**Summary report on: Protocol STH14971**

**CTA Number: 21304/0231/001-0001**

**Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust**

**Title: A pilot study of the effects of glucocorticoid receptor antagonism in patients with cortisol secreting adrenal incidentalomas**

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Aims/hypothesis: Adrenal incidentaloma (AI) are very common, but optimal management of patients with AI and low-grade excess cortisol secretion is not established. Uncontrolled studies reporting outcomes of adrenalectomy suggest improvements in cardiovascular risk, but all are subject to selection bias, and it is unclear if benefits are due to removal of excess cortisol. We reasoned that short-term use of mifepristone, a rapidly-acting glucocorticoid receptor (GR) antagonist, could improve GR-mediated cardiovascular and metabolic risk, with the ultimate aim of devising an individualised means of selecting those most likely to benefit from surgical intervention.

Methods: In a prospective open label pilot study, six patients with mild cortisol excess from adrenal incidentalomas (mean serum cortisol post 1 mg ONDST was 79.8 nmol/l) were treated with mifepristone 200 mg twice/day for up to 8 weeks. Primary end-points were 2-h glucose from OGTT and resting/24-h BP at 4 weeks. Secondary end-points included insulin sensitivity, fasting and AUC insulin and glucose at 4 weeks, resting/24-h BP at 8 weeks, serum 0900 h ACTH/cortisol and salivary 0900/2300 h cortisol at 4 and 8 weeks, lipids and bone markers at 8 weeks.

Results: All subjects showed clear biochemical evidence of GR antagonism, with significant elevations of serum and salivary cortisol, and plasma ACTH. As a group, at 4 weeks, there was a significant improvement in all indices of insulin sensitivity/resistance including HOMA-IR (3.16 vs 2.3; *P*=0.05), HOMA-%β (147.6 vs 91.67; *P*=0.03) and Matsuda index (3.31 vs 4.98; *P*=0.03). In one subject, however, there was no improvement. Treatment with mifepristone did not cause any significant changes in fasting glucose, 2-hour glucose and AUC glucose. Fasting insulin levels and AUC insulin were less in all individuals at follow up compared to baseline.

There were no significant changes in resting/24 h BP, mean serum osteocalcin levels and urine NTX/Creat.

Five patients completed the study to week four. One developed clinical symptoms of lassitude and fatigue at end of week two, whilst another developed similar symptoms at the end of week four. The patients were not admitted to hospital and neither of them required treatment for these episodes. Neither of the cases experienced a fall in blood pressure, nor did they develop postural hypotension. A third patient developed a urinary tract infection and side effects from antibiotics at week seven. These three patients were withdrawn from the study. There were no serious adverse

effects from mifepristone. Maximal effects of the drug, as expected from drug PK characteristics, were achieved by 4 weeks.

No haematological side effects were identified. There were no significant electrolyte changes at week 4 compared to baseline. There were no significant changes in cholesterol, LDL, triglycerides or HDL at end study compared to baseline but there was a significant reversible change in thyroid stimulating hormone (TSH) (1.45 vs 4.07 mU/l; $p = 0.03$).

Conclusions/interpretation: Short-term GR antagonism with mifepristone improves insulin sensitivity in some, but not all, patients with mild cortisol excess. Larger studies are needed, but our data suggest that GR antagonism may form the basis of a clinical tool to stratify patients for intervention in an individualised manner.