January 7, 2019

Poxel Announces Presentation of PXL065 Data at the 2019 NASH-TAG Conference

- **Presentation highlighted different stereoisomer properties of pioglitazone and other thiazolidinediones (TZDs)**
- **Data observed suggests a more favorable profile for PXL065 versus pioglitazone and other TZDs 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 an oral presentation, including data for PXL065, the deuterium-stabilized R-stereoisomer of pioglitazone, was made at the 2019 NASH-TAG Conference. The presentation titled “PXL065, Pioglitazone (pio), and Thiazolidinediones (TZDs): Unravelling Pio’s superior efficacy for NASH and role of stereoisomers” was given on January 5, 2019 in Park City, Utah.

The presentation highlighted key aspects related to the pharmacokinetic (PK) and pharmacodynamic (PD) role of stereoisomers within the class of compounds known as TZDs and the potential relevance for the treatment of NASH. Representative TZDs included rosiglitazone, pioglitazone and lobeglitazone, all of which are a mixture of interconverting R- and S- stereoisomers that have exhibited varying levels of efficacy for NASH in animal and/or human studies.

Key findings presented included: 1) a comparison of the striking species-dependent stereoselectivity of the PK for pioglitazone with other TZDs, 2) a comparison of unexpected differences in peroxisome proliferator-activated receptor gamma (PPARγ) activity with the eight stereoisomers that make up pioglitazone and its two active metabolites and 3) stabilization of pioglitazone’s stereoisomers with deuterium to characterize and identify R-pioglitazone as the preferred stereoisomer for the treatment of NASH.

Data presented demonstrated that each stereoisomer of pioglitazone and its active metabolites exhibits different PPARγ activity. The presentation also included data showing that PXL065 is a mitochondrial pyruvate carrier (MPC) inhibitor without PPARγ activity in a cofactor recruitment assay. In mouse models, PXL065 demonstrated the hepatic benefits observed with pioglitazone in NASH patients. In preclinical models, PXL065 exhibited little or no weight gain or fluid retention, side effects mainly associated with the PPARγ active, S-pioglitazone.

“While PPARγ activation has historically been identified as the driver of TZD benefits, a

mitochondrial modulatory effect may better explain the benefits for NASH," said Thomas Kuhn, CEO of Poxel. "Because the mechanism of action for PXL065 is known to target MPC inhibition, PXL065 is expected to have beneficial effects on ballooning, inflammation and steatosis, which are key components for treating patients with NASH."

Pioglitazone (Actos®*), a drug approved for the treatment of type 2 diabetes, has demonstrated therapeutic efficacy for NASH, even in patients with advanced fibrosis. 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 offers a proprietary new approach for the treatment of NASH. PXL065 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-related side effects that are thought to be associated with S-pioglitazone.

About the PXL065 Results

PPARγ activity and MPC inhibition were measured *in vitro.* Single and multi-dose PK studies were conducted in mouse, rat and dog. Weight gain and edema were evaluated in C57BL/6J mice and NASH efficacy was assessed in diet-induced mouse models.

Safety, tolerability and PK of 22.5 mg PXL065 were compared to 45 mg Actos® in a single-dose Phase 1a study. In man, PK results and modelling predict that 15 mg of PXL065 has the potential to provide efficacy for NASH similar to 45 mg Actos® with little or no weight gain or fluid retention. As part of the Phase 1 program, additional single doses are currently being studied and will be followed by a multiple ascending dose trial.

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 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[1]. 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).[2] 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 (R- and S-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 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. Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315
2. J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357

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