**INTRODUCTION**

A major function of the gastrointestinal (GI) tract is to maintain intestinal water/sodium (Na+) homeostasis through blood flow, secretory and absorptive mechanisms. In Chronic Kidney Disease patients, deficient renal Na+ clearance exacerbates fluid overload contributing to hypertension and accelerating cardiac and renal dysfunction. Na2+ is a Na+/H+ antport protein located on the apical membrane of intestinal epithelial cells [1]. RDX5791, a non-systemic drug, potently inhibits NHE3-mediated intestinal Na+ transport leading to enhanced fecal excretion and reduced urinary excretion of this ion. The purpose of this study was to evaluate the safety, tolerability and pharmacodynamics (PD) of different RDX5791 dosing regimens. The results demonstrate that RDX5791 has the potential to normalize hydration in patients with chronic kidney disease and/or heart failure.

**BACKGROUND**

RDX5791 is a potent inhibitor of both rat and human NHE3 and exhibits minimal systemic absorption in multiple species [2]. Through local inhibition of Na+ re-uptake in the lumen of the intestine, RDX5791 causes a shift in Na+ excretion from the kidneys to the GI tract. In rodents, RDX5791 induces a dose-dependent reduction in urinary Na+ and corresponding increase in fecal Na+ [2]. Prophylactic or interventional administration of RDX5791 to 5/6th nephrectomized rats (Nx) on a high Na+ diet results in a dose-dependent reduction in blood pressure, proteinuria and left ventricular hypertrophy [3]. Alone and combined with enalapril, RDX5791 provides cardiac and renal protective effects in salt fed Nx rats as measured by SBP, DBP, proteinuria, pulse wave velocity and other methods [4]. In a randomized, double-blind, placebo-controlled, single ascending dose phase 1a study in 80 healthy male and female volunteers, RDX5791 was well tolerated at all doses tested (10-900 mg) and exhibited pharmacodynamic activity consistent with its mechanism of action [5].

**OBJECTIVES**

1. To evaluate the safety, tolerability and PD activity of RDX5791 in healthy subjects.
2. To evaluate the impact of various dosing regimens on urinary Na and fecal Na.
3. To titrate RDX5791 to effect, i.e. individualize dose in order to augment the responder rate within a given cohort.
4. To monitor the effect on urinary potassium (K+) and calcium (Ca++)

**METHODS**

1. Randomized double-blind, placebo-controlled study performed in an in-patient clinical pharmacology unit.
2. 105 healthy volunteers (19-75 years old), 7 cohorts (12 subjects, 3 placebo).
3. Controlled diet with 200 - 250 mmol Na+/day (+1500 mg Na/meal).

**RESULTS**

Comparing 7 days of cumulative fecal vs. urine Na+

- Urine and blood chemistry:
  1. RDX5791 had no significant effect on urine K+, urine Ca++, and urine pH.
  2. Blood electrolyte levels (Na+, K+, Ca++, Mg++) were not affected by treatment.
  3. Plasma aldosterone exhibited a slight transient increase, within the normal range, and returned to baseline levels during the treatment period.

**DISCUSSION**

RDX5791 was very well tolerated. Fecal sodium increased within the first day of dosing, was sustained during the 7-day treatment period and returned to baseline when the drug was withdrawn on day 8. The reduction of urinary Na+ followed the same trend. Multiple dosing regimens (bid, tid) produced a 2-3 fold greater response than QD dosing. A higher response rate was achieved by titrating the drug to effect (not shown). Heart rate and stool frequency were increased but remained within the normal range. Subjects did not report urgency. The cumulative Na+ excreted over 7 days (corrected from placebo) was ~350 mmol (fecal) and ~400 mmol (urine), respectively. The concentration of Na+ in the stool was similar to the normal concentration of Na+ in plasma (not shown). Treated subjects tended to reduce their fluid intake vs. placebo (not shown). RDX5791 did not induce any significant changes in K+, Ca++, nor did it alter acid base status.

**CONCLUSIONS**

- RDX5791 demonstrated excellent safety due to its non-systemic profile.
- RDX5791 induced a significant increase in stool Na+ with a concomitant decrease in urine Na+.
- Twice-a-day dosing elicited a significantly greater response than once-a-day dosing.
- Fecal Na+ output increased rapidly upon initiation of drug treatment and rapidly returned to baseline levels after drug discontinuation.
- The PD effect was sustained during the 7 days of treatment.
- On a weekly basis, RDX5791 has the potential to remove ~280-350 mmol of Na+, i.e. about 2-2.5 L of extracellular fluid.
- RDX5791 is being developed for the management of fluid overload in ESRD, CRF and heart failure.

**REFERENCES**