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

Matthew J. Budoff, MD[1], Timothy M.E. Davis, BScMed (Hons), MB BS, DPhil (Oxon)[2], Alexandra G. Palmer, BSc[3], Robert Frederich, MD, PhD[4], David E. Lawrence, PhD[5], Jie Liu, MD[6], Ira Gantz, MD[6], Giuseppe Derosa, MD, PhD[7].
[1]Lundquist Institute, Torrance, CA, USA, [2]University of Western Australia, Crawley, Australia, [3]Pfizer Inc., Groton, CT, USA, [4]Pfizer Inc., Collegeville, PA, USA, [5]Pfizer Inc., New York, NY, USA, [6]Merck & Co., Inc., Kenilworth, NJ, USA, [7]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.

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

Ildiko Lingvay, MD[1], Michelle D. Greenberg, BSc[2], Silvina Gallo, MD[3], Harry Shi, MS[4], Jie Liu, MD[5], Ira Gantz, MD[5].
[1]UT Southwestern Medical Center, Dallas, TX, USA, [2]Pfizer Inc., Groton, CT, USA, [3]Pfizer Deutschland GmbH, Berlin, Germany, [4]Pfizer Inc., New York, NY, USA, [5]Merck & Co., Inc., Kenilworth, NJ, USA.