Brand Name: Farxiga

Generic Name: Dapagliflozin

Manufacturer: Astra-Zenica

Drug Class [1,2]: Antidiabetic agent, SGLT2 Inhibitor

Uses:

Labeled Uses[1,2,3,4]: Improving glycemic control in adults with type 2 diabetes.

Mechanism of Action[1,2,3,4,5]: Dapagliflozin works in the proximal renal tubules by inhibiting sodium-glucose cotransporter 2 (SGLT2). SGLT2 is involved in glucose reabsorption. Inhibition of SGLT2 results in increased excretion of glucose leading to a reduction in blood glucose plasma concentrations.

Pharmacokinetics[1,2,3,4]:

T_{max}	2 hours
$t_{½}$	13 hours
Clearance	75% urine 21% feces
Protein binding	91%
Bioavailability	78%

Metabolism[1,2,3]: Dapagliflozin is mainly metabolized by UGT1A9. CYP3A4 plays a minor role in its metabolism.

Elimination[1,2,3]: Dapagliflozin is mainly eliminated as metabolites of the parent drug in urine and feces (75%), the primary metabolite is Dapagliflozin 3-O-glucouronide. A portion of the parent drug is excreted in feces (15%) and urine (<2%).

Efficacy[6,7,8]:

List JF, Woo V, Morales E, Tang W, Fiedorek TF. Sodium-Glucose Cotransport Inhibition With Dapaglifozin in Type 2 Diabetes. Diabetes Care. 2009;32:650-657.

Study Design: Prospective, Multicenter randomized, parallel-group, double blind, placebo controlled study.

Description: This study consisted of drug-naïve type 2 diabetes patients from ages 18 to 79 and A1C's between 7-10%. Participants were taken from 133 sites from various countries. The patients in the study were randomly assigned to dapagliflozin, 2.5, 5, 10, 20, or 50mg, placebo or metformin XR. The metformin XR was started at 750mg titrated up to 1500 mg by week 2. Patients with a FBG > 240 at weeks 4 and 6, >220 at weeks 8, or >200 at week 10 were discontinued from the study. The primary objective of the study was to compare mean A1C change from baseline for dapaglifozin groups vs. placebo after 12 weeks. During the trial safety and efficacy was assessed at each study visit. The patients in the study had clinic visits at weeks 1, 2, 4, 6, 8,10, and 12. They had follow up appointments at weeks

14 and 16. Oral glucose tolerance testing was performed and fasting blood and urine samples were collected after a minimum 10 hour fast. Patients had their vitals checked along with a physical exam and adverse event assessment at each clinic visit. The study resulted in all dapagliflozin groups achieving significant reductions in mean A1C change from placebo. Results ranged from -0.55 to -0.90% (dapagliflozin), -0.18% (placebo), and -0.73% (metformin). No log-linear dose-response relationship was demonstrated (P_{trend}=0.41). Proportions of patients achieving A1C<7% at week 12 ranged from 40 to 59% (dapagliflozin), 32% (placebo), 54% (metformin). The comparison versus placebo statistically significant only for the 50mg group (P < 0.01). Of the 389 patients who were randomly assigned in the study 348 completed week 12. Dapagliflozin showed a decrease in FPG by the end of week one. Dapagliflozin treatment groups also showed a decrease in total body weight and an increase in urinary glucose excretion. During the trial no deaths were reported and adverse events amongst patients were similar amongst all groups. Hypoglycemic events were reported in 6-10% of dapagliflozin patients, 4% placebo, and 9% of metformin treated patients.

Limitations: The study was sponsored by Bristol-Myers Squibb and Astra-Zenica which is the manufacturer of dapagliflozin. There are authors of the study have been affiliated with the manufacturer of dapagliflozin in the past. . There were no other conflicts of interest in regards to this study. Patients whose A1C did not decrease to below a certain level at specific points during the study were dis-enrolled from the trial and treated with additional diabetic medications. No analysis was conducted for the most common, relevant AEs and hypoglycemia. Statistical analysis was performed on all patients treated in the trial and missing values were tracked via last observation carried forward. Intent to treat method was used and is beneficial in that it mimics clinical practice more closely. Fifty patients per treatment group provided 82% power to detect a mean 0.7% difference in A1C between dapagliflozin groups and placebo. The dapagliflozin 10mg arm only had 47 patients randomly assigned with 40 patients completing the trial. This would result in a higher chance of making a Type II Error and reduce the chance of having statistically significant study results. In addition, the difference between dapagliflozin and metformin were not statistically analyzed.

Conclusion: Over the course of a 12-week trial dapagliflozin decreased serum A1C, FPG, and PPG levels in type 2 diabetic patients in all treatment groups. Not all patients enrolled in the study completed the trial. However, of the patients that were enrolled no deaths were reported. Dapagliflozin did have a diuretic effect during the study and no effect on renal function was observed during the trial. Long term effects on renal function need to be established with further testing. The adverse events of patients in all treatment groups were deemed similar throughout. However, no analysis was conducted for relevant adverse events such as UTI's. Weight loss amongst dapagliflozin treatment groups was observed throughout the trial with higher doses of dapagliflozin, 20mg and 50mg, resulting in greater weight reduction. The weight loss across dapagliflozin treatment groups resulted in p values of <0.001 across the board. Resulting in less than a 0.1% chance that the results were due to chance. Overall, dapagliflozin improved hyperglycemia in type 2 diabetic patients by reducing A1C, FPG, and PPG levels and further studies are needed in oorder to fully assess the safety and efficacy of dapagliflozin.

Ferrannini E, Ramos SJ, Salsalli A, Tang W, List JF. Dapagliflozin Montherapy in Type 2 Diabetic Patients with Inadequate Glycemic Control by Diet and Exercise. Diabetes Care. 2010;33:2217-2224

Study Design: 24-week parallel-group, double-blind, placebo-controlled phase 3 trial.

Description: This 24-week trial included men and women ages 18-77 with type 2 diabetes and A1Cs between either 7-10% and 10-12%. The study was conducted between September 2007 and July 2008 at 85 sites in US, Canada, Mexico, and Russia. Patients with an A1C of 7-10% were given once daily

placebo or dapagliflozin 2.5, 5, or 10mg tablets. Patients with an A1C of 10.1-12% were given dapagliflozin 5 or 10mg tablets. No placebo group was used because of the patient's elevated A1C levels in this group. Patients had a 2 or 1 week diet/exercise placebo lead in. Patients with A1C's between 10-12% had a 1 week lead in. Primary outcome measures included change in A1C from baseline to the conclusion of the 24 week trial. Secondary outcome measures included a decrease in FBG and body weight baseline to the conclusion of the 24 week trial. Patients were assessed throughout the trial for safety by taking vital signs, monitoring of adverse events, and laboratory measurements. A total of 485 patients with an A1C of 7-10% were randomly assigned to the main treatment cohort and 74 patients were assigned to the high A1C cohort. The main treatment cohort resulted in an overall A1C reduction by the end of the 24 week trial. Reductions ranged from -0.58 to -0.89% with dapagliflozin compared to -0.23% with placebo. The authors of the study concluded that the decrease in A1C was statistically significant with 5 and 10mg dapagliflozin versus placebo ($P=0.0005$ and $P<0.0001$). By the end of the study a higher percentage of patients in the dapagliflozin arm had an A1C of <7% (41, 44, and 51% with 2.5, 5, and 10mg dapagliflozin versus 32% with placebo). It was reported that reductions in A1C were observed as early as week 1. Patients during the trial also showed a greater amount of weight loss with dapagliflozin when compared to placebo. In the exploratory high A1C evening dose cohort reductions in A1C, FPG, and body weight were similar to the main treatment cohort. Furthermore, patients in the exploratory high A1C cohort showed a greater reduction in A1C, FPG, and weight loss over the course of the 24 week trial. Adverse events were monitored throughout the trial and were similar across the cohorts. However, adverse events were not statistically analyzed and signs and symptoms associated with UTIs and genital infections were more frequently reported in the dapagliflozin arms.

Limitations: The study was funded by Bristol-Myers Squibb and AstraZeneca which is the manufacturer of the dapagliflozin. There are authors of the study that have been affiliated with the manufacturer of dapagliflozin in the past. . There were no other conflicts of interest reported for this trial. There is no power listed for the study. The authors do mention that no p values were reported for end points in exploratory cohorts but that was per the study design. The main limitation in the trial was self-reporting. Patients were instructed to self monitor their blood glucose daily and to report any unusually high or low blood glucose reading. This could lead to biased results and inaccurate results. Weight loss amongst dapagliflozin patients was also observed throughout the trial. However, there was no p-values reported. A placebo effect in regards to weight loss was possible due to the greater impact of diet and exercise counseling, as noted by the authors, on motivated patients with newly diagnosed type 2 diabetes during a clinical trial.

Conclusion: In the treatment of type 2 diabetes dapagliflozin lowered A1C, FPG, and resulted in weight loss amongst patients being treated with the medication. Dapagliflozin did show the ability to cause weight loss. However, the progressive weight loss seen throughout the trial had not reached a plateau by the end of the study. The adverse event profile of dapagliflozin included UTIs and genital infections. These were more frequently reported in the dapagliflozin arm. Taking into consideration patient's ongoing weight loss at the end of the trial and a potential to cause UTIs and genital infections more studies should be conducted focusing on these specific areas. Overall, dapagliflozin showed that it did result in a decrease in hyperglycemia (A1C and FPG) in medication naïve type 2 diabetic patients.

Nauck MA, Prato DS, Meier JJ, Duran-Garcia S, Rowedder K, Et al. Dapagliflozin Versus Glipizide as Add-on Therapy in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control With Metformin.[8] Diabetes Care. 2011;34:2015-2022

Study Design: 52-week, double-blind, multicenter, active-controlled, non-inferiority trial

Description: This study took place at 95 sites in 10 different countries. The patient profile includes men and women aged ≥18 years at enrollment with an A1C between 6.5-10%. A maximum of 25% of randomized patients had a baseline HbA_{1c} <7%. Further criteria included a fasting plasma glucose (FPG) ≤15 mmol/L and C-peptide concentration of ≥0.33 nmol/L. The study had an 18 week titration period and 34 week maintenance period. Patients in the trial were initially stabilized on metformin 1,500-2,500mg daily. Patients were then double blinded and placed on either glipizide or dapagliflozin. Patients were titrated up every 21 days until the max dosage of each drug was reached. Patient's not achieving adequate glycemic control were discontinued from the trial. The primary endpoint of the study was absolute change in HbA1c. Secondary endpoints included change in TBW, reports of hypoglycemia, and proportion of patients a TBW decrease of > 5%. Patient's safety was monitored throughout the study via laboratory tests, physical exams, electrocardiographic tests, and creaatinine clearance. Dapagliflozin produced a long-term HbA_{1c} mean reduction at 52 weeks that was numerically identical and statistically noninferior to the sulfonylurea glipizide in patients poorly controlled with metformin monotherap in addition to decreasing blood pressure and increasing weight loss. The study resulted in an HbA1c adjusted mean change for dapagliflozin (-0.52) (95% CI-0.60 to-0.44) and glipizide (-0.52) (95% CI -0.60 to -0.44) that was statistically non-inferior. . Dapagliflozin produced a long-term HbA1c mean reduction at 52 weeks that was numerically identical and statistically noninferior to the sulfonylurea glipizide in patients poorly controlled with metformin monotherapy in addition to decreasing blood pressure and increasing weight loss. Furthermore, the patients taking dapagliflozin lost weight whereas glipizide patients gained weight. It is also important to note that fewer hypoglycemic events occurred with dapagliflozin compared with glipizide and metformin. The proportion of patients with at least one episode of hypoglycemia at 52 weeks and was documented with a difference versus glipizide plus metformin; (-37.2%) (95 CI of difference -42.3 to -21.2; P < 0.0001). Furthermore, there was a higher proportion of patients in the dapagliflozin arm that reported UTIs and genital infections.

Limitations: Multiple contributors to the study had worked for Astra Zeneca and Astra Zeneca sponsored the trial. Within the study there are no baseline characteristics of the patient's listed, time specific criteria caused patients to be excluded from the trial and an adverse event analysis was not conducted.

Conclusion: Over the course of the 52 week trial dapagliflozin produced an HbA1c mean reduction at 52 weeks that was numerically identical and statistically non-inferior than glipizide. In addition, dapagliflozin produced significant weight loss and less hypoglycemic events when compared to glipizide. As with previous studies reports of UTIs and genital infections were reported. These specific adverse effects should be reviewed based upon their occurrence in other trails. Dapagliflozin was found to be non-inferior to glipizide in treating patients with type 2 diabetes already taking metformin. The safety and efficacy during the trial, of dapagliflozin was very similar to that of glipizide.

Contraindications[1, 2, 3, 4]:

Severe renal impairment

CRCL <60ml/min

Precautions[1,2,3,4,5]:

Genital mycotic infections: Patients may be at increased risk for Vulvovaaginal infections.

Hypersensitivity reactions: Angioedema or uticaria may occur.

Hypotension: Use with caution in patients on anti-hypertensive medications. Dapagliflozin may cause symptomatic hypotension due to fluid volume depletion. It is recommended to assess volume status before starting dapagliflozin in patients at risk for hypotension.

Lipid abnormality: May cause elevation in LDLs.

Renal Impairment: Should not be used in patients with CRCL <60ml/min due to less efficacy and increased risk of bone fractures.

Bladder Cancer: Not recommended in patient with active bladder cancer due to increased frequency in newly diagnosed bladder cancer in patients taking dapagliflozin.

Adverse Effects:

Occurring in >10% of patients

Endocrine & Metabolic

Mild Hypoglycemia (40% to 43%)

Occurring in >1% to <10% of patients

Endocrine & Metabolic

Dyslipidemia (2% to 3%)
Hypovolemia (1%)
Increased serum phosphate (2%)

Gastrointestinal

Constipation (2%)
Nausea (3%)

Genitourinary

Dysuria (2%)
Fungal Vaginosis (7% to 8%)
Genitourinary fungal infection (3%)
Increase Urine Output (3% to 4%)
UTI (4% to 6%)

Hematologic

Increased Hematocrit (>55%) (1%)

Infection

Influenza (2% to 3%)

Neuromuscular & Skeletal

Limb pain (2%)
Back pain (3% to 4%)

Respiratory

Nasopharyngitis (6% to 7%)

Drug Interactions[1,2,3,4,5]:

Inhaled and Systemic corticosteroids, Loop diuretics, Thiazide diuretics

Hypoglycemic effect of dapagliflozin may be diminished

Duloxetine

Possible enhancement of orthostatic hypotensive effect of duloxetine

Hypotensive agents

Possible enhancement hypotension

SSRIs, MAO inhibitors, Salicylates, Pegvisomant

Possible enhancement of hypoglycemic effects of dapagliflozin

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

Initial dose: 5mg/day
Dosage titration: Increase to 10mg/day

Pediatrics

Safety not established.

Renal impairment

Not recommended in patients with CRCL <60ml/min

Conclusion:

Dapagliflozin was found to increase glycemic control in 3 separate clinical trials. Dapagliflozin was approved by the FDA in January 2014 for the treatment of Type 2 Diabetes Mellitus. There may be a link to bladder cancer in patients taking dapagliflozin. Severe renal impairment is a contraindication to the use of dapagliflozin and dapagliflozin has the potential to cause hypotension. Although approved by the FDA in January 2014 the link to bladder cancer is of concern and further testing should be done to further investigate the link between the two. Weight loss has also been shown with dapagliflozin in clinical trials. However, the exact link between weight loss and dapagliflozin is not known. In one clinical trial patients being treated with dapagliflozin were shown to be still losing weight at the end of the trial. During clinical trials one of the more common side effects that patients experienced were UTIs and genital infections. This raises concern as well and requires further studies. Overall, dapagliflozin has shown to be effective in improving glycemic control in type 2 diabetes patients. Dapagliflozin may have a place in therapy as a second line or add on agent for patients who have not been able to achieve glycemic control with their current therapy. Dapagliflozin appears to cause weight loss in patients. If further clinical trials prove that this is a safe and effective form of weight loss overweight patients who have not been able to achieve glycemic control could benefit from the addition of the drug. Regardless of the indication dapagliflozin is contraindicated for use in patients with renal failure or who are on dialysis.

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