FIRST-TIME-IN-HUMAN PHASE I CLINICAL TRIAL IN HEALTHY VOLUNTEERS WITH SNF472, A NOVEL INHIBITOR OF VASCULAR CALCIFICATION

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INTRODUCTION

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.

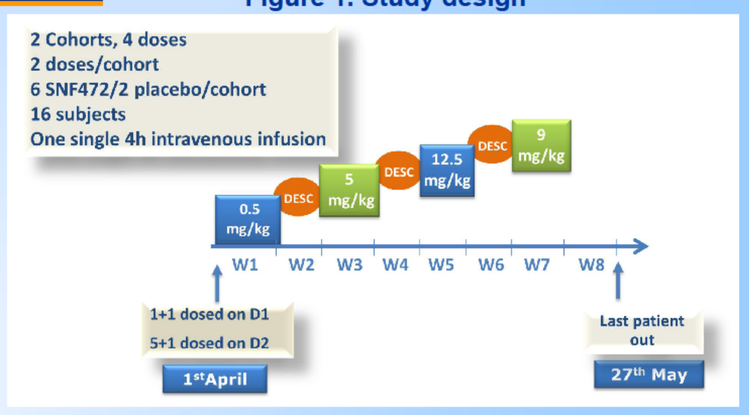
AIM

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 6:2 ratio to receive SNF472 or placebo, respectively. Each cohort participated in two treatment periods (TP). Subjects 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 TPs 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.

Figure 1. Study design



Fasting subjects received a single i.v. dose of either SNF472 or placebo over a 4-hour period in the morning of day 1 of each TP. Safety monitoring (vital signs, 12 lead ECG, and safety laboratory assessments), serial blood, and urine samples for PK were performed at specific time points during the TPs. Extensive ECG assessments were undertaken and subjects were monitored for hypocalcaemia by clinical signs and blood calcium measurements during TPs. Subjects were discharged from the Clinical Unit (CU) on day 3 of each TP after all the assessments had been completed. Subjects returned to the CU on day 4 after each TP for PK blood samples and safety assessments, and on day 7 for safety assessments. Subjects returned to the CU on day 14 after TP2 for a follow-up visit.

SNF472 was quantified in all PK samples by tandem mass spectrometry after separation in gradient reversed-phase chromatography **(Tur et al. J Chromatogr B 2014; 928:146-54).**

PD assessed the potential for ex vivo formation of HAP crystals in plasma samples obtained at baseline and around the t_{max} at the end of the 4-hour of infusion.

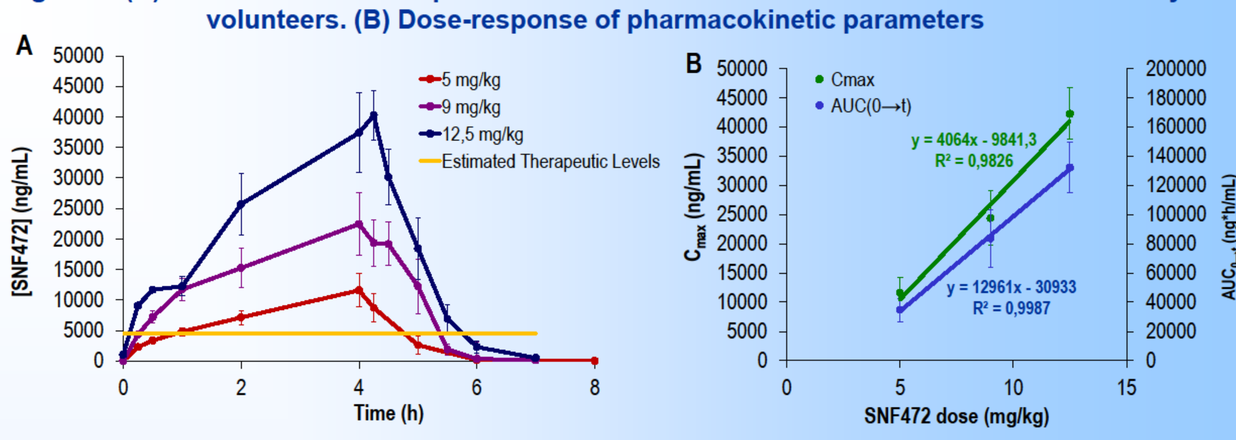
RESULTS

Pharmacokinetics - Single doses of SNF472 at 5, 9 and 12.5 mg/kg produced measurable SNF472 concentrations (Figure 2A), whilst C_{max} and AUC parameters increased in a slightly more than dose proportional manner (Figure 2B). Maximum mean plasma concentrations of 10-fold the anticipated EC_{50} were achieved. The PK stopping criterion (C_{max} of 127,291 ng/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-compartments behavior for SNF472, with a short distribution half-life ($t_{½}$) of around 30 minutes and a longer elimination $t_{½}$ of around 2 hours. The total amount of SNF472 excreted in urine accounted for less than 1% of the total administered dose.

Table 1. Pharmacokinetic parameters of SNF472 after 4-hour intravenous infusion in healthy volunteers

Statistic	t_{max} (min)	C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)	AUC_{0-inf} (ng*h/mL)	$\%AUC_{ex}$ (%)	λ_z (1/h)	$t_{1/2}$ (min)	Vz (mL)	CL (mL/h)
C2TP1 - 5 mg/kg									
Mean	240	11571	34819	42475	2.8	1.782	24	6339	11679
SD	1	6653	19407	20580	2.1	0.335	4	2244	6125
C2TP2 – 9 mg/kg									
Mean	214	24394	83686	89896	9.0	1.222	54	12446	8749
SD	76	11499	48680	43951	18.5	0.503	59	16516	3451
C1TP2 – 12.5 mg/kg									
Mean	252	42207	132161	133659	1.2	1.531	29	5832	8493
SD	8	10785	42195	42456	0.8	0.431	8	2316	3066

Figure 2. (A) Pharmacokinetics of plasma SNF472 after 4-hour intravenous infusion in healthy volunteers. (B) Dose-response of pharmacokinetic parameters



Results represent mean ± SEM

Safety - Good systemic tolerability was observed at all dose levels. The only adverse event (AE) of note was local irritation and mild pain at the infusion site, which cleared within 1-2 days. As 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 Analogue 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 dialysis 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 the 9 mg/kg and 12.5 mg/kg doses (Figure 4).

Table 2. Summary of safety findings after SNF472 4-hour intravenous infusion in healthy volunteers

Dose (mg/kg)	i.v. concentration (ng/mL)	Plasma levels Cmax (ng/mL)	Safety	
			Local tolerability	ECG, vital signs, CS
0.5	0.8	< 500	2/8 Mild	No effects
5	8	11496	5/8 Mild	No effects
9	0.7	26661	3/8 Mild	No effects
12.5	1	40433	4/7 Moderate	No effects

Figure 3. Ionised calcium levels after SNF472 4-hour intravenous infusion

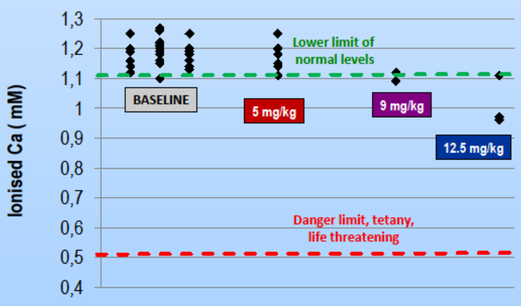
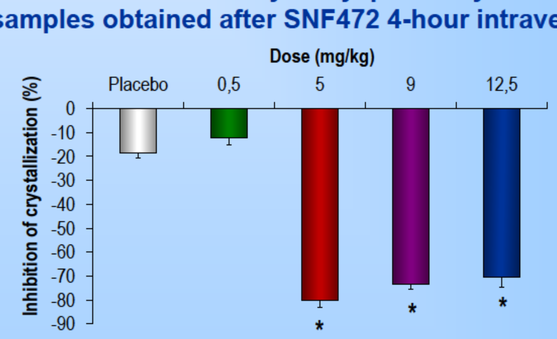


Figure 4. Ex vivo inhibition of hydroxyapatite crystallization in human plasma samples obtained after SNF472 4-hour intravenous infusion



Results repreemt mean ± SEM. Statistical analysis: One-way ANOVA. (*) Differences vs. placebo and 0.5 mg/kg, p < 0.05

CONCLUSIONS

1. SNF472 first human data shows acceptable pharmacokinetics and a wide safety profile
2. SNF472 shows a maximal inhibition effect on ex vivo hydroxyapatite formation at 5 mg/kg
3. SNF472 shows a wide safety margin in terms of hypocalcaemic adverse events
4. SNF472 presents a novel approach to inhibit cardiovascular calcification

L6) Dialysis. Bone disease

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L6) Dialysis. Bone disease.
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