of the hormone leptin, improves glycemia in patients with Rabson-Mendenhall Syndrome. We measured HbA1c in 11 patients with Rabson-Mendenhall Syndrome treated with high-dose metreleptin (≥0.15 mg/kg/day) after 6, 12, 18, 24, 36, 48, and 60 months, and at last follow up in patients treated >60 months (mean 90 months). We measured HbA1c over a comparable time frame in 7 untreated patients with Rabson-Mendenhall syndrome. 5 of these patients were also in the treatment group and were studied prior to starting metreleptin treatment or after metreleptin withdrawal. 2 patients in the untreated cohort were never treated with high-dose metreleptin. We calculated change in A1c from baseline at each of these timepoints in both the treated and untreated groups. At baseline the treatment group had similar age (13.8±5.0 vs 11.3±5.3 years, P=0.35) and trended toward higher A1c (10.7%±1.5 vs 8.9%±2.3%, P=0.08). All analyses were therefore adjusted for baseline A1c. In the untreated group, A1c increased non-significantly over time (P=0.2). Least-square mean change in A1c from baseline was 0.2%±1.4%, 0.2%±1.6%, 0.8%±1.5%, 1.0%±1.5%, 1.8%±1.5%, 1.5%±1.5%, 0.9%±1.4%, and 2.4%±1.4%. at 6, 12, 18, 24, 36, 48, and ~90 months of follow-up. During high-dose metreleptin treatment, A1c decreased non-significantly over time (P=0.2). Least square mean change in A1c from baseline was -1.9%±1.7%, -1.4%±1.8%, -1.0%±1.7%, -1.1%±1.7%, -1.1%±1.7%, -1.5%±1.7%, -0.6%±1.7%, and -0.2%±1.7% at 0, 6, 12, 18, 24, 36, 48, and ~90 months of follow-up. Reductions in A1c after metreleptin were statistically significant at months 6 (p=0.009), 12 (p=0.03), and 48 (p=0.04). Over time, A1c was 1.4% higher in the untreated group vs. the metreleptin treated group (P=0.04). These results suggest that treatment with metreleptin may lower A1c over time in patients with Rabson-Mendenhall syndrome. Better glycemic control, as indicated by lower average HbA1c levels, may reduce the risk of diabetic complications over time.

Diabetes Mellitus and Glucose Metabolism

CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE

Efficacy and Safety of Ertugliflozin in Patients With Type 2 Diabetes Mellitus and Established Cardiovascular Disease Treated With Metformin and Sulfonylurea

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Introduction: Ertugliflozin (ERTU), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). **Aim:** As a pre-specified sub-study of the Phase 3 VERTIS CV trial (NCT01986881), the efficacy and safety of ERTU were assessed in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) inadequately controlled with metformin and sulfonylurea (SU). **Methods:** Patients with T2DM, established ASCVD, and HbA1c 7.0–10.5% on stable metformin (≥1500 mg/day) and SU doses as defined per protocol were randomized to once-daily ERTU (5 mg or 15 mg) or placebo. The primary sub-study objectives were to assess the effect of ERTU on HbA1c compared with placebo and to evaluate safety and tolerability during 18-week follow-up. Key secondary endpoints included proportion of patients achieving HbA1c <7%, fasting plasma glucose (FPG), body weight, and systolic blood pressure. Changes from baseline at Week 18 for continuous efficacy endpoints were assessed using a constrained longitudinal data analysis model. **Results:** Of the 8246 patients enrolled in the VERTIS CV trial, 330 patients were eligible for this sub-study (ERTU 5 mg, n=100; ERTU 15 mg, n=113; placebo, n=117). Patients had a mean (SD) age of 63.2 (8.4) years, T2DM duration 11.4 (7.4) years, estimated glomerular filtration rate 83.5 (17.8) mL/min/1.73 m^2, and HbA1c 8.3% (1.0) (67.4 [10.6] mmol/mol). At Week 18, ERTU 5 mg and 15 mg were each associated with a significantly greater least squares mean (95% CI) HbA1c reduction from baseline versus placebo; the placebo-adjusted differences for ERTU 5 mg and 15 mg were –0.7% (–0.9, –0.4) and –0.8% (–1.0, –0.5), respectively (P<0.001). A higher proportion of patients in each ERTU group achieved HbA1c <7% relative to placebo (P<0.001). ERTU significantly reduced FPG and body weight (P<0.001, for each dose versus placebo), but not systolic blood pressure. Adverse events were reported in 48.0%, 54.9%, and 47.0% of patients in the ERTU 5 mg, 15 mg, and placebo groups, respectively. Genital mycotic infections were experienced by significantly higher proportions of male patients who received ERTU 5 mg and 15 mg (4.2% and 4.8%, respectively) versus placebo (0.0%; P≤0.05) and by a numerically, but not significantly, higher proportion of female patients who received ERTU 15 mg (10.3%) compared with placebo (3.8%) (P=0.36). The incidences of symptomatic hypoglycemia were 11.0% (5 mg), 12.4% (15 mg), and 7.7% (placebo), and of severe hypoglycemia 2.0% (5 mg), 1.8% (15 mg), and 0.9% (placebo). **Conclusion:** Among patients with T2DM and ASCVD, ERTU (5 mg and 15 mg) added to metformin and SU for 18 weeks improved glycemic control (HbA1c and FPG) and reduced body weight, and was generally well tolerated with a safety profile consistent with the SGLT2 inhibitor class.

Diabetes Mellitus and Glucose Metabolism

CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE

Efficacy and Safety of Ertugliflozin in Patients With Type 2 Diabetes Mellitus and Established Cardiovascular Disease Using Insulin

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Introduction: Ertugliflozin (ERTU), a sodium-glucose cotransporter 2 inhibitor, is approved as an adjunct to diet and exercise to improve glycemic control in patients (pts) with type 2 diabetes mellitus (T2DM). **Aim:** As part of the VERTIS CV trial (NCT01986881), the efficacy and safety of ERTU were assessed in pts with T2DM and established atherosclerotic cardiovascular disease (ASCVD) inadequately controlled by insulin. **Methods:** Pts were randomly assigned to placebo (PBO), ERTU 5 mg or 15 mg once daily. A pre-specified sub-study was conducted in pts on a stable dose of insulin ≥20 units/day (± metformin). The primary endpoint was HbA1c change from baseline at 18 weeks. Key secondary endpoints included proportion of patients achieving HbA1c <7%, fasting plasma glucose (FPG), body weight (BW), and systolic blood pressure (SBP). Changes from baseline at Week 18 for continuous efficacy endpoints were assessed using a constrained longitudinal data analysis model. HbA1c reduction was also assessed in subgroups based on baseline HbA1c, age, sex, race, ethnicity, and use of metformin. **Results:** Of 8246 pts randomized in VERTIS CV, 1065 pts (ERTU 5 mg: 348; ERTU 15 mg: 370; PBO: 347) with T2DM and ASCVD were included in the sub-study. Mean baseline characteristics were similar across treatment groups; age 64.8 years, T2DM duration 16.7 years, HbA1c 8.4%, and eGFR 73.7 mL/min/1.73 m^2. At baseline, 40.6% of pts were on insulin alone, 59.4% were receiving insulin + metformin; median (range) insulin dose was 58.0 (20–350) units/day. At Week 18, least squares mean change (95% confidence interval) from baseline in HbA1c was significantly greater with ERTU 5 mg and 15 mg vs PBO. PBO-adjusted differences were −0.6% (−0.7, −0.4) and −0.7% (−0.8, −0.5), for ERTU 5 mg and 15 mg, respectively (P<0.001 for both). HbA1c reductions were greater with ERTU vs PBO for all subgroups including by use of metformin. At Week 18, 10.7%, 20.7%, and 21.1% of pts with PBO, ERTU 5 mg and 15 mg, respectively, achieved HbA1c <7.0%. ERTU 5 mg and 15 mg significantly reduced FPG, BW, SBP, and ERTU 15 mg led to a small reduction in total daily insulin dose. The overall incidence of adverse events and serious adverse events was similar across treatment groups. In women, the incidences of genital mycotic infections was higher with ERTU 5 mg (3.4%; P=0.05) and ERTU 15 mg (3.6%; P=0.04) vs PBO (0.0%). The incidences of urinary tract infections (3.2–4.1%), symptomatic hypoglycemia (26.4–28.5%), and severe hypoglycemia (3.5–5.1%) were similar across treatment groups. The incidences of hypovolemia were low (1.4–2.4%) and similar across treatment groups. **Conclusion:** ERTU added to insulin (± metformin) led to greater reductions from baseline in HbA1c, FPG, BW, and SBP, and a higher proportion of pts achieving HbA1c <7.0%, vs PBO at 18 weeks in pts with T2DM and ASCVD, without increasing the risk of hypoglycemia.

Diabetes Mellitus and Glucose Metabolism

CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE

Efficacy of Dulaglutide Expanded Doses by Baseline A1C Categories: Post Hoc Analysis of AWARD-11

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The AWARD-11 trial demonstrated the safety and efficacy of dulaglutide (DU) once weekly doses of 3 mg and 4.5 mg compared to DU 1.5 mg in patients with type 2 diabetes (T2D) inadequately controlled with metformin monotherapy. This exploratory post hoc analysis of AWARD-11 assessed the effect of dulaglutide on A1C reduction by clinically-relevant baseline A1C subgroups (<8%; 8%-<9%; 9%-<10%; ≥10%) and the proportion of patients achieving A1C <7% in these subgroups through 36 and 52 weeks. Patients were randomized to once weekly DU 1.5 mg (n=612), 3 mg (n=616), or 4.5 mg (n=614). All patients initiated once weekly DU 0.75 mg for 4 weeks, followed by stepwise dose escalation every 4 weeks to the randomized dose. A mixed effects model for repeated measures was used within the A1C subgroups to assess the change in A1C from baseline at 36 and 52 weeks. A longitudinal logistic regression model was used within subgroups to analyze the proportion of patients achieving A1C <7% at 36 and 52 weeks. Efficacy analyses used data collected up to initiation of rescue medication or premature treatment discontinuation, if either occurred. DU 1.5 mg reduced A1C across all baseline A1C categories at 36 weeks (range, -1.0 to -2.2%) and effects were sustained through 52 weeks (range, -1.0 to -2.1%). A1C reductions were greater in patients randomized to DU 3 mg or 4.5 mg versus 1.5 mg in each A1C subgroup, with greater dose-related improvements in patients with higher baseline A1C through 36 weeks (A1C subgroup, least-squares mean change in A1C [%] with 1.5 mg, 3 mg, and 4.5 mg, respectively: A1C<8%, -1.0, -1.2, -1.2; A1C 8-<9%, -1.4, -1.6, -1.8; A1C 9-<10%, -2.1, -2.2, -2.3; A1C ≥10%, -2.2, -2.5, -3.2; interaction p<0.001). More patients randomized to 3 mg or 4.5 mg achieved A1C <7% versus those on 1.5 mg at 36 weeks regardless of baseline A1C, but the difference across dose groups was greater at higher baseline A1Cs. Over half of patients randomized to DU 4.5 mg achieved A1C <7% in every baseline A1C category (A1C<8%, 75%, 87%, 83%; A1C 8-<9%, 61%, 64%, 73%; A1C 9-<10%, 46%, 51%, 64%; A1C ≥10%, 19%, 33%, 55% for DU 1.5 mg, 3 mg, and 4.5 mg, respectively; interaction p=0.096). Similar patterns of dose-related improvement in A1C and proportions of patients achieving A1C <7% across baseline A1C categories were observed at 52 weeks. Gastrointestinal adverse events were similar between A1C subgroups. Glycemic control as measured by A1C and proportion of patients achieving A1C <7% was improved with DU dose escalation from 1.5 mg to 3 mg or 4.5 mg across a spectrum of clinically relevant baseline A1C categories without increasing incidence of GI adverse events. Patients at higher baseline A1Cs (9%-<10% and ≥10%) had larger dose-related improvements in glycemic control than those at lower baseline A1Cs (<8% and 8%-<9%). The majority of patients randomized to DU 4.5 mg achieved glycemic target across all categories of baseline A1C.