February 27, 2018

Poxel Presents Preclinical Proof-of-Concept Data for PXL770 in Non-Alcoholic Steatohepatitis (NASH) at Global NASH Congress 2018

- **PXL770 is observed to significantly reduce liver steatosis and NAS score following eight weeks of treatment vs control**

- **PXL770 is observed to significantly reduce expression of a panel of key genes associated with fibrosis**

LYON, France--(BUSINESS WIRE)-- POXEL SA (Euronext: POXEL - FR0012432516), a biopharmaceutical company focused on the development of innovative treatments for metabolic disorders, including type 2 diabetes, and liver diseases, including non-alcoholic steatohepatitis (NASH), today announced the poster presentation of proof-of-concept data for PXL770 in a biopsy-confirmed model of diet-induced NASH at the Global NASH Congress 2018 held in London, February 26-27, 2018. The results highlight PXL770 as a novel therapeutic approach in non-alcoholic fatty liver diseases (NAFLD), improving core disease symptoms. PXL770 directly activates adenosine monophosphate-activated protein kinase (AMPK), an enzyme that controls whole-body energy metabolism, de novo lipid synthesis, fatty acid oxidation and inflammation[1]. PXL770 is currently being assessed in a Phase 1b multiple ascending dose study in healthy volunteers.

"The preclinical data are compelling and consistent with what we can expect from a compound targeting AMPK activation. These results validate the unique potential PXL770 offers in NAFLD diseases, which represent a range of significant and unmet medical needs," said Thomas Kuhn, CEO of Poxel. "Pending successful completion of our ongoing Phase 1b program, we are planning to initiate a Phase 2a proof-of-concept study in patients with NAFLD, a condition in which fat builds up in the liver. This study is expected to begin during the second half of 2018. We are also exploring other metabolic diseases for proof-of-concept studies for PXL770."

Through its unique mechanism of action (MOA) that directly activates AMPK, PXL770 acts on a very important biological target. This target, which plays a key role as a master regulator of cellular energy, has the potential to treat numerous chronic metabolic diseases, including diseases that affect the liver, such as NASH,[2] which is a severe form of NAFLD. This target is important because it has the potential to trigger benefits on the three key pathophysiology processes involved in NASH development: liver steatosis, inflammation and fibrosis. PXL770 may also be differentiated from other compounds in development for liver

diseases since AMPK activation has the potential to also treat NASH comorbidities, specifically targeting cardiovascular risk factors, such as hyperglycemia, insulin resistance, dyslipidemia, inflammation, and obesity.

PXL770 Study Results

In this study, Poxel researchers assessed the effect of PXL770 in a diet-induced (high fat, fructose and cholesterol for 41 weeks) obesity NASH (DIO-NASH) mouse model with biopsy at baseline and at the end of the treatment period. Mice were treated orally with PXL770 35 or 75 mg/kg twice-daily for 8 weeks (n=12) or with vehicle for the control group.

DIO-NASH mice elicited characteristics of NASH, including steatohepatitis (NAS=7), liver fibrosis (score=2), elevated liver triglycerides (x26), elevated plasma cholesterol (x3.5) and ALT (x8) compared to normal diet chow mice. As expected, PXL770 increased AMPK activity (P-AMPK/AMPK, +128%, $p<0.05$ and +143%, $p<0.001$ at 35 and 75mg/kg respectively) in the liver. Compared to the control group, PXL770 slightly decreased body weight at the highest dose (-5%, $p<0.05$), reduced liver weight (-23%, $p<0.01$; -33%, $p<0.001$) and epididymal fat depot weight (-25%, $p<0.01$; -37%, $p<0.001$) at 35 and 75 mg/kg respectively. PXL770 also decreased plasma free fatty acid (-37% and -38%, $p<0.01$), plasma cholesterol (-33% and -34%, $p<0.01$) and alanine aminotransferase (-68% and -79%, $p<0.01$) at 35 and 75 mg/kg, respectively.

Both PXL770 doses significantly reduced the non-alcoholic fatty liver disease (NAFLD) activity score (NAS), which is commonly used to measure changes in NAFLD based on histological changes (-32% and -44% at 35 and 75mg/kg, respectively), decreasing steatosis, inflammation and hepatocellular ballooning. The benefit on liver steatosis was confirmed by the reduction of liver triglycerides (-36%, $p<0.001$ and -42 %, $p<0.001$ at 35 and 75mg/kg, respectively). Furthermore, PXL770 strongly down-regulated expression of a panel of key genes involved in fibrosis e.g., type I (-65% and -68%, $p<0.01$) and type III (-60 and -63%, $p<0.01$) collagen gene expression at 35 mg/kg and 75 mg/kg, respectively.

Together, these results highlight the beneficial effect of AMPK activation in the NASH model and the potential of PXL770 as a promising novel treatment option in NAFLD and, in particular, NASH.

The poster titled "PXL770, a new direct AMP Kinase activator, demonstrates promising effects for treatment of non-alcoholic steatohepatitis" is available on the Company's website under "Scientific Publications" or by using the following link http://www.poxelpharma.com/en_us/product-pipeline/posters.

About NASH

Non-alcoholic steatohepatitis (NASH) is a metabolic disease with no clear disease origin that is quickly becoming a worldwide epidemic. It is characterized by the accumulation of fat in the liver causing inflammation and fibrosis. The disease can be silent for a long period of time, but once it accelerates, severe damage and liver cirrhosis can occur, which can significantly impact liver function or can even result in liver failure or liver cancer. Typical risk factors for NASH include obesity, elevated levels of blood lipids (such as cholesterol and triglycerides) and diabetes. Currently no curative or specific therapies are available.

About PXL770

PXL770 is a first-in-class direct adenosine monophosphate-activated protein kinase (AMPK) activator. AMPK is a central regulator of multiple metabolic pathways leading to the control of lipid metabolism, glucose homeostasis and inflammation. Based on its central metabolic role, targeting AMPK offers the opportunity to pursue a wide range of indications to treat chronic metabolic diseases, including diseases that affect the liver, such as non-alcoholic steatohepatitis (NASH).

About Poxel SA

Poxel uses its development expertise in metabolism to advance a pipeline of drug candidates focused on the treatment of metabolic disorders, including type 2 diabetes and non-alcoholic steatohepatitis (NASH). We have successfully completed our Phase 2 clinical program for our first-in-class lead product, Imeglimin, which targets mitochondrial dysfunction, in the U.S., Europe and Japan, and the Phase 3 **T**rials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) program in Japan is underway. Our second program, PXL770, a direct adenosine monophosphate-activated protein kinase (AMPK) activator, is completing Phase 1 development. Based on this central metabolic role, targeting AMPK offers the opportunity to pursue a wide range of indications to treat chronic metabolic diseases, including diseases that affect the liver, such as NASH. We intend to generate further growth through strategic partnerships and pipeline development. (Euronext: POXEL, www.poxelpharma.com)

[1] Source: Day E.A et al., (2017) Trends Endocrinol Metab. 28, 545-560

[2] Source: Smith B. K et al., (2016) Am J Physiol Endocrinol Metab 311, E730 – E740

View source version on businesswire.com:
http://www.businesswire.com/news/home/20180226005544/en/

Poxel SA
Jonae R. Barnes, +1-617-818-2985
Senior Vice President, Investor Relations and Public Relations
jonae.barnes@poxelpharma.com
or
Investor relations / Media - EU/US
Trophic Communications
Gretchen Schweitzer or Stephanie May
+49 89 238 877 34 or +49 171 185 56 82
may@trophic.eu
or
Investor relations / Media - France
NewCap
Florent Alba/Nicolas Merigeau, +33 1 44 71 98 55
poxel@newcap.fr

Source: POXEL SA