A PHASE 1B/2A RANDOMISED, PLACEBO-CONTROLLED CLINICAL TRIAL WITH SNF472 IN HAEMODIALYSIS PATIENTS

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Introduction to SNF472

- IP6: myo-inositol hexaphosphate (MW = 792 Da)
- IP6: potent modulator of calcification
- Natural nutritional ingredient, GRAS listed
- Low oral availability (highly polar)
- IP6 found in blood
- Physiological levels: blood < 0.3 uM
- SNF472: modified IP6 salt, i.v. formulation
- Expected therapeutic activity at concentrations 2-3 uM
- SNF472 in clinical development for cardiovascular calcification in ESRD dialysis patients and calciphylaxis
The relevance of cardiovascular calcification

- Progression of CACs predicts CV events and all-cause mortality

General Population

- Accelerated progression > 75th percentile
- Progression absent-moderate

CKD2-5

- Progression absent-moderate

CKD5-ESRD

- All-cause mortality according to CAC progression

Budoff et al J Am Coll Cardiol 2010

Russo et al Kidney Int 2011

Bellasi 2012, oral communication
SNF472 directly inhibits the final common step.
SNF472: Therapeutic margin

- In vitro efficacy
- In vivo efficacy (EC50)
- Bolus/Side effects: ↓Ca

[Ca] in blood = 2200-2700 μM
SNF472: Therapeutic margin

- **In vitro efficacy**
  - Bolus/Side effects: ↓Ca

- **In vivo efficacy (EC50)**
  - \([\text{Ca}] = 2200-2700 \mu M\)

- **Selective and potent binding to HAP**
  - Stop HAP crystall growth

- **SNF472: Therapeutic margin**
  - Start chelating free calcium in blood
  - EFFICACY
  - CHELATION
  - X 100

- [SNF472] (ng/ml)
  - 3·10^5
  - 10^5
  - 3·10^4
  - 10^4
  - 3·10^3
  - 10^3
  - 3·10^2

- [SNF472] (μM)
  - 450
  - 150
  - 45
  - 15
  - 4.5
  - 1.5
  - 0.45
Phase 1 Clinical Trials

PHASE 1a
1) SAD, 2 cohorts 16 male HV
   0.5 mg/kg
   5 mg/kg
   DESC
   9 mg/kg
   12.5 mg/kg

2) SD
   8 male HD patients
   9 mg/kg

PHASE 1b
1) Multiple ascending dose (MAD), 8 male HD patients, 1-week treatment periods
   5 mg/kg
   DESC
   12.5 mg/kg
   DESC
   20 mg/kg

2) Repeated dose, 8 male HD patients, 1 month
   10 mg/kg
   1-month cohort
   3 mg/kg
   DESC
   1 mg/kg
   DESC
Phase 1b: Design

1) Cohort 1: Multiple ascending dose
   8 HD (2 placebos; 6 actives), 1 week treatment

2) Cohort 2: Repeated dose
   8 HD (2 placebos; 6 actives), 4 weeks treatment

- SNF472 administered for 4h infusion through the dialysis machine, pre-filter
- Dosed in each dialysis session
- Assessments performed all along the study in each dialysis session, with special intensity for cohort 1 on day 1 and 5, and for cohort 2, on week 1 and week 4.
- Assessments: Safety, Tolerability, PK and PD
Phase 1b: PK data Cohort 1

- Similar exposure in Healthy Volunteers (HV) and hemodialysis (HD) patients
- Dose linearity in terms of Cmax and AUC
- Minimum deviation at 20 mg/kg (day 5) ➔ methodological error during blood sampling

CONCLUSIONS: NO ACCUMULATION / LINEAR AND PREDICTABLE PK
Phase 1b: PK data Cohort 2

Similar plasma exposure after 1-month of repeated dosing of 10 mg/kg (tiw)

CONCLUSION: NO ACCUMULATION AFTER 1 MONTH
**Phase 1b: Safety**

- **Only one SAEs- not related / blind not broken / stopping criteria not met**
- **No systemic side effects and no ionized calcium reduction**
- **No local irritation, drug diluted through dialysis tubing**
- **High variability in terms of QTcB (both increases and decreases)**
- **Placebos cover all the range of ΔQTcB seen in all subjects**
- **No test item correlation ΔQTcB vs Cmax**

**CONCLUSION: GOOD SAFETY AND TOLERABILITY**
SMELLING EFFICACY?
Pharmacodynamic measurements

Measures blood calcification propensity ex-vivo
Estimates the effect of drugs on calcification potential

- 80 ml plasma
- 0.15 M NaCl, pH 7.40
- + 12.5 mM Ca\(^{2+}\)
- + 1.5 mM HPO\(_4^{2-}\)
- 30 minutes
- 750 r.p.m.
- Room temperature
- Light scattering
- Reading at 550 nm
- Every 3 minutes

**Pharmacodynamic measurements**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Efficacy (%)</th>
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<tbody>
<tr>
<td>SNF472</td>
<td></td>
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<tr>
<td>Pyrophosphate</td>
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</tr>
<tr>
<td>Ibandronate</td>
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<tr>
<td>Pamidronate</td>
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<td>Citrate</td>
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<td>Fetuin</td>
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Phase 1b: PD data

- **Cohort 1**

- **Cohort 2**

- **Maximum effects from 5 mg/kg**
- **Steep dose-response curve**
- **PD effects maintained over time (1 month)**
Conclusions

- First-in-human trials with SNF472 in HV and HD patients up to one month treatment completed
- Adequate PK profile, suggesting low SNF472 clearance through the dialysis membrane
- SNF472 reduces vascular calcification in animal models and calcification propensity in HD patients dose-dependently.
- Plateau of calcification propensity inhibition from 3 mg/kg (10000 ng/mL; 15 uM)
- Good safety at all tested doses, up to 20 mg/kg (70000ng/mL; 105 uM)
- Data supports continuation of the clinical program in CUA and ESRD dialysis patients
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THANKS!!!!!!!!!!