SNF472 is an intravenous (i.v.) formulation of myo-inositol-hexaphosphate (phytate). It is a selective calcification inhibitor exerting its effect through binding to hydroxyapatite crystal (HAP) growing sites. It is being developed, as an orphan drug, for the treatment of calciphylaxis. It is also being developed to inhibit the progression of cardiovascular calcification in patients with end stage renal disease on haemodialysis, to prevent cardiovascular events (including mortality). It has been extensively studied in non-clinical models for efficacy, safety, pharmacokinetics and toxicity, and shows a promising profile supporting progression to studies in humans.

**AIM**

The aim of this randomised, double-blind, placebo-controlled, first-time-in-human (FTIH) study was to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending i.v. doses of SNF472 in healthy male volunteers.

**MATERIALS AND METHODS**

Sixteen healthy male subjects were divided into two cohorts (C) with 8 subjects each. Cohorts were randomised in a 2:6 ratio to receive SNF472 or placebo, respectively. Each cohort participated in two treatment periods (TP). Subgroup were dosed in sequential, consecutive subgroups within each cohort. The first subgroup consisted of two sentinel subjects; one subject received SNF472 and one subject received placebo. Subgroup 2 was dosed at least 24 hours after Subgroup 1. C1 and C2 were interlocking cohorts, such that TP alternated between cohorts. Successive TPs between C1 and C2 were separated by at least 7 days. The administered SNF472 doses were: 0.5 mg/kg, 5 mg/kg, 9 mg/kg and 12.5 mg/kg. The study included a screening visit, two treatment periods, and a follow-up visit. The maximum expected duration for an individual subject in this part of the study, including screening and follow-up, was approximately 7 weeks.

**RESULTS**

Pharmacokinetics - Single doses of SNF472 at 5, 9 and 12.5 mg/kg produced measurable SNF472 concentrations (Figure 2A), whilst C<sub>max</sub> and AUC parameters increased in a slightly more than dose proportional manner (Figure 2B). Maximum mean plasma concentrations of 10-fold the anticipated EC<sub>50</sub> were achieved. The PK stopping criterion (C<sub>max</sub> of 127.291 nM/mL) was not met for any of the subjects studied. At all doses, steady state was not achieved at the end of infusion, as seen in Figure 2A. This suggests a 2-compartmental behavior for SNF472, with a short distribution half-life (t<sub>1/2</sub>) of around 30 minutes and a longer elimination half-life of around 2 hours. The total amount of SNF472 excreted in urine accounted for less than 1% of the total administered dose.

Safety - Good systemic tolerability was observed at all doses. The only adverse event (AE) of note was local irritation and mild pain at the infusion site, which cleared within 1-2 days. This appears to be related to the local concentration in the vein at the infusion site, it is not expected to be an issue in haemodialysis patients as the drug will be administered into the tubing delivering blood to the dialysis column. There were no serious AEs, no deaths, and no withdrawals due to AEs during the study. No meaningful differences were observed for data reported from the clinical laboratory tests. 12-Lead ECGs, physical examinations, Visual Analog Scale (VAS) tests, and Orthostatic hypotension tests (Table 2). Ionised calcium levels were measured, although several errors occurred in terms of sampling and analysis. The data suggested a possible dose-related decrease as shown in Figure 3. There were however no clinical features of hypocalcaemia or clinically relevant increases in QTc observed with any of the three doses evaluated. Furthermore, in the intended therapeutic situation (infusion during dialysis), the ionized Ca concentration in the blood will be stabilised by the Ca concentration in the dialysate fluid.

Pharmacodynamics - PD assessments showed an 80% inhibition at 5 mg/kg SNF472 on the blood potential to calcify, which appeared to be a plateau as the effects were similar for 9 mg/kg and 12.5 mg/kg doses (Figure 4).