, these changes persisted (eGFR: DUFORZIG 10 mg −3,50 mL/min/1,73 m^2 and placebo −2,38 mL/min/1,73 m^2). With DUFORZIG 10 mg, this eGFR reduction was evident at week 1 and remained stable through week 104, while placebo-treated patients had a slow continuous decline through week 52 that stabilized through week 104. At week 52 and persisting through week 104, greater increases in mean PTH and serum phosphorus were observed in this study with DUFORZIG 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of potassium of ≥ 6 mEq/L were more common in patients treated with placebo (12,0 %) than those treated with DUFORZIG 5 mg and 10 mg (4,8 % for both groups) during the cumulative 104-week treatment period. The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group (14,3 %) than for the DUFORZIG groups (6,9 % and 6,7 % for the 5 mg and 10 mg groups, respectively). Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to week 104 of which 8 occurred in the DUFORZIG 10 mg group, 5 occurred in the DUFORZIG 5 mg group, and none occurred in the placebo group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1,73 m^2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. No imbalance in bone fractures was observed in the safety analysis of the 12-study pool data and no bone fractures were reported in the dedicated study of patients with eGFR ≥ 45 to < 60 mL/min/1,73 m^2 (CKD 3A).

Use in elderly patients with type 2 diabetes

A total of 2 403 (26 %) of 9339 treated patients with type 2 diabetes mellitus were 65 years and older and 327 (3,5 %) patients were 75 years and older in a pool of 21 double-blind, controlled,

clinical studies of DUFORZIG assessing the safety and efficacy of DUFORZIG in improving glycaemic control. After controlling for level of renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. Overall, the proportion of patients reporting adverse events was consistent between those ≥ 65 and < 65 years of age.

Clinical trial information – heart failure

Clinical efficacy

DAPA-HF study: Heart failure with reduced left ventricular ejection fraction (LVEF ≤ 40 %)

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) was an international, multicentre, randomised, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40 %) to determine the effect of DUFORZIG compared with placebo, when added to background standard of care therapy, on the incidence of CV death and worsening heart failure.

Of 4 744 patients, 2 373 were randomised to DUFORZIG 10 mg and 2 371 to placebo and followed for a median of 18 months. The mean age of the study population was 66 years, 77 % were male, 70 % white, 5 % black or African American and 24 % Asian.

At baseline, 67,5 % patients were classified as NYHA class II, 31,6 % class III and 0,9 % class IV, median LVEF was 32 %, 42 % of the patients in each treatment group had a history of type 2 diabetes mellitus, and an additional 3 % of the patients in each group were classified as having type 2 diabetes mellitus based on a HbA1c ≥ 6,5 % at both enrolment and randomisation.

Patients were on standard of care therapy; 9 4% of patients were treated with ACE inhibitor, ARB,

or angiotensin receptor-neprilysin inhibitor (ARNI, 11 %), 96 % with beta-blocker, 71 % with mineralocorticoid receptor antagonist (MRA), 93 % with diuretic and 26 % had an implantable device (with defibrillator function).

Patients with eGFR ≥ 30 mL/min/1,73 m^2 at enrolment were included in the study. The mean eGFR was 66 mL/min/1,73 m^2, 41 % of patients had eGFR < 60mL/min/1,73 m^2 and 15 % had eGFR < 45 mL/min/1,73 m^2.

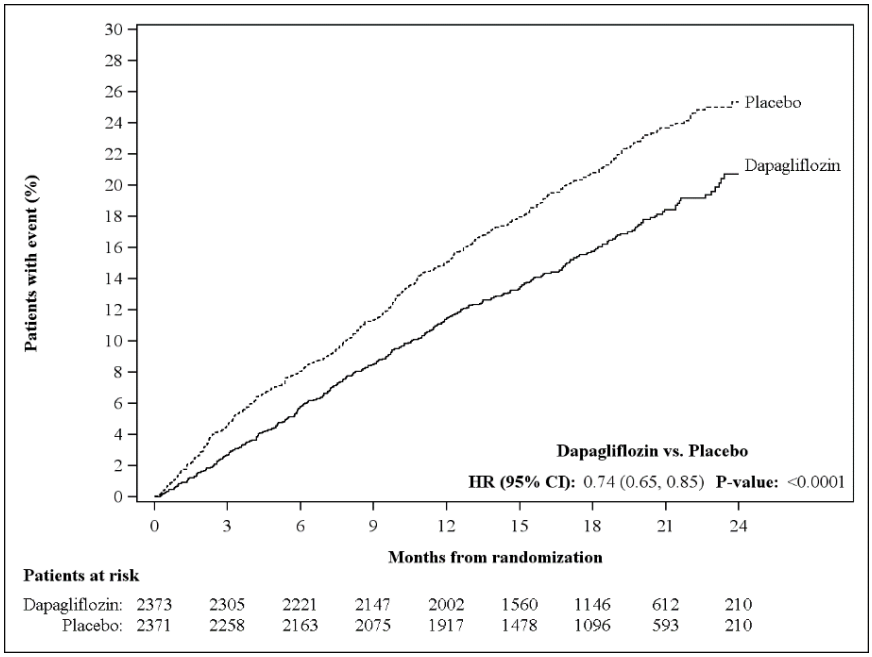
The DAPA-HF outcomes study compared DUFORZIG versus placebo in a population representative of that found in clinical practice. The overall study objective was to determine whether DUFORZIG prevents cardiovascular death and worsening heart failure, and if DUFORZIG improves heart failure symptoms.

Cardiovascular death and worsening heart failure

DUFORZIG 10 mg was superior to placebo in preventing CV death and worsening heart failure, with consistent treatment effect on primary and secondary endpoints.

DUFORZIG reduced the incidence of the primary composite endpoint of CV death, hospitalisation for heart failure or urgent heart failure visit (HR 0,74 [95 % CI 0,65; 0,85]; p < 0,0001). The number needed to treat per year was 26 (95 % CI 18, 46). The DUFORZIG and placebo event curves separated early and continued to diverge over the study period (Figure 15).

Figure 15 Time to first occurrence of the composite hospitalisation of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit

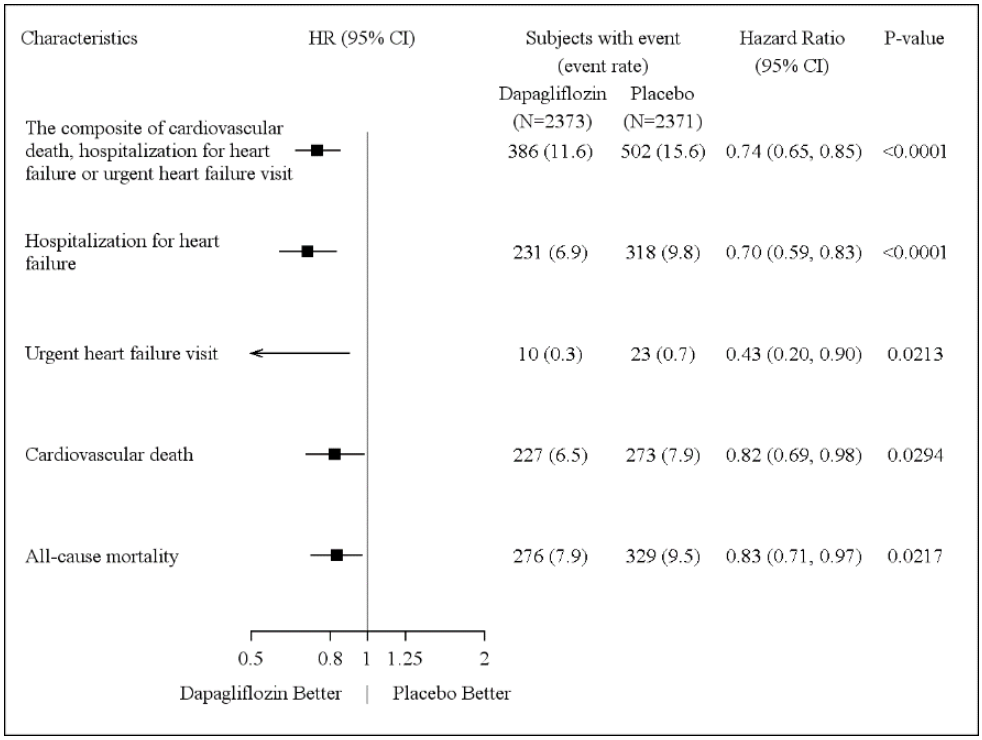


An urgent heart failure visit was defined as an urgent, unplanned, assessment by a medical practitioner, e.g. in an emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

Patients at risk is the number of patients at risk at the beginning of the period.

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 16). There were few urgent heart failure visits. DUFORZIG also reduced the incidence of cardiovascular death or hospitalisation for heart failure (HR 0,75 [95 % CI 0,65; 0,85], p < 0,0001).

Figure 16 Treatment effects for the primary composite endpoint, its components and all-cause mortality



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a medical practitioner, e.g. in an emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

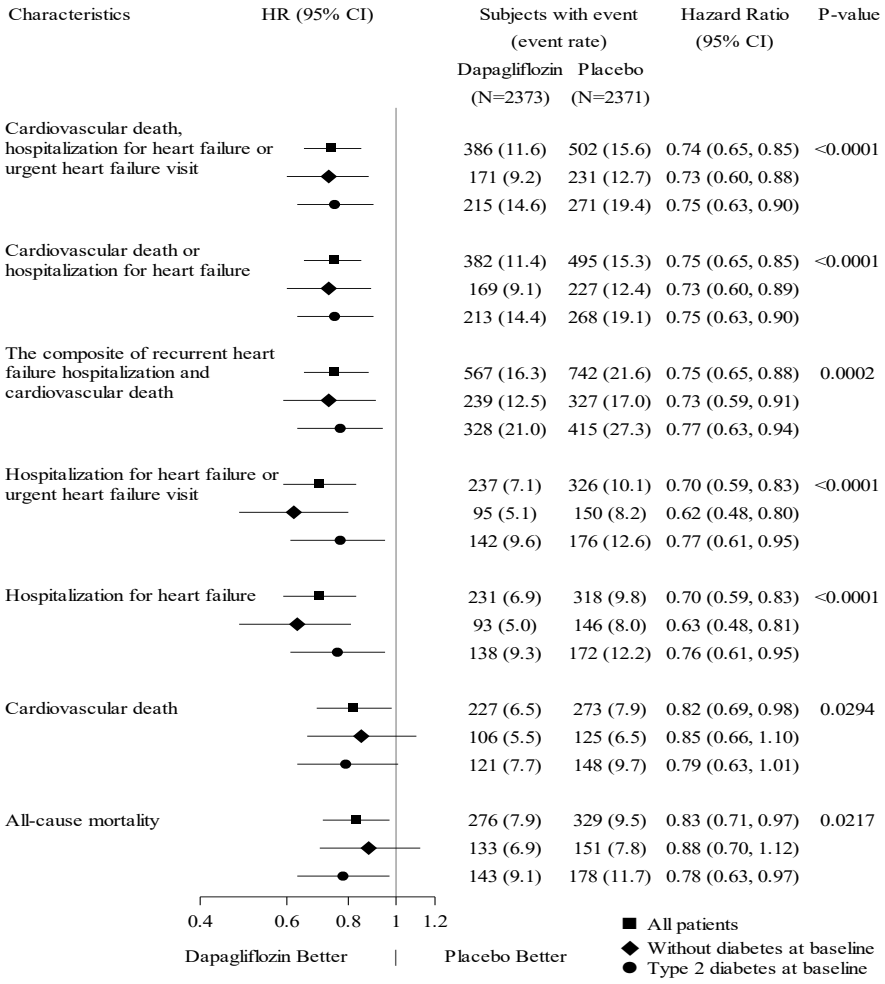
P-values for single components and all-cause mortality are nominal.

DUFORZIG also reduced the total number of events of hospitalisations for heart failure (first and recurrent) and cardiovascular death; there were 567 events in the DUFORZIG group versus 742 events in the placebo group (Rate Ratio 0,75 [95 % CI 0,65; 0,88]; p = 0,0002).

The treatment benefit of DUFORZIG was observed in heart failure patients both with type 2 diabetes mellitus and without diabetes (Figure 17).

Figure 17 Treatment effects in all patients, in patients with type 2 diabetes mellitus and in

patients without diabetes



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a medical practitioner, e.g. in an emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

For the composite of recurrent hospitalisations for heart failure and cardiovascular death, rate ratios are presented rather than hazard ratios and the numbers of events are shown rather than subjects with event.

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

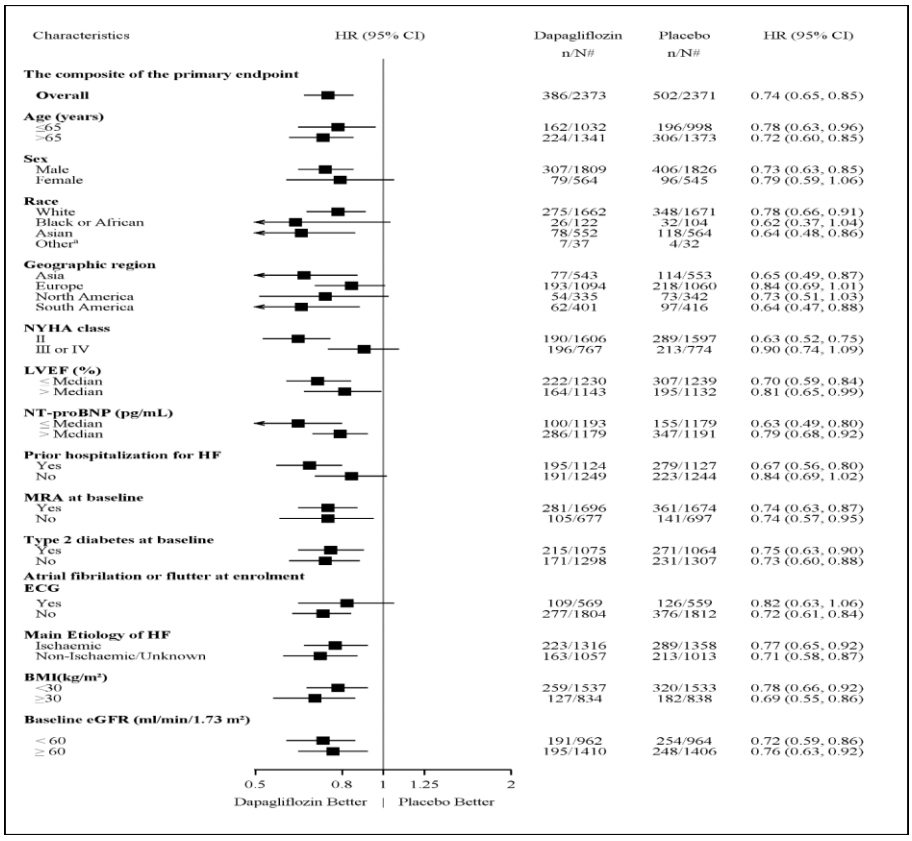
Event rates are presented as the number of subjects with event per 100 patient years of follow-up, or, for the composite of recurrent heart failure hospitalisations and CV death, as the average

number of events per 100 patient years.

P-values for components of the primary composite endpoint and for all-cause mortality are nominal.

The treatment benefit of DUFORZIG over placebo on the primary endpoint was also consistent across other key subgroups (Figure 18).

Figure 18 Treatment effects for the primary composite endpoint by sub-groups



[a] Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide. HF = Heart failure

Patient reported outcome – heart failure symptoms

The treatment effect of DUFORZIG on heart failure symptoms was assessed by the Total Symptom Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), which quantifies heart failure symptom frequency and severity, including fatigue, peripheral oedema, dyspnoea and orthopnoea. The score ranges from 0 to 100, with higher scores representing better health status. Treatment with DUFORZIG resulted in a statistically significant and clinically meaningful benefit over placebo in heart failure symptoms, as measured by change from baseline at month 8 in the KCCQ-TSS, (Win Ratio 1,18 [95 % CI 1,11; 1,26]; p < 0,0001). Both symptom frequency and symptom burden contributed to the results. Benefit was seen both in improving heart failure symptoms and in preventing deterioration of heart failure symptoms.

In responder analyses, the proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months, defined as 5 points or more, was higher for the DUFORZIG treatment group compared with placebo. The proportion of patients with a clinically meaningful deterioration, defined as 5 points or more, was lower for the DUFORZIG treatment group compared to placebo. The benefits observed with DUFORZIG remained when applying more conservative cut-offs for larger clinically meaningful change (Table 14).

Table 14 Number and percent of patients with clinically meaningful improvement and deterioration on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	**Dapagliflozin 10 mg n[a] = 2086**	**Placebo N[a] = 2062**		
Improvement	**n (%) improved[b]**	**n (%) improved[b]**	**Odds ratio[c] (95% CI)**	**p-value[f]**
≥ 5 points (small improvement)	1 198 (57,4)	1 030 (50,0)	1,15 (1,08; 1,23)	< 0,0001

≥ 10 points (moderate to large improvement)	1 124 (53,9)	968 (46,9)	1,15 (1,08; 1,22)	< 0,0001
≥ 15 points (large improvement)	1 120 (53,7)	984 (47,7)	1,14 (1,07;1,22)	< 0,0001
Deterioration	**n (%) deteriorated[d]**	**n (%) deteriorated[d]**	**Odds ratio[e] (95% CI)**	**p-value[f]**
≥ 5 points (small deterioration)	524 (25,1)	682 (33,1)	0,84 (0,78; 0,90)	< 0,0001
≥ 10 points (moderate to large deterioration)	385 (18,5)	495 (24,0)	0,85 (0,79; 0,92)	< 0,0001

[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months.

[b] Number of patients who had an observed improvement of at least 5, 10 or 15 points from baseline. Patients who died prior to the given timepoint are counted as not improved. Patients with a KCCQ-TSS at baseline which was too high for them to experience an improvement were defined as improved if they remained there at 8 months.

[c] For improvement, an odds ratio > 1 favours dapagliflozin 10 mg.

[d] Number of patients who had an observed deterioration of at least 5 or 10 points from baseline. Patients who died prior to the given timepoint are counted as deteriorated. Patients with a KCCQ-TSS at baseline which was too low for them to experience a deterioration were defined as deteriorated if they remained there at 8 months.

[e] For deterioration, an odds ratio < 1 favours dapagliflozin 10 mg.

[f] p-values are nominal.

Nephropathy

There were 28 and 39 events of the composite of confirmed sustained ≥ 50 % eGFR decrease, ESKD, or renal death in patients in the DUFORZIG and placebo groups, respectively, (HR 0,71 [95

% CI 0,44; 1,16]).

All-cause mortality

The incidence of all-cause mortality was lower in the DUFORZIG treatment group compared with placebo (HR 0,83; [95 % CI 0,71; 0,97], Figure 16.

DELIVER study: Heart failure with left ventricular ejection fraction > 40 %

Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) was an international, multicentre, randomised, double-blind, placebo-controlled study in patients aged ≥ 40 years with heart failure (NYHA class II-IV) with LVEF > 40 % and evidence of structural heart disease to determine the effect of DUFORZIG compared with placebo on the incidence of CV death and worsening heart failure.

Of 6 263 patients, 3 131 were randomised to DUFORZIG 10 mg and 3 132 to placebo and followed for a median of 28 months. The study included 654 (10 %) subacute heart failure patients (defined as randomised during hospitalisation for heart failure or within 30 days of discharge).

The mean age of the study population was 72 years, 56 % were male, 71 % white, 3 % black or African American and 20 % Asian.

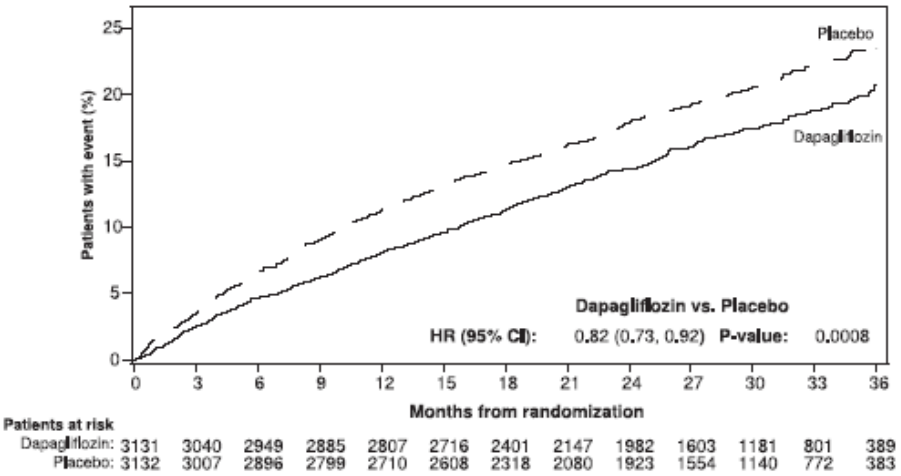
At baseline, 75 % patients were classified as NYHA class II, 24 % class III and 0,3 % class IV. Median LVEF was 54 %, 34 % of the patients had LVEF ≤ 49 %, 36 % had LVEF 50 – 59 % and 30 % had LVEF ≥ 60 %. In each treatment group, 45 % had a history of type 2 diabetes mellitus. Baseline therapy included ACE inhibitor/ARB/ARNI (77 %), beta-blockers (83 %) diuretics (98 %) and MRA (43 %).

Patients with eGFR ≥ 25 mL/min/1,73 m^2 at enrolment were included in the study. The mean eGFR

was 61 mL/min/1,73 m^2, 49 % of patients had eGFR < 60 mL/min/1,73 m^2, 23 % had eGFR < 45 mL/min/1,73 m^2, and 3 % had eGFR < 30 mL/min/1,73 m^2.

DUFORZIG was superior to placebo in reducing the incidence of the primary composite endpoint of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit (HR 0,82 [95 % CI 0,73; 0,92]; p=0,0008) (Figure 19).

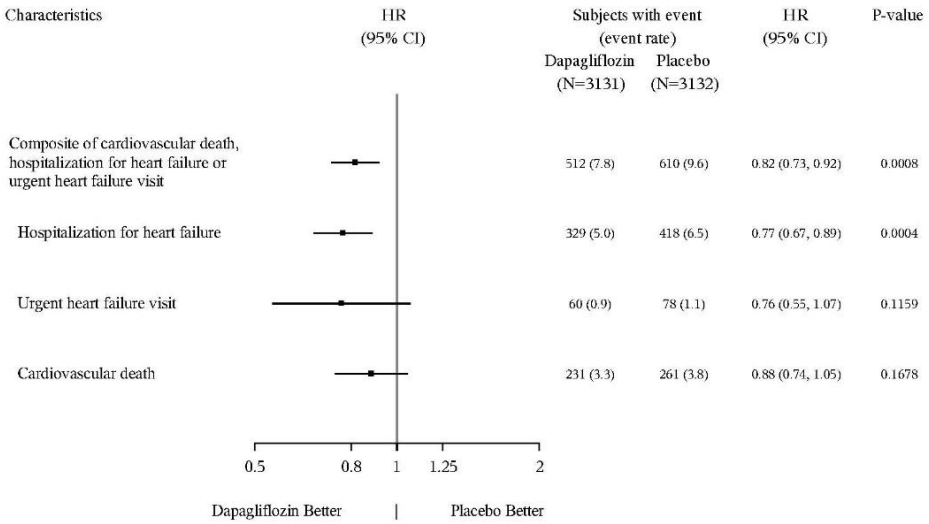
Figure 19 Time to first occurrence of the composite of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a medical practitioner, e.g. in an emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
Patients at risk is the number of patients at risk at the beginning of the period.

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 20).

Figure 20 Treatment effects for the primary composite endpoint and its components



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a medical practitioner, e.g. in an emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

DUFORZIG was superior to placebo in reducing the total number of heart failure events (first and recurrent hospitalisation for heart failure or urgent heart failure visits) and cardiovascular death; there were 815 events in the DUFORZIG group versus 1 057 events in the placebo group (Rate Ratio 0,77 [95 % CI 0,67; 0,89]; p=0,0003).

The treatment benefit of DUFORZIG over placebo on the primary endpoint was observed across subgroups of patients with LVEF ≤ 49 %, 50 – 59 %, and ≥ 60 %. Effects were also consistent across other key subgroups categorised by e.g. age, gender, NYHA class, NT-proBNP level, subacute status, and type 2 diabetes mellitus status.

Patient reported outcome – heart failure symptoms

Treatment with DUFORZIG resulted in a statistically significant benefit over placebo in heart failure

symptoms, as measured by change from baseline at Month 8 in the KCCQ-TSS, (Win ratio 1,11 [95 % CI 1,03; 1,21]; p=0,0086). Both symptom frequency and symptom burden contributed to the results.

In responder analyses, clinically meaningful deterioration, defined as 5 points or more, was lower for the DUFORZIG treatment group compared with placebo. The benefit observed with DUFORZIG remained when applying a more conservative cut-off. The proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months did not differ between treatment groups (Table 15).

Table 15 Number and percent of patients with clinically meaningful deterioration and improvement on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	**Dapagliflozin 10 mg n[a]=1316**	**Placebo n[a]=1311**		
Deterioration	**n (%) deteriorated[b]**	**n (%) deteriorated[b]**	**Odds ratio[c] (95 % CI)**	**p-value**
≥ 5 points (moderate deterioration)	264 (24,1)	317 (29,1)	0,78 (0,64, 0,95)	0,0127
≥ 14 points (large deterioration)	148 (13,5)	201 (18,4)	0,70 (0,55, 0,88)	0,0026
Improvement	**n (%) improved[d]**	**n (%) improved[d]**	**Odds ratio[e] (95 % CI)**	**p-value[f]**
≥ 13 points (small to moderate improvement)	531 (48,4)	498 (45,6)	1,13 (0,95, 1,33)	0,1608

≥ 17 points (large improvement)	486 (44,3)	478 (43,8)	1,06 (0,89, 1,26)	0,5137

[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months. Number includes patients with an 8-month assessment (Visit 5) planned or performed prior to 11 March 2020, when COVID-19 was declared a pandemic by the WHO. Data for patients with planned but not performed assessment prior to 11 March 2020 was imputed.

[b] Number of subjects who died prior to the given time point or had an observed deterioration from baseline equal to or exceeding the given threshold. Patients with a KCCQ-TSS at baseline which was too low to possibly experience a deterioration were defined as deteriorated if their score at 8 months was not higher than baseline.

[c] For deterioration, an odds ratio < 1 favours dapagliflozin 10 mg.

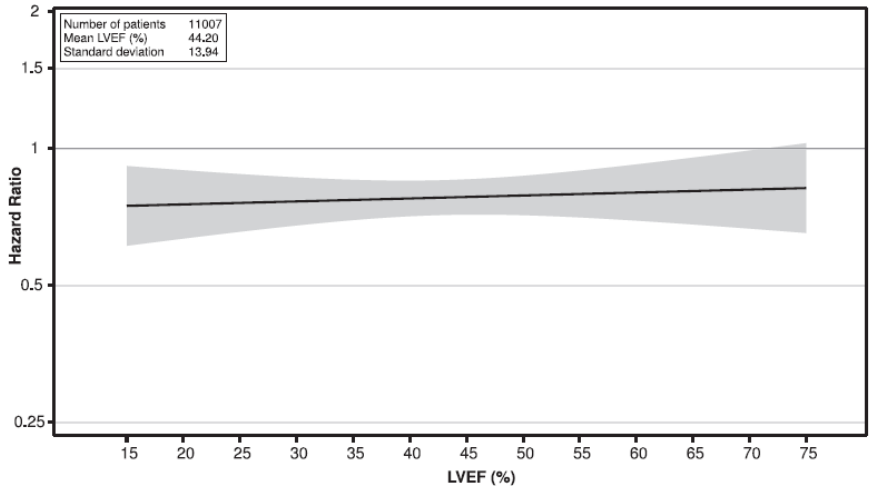
[d] Number of subjects who had an observed improvement of at least 13 or 17 points from baseline. Patients who died prior to the given timepoint are counted as not improved. Patients with a KCCQ-TSS at baseline which was too high to possibly experience an improvement were defined as improved if their score at 8 months was not lower than baseline.

[e] For improvement, an odds ratio > 1 favours dapagliflozin 10 mg.

Heart failure across DAPA-HF and DELIVER studies

In a pooled analysis of DAPA-HF and DELIVER, the treatment effect of DUFORZIG on the composite endpoint of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit was consistent across the LVEF range (Figure 22).

Figure 22 Treatment effect for the primary composite endpoint (cardiovascular death, hospitalisation for heart failure or urgent heart failure visit) by baseline LVEF

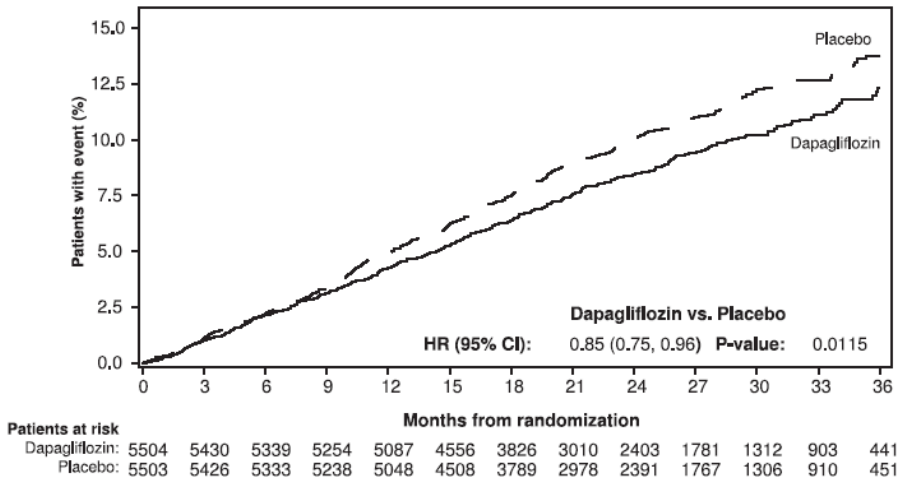


Definitions of the primary endpoints from each study are used. In DAPA-HF the primary endpoint included death with undetermined cause of death. In DELIVER the primary endpoint did not include death with undetermined cause of death.

Data for LVEF between 15 % and 75 % are presented in the figure. At baseline, 0,5 % of patients had LVEF < 15 % and 0,7 % had LVEF > 75 %.

In a pre-specified subject level pooled analysis of the DAPA-HF and DELIVER studies, DUFORZIG compared with placebo reduced the risk of cardiovascular death (HR 0,85 [95 % CI 0,75; 0,96], p=0,0115) (Figure 23). Both studies contributed to the effect.

Figure 23 Time to first occurrence of cardiovascular death (pooled analysis of DAPA-HF and DELIVER studies)



Definitions of CV death from each study is used. In DAPA-HF, CV death included death with undetermined cause of death. In DELIVER, CV death did not include death with undetermined cause of death.

Patients at risk is the number of patients at risk at the beginning of the period.

Clinical trial information - chronic kidney disease

Clinical efficacy

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD) was an international, multicentre, event-driven, randomised, double-blind, parallel-group, placebo-controlled study comparing DUFORZIG with placebo, when added to background standard of care therapy, in chronic kidney disease (CKD) patients with eGFR ≥ 25 to ≤ 75 mL/min/1,73 m^2 and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5 000 mg/g). The primary objective was to determine the effect of DUFORZIG compared with placebo in reducing the incidence of the composite endpoint of ≥ 50 % sustained decline in eGFR, end stage kidney disease (ESKD) (defined as sustained eGFR < 15 mL/min/1,73 m^2, chronic dialysis treatment or receiving a renal transplant), CV or renal death.

A total of 4 304 patients were randomised to DUFORZIG 10 mg (N = 2 152) or placebo (N = 2152)

once daily and followed for a median of 28,5 months. Treatment was continued if eGFR fell to levels below 25 mL/min/1,73 m^2 during the study and could be continued in cases when dialysis was needed.

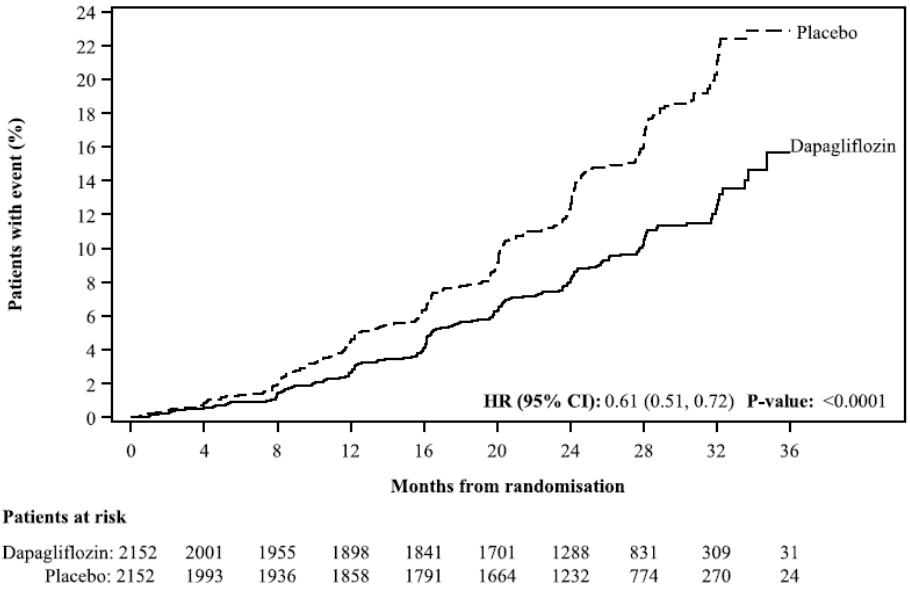
At baseline, mean eGFR was 43,1 mL/min/1,73 m^2 and median UACR was 949,3 mg/g, 44,1 % of patients had eGFR 30 to < 45 mL/min/1,73 m^2 and 14,5 % had eGFR < 30 mL/min/1,73 m^2. 67,5 % of the patients had type 2 diabetes mellitus.

Patients were on standard of care (SOC) therapy; 97,0 % of patients were treated with an angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker (ARB).

The mean age of the study population was 61,8 years, 66,9 % were male, 53,2 % white, 4,4 % black or African American, and 34,1 % Asian.

DUFORZIG was superior to placebo in reducing the incidence of the primary composite endpoint of ≥ 50 % sustained decline in eGFR, reaching ESKD, CV or renal death (HR 0,61 [95 % CI 0,51; 0,72]; p < 0,0001). The number needed to treat per 27 months was 19 (95 % CI 15, 27). Based on the Kaplan-Meier plot, the DUFORZIG and placebo event curves began to separate early (4 months) and continued to diverge over the study period (Figure 24).

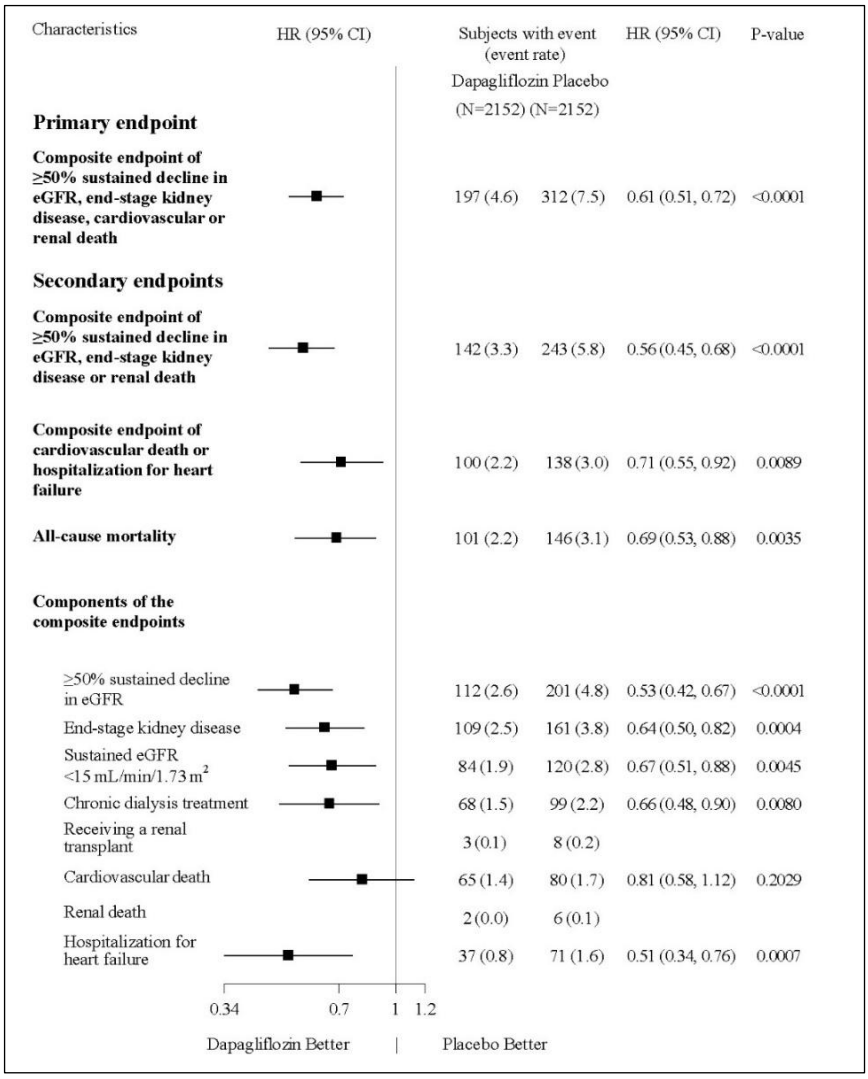
Figure 24 Time to first occurrence of the primary composite endpoint, ≥ 50 % sustained decline in eGFR, ESKD, CV or renal death



Patients at risk is the number of patients at risk at the beginning of the period.

All four components of the primary composite endpoint individually contributed to the treatment effect (Figure 25). DUFORZIG also reduced the incidence of the composite endpoint of ≥ 50 % sustained decline in eGFR, ESKD or renal death (HR 0,56 [95 % CI 0,45; 0,68]; p < 0,0001), the composite endpoint of CV death and hospitalisation for heart failure (HR 0,71 [95 % CI 0,55; 0,92], p = 0,0089), and all-cause mortality (HR 0,69 [95 % CI 0,53; 0,88], p = 0,0035).

Figure 25 Treatment effects for the primary and secondary composite endpoints, their individual components, and all-cause mortality



The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

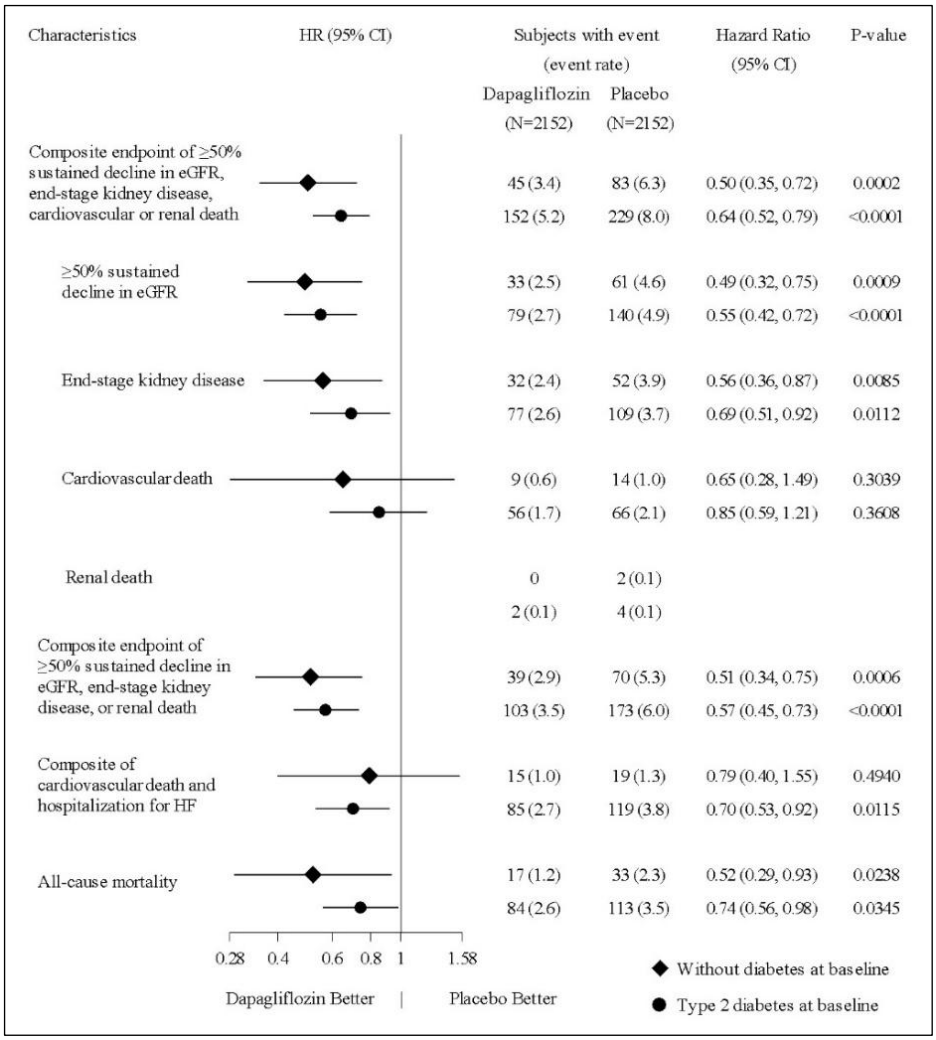
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

P-values for components of the composite endpoints are nominal.

The treatment effect of DUFORZIG was consistent in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes (Figure 26).

Figure 26 Treatment effects in patients with type 2 diabetes mellitus and in patients without diabetes



The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

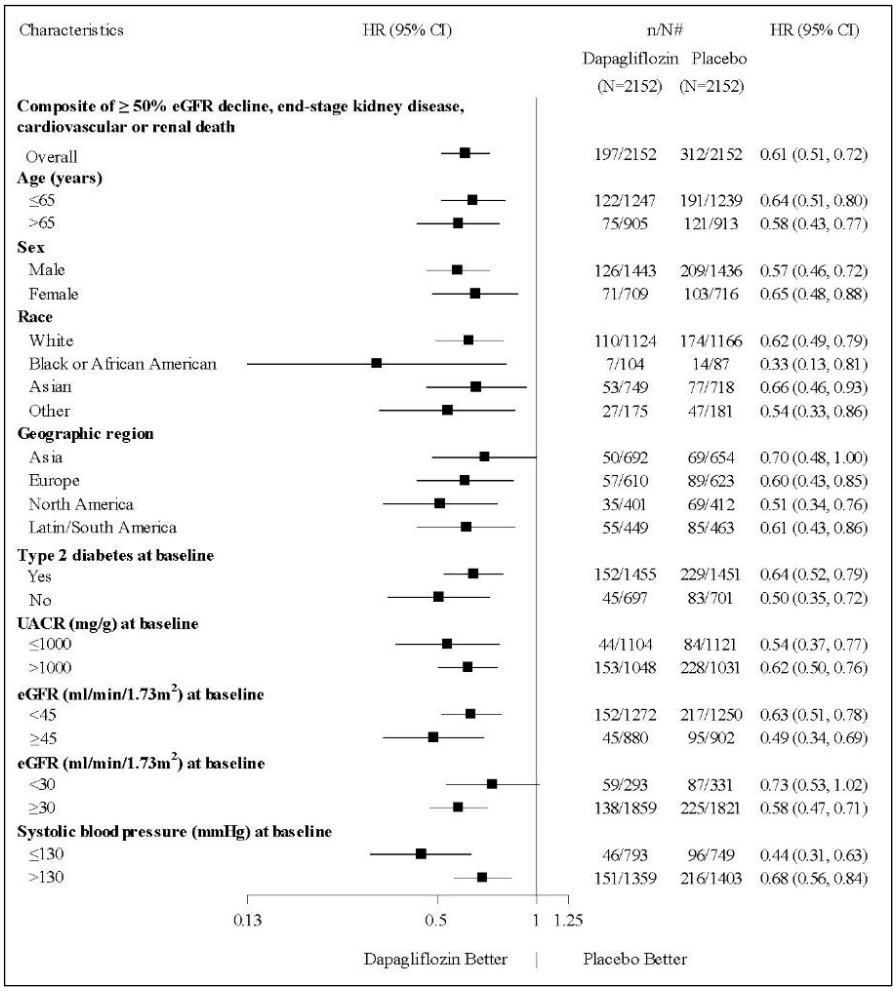
Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

P-values are nominal.

The treatment benefit of DUFORZIG over placebo on the primary composite endpoint was consistent across key subgroups (Figure 27).

Figure 27 Treatment effects for the primary composite endpoint by sub-groups



n/N# Number of subjects with event/number of subjects in the subgroup.

The treatment benefit of DUFORZIG was also observed for exploratory endpoints;

- A greater reduction in UACR was demonstrated for DUFORZIG compared with placebo. The effect was observed as early as 14 days and was maintained throughout the study. At 36 months, the adjusted mean percent change from baseline in UACR (mg/g) was 41 % in patients treated with DUFORZIG and 20 % in patients treated with placebo, with a difference between treatment groups of 26,3 % ([95 % CI 36,8; 14,0], nominal p = 0,0001).
- The incidence of doubling of serum creatinine since the most recent laboratory measurement

(an evaluation of acute worsening in kidney function), was reduced in the DUFORZIG group compared with the placebo group (HR 0,68 [95 % CI 0,49; 0,94], nominal p = 0,0187).

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50 % and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Biotransformation

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12,9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O- glucuronide accounted for 61 % of a 50 mg [^{14}C]- dapagliflozin dose and was the predominant medicine-related component in human plasma, accounting for 42 % [based on $AUC_{(0\text{-}12\ h)}$] of total plasma radioactivity, similar to

the 39 % contribution by parent compound. No other metabolite accounted for > 5 % of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism was a minor clearance pathway in humans.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent compound.

Special population

Renal impairment

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin that were 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin

exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

Hepatic impairment

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see section 4.4).

Age

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥ 18 to < 40 years [n = 105] and elderly: ≥ 65 years [n = 224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥ 40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10,4 % lower than in the reference group [90 % CI: 87,9; 92,2 %] and 25 % higher in elderly patients compared to the

reference group [90 % CI: 123; 129 %]. These differences in systemic exposure were considered not to be clinically meaningful.

Paediatric and adolescent

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Body weight

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥ 120 kg, n = 91) were estimated to be 78,3% [90 % CI: 78,2; 83,2 %] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥ 120 kg) is recommended.

Subjects with low body weights (< 50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29 % higher than subjects with the reference group body weight. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (< 50 kg) is recommended.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0,5, 2, and 10 mg/kg/day for both

males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72 × (males) and 105 × (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131 × (males) and 186 × (females) the human AUC at the MRHD.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an *in vitro* clastogenicity assay, but only in the presence of S9 activation and at concentrations ≥ 100 µg/mL. Importantly, dapagliflozin was negative for clastogenicity *in vivo* in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples > 2 100 × the human exposure at the MRHD. These studies, along with the absence of tumour findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days), and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤ 1 708 × and 998 × the MRHD in males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

Teratogenicity and impairment of early development

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15× the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of prenatal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups). Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1 415 × and 137 ×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 × the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19 × the human value at the MRHD.

In additional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1 191× the MRHD. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at doses up to 75 mg/kg/day (1 441× the MRHD). Doses ≥ 150 mg/kg/day (≥ 2 344× the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal

toxicity included mortality, adverse clinical signs, and decrements in body weight and food consumption. Developmental toxicity consisted of increased embryo-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centra, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Animal toxicology

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose, and included decreases in body weights and/or body weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤ 25 mg/kg/day (≥ 346 × the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥ 3 200 × the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than, or approximately equal to, anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium) was only observed at high-exposure multiples (≥ 2 100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥ 3 200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12 month dog study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Crospovidone

Lactose anhydrous

Magnesium stearate

Microcrystalline cellulose

Silicon dioxide.

Film-coating

Hydrolysed polyvinyl alcohol

Titanium dioxide

Polyethylene glycol

Talc

Iron oxide yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months Bristol-Myers Squibb

36 months AstraZeneca Pharmaceuticals

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Silver aluminium/aluminium foil blister packs of 14, 28, 30, 90 and 98 tablets packed in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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AstraZeneca Logo

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