Pharmacokinetic and pharmacodynamic evaluation of a new vascular calcification inhibitor (INS-3001) in rats

M. Maillard¹, D. Mordasini, D¹. Spaggiari², O. Phan¹, M. Ivarsson³, R. Maj³, L.A. Décosterd², M. Burnier¹

¹Service of nephrology, and ²Service of clinical pharmacology, Lausanne University Hospital, Lausanne, Switzerland

³Inositec AG; Zurich, Switzerland
Disclosures

• The present study was granted by the Swiss Innovation Agency, (Commission for Technology and Innovation)

• Apart Dr Ivarsson, Founder and CEO and Dr Maj, Head of Development of Inositec AG, no disclosure
Vascular calcification (VC): Clinical implication

Clinical evidence
- High prevalence in CKD patients
- VC increase mortality and morbidity in CKD patients

Strategies to control
- Phosphate binders (non-calcium containing PB)
- Calcimimetics
  
  \textbf{Myo-inositol hexakisphosphate (IP6)}
  (still in clinical development)

But: IP6 has a poor PK profile
- need 4 hrs i.v. infusion to overcome it

\[ \text{[JAMA Cardiol 2017;2:635]} \]
\[ \text{[PLoS One 2018;13:1]} \]
INS-3001: a novel inhibitor of vascular calcification

**Mechanism of action**
Coating of calcifications to hinder apposition of further material (not chelation of ionic Ca²⁺)

*See also poster FR-PO487*

inositec
In vivo assessment of inhibitory efficacy on VC: Vit D-excess model

Animal
- Sprague-Dawley male rats

Feeding
- High-phospho (1.3%), normal calcium (0.7%) and low protein (2.5%) diet

Calcification induction
- High dosage of Vit D (300kUI/kg) sc, once a day, from D1 to D5 in the morning

Sacrifice
- Day 12

Calcification evaluation
- VC macroscopically assessed with alizarin red staining of whole aorta and ICP-EOS characterization of Ca content of abdominal aorta and carotids expressed as mg of Ca²⁺ per g of dry tissue weight

Other biochemical parameters
- Plasma calcium, phosphate and creatinine

Calcium
- Sham VitD

Phosphate
- Sham VitD

Creatinine
- Sham VitD

BW change
- Sham VitD

Abd. aorta
- Sham VitD

Carotids
- Sham VitD

VitD-induced Vascular calcification (mean ± sem)

VitD Sham VitD
In vivo activity of INS-3001 in non-uremic rat model of VC

- Protocol:
  - INS-3001  30 mg/5ml/kg bid (n=11)
  - NaCl 0.9% 5ml/kg bid (n=10)
  - IP6 30mg/5ml/kg bid (n=6)

- INS-3001 treatment statistically blunt the Vit D-induced decrease of renal function

- No modification on other measured biochemical parameters (Plasma Ca^{2+} or PO_{4}^{3-})
In vivo efficacy of INS-3001 on VitD-induced VC in non-uremic rat model at sacrifice

- INS-3001 reduces bulk calcium content in vascular tissues
- IP6 treatment could not be completed according to schedule due to local reactions at injection site
- Direct comparison of effect on vascular calcification not possible but INS-3001 clearly non-inferior to IP6

Graphs showing calcium content in Carotids and Abd. aorta for CTRL, INS-3001, and IP6.
Assessment of the PKs of INS-3001 in a rat model of uremia

**Animals**
- Sprague-Dawley male rats

**Uremia induction**
- 0.3% adenin added to high-phosphore (1.3%) normal calcium (0.7%) and low protein (2.5%) diet

**Sacrifice**
- 8 weeks
Assessment of the PKs of a single dose (10mg/kg) of INS-3001 in our adenine-model

Groups (10 mg/kg dose)
- INS-3001 i.v. in non-uremic rats (n=6)
- INS-3001 s.c. in non-uremic rats (n=6)
- INS-3001 i.v. in uremic rats (n=6)
- INS-3001 s.c. in uremic rats (n=6)

• No difference in BW at the moment of PK measurements

LC-MS analyses
- TSQ QuantivaTM® (Thermo Fisher)
- XBridge BEH Amide, 2.1 x 50 mm, 2.5 μm (Waters)
- NH4OAc 20 mM pH=5/MeCN

: inositec
INS-3001 single dose (10mg/kg) PKs data

- INS-3001 displayed high s.c. bioavailability
- Cmax remained unchanged whatever the uremic status
- Uremic rats displayed higher AUC, mean residence time T1/2 and Tmax (not shown) than non-uremic controls which in turn influences the total clearance
- Lower Vd in the uremic state

- IP6 in non-uremic rats: T1/2: <10 min
- IP6 Cmax and AUC decreased by 3-4 fold due to uremia

Conclusion

- INS-3001 is a potent inhibitor of vascular calcification after Vitamin D overdose in rats
- INS-3001 has a beneficial effect on the renal function
- The uremic state appeared to significantly influence the rat plasma PKs of INS-3001 after s.c. and i.v. administration
- Our data suggests that uremia extends plasma exposure of INS-3001 without increasing peak plasma levels
- Therefore therapeutic levels can be attained following s.c. administration in the context of uremia
Thank you for your attention