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Poxel Presents New Preclinical Proof-of-Concept Results for PXL770 at the 3rd Annual Global NASH Congress

- **PXL770, a novel direct AMP kinase activator, observed to reduce liver inflammatory cells, which may contribute to an improvement of fibrogenesis, in a preclinical NASH model**
- **Clinical results from the PXL770 PK/PD trial and Phase 2a study expected in 2Q and 3Q of 2020, respectively**

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 that new preclinical proof-of-concept results for PXL770 for the treatment of NASH were reported in an oral presentation during the 3rd Annual Global NASH Congress held in London, February 10-11, 2020. The results highlight PXL770 as a potentially novel therapeutic approach for the treatment of NASH, improving core aspects of disease pathophysiology.

Inflammation is known as a core component of the pathophysiology of NASH and as a major contributing factor leading to fibrogenesis. In addition to known effects to suppress hepatic steatosis, published literature suggests the involvement of adenosine monophosphate-activated protein kinase (AMPK) in the modulation of inflammatory responses. In a preclinical diet-induced obese (DIO)-NASH model, treatment with PXL770, a direct AMPK activator clinical candidate, improved inflammation score assessed by histology. More specific observations included a decrease in multiple subtypes of inflammatory cells in the liver, including macrophages and B-lymphocytes in addition to suppression of elevated chemokine (MCP-1) levels, which correlated with the decrease in liver monocyte-derived macrophages. These effects may contribute to the concomitant improvement of fibrogenesis measured in this study. PXL770 is currently being assessed in a pharmacokinetic and pharmacodynamic (PK/PD) trial and a Phase 2a efficacy and safety study for the treatment of NASH.

“Based on results from multiple preclinical models for PXL770 and published literature that are consistent with potential clinical beneficial effects, we believe that AMPK activation could play a beneficial role in the metabolic and inflammatory pathways that lead to liver injury and NASH,” said Thomas Kuhn, CEO of Poxel. “We look forward to seeing whether this novel mechanism translates into results in patients as we near upcoming clinical readouts from our PXL770 PK/PD trial and Phase 2a study, which are currently expected in the second and

third quarter of 2020, respectively."

"Through its unique mechanism of action that directly activates AMPK, PXL770 modulates a master regulator of cellular energy," said David Moller, MD, CSO of Poxel. "Our new preclinical data highlights the potential of PXL770 to treat the root causes of NASH by also decreasing liver inflammation with the potential to improve downstream effects on fibrogenesis; thus, we envision that this target may trigger benefits on many aspects of NASH pathophysiology: liver steatosis, inflammation, ballooning 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 by specifically targeting cardiovascular risk factors, such as hyperglycemia, insulin resistance, dyslipidemia and obesity.

PXL770 Study Results

In this study, Poxel assessed the effect of PXL770 in a diet-induced (high fat, fructose and cholesterol for 34 weeks) obese NASH (DIO-NASH) mouse model. DIO-NASH mice with biopsy-confirmed steatosis (score ≥2) and fibrosis (stage ≥F1) received 75 mg/kg of PXL770 orally twice daily for 8 weeks versus vehicle treatment in the control group.

Compared to mice on a normal chow diet, DIO-NASH mice exhibited liver inflammation with increased total liver leucocytes (myeloid and lymphoid cells) and liver fibrosis. Compared to control mice, PXL770 decreased liver inflammation score and decreased liver inflammatory cells, particularly macrophages, as described in the table below.

PXL770 effects on liver inflammation

Total liver leucocytes: -40% p<0.05	
Total liver myeloid cells *(CD45CD11b^{+})*: -42%, p<0.05 Monocyte/macrophages cells *(Ly6C^{++})*: -49%, p<0.05 Resident myeloid cells *(F4/F80^{high}CD11^{low})*: -60%, p<0.05 Liver macrophages markers • Galectin-3 (% fractional area): 2.5 vs 4.1 in ctrl, p<0.0001 • CD68 (mRNA): -34%, p<0.01	Total liver lymphoid cells *(CD45CD11b^{-})*: -39%, p<0.05 Total liver B-cells: -50%, p<0.01 Total liver T-cells: tendency to be reduced

N = 8 to 12

As described in the literature, both liver monocytes-macrophages and B-cells promote fibrogenesis. The reduction in inflammatory cells observed with PXL770 may contribute to the benefits of PXL770 reported on fibrogenesis as described in the table below:

PXL770 effects on fibrogenic markers

TGF β (mRNA): -30%, p<0.05
PDGF (mRNA): -30%, p<0.05
aSMA positive staining: -39%, p<0.01
Col1A1 (mRNA): -68%, p<0.001
TIMP-1 (mRNA): -60%, p<0.001

N = 8 to 12 depending on the parameter

In this study, PXL770 reduced total inflammatory liver cells, which may contribute to observed improvements in fibrogenesis. Poxel believes these benefits induced by PXL770 appear promising for the treatment of NASH.

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 type 2 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)[1].

About Poxel SA

Poxel is a **dynamic biopharmaceutical company** that uses its extensive expertise in developing **innovative drugs for metabolic diseases**, with a focus on **type 2 diabetes** and **non-alcoholic steatohepatitis (NASH)**. In its mid-to-late stage pipeline, the Company is currently advancing three drug candidates as well as earlier-stage opportunities. **Imeglimin**, Poxel's first-in-class lead product, targets mitochondrial dysfunction. Together, with its partner Sumitomo Dainippon Pharma, Poxel successfully completed 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. Poxel also established a partnership with Roivant Sciences for Imeglimin's development and commercialization in countries outside of the partnership with Sumitomo Dainippon Pharma, including the U.S. and Europe. **PXL770**, a first-in-class direct adenosine monophosphate-activated protein kinase (AMPK) activator, is in a Phase 2a proof-of-concept program for the treatment of NASH. PXL770 could also have the potential to treat additional metabolic diseases. **PXL065** (deuterium-stabilized R-pioglitazone), a mitochondrial pyruvate carrier (MPC) inhibitor, is advancing into a Phase 2 clinical trial for the treatment of NASH. Poxel also has additional earlier-stage programs targeting metabolic, specialty and rare diseases. The Company intends to generate further growth through strategic partnerships

and pipeline development. Listed on Euronext Paris, Poxel is headquartered in Lyon, France, and has subsidiaries in Boston, MA, and Tokyo, Japan. For more information, please visit: www.poxelpharma.com.

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

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