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Poxel Announces Initiation of Part 2 of Phase 1a Study for PXL065, which is being Developed for the Treatment of NASH

- **PXL065 data to date suggest the potential for a favorable profile for the treatment of 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 that Part 2 of the Phase 1a study for PXL065, a deuterium-stabilized R-stereoisomer of pioglitazone, has been initiated. This second part of the Phase 1a study will enroll six healthy subjects per group, with a primary objective to assess safety and tolerability and a secondary objective to assess dose proportionality. This Phase 1a trial, which was discussed with the U.S. Food and Drug Administration (FDA) in a pre-Investigational New Drug Application (IND) meeting, was designed to include two single oral doses and potentially up to three additional doses of PXL065.

In Part 1 of the Phase 1a study, which was presented during the 2018 American Association for the Study of Liver Diseases (AASLD) meeting, twelve healthy subjects received a single oral dose of 22.5 mg PXL065 or 45 mg Actos®*. In this study, PXL065 was shown to be safe and well-tolerated with no adverse events. Based on the pharmacokinetic (PK) results, modeling predicts that a 15 mg dose of PXL065 may provide a similar exposure of R-pioglitazone as a 45 mg dose of the parent drug, pioglitazone (Actos), which suggests it should show similar efficacy with an improved safety profile, including reduced weight gain and fluid retention.

“Nonalcoholic fatty liver disease (NAFLD) is reaching epidemic proportions worldwide and is the most common chronic liver condition in obese patients with prediabetes or type 2 diabetes mellitus,” said Kenneth Cusi, MD, Chief of the Division of Endocrinology, Diabetes & Metabolism in the Department of Medicine at the University of Florida. “Because the mechanism of action for PXL065 is known to target mitochondrial pyruvate carrier (MPC) inhibition, PXL065 is expected to have beneficial effects on insulin resistance and inflammation, which are key components for treating steatohepatitis in patients with NASH.”

“Shortly after signing the acquisition agreement with DeuteRx for PXL065, the IND for PXL065 was transferred to Poxel, and we subsequentially initiated Part 2 of the Phase 1a study. Data generated from this latest study of PXL065, including the PK results and modeling work based on the highest approved dose of pioglitazone, should enable us to establish optimal doses for the next phase of development,” said Thomas Kuhn, CEO of Poxel.

“The underlying pathophysiological mechanisms that contribute to the development and progression of NAFLD and NASH are highly complex and support the need for the development of novel therapies acting on different targets. We believe that addressing a variety of relevant pathways, such as mitochondrial pyruvate carrier (MPC) inhibition with PXL065 and direct adenosine monophosphate-activated protein kinase (AMPK) activation with PXL770, could yield greater success in the treatment of NASH,” continued Thomas Kuhn. “We look forward to advancing both of our programs for the treatment of NASH into proof-of-concept studies in 2019.”

Pioglitazone, a drug approved for the treatment of type 2 diabetes has demonstrated therapeutic efficacy for NASH, even in patients with advanced fibrosis. Pioglitazone is the only drug recommended for biopsy-proven NASH patients by the Practice Guidelines published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[1] However, its therapeutic use and potential have been limited due to the PPARγ-related side effects of weight gain, bone fractures and fluid retention. PXL065, a novel patent-protected drug candidate, offers an expected new approach for the treatment of NASH and has the potential to preserve the pharmacological benefits of pioglitazone required for the treatment of NASH, such as a reduction of hepatic steatosis, inflammation, ballooning and fibrosis and could reduce PPARγ agonism and the associated side effects that are thought to be related to S-pioglitazone.

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 PXL065
PXL065, formerly DRX-065, is deuterium-stabilized R-pioglitazone. Pioglitazone is the most extensively studied drug for NASH and has demonstrated “resolution of NASH without worsening of fibrosis” in a Phase 4 trial[2]. Pioglitazone is the only drug recommended for biopsy-proven NASH patients by the Practice Guidelines published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[1] Pioglitazone’s use for NASH, however, has been limited due to the PPARγ-related side effects, which include weight gain, bone fractures and fluid retention.

Pioglitazone is a 1:1 mixture of two mirror-image compounds (stereoisomers) that interconvert *in vivo*. Using deuterium, DeuteRx stabilized each stereoisomer and characterized their dramatically different pharmacological properties. In *in vitro* studies, PXL065 has been shown to target MPC as an inhibitor. In preclinical models, PXL065 exhibits the anti-inflammatory activity and NASH efficacy associated with pioglitazone with little or no weight gain or fluid retention, side effects which are associated with the S-stereoisomer. Based upon preclinical and Phase 1 results to date, PXL065 is expected to exhibit a better therapeutic profile than pioglitazone for NASH.

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)[3].

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 Trials of Imeglimin for Efficacy and Safety (TIMES) program for the treatment of type 2 diabetes in Japan. Our partner Roivant Sciences is responsible for Imeglimin's development and commercialization in countries outside of Poxel's 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 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. PXL065 (deuterium-stabilized R-pioglitazone), a mitochondrial pyruvate carrier (MPC) inhibitor, is in Phase 1 and being developed for the treatment of NASH. Poxel also has additional earlier-stage programs, including deuterated drug candidates for metabolic, specialty and rare diseases. We intend to generate further growth through strategic partnerships and pipeline development. (Euronext: POXEL, www.poxelpharma.com)

*Actos is the branded version of pioglitazone and a registered trademark of Takeda Chemical Industries, Ltd.

1. J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357

2. Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315)

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

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