PXL770, a direct AMPK activator for the treatment of NASH, shows a favorable PK, tolerability and safety profile in humans

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INTRODUCTION

- AMPK plays a key role in cellular energy homeostasis and appears as a potential target for the treatment of fatty liver diseases and NASH.
- PXL770 is a first-in-class direct adenosine monophosphate-activated protein kinase (AMPK) activator.
- In pharmacological experiments, PXL770 was shown to improve metabolic syndrome and NASH in a number of dedicated animal models.
- In vitro studies showed that PXL770 is an inhibitor of one efflux transporter (BCRP) and two uptake transporters (OATP1B1 and OATP1B3)

OBJECTIVES

- To assess the safety, tolerability and pharmacokinetics (PK) of PXL770 following single ascending doses (SAD) and multiple ascending doses (MAD) in healthy Caucasian male subjects
- To determine the exposure–response (E-R) relationship between plasma concentrations of PXL770 and changes from baseline in QTcF
- To assess the drug-drug interaction (DDI) of PXL770 with rosuvastatin, a probe substrate of BCRP, OATP1B1 and OATP1B3 transporters

METHODS

- Two randomized, double-blinded, placebo-controlled studies of SAD (study 1) and MAD including an open-label part to assess the DDI with rosuvastatin (study 2)
  - **SAD** : 30, 60 mg (6 active, 2 placebo), 125, 250, 375 and 500 mg (9 active, 3 placebo)
  - **MAD** : 60, 125, 250, 375 and 500 mg qd and 125 mg bid (6 active, 2 placebo) - one single dose (Day 1) and repeated treatment for 10 days (Day 5 to Day 14)
  - **DDI** : Single dose of rosuvastatin (10 mg) before and after a treatment of PXL770 (250 mg qd) for 7 days (12 subjects)
- Safety: Adverse events (AE), vital signs, physical exams, safety laboratory, 12-lead electrocardiogram (ECG), 3-lead telemetry and 12-lead Holter recording
- E-R modeling: Holter extracted ECGs were used to predict baseline and placebo adjusted QTcF (ΔΔQTcF) and its 90% Confidence Interval (90%CI) at the mean PXL770 maximum concentration (C_{max}) for each dose level
- PXL770 and Rosuvastatin concentrations: Validated LS-MS/MS methods
- PK parameters : non–compartimental analysis (Phoenix WinNonlin®)

RESULTS

Demographics and baseline characteristics

Table 1: Basal demographics

	SAD	MAD	DDI
N*	64	48	12
Age (years) Mean (SD)	36.8 (10.4)	36.8 (9.1)	41 (9.3)
BMI (kg/m²) Mean (SD)	24.7 (2.5)	24.3 (2.6)	24.1 (2.3)

*All were Caucasian male subjects

Safety and tolerability

In SAD and MAD (DDI) studies:

- Safety profile of PXL770 was good across the dose ranges tested
- No Serious Adverse Event (SAE) nor AE leading to discontinuation
- No clinically significant findings in 12-lead ECG, Holter ECG or telemetry, in vital signs and in safety laboratory
- The maximal tolerated dose was not reached

Table 2: Treatment Emergent Adverse Events (TEAE) – number of events (% of subjects)

	SAD							MAD							DDI	
Dose (mg)	Pbo	30	60	125	250	375	500	Pbo	60 od	125 od	250 od	125 bid	375 od	500 od	250 od	250 od + Rosuvastatin 10
N	16	6	6	9	9	9	9	12	6	6	6	6	6	6	12	12
TEAE	6 (19%)	2 (33%)	0	2 (22%)	4 (44%)	2 (22%)	1 (11%)	7 (50%)	3 (33%)	2 (17%)	7 (83%)	7 (83%)	11 (67%)	11 (67%)	1 (8%)	3 (17%)
SAE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TEAE with drawal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Related TEAE	3 (6%)	0	0	0	1 (11%)	0	0	2 (17%)	2 (33%)	0	4 (50%)	2 (33%)	5 (50%)	8 (50%)	0	0

- SAD : one related TEAE (mild dizziness) at 250 mg
- MAD : Most of related TEAEs were from the gastrointestinal system (abdominal pain or discomfort) or central nervous system (headache)

Exposure-Response modeling (QT/QTc)

- Over the whole range of doses investigated in the SAD and MAD, the upper bounds of the 90%CI of estimated ΔΔQTcF were never above the 10 msec threshold of regulatory concern
- It can be concluded that PXL770 is unlikely to induce QT/QTc prolongation over the entire tested dose ranges

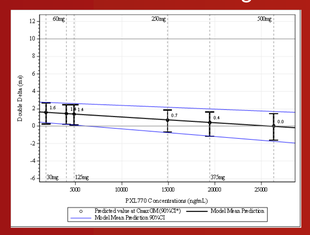

Figure 1: Estimated ΔΔQTcF (with 90% CI) vs PXL770 concentrations after single dose

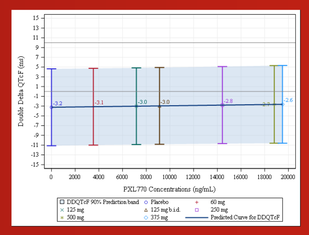

Figure 2: Estimated ΔΔQTcF (with 90% CI) vs PXL770 concentrations after repeated doses

Pharmacokinetics

- Rapid absorption and distribution
- T_{max} around 1.5-3 h
- Bi-phasic elimination with a first rapid phase and a second much slower phase.
- Terminal half-life around 25 h
- Suspected entero-hepatic recirculation
- Almost no urinary excretion

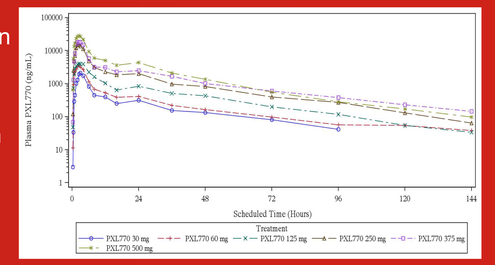

Figure 3: Mean plasma concentration versus time profiles of PXL770 after single oral administration

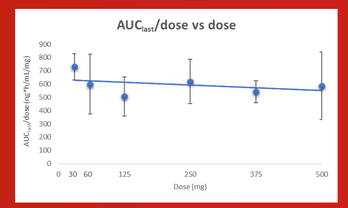

Figure 4: Mean dose-normalised AUC_{last} vs dose after single oral administration

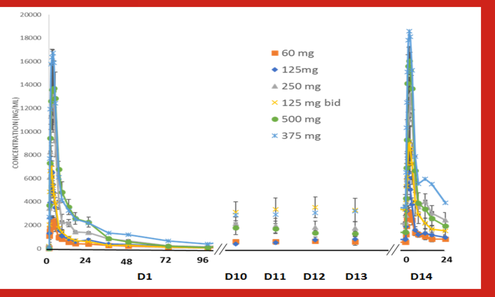

Figure 5: Mean plasma concentration versus time profiles of PXL770 after multiple oral administrations

- C_{max} and Area Under the Curve (AUC) increased in a dose dependent manner following oral single administration with moderate inter-individual variability
- After multiple administrations, the increase in plasma exposure was also dose-dependent up to the dose of 375 mg and less than dose-proportional at the dose of 500 mg, suggesting a potential saturation in the absorption process
- Steady state reached after 5 to 8 days
- Time-invariant PK
- No accumulation on the C_{max} and a modest accumulation on the AUC

- Rosuvastatin mean C_{max} and AUC were not affected by PXL770 as slope estimates were around one and the 90%CI fell entirely between the bioequivalence ranges of 80%-125%
- No effect of PXL770 on T_{max} of rosuvastatin

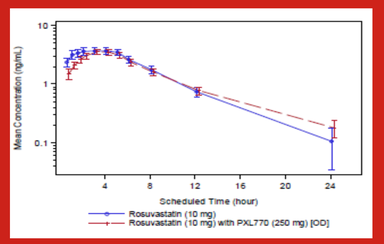

Figure 6: Mean plasma concentration versus time profiles of rosuvastatin with or without PXL770

CONCLUSIONS

- PXL770 is safe and well tolerated up to 500 mg after single and multiple administrations
- PXL770 does not induce any QT/QTc interval prolongation up to 500 mg
- PK is linear and dose-dependent up to 375 mg
- No Drug-Drug Interaction between PX770 and Rosuvastatin

AMPK MEETING 2018 – TORONTO 30 September -04 October 2018