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Poxel Announces Favorable Results for PXL770 Phase 1b Multiple Ascending Dose Trial and Drug-Drug Interaction Study

- **PXL770 observed to have a favorable safety and pharmacokinetic profile in the complete Phase 1 program**
- **PXL770 is advancing into a Phase 2a proof-of-concept program for NASH**

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 non-alcoholic steatohepatitis (NASH), today announced favorable results from the PXL770 Phase 1b two-part study that included a multiple ascending dose (MAD) trial and a drug-drug interaction study. PXL770 is a first-in-class, oral, direct adenosine monophosphate-activated protein kinase (AMPK) activator that is advancing into a Phase 2a proof-of-concept program for the treatment of NASH. Liver diseases, such as NASH, are growing in prevalence, and there are no regulator-approved treatments available.

“We are pleased with the outcome of the PXL770 Phase 1 program. We believe that PXL770’s unique mechanism of action has the potential to treat the underlying root causes of fatty liver diseases, including liver steatosis, inflammation and fibrosis, as well as provide benefits for co-morbidities, including those related to cardiovascular disease,” said Thomas Kuhn, CEO of Poxel. “We are planning to initiate a Phase 2a program in patients with nonalcoholic fatty liver disease (NAFLD), a condition in which fat builds up in the liver. We are also exploring other metabolic diseases for proof-of-concept studies for PXL770.”

The MAD trial included 48 subjects and evaluated the safety, tolerability and pharmacokinetics (PK) of PXL770 administered once- or twice-daily after 10-day repeated administration in six dose groups ranging from 60 mg to 500 mg. In this study, there were no serious adverse events or adverse events leading to withdrawal. PXL770 was well tolerated up to the highest dose tested of 500 mg, which was reached because none of the dose escalation safety stopping criteria was met. In this study, electrocardiogram (ECG) was investigated at all doses, and PXL770 did not induce prolongation of the TQT interval (a cardiac safety measurement), nor changes in any other ECG parameters. The PK (Cmax and AUC) of PXL770 was shown to be linear with a trend for saturation at the highest dose tested.

In addition to the MAD trial, a drug-drug interaction study was also conducted with rosuvastatin, a statin drug and probe substrate for organic anion transporting polypeptide (OATP) transporters, which can cause PK drug–drug interactions. In this study 12 subjects were administered 250 mg doses of PXL770 once-daily and the standard dose of rosuvastatin. The results demonstrated the lack of PK interaction between PXL770 and OATP substrates.

Based on the favorable results in the Phase 1b and the favorable safety and tolerability profile in the single ascending dose Phase 1a study, the Company is preparing to initiate a Phase 2a proof-of-concept program. This program will include a randomized, double-blind, placebo-controlled, parallel-group study that will assess the efficacy and safety of PXL770 versus placebo in approximately 100 patients with NAFLD with or without type 2 diabetes. The primary endpoint of the study will be defined as the relative percent change from baseline in liver fat content, as assessed using magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) after 12 weeks of treatment. Secondary parameters will explore the role of PXL770 on lipid metabolism and glucose control. The Phase 2a program will also include a mechanistic component that will assess the effect of PXL770 on the inhibition of lipolysis (release of FFA from triglycerides stored in the adipose tissue) and hepatic *de novo* lipogenesis (triglycerides synthesis from glucose precursors).

During the second half of 2018, preparation for the Phase 2a program for PXL770 will include filing an Investigational New Drug Application with the U.S. Food and Drug Administration, manufacturing of drug product and validation of clinical sites.

Through directly activating AMPK, PXL770 acts on an important biological target. AMPK is a master regulator of

cellular energy and its activation has the potential to treat numerous chronic metabolic diseases, including diseases that affect the liver, such as NASH,[1] 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.

In the PXL770 Phase 1a single ascending dose (SAD) study, safety, tolerability and pharmacokinetics of six doses of PXL770 were assessed in 64 healthy male subjects. The results demonstrated that PXL770 exhibited a favorable safety and tolerability profile with no serious adverse events reported nor safety signals. PK assessment showed that PXL770 plasma exposure (Cmax and AUC) increased in a dose dependent manner following oral administration with moderate inter-individual variability.

Data results presented at the Global NASH Congress 2018 in February highlighted the beneficial effect of AMPK activation in a diet induced NASH mouse model and the potential of PXL770 to act on liver steatosis and inflammation as well as adipose tissue lipolysis and inflammation. This data 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 the Phase 2 clinical program for our first-in-class lead product, Imeglimin, which targets mitochondrial dysfunction, in the U.S., Europe and Japan. Together, with our partner Sumitomo Dainippon Pharma, we are conducting the Phase 3 **T**rials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) program for the treatment of type 2 diabetes in Japan. Our partner Roivant Sciences will be responsible for Imeglimin's development and commercialization in countries outside of Poxel's partnership with Sumitomo Dainippon Pharma, including the U.S. and Europe. Our second program, PXL770, a first in class direct adenosine monophosphate-activated protein kinase (AMPK) activator, is advancing into a Phase 2a proof-of-concept program for the treatment of NASH. PXL770 could also have the potential to treat additional metabolic diseases. We intend to generate further growth through strategic partnerships and pipeline development. (Euronext: POXEL, www.poxelpharma.com)

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

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