PXL770, a direct AMPK activator, shows favorable cardiac safety profile

Sophie Hallakou-Bozec[1]; Pascale Gluais-Dagorn[1]; Herve Giorgi[1]; Pascale Fouqueray[1] and Sebastien Bolze[1] [1]Poxel, 259-261 avenue Jean Jaurès, 69007 Lyon, France

Background

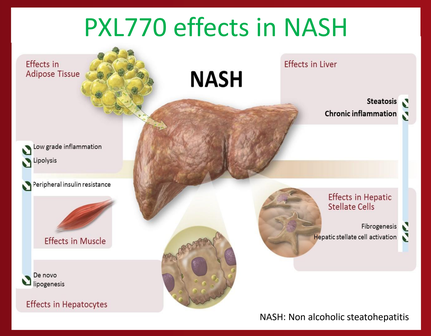
Adenosine monophosphate-activated protein kinase (AMPK) is described as a major regulator of cellular energy homeostasis and its activation is expected to show beneficial effects in metabolic and cardiovascular diseases. However, several observations have raised a potential concern of supraphysiologic AMPK activation in the heart:

- First, human with mutation of regulatory γ2-subunit of AMPK (PRKAG2 gene) develop a cardiac hypertrophy and a glycogen storage cardiomyopathy associated with a familial form of Wolff-Parkinson-White syndrome (ventricular preexcitation syndrome).
- Second, the systemic pan-AMPK activator MK-8722 was reported to induce a reversible cardiac hypertrophy as well as independent glycogen accumulation after 1 month of treatment in 2 animal species (Myers et al. Science 357, 507-511 (2017).

PXL770 is a first-in-class direct AMPK activator

PXL770 allosterically activates the AMPK with a more potent effect on β1-containing heterotrimers (EC50 ~ 50nM) than β2-containing heterotrimers (EC50 ~ 1 µM) and protects AMPK against dephosphorylation.

PXL770 showed benefits in DIO-NASH mice model and is in clinical development in NASH.



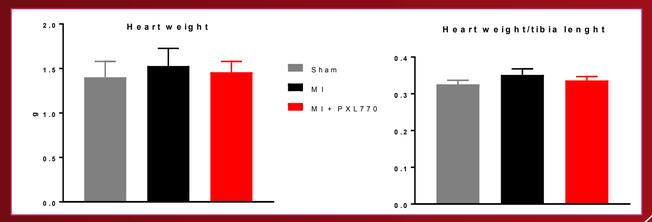
Objectives

To report the results of non-clinical evaluation of PXL770 effects on cardiac safety

Pharmacological study

4-month twice daily oral treatment with PXL770 75 mg/kg in rat model of heart failure (HF) induced by complete coronary artery occlusion.

No effect of PXL770 treatment on heart weight in rat model of HF



Safety pharmacological studies

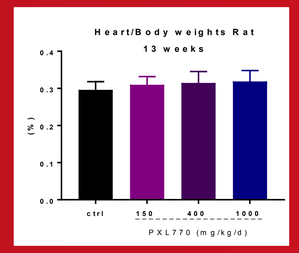
- Ability of PXL770 to bind hERG and effect on hERG current (hERG protein was stably expressed in HEK-293 cells)
  - PXL770 up to 500 µM did not displace ligand binding to the hERG channel protein.
  - No relevant effect on the hERG tail current amplitude up to 52µM.
- Effect of PXL770 on cardiovascular parameters in dogs (conscious dogs instrumented with radio-telemetry devices)
  - PXL770 at single dose up to 500 mg/kg had no significant effect on blood pressure or electrocardiographic (ECG) parameters.

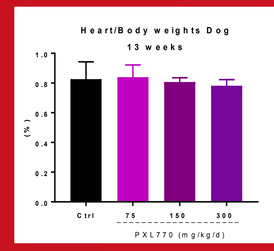
Toxicological studies

Studies design

Animal	Dose (mg/kg/d) PO	Duration	Criteria
Rat (10M+10F)	Up to 1000	13 weeks	- Heart weight - Heart glycogen deposit (Shiff Periodic Acid (PAS) staining
Dog (3M+3F) M: male F: female	Up to 300	13 weeks	- External telemetry from 1h before dosing until 20h post dosing. 15 consecutive ECG complexes were analysed at the following time-points: 30min before dosing then 1, 2, 4, 6, 16h postdose on D-12, D2 and D89. HR, ECG intervals and incidence of cardiac arrhytmias were assessed - Heart weight - Heart glycogen deposit (Shiff Periodic Acid (PAS) staining)

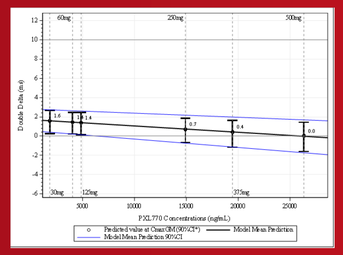
- After 13-week PXL770 administration:
  - No increase in heart weight,
  - No change in heart rate and QTc interval,
  - No electrocardiographic abnormality,
  - No evidence of PXL770 treatment related changes for myocardial glycogen deposits.



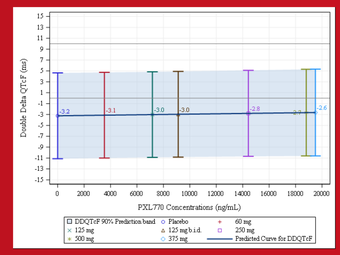


Single ascending doses (30 to 500 mg) and multiple ascending doses (60 to 500 mg qd and 125 mg bid over 10 days) in healthy male subjects

- Safety profile of PXL770 was good across the dose ranges tested.
- No clinically significant findings in 12-lead ECG, Holter ECG or telemetry.
- Exposure-response modeling (QT/QTc):
  - No QT/QTc prolongation over the entire tested dose ranges
  - Estimated ΔΔQTcF were never above the regulatory threshold of 10 ms



Estimated ΔΔQTcF (with 90% CI) vs PXL770 concentrations after single dose



Estimated ΔΔQTcF (with 90% CI) vs PXL770 concentrations after repeated doses

Conclusion

Non clinical pharmacology and toxicology studies with PXL770 up to the dose of 500 mg/kg single dose or 300 mg/kg once daily over 13 weeks did not evidence cardiac hypertrophy, accumulation of glycogen in the myocardium or ECG abnormalities.

This good cardiac safety was confirmed in healthy subjects where no adverse effects were observed on extensive ECG recordings analysis after PXL770 administration up to 500mg qd over10-day.

PXL770 exhibit a good cardiac safety and is now ready to enter phase 2 program in likely NASH subjects.

poxel
Excellence in achieving PoC