**THE PROTEKT STUDY – A PHASE IIA, RANDOMISED, CONTROLLED, OPEN-LABEL TRIAL OF ROSUVASTATIN FOR THE PREVENTION OF AMINOGLYCOSIDE-INDUCED KIDNEY TOXICITY IN CHILDREN WITH CYSTIC FIBROSIS**

**Background and purpose**

Aminoglycoside antibiotics are commonly used for the treatment of respiratory exacerbations in CF, but their use can be complicated by nephrotoxicity. Megalin-mediated endocytosis is the principal pathway for the accumulation of aminoglycosides in proximal tubule epithelial cells (Schmitz C, et al. J Biol Chem. 2002;277:618-22), resulting in kidney toxicity. Activation of this pathway depends on intermediates derived from mevalonate, the product of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reduction, catalysed by HMG-CoA reductase (Khwaja A, et al. Lancet. 2000;355:741-4). We have demonstrated *in vitro* that inhibition of HMG-CoA reductase by statins reduces uptake of aminoglycosides in proximal tubule epithelial cells, leading to a reduction in toxicity (Antoine DJ, et al. Biochem Pharmacol. 2010;79:647-54). The protective effect of statins on aminoglycoside nephrotoxicity has also been shown in vivo in two animal models. PROteKT investigates the potential of repurposing a statin to prevent aminoglycoside-induced nephrotoxicity in humans.

**Study design**

Children with CF were recruited at 13 paediatric CF centres in the UK. Participants were randomised equally to either receive rosuvastatin 10mg once daily or no intervention (control), throughout a clinically indicated course of treatment with intravenous (IV) tobramycin. Participants provided urine samples for biomarker analysis at baseline, daily during tobramycin exposure and at a follow-up assessment 3-5 weeks later.

**Patient selection criteria**

Eligible participants were children age 6 to 18 years inclusive with a diagnosis of cystic fibrosis (established by sweat test or genotype), due to have a planned, clinically indicated, course of treatment with IV tobramycin.

**Primary and secondary outcome measures**

The primary outcome measure was the difference in mean fold-change in urinary KIM-1 (a biomarker of proximal tubule injury) from baseline to ‘highest value’ concentration during exposure to tobramycin between the rosuvastatin treated arm and control arm. Secondary outcomes were measured at baseline, three formal assessments during tobramycin exposure, and at the follow-up visit, and included change in serum creatinine and estimated GFR; change in urinary NGAL; serious adverse events; difference in tobramycin concentrations; difference in FEV1 and C-Reactive Protein; plasma rosuvastatin concentrations in the intervention arm.

**Results**

The study has completed recruitment, reaching its target of 50 patients. Analysis is ongoing and it is anticipated that final results will be available by October 2017.