Cardiovascular safety and efficacy of exenatide once-weekly in patients with moderate renal dysfunction in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

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Background and aims: EXSCEL, a multinational, randomized, placebo-controlled cardiovascular (CV) outcome trial of 2 mg once-weekly exenatide added to usual care, demonstrated CV safety in patients with type 2 diabetes (T2D) with or without previous CV disease. We report the impact of exenatide on confirmed CV outcomes, all-cause mortality, and key CV safety parameters according to baseline renal function (moderate dysfunction [<60 mL/min/1.73m2] and within Stage 3 [3a: eGFR 45-59 or 3b: 30-44 mL/min/1.73m2] chronic kidney disease).

Materials and methods: For the subgroups by baseline renal function, Cox proportional hazards models were fit to the time to first event of the three-component major adverse CV event (MACE-3) composite outcome (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke). Secondary outcomes were time to all-cause mortality, death from CV cause, nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome.

Results: Of 14,752 patients in the ITT population, 3191 (22%) had eGFR<60, 2288 (16%) had eGFR 45-59 and 889 (6%) had eGFR 30-44 mL/min/1.73m2. Participants with moderate renal dysfunction had a higher mean age (67 vs 61 years) and longer duration of T2D (median [IQR] 14 [9,21] vs 11 [6,17] years). In univariate subgroup analyses, there was no significant interaction between randomized treatment and renal function, either based on eGFR thresholds (± 60 mL/min/1.73m2; p for interaction = 0.12) or on CKD stages (p for interaction = 0.51). In those with eGFR <60 mL/min/1.73m2, first MACE-3 events occurred in 283 (18.1%) participants in the exenatide group and 284 (17.5%) in the placebo group (hazard ratio [HR] 1.01, 95% CI 0.86-1.19). HR and 95% CI for other important CV outcomes are shown in the Table.

Conclusion: In patients with moderate renal dysfunction, 2 mg once-weekly exenatide had a neutral impact on CV outcomes. In univariate analyses unadjusted for multiplicity, modest risk reductions were seen with exenatide in those with baseline eGFR ≥60mL/min/1.73m2 for MACE-3, all-cause mortality, CV death and fatal or non-fatal stroke.

Clinical Trial Registration Number: NCT01144338
Supported by: AstraZeneca (Gaithersburg, MD)