Randomised, double-blind trial of dual add-on saxagliptin plus dapagliflozin vs saxagliptin or dapagliflozin add-on alone in poorly controlled type 2 diabetes on metformin

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Background and aims: SGLT2 and DPP-4 inhibitors have complementary mechanisms of action that can potentially improve glucose control with weight loss and a low risk of hypoglycaemia. We compared the efficacy and safety of dual add-on of saxagliptin (SAXA) and dapagliflozin (DAPA) with SAXA and DAPA alone in patients with type 2 diabetes mellitus (T2DM) poorly controlled with metformin.
Materials and methods: In this 24-week, multicenter, randomized, double-blind, active-controlled trial, adults with T2DM and A1C ≥8.0% and ≤12.0%, received SAXA 5 mg and DAPA 10 mg once daily compared with SAXA and placebo (PBO) or DAPA and PBO on background of metformin XR ≥1500 mg/d. The primary end point was the adjusted mean change in A1C from baseline to week 24. Safety and tolerability assessments included adverse events (AEs) and hypoglycaemia.
Results: A total of 534 patients were randomized. Mean ± SD A1C at baseline in SAXA+DAPA, SAXA+PBO, and DAPA+PBO groups was 8.9 ± 1.2%, 9.0 ± 1.1%, and 8.9 ± 1.2%, respectively. Adjusted mean reduction from baseline in A1C was -1.47% in SAXA+DAPA compared with -0.88% in SAXA+PBO (difference −0.59%; 95% CI [-0.81, -0.37]; *P*<0.0001) and -1.20% in DAPA+PBO (difference −0.27%; 95% CI [-0.48, -0.05]; *P*<0.02). The adjusted mean proportion of patients achieving A1C <7% was 41% in SAXA+DAPA compared with 18% in SAXA+PBO (difference of 23%; 95% CI [15, 32]) and 22% in DAPA+PBO (difference of 19%; 95% CI [10, 28]). AEs occurred in 48.6%, 52.8%, and 48.6% of patients in the SAXA+DAPA, SAXA+PBO, and DAPA+PBO groups, respectively. Urinary and genital infections occurred with the expected frequency previously reported. Incidence of hypoglycaemia was 1.1%, 0.6%, and 1.1%, respectively with no episodes of major hypoglycaemia.
Conclusion: This first report of triple therapy, adding a well-tolerated combination of DPP-4 and SGLT2 inhibitors to background metformin therapy in patients with T2DM poorly controlled with metformin, demonstrated that the dual add-on combination of SAXA and DAPA had greater improvements in glucose control than each component alone. More than 40% of poorly controlled T2DM patients receiving SAXA+DAPA achieved an A1C goal of <7%, with weight loss similar to DAPA alone and with very low hypoglycaemia risk.
Clinical Trial Registration Number: NCT01606007
Supported by: BMS and AstraZeneca