The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial.

Patients with type 2 diabetes and nephropathy have high cardiorenal morbidity and mortality despite optimum treatment including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.
blockers (ARBs). Residual risk is related to residual albuminuria. We assessed whether CCX140-B, a selective inhibitor of C-C chemokine receptor type 2 (CCR2), could further reduce albuminuria when given in addition to standard care, including ACE inhibitors or ARBs. In this randomised, double-blind, placebo-controlled clinical trial, we recruited patients from 78 research centres in Belgium, Czech Republic, Germany, Hungary, Poland, and the UK. We enrolled patients with type 2 diabetes aged 18-75 years with proteinuria (first morning void urinary albumin to creatinine ratio [UACR] 100-3000 mg/g), estimated glomerular filtration rate of 25 mL/min per 1.73 m(2) or higher, and taking stable antidiabetic treatment and ACE inhibitors or ARBs, for at least 8 weeks before study entry. Patients were stratified based on baseline UACR and renal function (estimated glomerular filtration rate), and then randomly assigned (1:1:1) via an interactive web response system with a minimisation algorithm to oral placebo, 5 mg CCX140-B, or 10 mg CCX140-B once a day. The 12-week dosing period in the initial protocol was extended to 52 weeks by protocol amendment. The primary efficacy measure was change from baseline in UACR during 52 weeks in the modified intention-to-treat population (all patients with uninterrupted dosing, excluding patients who stopped dosing at week 12 either permanently under the original protocol, or temporarily because of delay in approval of the protocol amendment). We did safety analyses on all randomly assigned patients who received at least one dose of study drug. According to a prespecified analysis plan, we analysed the primary endpoint with one-sided statistical testing with calculation of upper 95% confidence limits of the differences between active and control. This trial is registered with ClinicalTrials.gov, number NCT01447147. The study ran from Dec 7, 2011 (first patient enrolled), until Aug 4, 2014. We enrolled 332 patients: 111 were assigned to receive placebo, 110 to 5 mg CCX140-B, and 111 to 10 mg CCX140-B. Of these, 192 were included in the modified intention-to-treat population. UACR changes from baseline during 52 weeks were -2% for placebo (95% CI -11% to 9%), -18% for 5 mg CCX140-B (-26% to -8%), and -11% for 10 mg CCX140-B (-20% to -1%). We recorded a -16% difference between 5 mg CCX140-B and placebo (one-sided upper 95% confidence limit -5%; p=0.01) and a -10% difference between 10 mg CCX140-B and placebo (upper 95% confidence limit 2%; p=0.08). Adverse events occurred in 81 (73%) of 111 patients in the placebo group versus 71 (65%) of 110 patients in the CCX140-B 5 mg group and 68 (61%) of 111 patients in the CCX140-B 10 mg group; there were no renal events during the study. Our data suggest that CCR2 inhibition with CCX140-B has renoprotective effects on top of current standard of care in patients with type 2 diabetes and nephropathy. ChemoCentrx.