London New Drugs Group
APC / DTC Briefing Document

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DAPAGLIFLOZIN

Contents

Produced for the
London New Drugs Group by:

Alexandra Denby,
Regional MI Manager
Medicines Information Service
Northwick Park Hospital
Middlesex
HA1 3UJ

Tel: 020 8869 3551
nwlh-tr.medinfo@nhs.net

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Summary

The drug and the review

- Dapagliflozin is a competitive, reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2), in the proximal convoluted tubule. It reduces glucose reabsorption by the kidneys and increases urinary glucose excretion.
- In November 2012 dapagliflozin (Forxiga) was launched in the UK for type 2 diabetes mellitus. Dapagliflozin 10mg is indicated for use in adults for, a) monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance, and b) in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- This review evaluates the clinical trials submitted for the licensing application.

Background

- The prevalence of type 2 diabetes varies according to factors such as ethnic group and degree of social deprivation. For example, in the general population, the prevalence is 3.4 to 4.3% in women and men ≥55 years of age. However, higher a prevalence is see in Black patients of Caribbean origin (8.4 to 10%), and Indian patients (5.9 to 10.1%), but a lower prevalence is seen in Chinese patients (3.3 to 3.8%) and Irish patients (2.3 to 3.6%).
- There are a number of treatment options for type 2 diabetes, if HbA1c is ≥6.5% after a trial of lifestyle measures. NICE guidance recommends starting treatment with metformin, or a sulfonylurea in patients who are not overweight or who cannot take metformin. If HbA1c rises to ≥6.5%, metformin can be combined with a sulfonylurea. Alternatively, either metformin or a sulfonylurea can be combined with pioglitazone, a gliptin or an insulin secretagogue. Once HbA1c is ≥7.5%, pioglitazone or insulin can be added, or sitagliptin, exenatide or liraglutide can be used in specific patients.
- The NICE Technology Appraisal for dapagliflozin is anticipated June 2013.

Literature

- Medline (dapaflozin.af) and Embase (DAPAGLIFLOZIN/) databases were searched and Bristol Myers Squibb provided details of the trials submitted for licensing, a full bibliography and conference abstracts.

Efficacy studies and critical evaluation

Twelve phase III randomised, controlled studies were submitted for the marketing authorisation, one was in Japanese patients and not included in this review.

1) Monotherapy

- Three doses of dapagliflozin (2.5mg, 5mg and 10mg daily) were compared with placebo in 485 treatment-naïve patients in a 24 week study. The mean changes in HbA1c from baseline (primary endpoint) were -0.58 to -0.89% with dapagliflozin compared with -0.23% with placebo (p=0.005 with 5mg and p<0.0001 with 10mg, vs. placebo). Target HbA1c (<7.0%) was achieved in 41% (2.5mg), 44% (5mg), 51% (10mg) and 32% (placebo). Body weight reductions were similar with both dapagliflozin and placebo, which may reflect a greater impact of diet/exercise counselling in motivated patients.
- The following were not stated in the study: whether this was a superiority or non-inferiority study, what the power calculation was, which population (ITT or per protocol) was analysed and how many patients required rescue medication.

2) Low dose monotherapy

- This phase III study in 280 treatment-naïve patients is still on-going and no results have been published. Patients have been randomised to treatment with dapagliflozin 1mg, 2.5mg or 5mg daily, or placebo.

3) Comparison to sulfonylurea in patients inadequately controlled on metformin

- Dapagliflozin 2.5mg titrated up to 10mg/day was compared with glipizide 5mg titrated up to 20mg/day in 408 patients in a non-inferiority study. All received concurrent metformin 1500-2000mg/day. The primary endpoint was the change in HbA1c from baseline to week 52. Mean reductions were -0.52 with both dapagliflozin and glipizide. Weight loss occurred with dapagliflozin but weight gain occurred with glipizide.
- The change in HbA1c with glipizide was initially rapid, followed by a gradual increase, while the change seen with dapagliflozin was a gradual reduction. A longer follow-up is necessary to see if the identical reduction is sustained. Last observation carried forward (LOCF) analysis was used for HbA1c change from baseline, which assumes that the patient's condition remains static from the time of the observation. More patients treated with dapagliflozin than glipizide discontinued therapy due to adverse events because 13 patients treated with dapagliflozin had a creatinine clearance <60mL/min and had treatment stopped according to protocol.

4) Add-on to sulfonylurea

- Dapagliflozin 2.5mg, 5mg or 10mg, or placebo was added to glimepiride 4mg/day in a 24-week study in 597 patients. Mean reductions in HbA1c were -0.58 to -0.82% with dapagliflozin vs. -0.13% with placebo, p<0.0001. By week 48, the reductions were -1.31 to -1.80% vs. -0.43%. HbA1c <7.0% was achieved by more patients treated with 5mg and 10mg than placebo.
- Hypoglycaemic events occurred more frequently with the addition of dapagliflozin than placebo, but this is commonly seen when antidiabetic therapies are added to sulfonylureas. The study is limited by the use of the fixed dose of glimepiride and addition of rescue medication, rather than titration of the glimepiride dose. This reflects the different maximum doses in the EU (4mg/day) and US (8mg/day).

5) Add-on to metformin

- Dapagliflozin 2.5mg, 5mg, or 10mg, or placebo was added to metformin ≥1500mg/day in a 24 weeks study in 546 patients. Those completing the 24 weeks could continue into a long-term study for a total of 102 weeks. The primary efficacy dataset consisted of all randomised patients who received at least one dose of study medication and had at least one post-baseline measurement. The primary endpoint was the change from baseline in HbA1c at week 24. Mean reductions were significantly greater in the dapagliflozin groups than in the placebo group: -0.3% (placebo), -0.67% (2.5mg, p=0.0002), -0.70% (5mg, p<0.001) and -0.84% (10mg, p<0.0001); these reductions were sustained to week 102. At 24 weeks, HbA1c <7% was seen in 33-40.6% of patients treated with dapagliflozin vs. 25.9% treated with placebo.
- The study has several limitations. LOCF analysis was used for missing values which could bias results, but the number of missing values was low. The number of elderly patients was low and most patients were Caucasian, which may limit extrapolation of the data to patient subsets.

6) Add-on to metformin

- Two 24-week studies evaluated the efficacy of dapagliflozin 5mg (Study 1) and 10mg (Study 2) with or without metformin ≤2000mg/day in 598 and 638 patients. In both studies, the combination of both drugs was more efficacious than each drug used as monotherapy. The primary endpoint was change in HbA1c from baseline to week 24: mean changes with the combination were -2.05% (Study 1) and -1.98% (Study 2). Respective mean changes with dapagliflozin were -1.19% and -1.45%, and with metformin were -1.35% and -1.44%.

7) Add on to insulin

- 808 patients poorly controlled on insulin ≥30 units/day and with up to 2 oral antidiabetes drugs were treated with dapagliflozin 2.5mg, 5mg, or 10mg, or placebo for 24-48 weeks. Mean reductions from baseline in HbA1c (primary endpoint) were significantly greater with dapagliflozin 2.5mg (-0.79%), 5mg (-0.89%) and 10mg (-0.96%) than with placebo (-0.39%), p<0.001 for all dapagliflozin doses vs. placebo, at 24 weeks. These were sustained to week 104. Patients treated with dapagliflozin were less likely to require increased insulin doses. Hypoglycaemic events were more frequent in those treated with dapagliflozin than placebo.
- There are study limitations. Insulin doses were not titrated to target, but this study was designed to assess whether dapagliflozin improved glycaemic control. Most patients enrolled were Caucasian and effects may vary in other ethnic groups.

8) Add-on to glitazone

- The effects of dapagliflozin 5mg or 10mg, or placebo in 420 patients poorly controlled on pioglitazone were assessed in a 48 week study. Mean changes in HbA1c from baseline to week 24 (primary endpoint), were -0.42% with placebo, -0.82% with 5mg (p=0.0007 vs. placebo) and -0.97% with 10mg (p<0.0001 vs. placebo). At 48 weeks, the mean changes were -0.54%, -0.95% and -1.21% (p=not significant). Fasting plasma glucose reductions were significantly greater and weight increases were significantly less with dapagliflozin.

9) Patients with renal impairment

- Patients (n=252) with moderate renal impairment were treated with dapagliflozin 5mg or 10mg. The primary endpoint was the change in HbA1c from baseline: -0.32% with placebo, -0.41% with dapagliflozin 5mg and -0.44% with dapagliflozin 10mg. Glycaemic measurements were not significantly improved with dapagliflozin but the residual glucose excretion was enough to cause other dapagliflozin effects, such as weight loss, blood pressure reduction and uric acid reduction. Results have been published as a conference poster only.

10) Effects of dapagliflozin and metformin on body weight

- Body composition measurements were monitored in a 24-week study in 180 patients inadequately controlled on metformin. Dapagliflozin 10mg or placebo therapy was added. The primary endpoint was the change from baseline to week 24 in total body

weight. Mean weight loss with dapagliflozin was 2.08kg more than that lost with placebo (p<0.0001). Mean weight loss was greater in men (-2.76kg) than in women (-1.22kg, p=0.04) at week 24.

- The study has several limitations. No pre/peri menopausal women were recruited and the men were therefore around 5years younger and 12kg heavier, which may have explained the significant effect of sex on change in total body weight.

11) Triple therapy with sitagliptin and metformin

- Patients with inadequate control on sitagliptin 100mg ± metformin ≥1500mg were randomised to receive additional treatment with either dapagliflozin 10mg (n=223) or placebo (n=224) for 48 weeks. The primary endpoint was the mean change in HbA1c at 24 weeks and a greater reduction was seen with dapagliflozin treatment (mean difference -0.48%, p<0.0001). Differences in the individual strata were -0.56% (stratum 1, dapagliflozin + sitagliptin, p<0.0001) and -0.40% (stratum 2, triple therapy p<0.0001).

Safety

- In all studies, more patients treated with dapagliflozin than placebo had a higher incidence of events suggestive of genital infections and urinary tract infections. These resolved with standard care and rarely led to discontinuation. The presence of glucose in the urine has been shown to increase *E. coli* growth and epidemiological data show a link between increased urinary glucose excretion and UTI.
- When compared with glipizide, dapagliflozin had a 10-fold reduction in the number of hypoglycaemic episodes as well as sustained weight loss.
- In January 2012 the US FDA requested additional clinical data to allow a better assessment of the benefit-risk profile, especially in relation to a higher incidence of breast and bladder cancers reported in patients treated with dapagliflozin. Ten cases of bladder cancer and nine cases of breast cancer were reported in phase 2 and 3 studies. The FDA calculated the expected number of cases of each type of cancer, using US epidemiology data, which were lower than the number of reported cases in the dapagliflozin trials. The FDA does acknowledge that the use of such data reflects the US population, and not the study population, most of which were enrolled from outside of the US, and that the relative risk of the cancers could not be established with any degree of certainty using the currently available data.
- Specific safety issues regarding this tumour imbalance, the limited data in patients over 75 years of age, the use in patients at risk of volume depletion, hypotension and electrolyte imbalances have been addressed in the UK SPC and in the UK Risk Management Plan.
- There were at least 8 cases of liver-related test dysfunction with increased serum ALT and bilirubin. Only one was possibly related to dapagliflozin.

Potential benefits over existing technologies

- Dapagliflozin has a novel mechanism of action that is not reliant on insulin secretion and it is the only orally acting antidiabetic that does not rely on insulin.
- Weight loss has occurred in patients treated with dapagliflozin, which may be advantageous.
- There are additive effects when dapagliflozin is used concurrently with other anti-diabetes treatments.

Potential disadvantages over existing technologies

- A higher incidence of events suggestive of UTI and genital infections has occurred in patients treated with dapagliflozin.

Health Economics / Estimated cost per 100 000 population

- Healthcare professionals should contact Sudesh Basra, Market Access Marketing Manager: UK and Ireland; Cardiovascular and Metabolics, Bristol-Myers Squibb, directly to discuss the budget impact for their specific local health economy, sudesh.basra@bms.com
- The cost of dapagliflozin is £36.59 for 28 tablets (both 5mg and 10mg strengths).

Issues for consideration

- Dapagliflozin is the first SGLT2 inhibitor to be available in the UK.
- NICE technology appraisal is not due until June 2013.
- It may be a useful treatment choice in patients in whom weight loss would be advantageous.
- Dapagliflozin does not affect the natural progression of type 2 diabetes.
- The positive impact on glycaemic control, weight and hypoglycaemia risk is advantageous but the UTI prevalence and potential other toxicity, is worthy of caution.
- Patients should be carefully assessed before initiating dapagliflozin as a means of avoiding insulin therapy.
- The FDA is still investigating a potential increase in risk of breast and bladder cancers in patients treated with dapagliflozin. Specific safety issues regarding this tumour imbalance, the limited data in patients over 75 years of age, the use in patients at risk of volume depletion, hypotension and electrolyte imbalances have been addressed in the UK SPC and in the UK Risk Management Plan.

This document reflects the views of the London New Drugs Group and may not reflect those of the reviewers.

Background

In November 2012 dapagliflozin (Forxiga) was launched in the UK for the treatment of type 2 diabetes mellitus in adults.[1] Dapagliflozin 5mg and 10mg daily is indicated for use in adults with type 2 diabetes mellitus to improve glycaemic control as:[2]

- Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
- Add-on combination therapy: In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Type 2 diabetes

The prevalence of type 2 diabetes in the UK is increasing with the prevalence of obesity and decreased physical activity.[3] The prevalence varies according to factors such as ethnic group and degree of social deprivation. For example, in the general population, the prevalence is 4.3% in men ≥55 years of age and 3.4% in women ≥55 years. However, higher a prevalence is see in Black patients of Caribbean origin (10% and 8.4% respectively), and Indian patients (10.1% and 5.9% respectively), but a lower prevalence is seen in Chinese patients (3.8% and 3.3% respectively) and Irish patients (3.6% and 2.3% respectively).[3]

There are a number of treatment options for type 2 diabetes after a trial of lifestyle measures if HbA1c is ≥6.5%. NICE guidance recommends starting treatment with metformin, or a sulfonylurea in patients who are not overweight or if glucose levels are particularly high.[3;4] If HbA1c rises to ≥6.5%, metformin can be combined with a sulfonylurea. Alternatively, either metformin or a sulfonylurea can be combined with pioglitazone, a gliptin (such as sitaglitpin or vildagliptin, specific patients only) or an insulin secretagogue (repaglinide or nateglinide, or exenatide or liraglutide, specific patients only). Once HbA1c is ≥7.5%, pioglitazone or insulin can be added, or sitagliptin, exenatide or liraglutide can be used in specific patients.[3;4] Further details can be found in the BNF or NICE guidance. NICE guidance on dapagliflozin is not due until June 2013.[5]

Current oral antidiabetic treatments

Disease progression in type 2 diabetes is due to deteriorating glycaemic control due to declining beta-cell function. Treatments that depend on insulin supplementation or secretion can cause hypoglycaemia, weight gain, loss of insulin sensitivity and loss of effectiveness.[6] The following classes of oral antidiabetic drugs are currently available in the UK:[4]

- **Biguanide** (metformin): Decreases gluconeogenesis and increases peripheral utilisation of glucose, requires endogenous insulin so is only effective if there are some residual functioning pancreatic islet cells.
- **Sulfonylureas**, eg, glimepride, glicliazide: Augments insulin secretion, requires some pancreatic beta-cell activity.
- **Thiazolidinedione** (pioglitazone): Reduces peripheral insulin resistance, leading to reduced blood glucose concentration.
- **Oral secretagogues** (nateglinide and repaglinide): Stimulates insulin release and relies on functioning pancreatic beta-cells.
- **Dipeptidylpeptidase-4 inhibitors** (gliptins, e.g. saxagliptin, vildagliptin): Inhibit DPP-4 to increase insulin secretion (and requires some functioning pancreatic beta-cells) and lower glucagon secretion.
- Exenatide and liraglutide are **GLP-1 receptor agonists** which are given by subcutaneous injection. They bind to glucagon-like peptide (GLP)-1 receptors to increase insulin secretion, suppress glucagon secretion and slow gastric emptying.

Dapagliflozin

Dapagliflozin is a competitive, reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2), which is located in the proximal convoluted tubule.[7] It reduces glucose reabsorption by the kidneys and increases urinary glucose excretion.[8]

The kidney has three roles in glucose homeostasis: gluconeogenesis, uptake and use of glucose for its own energy needs and glucose reabsorption.[7] In the fasting state, about 20% of the total glucose output and about 10% of the total systemic glucose disposal can be attributed to the kidney. After meals, renal glucose uptake increases three-fold but the systemic glucose disposal changes very little. In a typical day, the kidney produces 15-55g of glucose via gluconeogenesis and uses between 25-35g of glucose. Healthy kidneys filter around 180g of glucose daily from the circulation and most (99%) is reabsorbed from the glomerular filtrate

in the proximal tubule. The kidney has the greatest effect on glucose homeostasis via this reabsorption.[7] In patients with type 2 diabetes, in the fasting state approximately 300% more glucose is released by the kidney into the circulation, and both fasting and postprandial glucose use is increased (two- to three-fold).[7]

Glucose is reabsorbed from the glomerular filtrate by SGLT1 and 2. SGLT2 is found on the surface of proximal tubule epithelial cells and mediates the majority of total glucose reabsorption (see figure 1, below).[7] Reabsorption of filtered glucose is directly proportional to the plasma glucose load; once plasma glucose concentrations exceed 180mg/dL, glucose that is not reabsorbed is excreted into the urine. Dapagliflozin has nearly 3000-fold selectivity for SGLT2 than for SGLT1[9] and by inhibiting SGLT2, glucose-reabsorption is reduced and urinary glucose excretion increased, with net caloric loss[8].

The resulting reduction plasma glucose reduces the glucose load filtered by the kidney, thereby limiting further glucose excretion. Dapagliflozin treatment may be associated with a lower propensity for hypoglycaemia than other oral antidiabetic treatments.[8]

Dose

The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. It can be taken at any time of day, with or without food. When dapagliflozin 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.[2]

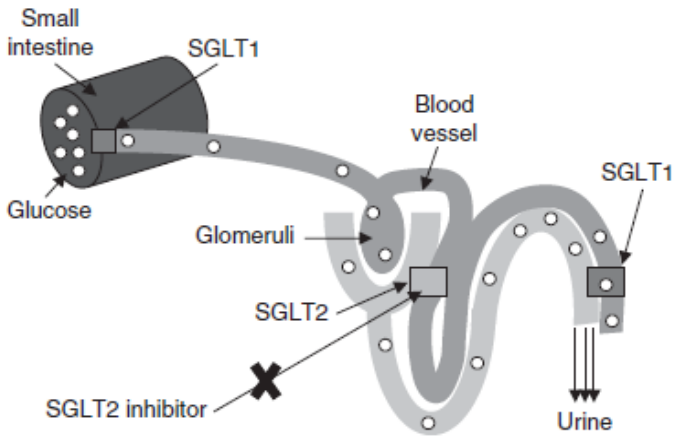
Dose in special populations

The efficacy of dapagliflozin is reduced in patients who have moderate renal impairment and likely absent in those with severe renal function. Dapagliflozin is therefore not recommended in patient with moderate to severe renal impairment. No dose adjustment is required in patients with mild renal impairment, or in patients with mild to moderate hepatic impairment. A starting dose of 5mg/day is recommended in patients with severe hepatic impairment, increased to 10mg/day if well tolerated. No dose adjustment is recommended in elderly patients but use in patients aged ≥75 years is not recommended due to limited data in this age group. No data are available on the safety and efficacy of dapagliflozin in children aged 0 to to <18 years.[2]

There are no data from the use of dapagliflozin in pregnant women and it is unknown whether it is excreted into human milk. Dapagliflozin should not be used during pregnancy or lactation. The effects of dapagliflozin on fertility have not been studied.[2]

Clinical efficacy: Phase III studies

Figure 1: Mechanism of action of sodium-glucose co-transporter 2 inhibitors in types 2 diabetes.[10]



Twelve phase III studies in patients with type 2 diabetes were submitted for the marketing authorisation application. The studies (apart from the one in Japanese patients) are summarised below and further details are in Appendix 1. All patients received dietary and lifestyle/exercise counselling and advice. Details below are on the trial design, primary endpoint and comments.

Monotherapy

Ferrannini et al[9] evaluated the efficacy of three doses of dapagliflozin in a 24-week, parallel-group, randomised, double-blind, placebo-controlled study. Treatment-naïve patients with HbA1c of 7-10% (n=485, mean age 35-65 years) were randomly assigned to one of seven treatment arms: placebo once daily, or 2.5mg, 5mg, or 10mg dapagliflozin once daily either in the morning (main cohort, n=274) or in the evening (exploratory cohort, n=211). Patients with HbA1c of 10.1-12% (high-HbA1c exploratory cohort, n=74) were randomised 1:1 to either 5mg or 10mg dapagliflozin (no placebo group because of the high HbA1c levels). Open-label rescue medication (metformin 500-2000mg/day) could be given as rescue medication if fasting plasma glucose (FPG) was >270mg/dL at week 4, or >240mg/dL at week 8, or >200mg/dL at weeks 12-24.

The primary endpoint (measured in the main cohort) was the change from baseline in HbA1c level at week 24: mean reductions were -0.58 to -0.89% with dapagliflozin vs. -0.23% with placebo (p=0.0005 with 5mg and p<0.0001 with 10mg, vs. placebo) (table 1). Reductions were apparent at week 4. Target HbA1c <7% was achieved in 41%, 44% and 51% of those treated with dapagliflozin 2.5mg, 5mg and 10mg respectively, and 32% in the placebo group. Reductions in FPG were significantly higher with dapagliflozin 5mg and 10mg than with placebo. Reductions in body weight were similar, which may be due to a greater impact of diet/exercise counselling in motivated patients. In the exploratory evening dose group, changes in HbA1c, FPG and body weight were similar to those seen in the main cohort. In the high HbA1c cohort, there were numerically greater reductions in the dapagliflozin group, compared to other cohorts. No major episodes of hypoglycaemia occurred in any group. A higher proportion of patients treated with any dose of dapagliflozin experienced events suggestive of a genital infection compared with placebo.

The following were not stated in the published study: whether this was a superiority or non-inferiority study, a power calculation, which population (intention to treat (ITT) or per protocol (PP)) was analysed and how many patients required rescue medication. Monotherapy with dapagliflozin resulted in significantly larger reductions in HbA1c and FPG than placebo. Patients with high baseline HbA1c may already present with glycosuria because their filtered glucose load may exceed the absorption capacity of the kidney. UTIs and genital infections resolved with standard care and rarely led to discontinuation.

Low dose monotherapy

A phase III study (NCT00736879) assessed the efficacy of low dapagliflozin in patients with type 2 diabetes not adequately controlled by diet and exercise.[11] Approximately 280 patients were randomised to treatment with dapagliflozin 1mg, 2.5mg or 5mg, or placebo. The primary endpoint was the change from baseline in HbA1c. Secondary endpoints included change from baseline in total body weight, FPG and waist circumference. No study results have been published yet.

Comparison to sulfonylurea in patients inadequately controlled on metformin

The study by **Nauck et al**[8] tested the efficacy, safety and tolerability of dapagliflozin against glipizide over 52 weeks in patients with type 2 diabetes inadequately controlled on metformin. Patients with HbA1c between 6.5 and ≤10% were randomised to treatment with either dapagliflozin 2.5mg titrated up to ≤10mg/day (n=406), or glipizide 5mg titrated up ≤20mg/day (n=408, mean age 51-69 years), over 18 weeks. Doses were increased if FPG ≥6.1mmol/L. All patients received metformin 1500-2500mg/day. The non-inferiority margin (upper limit of 95% CI for treatment difference in mean HbA1c change from baseline) was <0.35%. Last observation carried forward (LOCF) analysis was used for HbA1c and total body weight. To provide 90% power for the per protocol population and assuming a 25% exclusion, 373 patients per group were required.[12] Few patients treated with dapagliflozin discontinued due to inadequate glycaemic control (0.2%) compared with 3.6% treated with glipizide. A total of 77.9% of patients completed the study, 79.3% in the dapagliflozin arm and 76.9% in the glipizide arm.

Efficacy analyses included 98.2% of all randomised patients. Maintenance of efficacy, safety and tolerability at 104 weeks have been reported in a conference poster.[13]

During the 34-week maintenance phase no further up-titration was allowed but doses could be reduced. Treatment was discontinued if FPG was higher than pre-specified values at various timepoints during the study. The primary endpoint in the full analysis set (all randomised patients receiving ≥1 dose, baseline and post-baseline efficacy values) was the absolute change in HbA1c from baseline to week 52: mean reductions were -0.52 with both dapagliflozin and glipizide, mean difference 0.00 (-0.11 to 0.11) (table 2).[8] At 104 weeks the change in HbA1c was -0.32% with dapagliflozin and -0.14% with glipizide (mean difference -0.18%, 95% CI -0.33 to -0.02).[13] The initial weight loss seen with dapagliflozin and weight gain with glipizide at 52 weeks remained stable at 104 weeks, with a 5kg difference between the two groups.[13] A higher proportion of patients treated with dapagliflozin than placebo had signs of genital infections and UTI; most were reported in the first year of treatment and more often in women than in men.[13] Hypoglycaemic events occurred in 4.2% treated with dapagliflozin and 45.8% treated with glipizide at 104 weeks.[13]

The comparable efficacy of dapagliflozin to glipizide was achieved with a 10-fold reduction in number of hypoglycaemic episodes as well as sustained weight loss, albeit with a greater amount of signs and symptoms suggestive of genital and urinary tract infections. The change in HbA1c with glipizide was initially rapid, followed by a gradual increase, while the response with dapagliflozin was a gradual reduction. The use of LOCF data assumes that the patient remains static at this last observation and may not give a true reflection of the outcome. The reason why more patients treated with dapagliflozin discontinued the study due to AEs is because 13 patients treated with dapagliflozin had creatinine clearance <60ml/min and had treatment stopped. The mechanism by which dapagliflozin reduces blood pressure is unclear but may involve osmotic diuresis or sodium loss. Events suggestive of genital infections or UTIs were reported spontaneously and not all could be confirmed as infections.

Add on to sulfonylurea

Strojek et al[14] investigated the efficacy of dapagliflozin added to glimepiride therapy in a randomised, double-blind, placebo-controlled, parallel-group, 24 week study. Patients with inadequately controlled type 2 diabetes (HbA1c ≥7 to ≤10%, n=597, mean age 50-70 years) were treated with dapagliflozin 2.5mg, 5mg or 10mg/day, or placebo, plus glimepiride 4mg/day. The glimepiride dose could be reduced to 2mg/day or discontinued in order to alleviate hypoglycaemic events. Patients with inadequate control were treated with rescue therapy (metformin, or pioglitazone/rosiglitazone). In order to detect a 0.5% difference between dapagliflozin vs. placebo for changes from baseline to week 24 in HbA1c, 129 patients per group were needed to provide 90% power. Statistical testing was in a sequential manner: only those dapagliflozin groups significantly superior to placebo for the primary endpoint had statistical inference tested vs. placebo for the first secondary endpoint, etc. In total 91.5% completed the study; 3.1% and 2.1% of patients in the dapagliflozin and placebo groups withdrew because of adverse events. Seven patients discontinued due to serious adverse events: 2 in the placebo group and 5 in the dapagliflozin group

The primary endpoint was the change in HbA1c from baseline to week 24 in the full analysis set (all randomised patients who received ≥1 dose of study medication, had a baseline and ≥1 post-baseline value for ≥1 efficacy value): mean reductions were -0.58 to -0.82% with dapagliflozin vs. -0.13% with placebo, p<0.0001 (table 3). Rescue medication was required by 23 patients in the placebo group (15.9%) and 19 patients treated with dapagliflozin (4.2%). Dapagliflozin 5mg and 10mg produced sustained mean reductions in total body weight from baseline, but the reduction seen with 2.5mg was not significantly greater than that seen with placebo. Significantly more patients achieved an HbA1c <7.0% with dapagliflozin 5mg and 10mg than with placebo. Reductions in fasting plasma glucose were significantly greater with dapagliflozin 5mg and 10mg vs. placebo. Hypoglycaemic events were more frequent in the dapagliflozin group vs. placebo (7.1 – 7.9% vs. 4.8%). Higher proportions of patients treated with dapagliflozin than placebo had signs and symptoms suggestive of genital infections (5.5% vs. 0.7%), but

similar proportions had signs and symptoms suggestive of UTIs (5.3% vs. 6.2%).

The addition of dapagliflozin to glimepiride improved glycaemic parameters, with significant reductions in HbA1c with all 3 doses. Hypoglycaemic events occurred more frequently with the addition of dapagliflozin but this is commonly seen when antidiabetic therapies are added to sulfonylureas. Subgroup analyses showed that dapagliflozin reduced HbA1c at all levels of baseline HbA1c, produced equivalent efficacy in patients with high and low baseline BMI and in patients from Asia/Pacific vs. Europe. Sulfonylurea treatment is often associated with weight gain, so there is a potentially beneficial weight loss effect when combined with dapagliflozin. One study limitation is the use of a fixed glimepiride dose and addition of rescue medication, rather than titration of the glimepiride, reflecting the different maximum doses in the EU (4mg/day) and US (8mg/day). However, the glucose-lowering effect of sulfonylurea's can be obtained at half-maximal doses so in theory the patients in the study would have been exposed to a dose reflective of maximal clinical efficacy.

Add on to metformin

The efficacy and safety of dapagliflozin when added to metformin therapy was assessed by **Bailey et al** in a 24 week study.[15] Patients (n=546, mean age 52 -55 years) stable on a metformin dose of at least 1500mg/day for at least 8 weeks prior to enrolment were randomised to treatment with dapagliflozin 2.5mg, 5mg or 10mg, or placebo. Rescue medication, for patients with FPG over predefined levels at weeks 4-8, 8-12 or 12-24, was pioglitazone or acarbose; the number of patients requiring this was not stated. Those who completed the 24-week study could continue in a long-term study for a total of 102 weeks, results of which have been published in a conference poster.[16] With 129 patients per group, the study was powered to detect a difference in HbA1c of 0.5% between each dapagliflozin treatment group and the placebo group. The primary efficacy dataset consisted of all randomised patients who received at least one dose of study medication and had at least one post-baseline measurement. The last observation carried forward (LOCF) method was used for missing 24-week data. In total 88% of patients completed the study.

The primary endpoint was the change from baseline in HbA1c at week 24. Mean reductions were significantly greater in the dapagliflozin groups than in the placebo group: -0.3% (placebo), -0.67% (dapagliflozin 2.5mg, p=0.0002), -0.70% (dapagliflozin 5mg, p<0.001) and -0.84% (dapagliflozin 10mg, p<0.0001) (table 4).[15] These reductions were sustained through to week 102.[16] An HbA1c <7.0% at week 24 was achieved by more patients treated with dapagliflozin than with placebo, 33-40.6% vs. 25.9%. At week 102, a smaller proportion of patients had an HbA1c <7%, but this was achieved by more patients treated with dapagliflozin than placebo. The proportion of patients requiring rescue medication or discontinuing for failing to achieve glycaemic targets was higher in the placebo group (60.6%) than in the dapagliflozin groups (42 – 51%) at week 102, but in all groups the proportions were high. Significantly greater reductions in FPG and in bodyweight were seen in the dapagliflozin groups compared with the placebo group (see Appendix 1). Reductions in FPG continued in all 4 groups to week 102, but body weight reductions peaked around week 50. Hypoglycaemia occurred in similar proportions in each group at both 24 and 102 weeks. Signs and symptoms suggestive of UTIs were reported in similar proportions of each group at both time points, but more patients treated with dapagliflozin reported signs and symptoms suggestive of genital infections. One event suggested of a genital infection was reported by most patients but two patients experienced two and three events. Most were mild or moderate and resolved with self-treatment or conventional interventions. No meaningful changes in serum electrolytes, renal function or fasting lipids (apart from greater increases with HDL cholesterol and decreases in triglycerides with dapagliflozin) occurred.

The addition of dapagliflozin to metformin therapy improved glycaemic control and reduced both body weight and waist circumference; this was maintained over 102 weeks. The number of elderly patients in the study was low, and the patients were mainly Caucasian, which may limit extrapolation of data to patient subsets. LOCF analysis could bias the results but the number of missing values was low.

Henry et al[17] evaluated the efficacy of dapagliflozin and metformin-XR (extended release), combined or alone, in treatment-naïve patients in two randomised, double-blind, active-controlled 24-week studies (n=598 and 638, aged 18 -77 years). Dapagliflozin doses were 5mg in Study 1 and 10mg in Study 2. Metformin XR was titrated up to 2000mg/day. Patients were treated with dapagliflozin plus metformin, or dapagliflozin plus placebo or metformin plus placebo. Patients not achieving control could receive open-label rescue therapy with pioglitazone, sitagliptin or acarbose. With 190 patients per group there was 90% power to detect a difference in HbA1c of 0.4% between combination vs. monotherapy groups.

The primary endpoint was change in HbA1c from baseline to week 24, derived from patients with ≥1 dose of medication and ≥1 post-baseline measurement, using the LOCF method for missing values. In both studies, the combination of dapagliflozin plus metformin was more efficacious than either drug alone. Mean changes in HbA1c from baseline in Study 1 and Study 2 with the combination therapy were -2.05% and -1.98%, p<0.0001 vs. both dapagliflozin and metformin XR, both studies (table 5). Mean changes with dapagliflozin 5mg (Study 1) and 10mg (Study 2) were -1.19% and -1.45% respectively. Mean changes with metformin XR were -1.35% and -1.44%. Fewer patients in the combination and dapagliflozin groups need rescue therapy or discontinued. Reductions in fasting plasma glucose were significantly higher with the combination in both studies than with either monotherapy, and weight reductions were significantly greater with dapagliflozin 10mg, both alone and in combination with metformin XR, than with metformin XR monotherapy. Signs and symptoms suggestive of genital infections were higher in patients treated with dapagliflozin. Major hypoglycaemia was not reported in either study; neither dapagliflozin nor metformin is prone to causing hypoglycaemia. No bladder malignancies occurred in either study. One breast cancer was found 16 days after a patient had been randomised to dapagliflozin in study 1.

Add on to insulin

Wilding et al[18] evaluated the effects of dapagliflozin in patients with type 2 diabetes poorly controlled on insulin ≥30 units/day ± up to 2 oral antidiabetes drugs. A total of 808 patients (mean age 59.3) were randomised to add-on treatment with dapagliflozin 2.5mg, 5mg or 10mg, or placebo. Patients completing the 24-week primary efficacy phase (n=711) then continued to a 24-week site- and subject-blinded continuation phase (n=676). The insulin dose was increased if FPG was above set limits at specified time points (such as >13.3mmol/L during weeks 1-12) or if HbA1c was >8% during weeks 25-48. The primary endpoint was the change from baseline in HbA1c at week 24. Efficacy was based on the full analysis set – all patients receiving at least 1 dose of study medication and at least 1 post-baseline value for 1 efficacy value. The study was powered (153 patients per group, 90% power) to detect a difference of 0.5% between dapagliflozin and placebo for changes in HbA1c.

Significant mean reductions in HbA1c with dapagliflozin treatment were seen at weeks 24: -0.79% (2.5mg), -0.89% (5mg) and -0.96% (10mg) vs. -0.39% (placebo), (<0.001 for all dapagliflozin doses vs. placebo). These were sustained to week 48 (-0.79%, -0.96%, -1.01% and -0.47% respectively, p<0.001). Reductions in body weight were greater with dapagliflozin than with placebo (table 6). After 24 weeks 9.7 to 11.2% of patients treated with dapagliflozin vs. 29.2% treated with placebo required insulin up-titration (>5 unit increase in daily dose and >10% from baseline). Reductions in glycaemic parameters and body weight were sustained over 48 weeks. Maintenance of efficacy and safety and tolerability were assessed again at 104 weeks.[19] Mean changes in HbA1c and body weight showed significantly greater reductions in the dapagliflozin groups than in the placebo group at 104 weeks, and mean daily insulin doses were significantly lower in the dapagliflozin groups than in the placebo group (see table 6). The probability of insulin up-titration or discontinuation because of poor glycaemic control was consistently higher in the placebo group than in the dapagliflozin groups.

Signs and symptoms suggestive of UTIs and genital infections were more prevalent in the dapagliflozin groups than in the placebo group, with most events occurring in women during the first 24

weeks of treatment and few leading to discontinuation. Three bladder and three breast cancers occurred during the course of the study; a total of 15 malignancies occurred during the study with four within 90 days of starting the study drug (types not stated).

There are study limitations. Insulin doses were not titrated to target, although this study was designed to assess whether dapagliflozin improved glycaemic control which required baseline therapy to remain unchanged. Most patients (95%) were Caucasian. Potential concerns regarding breast and bladder cancer could not be evaluated due to lack of statistical power in this study. The study was not designed to determine long-term safety but 104 week data were presented in June 2012.[19]

Add on to glitazone

Rosenstock et al[20] evaluated the effects of dapagliflozin in patients inadequately controlled on pioglitazone (≥30mg/day) in a 24-week study with a subsequent 24-week extension. Patients (mean age 53.5) were randomised to treatment with dapagliflozin 5mg (n=141) or 10mg (n=140) or placebo (n=139), plus open-label pioglitazone 30-45mg/day. Open-label rescue of metformin or a sulphonylurea could be used if the patients fasting plasma glucose (weeks 4-24) or HbA1c (weeks 25-48) was above set levels at specific time points. No power calculation was carried out.

The primary endpoint of the study was change in HbA1c from baseline to week 24: mean changes were -0.82% with dapagliflozin 5mg (p=0.0007 vs. placebo) and -0.97% with 10mg (p<0.0001 vs. placebo), vs. -0.42 with placebo. At 48 weeks, mean changes were -0.95% and -1.21% vs. -0.54% (difference not statistically significant). Fewer patients treated with dapagliflozin required rescue medication or discontinued therapy due to lack of glycaemic control (11-18%) than with placebo (34%). Fasting plasma glucose reductions were significantly greater and weight changes were significantly smaller with dapagliflozin than placebo (table 7). Adverse events were reported in a similar proportion of patients in each group, with the exception of genital infection which were higher in the dapagliflozin groups. Events suggestive of UTI or genital infection responded to initial therapy without interrupting dapagliflozin treatment. One case of squamous cell bladder cancer was reported in a patient on day 144 (with a positive family history) taking dapagliflozin 5mg. No major episodes of hypoglycaemia occurred during the 48 weeks. Two patients in each dapagliflozin groups and one in the pioglitazone group had decreased renal function during the first 24 weeks, including increased serum creatinine (four events) and one event of decreased GFR. The addition of dapagliflozin to pioglitazone produced significant HbA1c reduction and mitigated weight gain and fluid retention due to pioglitazone without increasing the risk of hypoglycaemia.

Effects of dapagliflozin plus metformin on body weight

Weight loss seen with dapagliflozin may result from reduced body fat secondary to caloric loss or from fluid loss secondary to osmotic diuresis, or a combination of both. **Bolinder et al**[21] investigated the underlying components of the weight loss by monitoring body composition measurements during treatment with dapagliflozin 10mg or placebo in patients inadequately controlled by metformin alone. The 24-week study was followed with a 78-week extension period. Inclusion criteria included women aged 55-75 who were at least 5 years postmenopausal, and men aged 30 to 75, HbA1c 6.5 to 8.5%, and bodyweight no greater than 120kg (due to limitation imposed by DXA scanning equipment, used to assess body composition). Randomisation was stratified according to gender. The primary endpoint was the change from baseline to week 24 in total body weight. Key secondary endpoints included the change from baseline to week 24 in waist circumference, total fat mass measured by DXA scan and the proportion of patients achieving a weight reduction of ≥5%. If the primary endpoint was significant at a level p<0.05 then the results of the key secondary endpoint would be assessed. Primary and secondary endpoints were assessed on the full analysis set; all randomised patients who received at least one dose and had a baseline and at least one post-baseline efficacy value for at least one efficacy variable.

The mean weight loss achieved with dapagliflozin was significantly greater than that with placebo, difference -2.08kg, p<0.0001. In the dapagliflozin group mean change in total body weight from baseline showed a faster decline over the first few weeks followed by a more gradual decline that had

not plateaued by week 24 (table 8) Mean weight loss was greater in men (-2.76kg) than in women (-1.22kg) at week 24 (p=0.0481). The following secondary endpoints were reduced to a greater extent with dapagliflozin treatment vs. placebo (see Appendix 1, no. 6); waist circumference, fat mass, proportion with >5% body weight decrease, lean mass, HbA1c, FPG, visceral adipose tissue volume (VAT) and subcutaneous VAT.

Weight loss was achieved with dapagliflozin treatment, mainly accounted for by fat loss with significant reductions in abdominal and subcutaneous visceral adipose fat. The study has limitations. No pre- or perimenopausal women were recruited, in order to avoid rapid changes in bone mineral density that occurs around the time of the menopause. The men were therefore on average 5 years younger and 12kg heavier, which may have explained the significant effect of sex on change in total body weight. Patients were body weight over 120kg were excluded because they would not have been able to have DXA scans. Baseline HbA1c was low in this study so changes with dapagliflozin treatment were modest; this low baseline value was chosen to avoid discontinuations due to inadequate glycaemic control. The study was not able to elicit the precise mechanism of dapagliflozin-weight loss, and the effects of it on food intake and satiety is unknown.

Renal impairment

A phase 2/3 study (NCT00663260) has been carried out to determine whether dapagliflozin is effective in treating patients with type 2 diabetes and moderate renal impairment.[22] Results have been published as a conference poster only. Patients (n=252) with eGFR of 30-59mL/min were randomised to treatment with dapagliflozin 5mg, 10mg or placebo for 52 weeks. Patients could receive open-label rescue therapy (excluding metformin) to achieve glycaemic control. Mean baseline eGFR was 44.6mL/min/1.7m^2. Ten patients (4%) were classified as having CKD stage 4, 122 (48.4%) had CKD stage 3B, 109 (43.3%) had stage 3A and 11 (4.4%) had stage 2.

The primary endpoint was the change in HbA1c from baseline to week 24, which was -0.32 with placebo, -0.41 with dapagliflozin 5mg and -0.44 with dapagliflozin 10mg. Larger reductions in eGFR were seen in dapagliflozin-treated patients but eGFR tended to remain stable after an initial decrease. Larger reductions in fasting plasma glucose were achieved with dapagliflozin therapy (table 9). Greater weight loss was seen with dapagliflozin treatment. More patients treated with placebo than with dapagliflozin experienced at least one hypoglycaemic episode or a major episode of hypoglycaemia. Events suggestive of urinary tract infections occurred at a similar rate in all 3 groups, but those suggestive of a genital infection were more common in the dapagliflozin groups. Four patients treated with dapagliflozin 10mg had increased blood creatinine and renal failure occurred in one placebo-treated and one dapagliflozin 5mg-treated patient.

Glycaemic measures were not significantly improved with dapagliflozin therapy in patients with type 2 diabetes and moderate renal impairment. The residual glucose excretion was enough to cause some of the other dapagliflozin effects, such as weight loss, blood pressure reduction and uric acid reductions. An increase in fractures was seen in this study (10 patients treated with dapagliflozin had fractures vs. 0 for placebo) but has not been seen in other studies of dapagliflozin. Further research is needed to determine if the stabilisation of eGFR and eCrCL as well as reduced hyperkalaemia and marked abnormalities of albumin : creatinine ratio are potentially indicative of a renoprotective effect of dapagliflozin.

Triple therapy with sitagliptin and metformin

Jabbour et al[23] evaluated the efficacy and safety of dapagliflozin added to sitagliptin therapy in a randomised, double-blind, placebo-controlled study. Patients with inadequate control on sitagliptin 100mg ± metformin ≥1500mg were randomised to receive additional treatment with either dapagliflozin 10mg (n=223) or placebo (n=224) for 48 weeks. Patients were stratified according to metformin use (stratum 1: without or stratum 2: with).

Results have been published in poster format only. The primary endpoint was the mean change in HbA1c at 24 weeks and a greater reduction was seen with dapagliflozin treatment (mean difference -0.48%, p<0.0001). Differences in the individual strata were -0.56% (stratum 1, p<0.0001) and -0.40% (stratum 2, p<0.0001). Mean reductions in HbA1c were first seen at week 4 and continued

until week 48 in the overall cohort and in patients treated with triple therapy. For patients treated with dapagliflozin and sitagliptin, mean reductions in HbA1c were seen by week 4 but began to rise again at week 32, returning to baseline levels at week 48 (but still lower than mean HbA1c measurements in the placebo group). No comment is made by the investigators regarding this. Twice as many patients treated with dapagliflozin achieved an HbA1c <7% (35.4%, overall, 42.8% stratum 1 and 28% stratum 2), vs. placebo (16.6% overall, 17.2% stratum 1 and 16% stratum 2). Over 24 weeks, 18.8% of patients discontinued dapagliflozin treatment vs. 41.5% receiving placebo, because of lack of efficacy of FPG above pre-specified rescue criteria. Greater reductions in body weight were seen with dapagliflozin therapy: differences were -1.89kg (overall), -1.85kg (stratum 1) and -1.87kg (stratum 2), and these were sustained to week 48.

Adverse events were more common in the dapagliflozin group than placebo (66.2% vs. 61.1%) but hypoglycaemia was more frequent in the placebo group (6.2% vs. 5.3%). Renal impairment or failure occurred in twice as many patients treated with dapagliflozin (n=8, 3.6%) than with placebo (n=4, 1.8%). Genital infections and UTIs were also more common in dapagliflozin-treated patients (9.3% and 5.8%) than in placebo-treated patients (0.4% and 3.5%).

The trial details have been published in poster format only and this can make critical evaluation difficult. The additional of dapagliflozin to sitagliptin and metformin lead to a significant reduction in mean HbA1c compared with placebo, but the initial reduction seen when dapagliflozin was added to sitagliptin alone had returned to baseline levels after 48 weeks. As with the other studies, dapagliflozin treatment was associated with a higher incidence of genital infections and UTIs, and renal impairment. The renal events were all non-serious and reversible, and did not require treatment.

Adverse events

Overall 4287 patients were exposed to dapagliflozin and 1941 to control. The average duration of observation was 341 days and 316 days respectively.[24]

Urinary tract infections: Patients with type 2 diabetes mellitus have a predisposition to urinary tract infections (UTIs): the presence of glucose in urine has been shown to increase *E. coli* growth in vitro and epidemiological data show a link between increased urinary glucose excretion and UTI. Pooled data from 12 trials with dapagliflozin was evaluated for the presence of signs and symptoms suggestive of or clinical diagnosis of UTIs (n=4545).[25] Signs and symptoms of and clinical diagnoses of UTIs were higher with dapagliflozin 5mg and 10mg than with 2.5mg or placebo (see Table 1). These were more frequently reported in women than in men. Most events were mild-moderate.

Genital infections: Urinary glucose may also provide a favourable environment for genital micro-organisms and increase the risk of genital infections.[26] Active and directed questioning was carried out in 12 studies to identify possible genital infections (n=4545). Events suggestive of and more definitive events of diagnosed cases of genital infections were higher with all doses of dapagliflozin than with placebo (see table 1). Most patients with genital infections experienced one event, and most events were mild or moderate. Antifungal or antimicrobial treatment was required in 68-88% of cases in the dapagliflozin groups and 92% in the placebo group.

Malignancies

In the clinical studies, the relative risk associated with dapagliflozin for some tumours was above 1 (bladder, prostate, breast) but below 1 for others (e.g. blood, ovary, renal tract), not resulting in an overall increased tumour risk with dapagliflozin. The numerical imbalance of breast, bladder and prostate tumours must be considered with caution. These will be further investigated in post-marketing studies.[2]

Bladder cancer: Ten cases of bladder cancer in men were reported during the phase 2 and 3 studies, nine occurred in patients treated with dapagliflozin. Five men had haematuria at baseline, which suggests that the disease may have been present but undetected prior to enrolment. The clinical trials were not powered to statistically distinguish between 9 cases in the dapagliflozin arm and 1 in the placebo arm, but

Table 1: Pooled data showing incidence of UTIs[25] and genital infections[26]		Placebo (n=1393)	Dapagliflozin 2.5mg (n=814)	Dapagliflozin 5mg (n=1145)	Dapagliflozin 10mg (n=1193)
Events suggestive of UTI[25]	**Total**	4.5%	4.2%	7.3%	6.5%
Clinical diagnosed[25]	**Total**	3.7%	3.6%	5.7%	4.3%
	Women	6.6%	5.8%	9.6%	7.7%
	Men	1%	1.4%	1.6%	0.8%
Pyelonephritis[25]	**Total**	N=1	N=2	N=1	N=0
Events suggestive of a genital infection[26]	**Total**	2.1%	5.8%	7.0%	7.0%
Diagnosed genital infection[26]	**Total**	0.9%	4.1%	5.7%	4.8%
	Women	1.5%	5.8%	8.4%	6.9%
	Men	0.3%	2.4%	2.8%	2.7%

event rates for males significantly exceeded the expected rate in an age-matched reference diabetic population.[27] US Surveillance Epidemiology and End Results (SEER) data suggest that two cases of bladder cancer would be expected in the male dapagliflozin population based on a rate of 91.6 new cases per 100,000 years. The actual rate seen during the trials was 402 new cases per 100,000 years.

Mechanisms have been suggested to explain this increased risk: insulin has a mitogenic effect and increased blood insulin levels could stimulate tumour growth by increasing bioactive insulin-like growth factor-1, and changes in urine composition and bladder function as well as an increased risk of UTI are linked with an increased risk of bladder cancer.[27] There are limitations to the US review: cancer rates from SEER reflects the US population, but most participants were enrolled outside of the US and bladder cancer rates may differ; clinical trial populations are often highly pre-screened for certain co-morbidities which may result in an underestimated cancer incidence, but both of these limitations may result in a lower case count. However, the incidence may be higher because of increased surveillance in a clinical trial setting. The comparisons between a clinical trial population and a reference population should be interpreted carefully.[27]

Breast cancer: Nine cases of breast cancer were observed in dapagliflozin-treated patients vs. none in the comparator arms in the clinical trials.[28] The cases were a mixture of stage I and II and all diagnosed within a year of treatment initiation, with 2 diagnosed in the first 2 months. The natural history of breast cancer would suggest that the lesions were present in a clinically undetected state at the time of patient enrolment. SEER data was used to calculate the expected number of breast cancer cases in the dapagliflozin trials. A standardised incidence ratio (SIR) was calculated to evaluate the observed incidence from the trials with the expected incidence from SEER data. The expected incidence was 7.1, and the SIR was 1.27 for dapagliflozin-treated patients (95% CI 0.58 to 2.41). The total number of expected incidence cases in female patients in the comparator arms was 2.9; no SIR was calculated for the comparator arms because no cases of breast-cancer were reported in female comparator patients in the studies.

The FDA state limitations to the use of SEER data, which is based on the general US population.[28] The trials were conducted internationally, with about 20% enrolled from the US. The SEER data reflects only the US population and rates of breast cancer vary across countries, so estimates from SEER may not be applicable to all. Breast cancer identified in the dapagliflozin studies included all cases, irrespective of grade or stage, while SEER data only includes invasive breast cancer. An adjustment factor was used to obtain the incidence rate of breast cancer in type 2 patients from SEER; the patient population differs to that in the dapagliflozin trials and it is likely that the patient enrolled may have been healthier than general type 2 diabetes patient in SEER. This could have actually underestimated the SIR. The finding that no cases of breast cancer were observed in the control groups suggests that the study participants may have had a lower risk of breast cancer compared

with the general type 2 diabetes population; extrapolating this suggests that the actual number of cases seen in dapagliflozin-treated patients should therefore be lower than the expected number, but this was not the case. The FDA concluded that it was not feasible to establish the relative risk of breast cancer with dapagliflozin with any degree of certainty with the current available data.

Liver toxicity: There were at least eight cases of liver-related test dysfunction with increased serum ALT and bilirubin; five of these reported values that reached the laboratory threshold for potential Hy's Law cases.[24] Hy's Law cases have three components: (1) the drug causes hepatocellular injury shown by a higher incidence of 3 or more times the upper limit of normal for ALT or AST than the control or placebo, (2) subjects showing (1) also have a serum total bilirubin that is >2x ULN without cholestasis, (3) no other reason can be found to explain the combination of increase ALT/AST and bilirubin. This identifies a drug likely to cause serious liver injury. Of these eight cases, only one was possibly related to dapagliflozin therapy. Another 27 patients treated with dapagliflozin had potential liver toxicity, but none of these cases were thought to be related to dapagliflozin.

Health economics / budget impact model

Costs of dapagliflozin and other oral antidiabetes treatments are in table 2, below.

Healthcare professionals should contact Sudesh Basra, Market Access Marketing Manager: UK and Ireland; Cardiovascular and Metabolics, Bristol-Myers Squibb, directly to discuss the budget impact for their specific local health economy; mobile: +44 (0)7581 156657 or email: Sudesh.Basra@bms.com

Table 2: Costs of dapagliflozin and other oral antidiabetes treatments

	Dose[4]	Cost/28 or 30 days[32] (Drug Tariff unless stated)	Cost/year
Dapagliflozin	10mg/day (5mg in special populations)	28x5mg / 10mg: £36.59	£475.67
Metformin	500mg-2000mg daily	28x500mg: £0.88 (generic) 84x500mg: £1.41 (generic) 28x500mg SR: £ 2.66 (Glucophage SR®) 56x500mg SR: £5.32 (Glucophage SR®)	£11.44 (500mg/day) -
Glipizide	2.5mg-5mg daily, max 20mg daily	28x5mg: £1.26 (Minodiab®) 56x5mg: £5.26 (generic)	£16.38 (5mg/day) £65.52 (20mg/day)
Gliclazide	40mg-80mg daily, max 320mg daily	28x40mg: £3.36 (generic) 28x80mg: £1.06 (generic) 60x80mg: £1.39 (generic)	£43.68 (40mg/day) £8.34 (80mg/day) £33.36 (320mg/day)
Exenatide	5mcg-10mcg twice daily (Byetta) or 2mg per week (Bydureon)	£68.24 (250mcg/mL, 60 doses of either 5 or 10mcg, 30 days) (Byetta®) 4x£18.34: £73.36 (2mg vial, 1 dose, Bydureon®)[4]	£828.88 (5 or 10mcg/day) £953.68 (2mg/week)
Liraglutide	0.6mg to 1.8mg daily	£78.48 (6mg/mL, 6mLs, 20-60 days) (Victoza®)[4]	£470.88 (0.6mg/day) £1412.64 (1.8mg/day)
Nateglinide	60mg tds to 180mg tds	84x60mg: £22.71 (Starlix®) 84x120mg: £25.88 (Starlix®) 84x180mg: £25.88 (Starlix®)	£295.23 (60mg tds) £336.44 (120-180mg tds)
Pioglitazone	15mg-30mg once daily, max 45mg daily	28x15mg: £16.55 (generic) 28x30mg: £24.24 (generic) 28x45mg: £24.54 (generic)	£215.15 (15mg/day) £315.12 (30mg/day) £319.02 (45mg/day)
Repaglinide	1mg to 16mg daily	30x1mg: £1.20 (generic)[4] 90x1mg: £3.59 (generic)[4] 90x2mg: £3.59 (generic)[4]	£14.40 (1mg/day) £28.80 (2x1mg = 2mg/day) £43.08 (3x1mg = 3mg/day) £10.77 (2x2mg = 4mg/day) £57.44 (4x2mg = 8mg/day)
Saxaliptin	5mg daily	28x5mg: £31.60 (Onglyza®)	£410.80
Sitagliptin	100mg daily	28x100mg: £33.26 (Januvia®)	£432.38
Vildagliptin	50mg once or twice daily	56x50mg: £31.76 (Galvus®)	£206.44(50mg/day) £412.88 (100mg/day)

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Produced by the London New Drugs Group. Correspondence to Alexandra Denby, Regional MI Manager, London Medicines Information Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex. HA1 3UJ. e-mail: alexandra.denby@nhs.net. This document reflects the views of the LNDG and may not reflect those of the reviewers. The LNDG would like to thank Dr Keith Steer, Consultant Metabolic Physician, NWLH NHS Trust and Hon. Senior Lecturer in Clinical Medicine, ICSM, and Dr Daniel Darko, Consultant Physician, Diabetes & Endocrinology, Central Middlesex Hospital, for their comments on this review. Bristol Myers Squibb has commented on this review.

Embase: DAPAGLIFLOZIN/
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Appendix 1: Phase III studies

Table 1) Monotherapy [Ferrannini et al[9]]

- Two patients (placebo group) withdrew due to lack of efficacy. Seventeen patients in the dapagliflozin groups withdrew due to adverse events.

Group		Change from baseline to week 24			
		HbA1c (%)	FPG (mg/dL)	Weight (kg)	Urinary glucose: creatinine (g/g)
Main cohort (AM dose)	Placebo (n=75)	-0.23±0.10	-4.1±3.9	-2.2±0.4	0.96±2.87
	2.5mg (n=65)	-0.58±0.11	-15.2±4.2	-3.3±0.5	12.12±2.98
	5mg (n=64)	-0.77±0.11*	-24.1±4.3*	-2.8±0.5	17.68±3.28
	10mg (n=70)	-0.89±0.11†	-28.8±4.0†	-3.2±0.5	33.8±3.08
Exploratory cohort (PM dose)	2.5mg (n=67)	-0.83±0.11	-25.6±4.1	-3.8±0.5	24.24±3.07
	5mg (n=68)	-0.79±0.11	-27.3±4.2	-3.6±0.5	38.00±3.09
	10mg (n=76)	-0.79±0.10	-29.6±4.0	-3.1±0.4	45.80±2.86
High HbA1c	5mg (n=34)	-2.88±1.41	-77.1±53.4	-2.1±3.4	n/a
	10mg (n=39)	-2.66±1.26	-84.3±61.0	-1.9±3.5	n/a

* p<0.001 † p<0.0001

- **Exploratory analyses:** Mean HbA1c (%) in patients with baseline HbA1C ≥9%: -1.23±0.98 (2.5mg), -1.98±0.90 (5mg), -1.90±0.79 (10mg) vs. 0.16±2.50 (placebo). No p values were generated for endpoints in exploratory cohorts, as per study design.

Overall population

- No clinically meaningful changes in serum electrolytes or renal function seen.
- Greater blood pressure reductions were achieved with dapagliflozin treatment than with placebo, reflecting the diuretic effect of dapagliflozin. Systolic BP was reduced by 2.3-5.7 vs. 0.9mmHg, and diastolic BP reduced by 1-3.3 vs. 0.7mmHg.
- Hypoglycaemia occurred in two patients treated with placebo and six treated with dapagliflozin; none led to study discontinuation and no major episodes occurred.
- Events suggestive of UTIs occurred in three patients treated with placebo (4%) and 42/484 treated with dapagliflozin (8.6%).
- Events suggestive of genital infections occurred in one placebo-treated and 39/484 dapagliflozin-treated patients (1.3% vs. 8%).
- Safety data from the exploratory cohort were similar to those in the main cohort. Six patients treated in the evening experienced nocturia vs. none treated in the morning.

Table 2) Vs. glipizide, All pts received metformin [Nauck et al.[8;12;13]]

- Discontinuations due to hypoglycaemic events and major hypoglycaemic events occurred in glipizide group only (n=6 and n=3).

Dose at end of titration period	Dapagliflozin +MET (n=406)		Glipizide + MET (n=408)		Difference (95% CI)
Dapa 2.5mg / Glip 5mg[12]	19 (4.7%)		54 (13.2%)		
Dapa 5mg / Glip 10mg[12]	34 (8.4%)		51 (12.5%)		
Dapa 10mg / Glip 20mg[12]	353 (86.9%)		296 (72.5%)		
No 'down-titration'[12]	395 (97.3%)		343 (84.1%)		
	Dapagliflozin (n=400)		Glipizide (n=401)		
Endpoint (FAS)	Week 52[8;12]	Week 104[13]	Week 52[8;12]	Week 104[13]	At week 52
HbA1c, mean change, %	-0.52	-0.32	-0.52	0.14	0 (-0.11 to 0.11)
Change in FPG mmol/L	-1.24	-1.12	-1.04	-0.67	
Weight change, kg	-3.22	-3.70	+1.44	+1.36	4.65kg (-5.14 to -4.17, p<0.0001)
Weight reduction ≥5%	33.3%	-	2.5%	-	30.8% (26 to 35.7, p<0.0001)
≥ 1 hypoglycaemic episode	3.5%	-	40.8%	-	-37.2% (-42.3 to -21.2, p<0.0001)
Changes in SBP, mmHg	-4.3	-	+0.8	-	-5 (-6.7 to -3.4)
Change in DBP, mmHg	-1.6	-	-0.4	-	-1.2 (-2.3 to -0.2)
Change in urinary glucose mmol/L	141.2	-	-4.1	-	
Adverse events	Dapagliflozin (n=406)		Glipizide (n=408)		
	Week 52[8;12]	Week 104[13]	Week 52[8;12]	Week 104[13]	
Discontinuation due to AE	37 (9.1%)	40 (9.9%)	24 (5.9%)	31 (7.6%)	
≥1 Serious AE	35 (8.6%)	8 (2%)	46 (11.3%)	7 (1.7%)	
Genital infection*	50 (12.3%)		11 (2.7%)		
UTI*	44 (10.8%)		26 (6.4%)		
Renal impairment/failure	24 (5.9%)		14 (3.4%)		

* events suggestive of such infections

Appendix 1: Phase III studies

Table 3) Add on to glimepiride (GLI) [Strojek et al[14]]

Changes at week 24[14;33]	Placebo + GLI (n=145)	Dapa 2.5mg + GLI (n=154)	Dapa 5mg + GLI (n=142)	Dapa 10mg + GLI (n=151)
HbA1c, %	-0.13	-0.58	-0.63	-0.82
Difference vs. placebo†		-0.44 (-0.61 to -0.27)*	-0.49 (-0.67 to -0.32)*	-0.68 (-0.86 to -0.51)*
Body weight, kg	-0.72	-1.18	-1.56	-2.26
Difference vs. placebo†		-0.46 (-1.08 to 0.15), p=0.141	-0.84 (-1.47 to -0.21), p=0.0091	-1.54 (-2.17 to -0.92), p<0.0001
OGTT mmol/l	-0.33	-2.08	-1.78, p=0.0002	-1.94, p<0.0001
HbA1c<7%	13%	26.8%	30.3%, p=0.0001	31.7%, p<0.0001
FPG mmol/L	-0.11	-0.93	-1.18, p<0.0001	-1.58, p<0.0001
SBP / DBP, mmHg	-1.2 / -1.4	-4.7 / -1.1	-4.0 / -1.7	-5.0 / -2.8
Urine glucose mmol/L	-13.96	98.53	119.90	155.14
Rescue medication	23 (15.9%)	9 (5.8%)	7 (4.9%)	3 (2.0%)
Adverse events	**n=146**	**n=154**	**n=145**	**n=151**
≥1 Serious AE	7 (4.8%)	11 (7.1%)	10 (6.9%)	9 (6.0%)
Hypoglycaemic events	7 (4.8%)	11 (7.1%)	10 (6.9%)	12 (7.9%)
Genital infection‡	1 (0.7%)	6 (3.9%)	9 (6.2%)	10 (6.6%)
UTI‡	9 (6.2%)	6 (3.9%)	10 (6.9%)	8 (5.3%)
Renal impairment/failure	2 (1.4%)	1 (0.6%)	1 (0.7%)	0

* p<0.0001 † Difference (95% confidence interval) ‡ events suggestive of such infections
Change in body weight for dapagliflozin 2.5mg was not statistically significant: no further significant testing was carried out

Table 4) Add on to metformin (MET) [Bailey et al[15;16]]

Changes		Placebo + MET (n=137)	Dapa 2.5mg + MET (n=137)	Dapa 5mg + MET (n=137)	Dapa 10mg + MET (n=135)
HbA1c, %	**Week 24**	-0.30	-0.67, p=0.0002	-0.70, p<0.0001	-0.84, p<0.0001
	Week 102	0.02	-0.48	-0.58	-0.78
FPG mmol/L	**Week 24**	-0.33	-0.99, p=0.0019	-1.19, p<0.0001	-1.30, p<0.0001
	Week 102	-0.58	-1.07	-1.36	-1.58
Body weight, kg	**Week24**	-0.9	-2.2, p<0.0001	-3.0, p<0.0001	-2.9, p<0.0001
	Week102	+1.36	-1.10	-1.70	-1.74
Endpoints at week 24					
Reduction in waist circumference		-1.3cm	-1.7cm	-2.7cm	-2.5cm
HbA1c<7.0%		25.9%	33%, p=0.1775	37.5%, p=0.0275	40.6%, p=0.0062
HbA1c ≤6.5%		13.8%	20.7%, p= not tested	14.5%, p=0.8627	25.2%, p=0.0149
HbA1c in pts with baseline HbA1c ≥9.0%		N=22 9.12%	N=17 8.44%, p= not tested	N=34 8.16%, p=0.0068	N=18 8.16%, p=0.029
Rescue meds or discontinuation due to failure to achieve glycaemic targets, wk102		83 (60.6%)	71 (51.8%)	64 (46%)	57 (42%)
Adverse events to week 102		N=137	N=137	N=137	N=135
At least one AE		111 (81%)	111 (81%)	111 (81%)	111 (82.2%)
At least 1 serious AE		14 (10.2%)	15 (10.9%)	9 (6.6%)	14 (10.4%)
Hypoglycaemia (at least 1 event)		8 (5.8%)	5 (3.6%)	7 (5.1%)	7 (5.2%)
Major hypoglycaemia		0	0	0	0
Genital infection‡		7 (5.1%)	16 (11.7%)	20 (14.6%)	17 (12.6%)
UTI‡		11 (8.0%)	11 (8.0%)	12 (8.8%)	18 (13.3%)
Renal impairment or failure		2 (1.5%)	6 (4.4%)	4 (2.9%)	2 (1.5%)

‡ events suggestive of such infections
Difference in HbA1c <7.0% for dapagliflozin 2.5mg vs. placebo: not statistically significant: no further significant testing was carried out
Mean changes in urinary glucose excretion were 10.8 to 32.2g/g for dapagliflozin vs. -0.7g/g for placebo.

Appendix 1: Phase III studies

Table 5) Add-on or vs. metformin (MET) [Henry et al[17]]

	Study 1 (n=598)			Study 2 (n=638)		
Changes at week 24	**Dapa 5mg + MET (n=194)**	**Dapa 5mg + PBO (n=203)**	**MET + PBO (n=201)**	**Dapa 10mg + MET (n=211)**	**Dapa 10mg + PBO (n=219)**	**MET + PBO (n=208)**
HbA1c, %	-2.05*	-1.19	-1.35	-1.98*	-1.45	-1.44
FPG mmol/L	-3.39*	-2.33	-1.86	-3.35*	-2.58	-1.93
Weight, kg	-2.66†	-2.61	-1.29	-3.33†	-2.73†	-1.36
HbA1c <7.0%	96/185 (52.4%)‡	46/196 (22.5%)	68/195 (34.6%)	92/202 (46.6%)‡	69/216 (31.7%)	72/203 (35.2%)
Rescue meds or discontinuation	1 (0.5%)	15 (7.4%)	26 (12.9%)	3 (1.4%)	17 (7.8%)	28 (13.5%)
Genital infections	6.7%	6.9%	2.0%	8.5%	12.8%	2.4%
UTI	7.7%	7.9%	7.5%	7.6%	11%	4.3%

* p<0.0001 DAPA + MET vs. DAPA monotherapy and vs. MET monotherapy MET: Metformin PBO: Placebo
† p<0.0001 DAPA + MET and DAPA monotherapy vs. MET monotherapy
‡ Statistically significant vs. DAPA monotherapy and MET monotherapy. Genital infections and UTIs: signs and symptoms suggestive of these.

Table 6) Add on to insulin (INS) [Wilding et al[18;19]]

Mean changes at week 24	**Placebo + INS (n=197)**	**Dapa 2.5mg + INS (n=202)**	**Dapa 5mg + INS (n=211)**	**Dapa 10mg + INS (n=194)**
HbA1c, %	-0.39	-0.79*	-0.89*	-0.96*
Body weight, kg	0.43	-0.92*	-1.00*	-1.61*
Insulin dose (IU/d)	5.65	-1.95*	-0.63*	-1.18*
FPG mmol/L – vs. placebo		-0.65*	-1.12*	-1.10*
Insulin dose up-titrated†	29.2%	11.2%	10.6%	9.7%
Seated SBP / DBP mm/Hg	-3.56 / -1.86	-4.21 / -2.11	-5.93 / -3.04	-6.66 / -2.70
Mean changes at week 48				
HbA1c, %	-0.47	-0.79*	-0.96*	-1.01*
Body weight, kg	0.82	-0.96*	-1.00*	-1.61*
Insulin dose (IU/d)	10.54	-0.92*	-0.30*	-0.70*
FPG mmol/L – vs. placebo	-	-0.69*	-0.90*	-0.94*
Insulin dose up-titrated†	42.8%	21.7%	15.6%	15.3%
Seated SBP / DBP mm/Hg	-1.49 / -1.31	-5.30 / -2.96	-4.33 /-2.64	-4.09 / -2.85
Mean differences at week 104‡				
HbA1c, %	-	-0.21 (-0.41, -0.01)	-0.39 (-0.59, -0.18)	-0.35 (-0.56, -0.15)
Body weight, kg	-	-2.70 (-3.78, -1.65)	-2.74 (-3.80, -1.69)	-3.19 (-4.24, -2.14)
Mean daily insulin dose (IU/d)		-14.3U (-20.5, -8.0)	-16.8 (-23.1, -10.5)	-19.2 (-25.5, -12.9)
Insulin dose up-titrated†	50.4%	29.1%	26.5%	25.5%
Adverse events, week 48 unless stated				
Major hypoglycaemia	2 (1%)	3 (1.5%)	2 (0.9%)	3 (1.5%)
Total hypoglycaemia	102 (51.8%)	122 (60.4%)	118 (55.7%)	105 (53.6%)
Renal impairment/failure	3 (1.5%)	2 (1.0%)	6 (2.8%)	4 (2.0%)
Hypotension, dehydration or hypovolaemia	2 (1%)	5 (2.5%)	5 (2.4%)	3 (1.5%)
Genital infections, wk 24[19]	4 (2%)	10 (5%)	16 (7.5%)	18 (9.2%)
Genital infections, wk 48[19]	5 (2.5%)	13 (6.4%)	21 (9.9%)	21 (10.7%)
Genital infections, wk 104[19]	6 (3%)	15 (7.4%)	27 (12.7%)	18 (14.3%)
UTI, wk 24[19]	8 (4.1%)	15 (7.4%)	19 (9%)	17 (8.7%)
UTI, wk 48[19]	10 (5.1%)	16 (7.9%)	23 (10.8%)	20 (10.2%)
UTI, wk 104[19]	11 (5.6%)	17 (8.4%)	28 (13.2%)	17 (13.8%)

* p<0.001. † Discontinued therapy as glycaemic target not achieved or insulin dose increased ‡ Differences vs. placebo (95% CI)
Insulin dose increased if FPG >13.3 (wks 0-12), >12.2 (wks 12-24) or >9.9mmol/L (wks 25-48) or HbA1c >8% (wks 25-48).
Genital infections and UTIs: signs and symptoms suggestive of these

Appendix 1: Phase III studies			
Table 7) Add on to pioglitazone (PIO) [Rosenstock et al[20]]			
Mean change at week 24	**Placebo + PIO (n=139)**	**Dapagliflozin 5mg + PIO (n=141)**	**Dapagliflozin 10mg + PIO (n=140)**
HbA1c, %	-0.42	-0.82 (p=0.0007)	-0.97 (p<0.0001)
FPG (mmol/L)	-0.31	-1.38 (p<0.0001)	-1.64 (p<0.0001)
Weight (kg)	+1.4	+0.09 (p<0.0001)	-0.14 (p<0.0001)
Seated SBP/DBP mm/Hg	1.3 / 0.7	-0.8 / -1.0	-3.4 / -3.1
Mean change at week 48			
HbA1c	-0.54	-0.95	-1.21
FPG (mmol/L)	-0.73	-1.27	-1.84
Weight (kg)	+2.99	+1.35	+0.69
Adverse events			
Major hypoglycaemia	0	0	0
Total hypoglycaemia	1 (0.7%)	3 (2.1%)	0
Genital infections	4 (2.9%)	13 (9.2%)	12 (8.6%)
UTI	11 (7.9%)	12 (8.5%)	7 (5%)
Decreased renal function	1 (0.7%)	2 (1.4%)	2 (1.4%)
Peripheral oedema	9 (6.5%)	6 (4.3%)	3 (2.1%)
Bladder cancer	0	1 (0.7%)	0
Genital infections and UTIs: signs and symptoms suggestive of these.			

Table 8) Effects on body weight [Bolinder et al[21]]			
Change at 24 weeks	**Placebo + MET (n=91)**	**Dapagliflozin + MET (n=89)**	**Difference**
Mean weight loss	-0.88kg	-2.96kg	-2.08kg, p<0.0001
Waist circumference (cm)	-0.99	-2.51	-1.52, p=0.0143
Fat mass (kg)	-0.74 (n=79)	-2.22 (n=82)	-1.48, p=0.0001
Lean mass (kg)	-0.6	-1.1	-0.60 (p=0.0211)
Proportion with body weight decrease ≥5%	4.3%	30.5%	26.2%, p<0.0001
HbA1c	-0.10	-0.39	-0.28, p<0.0001
FPG (mmol/L)	0.13 (n=91)	-0.82 (n=88)	-0.95, p<0.0001
Visceral adipose tissue volume (VAT) (cm^3)	-39.2	-297.5	-258.4, p=0.0084
SC VAT (cm^3)	-121.4	-306.4	-184.9, p=0.0385

Appendix 1: Phase III studies			
Table 9) In patients with renal impairment [Kohan et al[22]]			
Mean changes at week 24	**Placebo (n=84)**	**Dapa 5mg (n=83)**	**Dapa 10mg (n=85)**
HbA1c, % [difference vs. PBO (95% CI)]	-0.32	-0.41 [-0.08 (-0.37, 0.20)]	-0.44 [-0.11 (-0.40, 0.45)]
FPG mg/dL [difference vs. PBO (95% CI)]	8.4	-5.2 [-13.6 (-29.7, 2.4)]	-0.6 [-9.0 (-25.0, 7.0)]
Body weight, kg [difference vs. PBO (95% CI)]	0.27	-1.54 [-1.81 (-2.68, -0.94)]	-1.89 [-2.16 (-3.03, -1.29)]
Mean changes at week 52			
HbA1c, % [difference vs. PBO (95% CI)]	-0.04	-0.33 [-0.29 (-0.76, 0.18)]	-0.34 [-0.30 (-0.77, 0.17)]
FPG mg/dL [difference vs. PBO (95% CI)]	-8.5	-15.4 [-6.9 (-30.9, 17.1)]	-17.3 [-8.7 (-32.3, 14.8)]
Body weight, kg [difference vs. PBO (95% CI)]	-0.08	-2.22 [-2.14 (-4.29, 0.02)]	-2.27 [-2.19 (-4.34, -0.05)]
eGFR mL/min/1.73m^3 [difference vs. PBO (95% CI)]	-1.35	-2.00 [-0.65 (-3.52, 2.22)]	-4.47 [-3.12 (-6.00, -0.24)]
Measured CrCL, mL/min [difference vs. PBO (95% CI)]	6.83	-1.91 [-8.75 (-16.45, -1.04)]	-6.11 [-12.94 (-20.65, -5.22)]
Adverse events, week 52			
At least one AE	73 (86.9%)	78 (94%)	74 (87.1%)
AE leading to discontinuation of study med	18 (21.4%)	11 (13.3%)	20 (23.5%)
Major hypoglycaemia	4 (4.8%)	0	2 (2.4%)
Hyperkalaemia	12 (14.3%)	10 (12%)	7 (8.2%)
Genital infections	3 (3.6%)	6 (7.2%)	6 (7.1%)
UTI	8 (9.5%)	7 (8.4%)	8 (9.4%)
Fracture	0	3 (3.6%)	7 (8.2%)
Hypotension, dehydration or hypovolaemia	4 (4.8%)	7 (8.4%)	8 (9.4%)
Renal event	2 (2.4%)	1 (1.2%)	5 (5.9%)
Blood creatinine raised	1 (1.2%)	0	4 (4.7%)
Renal impairment/failure	1 (1.2%) (Failure)	1 (1.2%) (Failure)	1 (1.2%) (Impairment)
Genital infections and UTIs: signs and symptoms suggestive of these.			