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Poxel Announces Favorable Results for PXL065 Phase 1a Single Ascending Dose Trial

- **PXL065 observed to have a favorable safety, tolerability and pharmacokinetic profile in the Phase 1a trial**
- **PXL065 is advancing into a Phase 1b multiple ascending dose trial to support a pivotal Phase 2 trial in 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 Phase 1a two-part study that included three single doses of PXL065 and a single dose of Actos®* (pioglitazone). PXL065, the deuterium-stabilized R-stereoisomer of pioglitazone, is a mitochondrial pyruvate carrier (MPC) inhibitor being developed for the treatment of NASH.

“We are pleased with the outcome of the PXL065 Phase 1a study which supports the preclinical studies and modelling showing 15 mg of PXL065 has the potential to provide an improved therapeutic profile over 45 mg Actos®,” said Thomas Kuhn, CEO of Poxel. “We are planning to initiate the Phase 1b multiple ascending dose (MAD) trial in healthy subjects during the second quarter of 2019 with completion expected in the third quarter. This study will be important in the development plan of PXL065, and the potential use of the 505(b)(2) regulatory pathway could provide an expedited development approach to a registration program.”

The Phase 1a study evaluated the safety, tolerability and pharmacokinetics (PK) of several doses of PXL065 compared to 45 mg Actos® in a total of 24 healthy subjects. In this study, PXL065 was observed to show a favorable safety and tolerability profile with no serious adverse events. PK assessment showed that PXL065 plasma exposure (Cmax and AUC) increased in a dose-proportional manner up to 22.5 mg following oral administration with moderate inter-individual variability. Furthermore, stabilization of R-pioglitazone with deuterium was confirmed at all doses tested.

“As a hepatologist, I participated in early Phase 2 clinical trials with pioglitazone in biopsy-proven NASH patients. Although pioglitazone has achieved the most compelling treatment effects to date for resolution of NASH without worsening of fibrosis, it is only prescribed by a small percentage of physicians, around 14%[1], for biopsy-proven NASH patients. The primary reason for this is pioglitazone’s side effect of weight gain,” said Stephen A. Harrison, MD, Visiting Professor of Hepatology, Radcliffe Department of Medicine, University of Oxford, UK. “I am excited about the potential for an improved therapeutic profile for PXL065 for the treatment of NASH, particularly the opportunity for reduced weight gain.”

Based on the favorable results in the Phase 1a study, the Company is preparing to initiate a Phase 1b MAD trial. This double-blind, randomized, placebo-controlled study will assess the safety, tolerability and PK in healthy subjects after 7 days of dosing with several doses of PXL065 versus 45 mg Actos®.

During the remainder of 2019, preparation for the pivotal Phase 2 program of PXL065 in biopsy-proven NASH patients will also include a pre-Investigational New Drug meeting with the U.S. Food and Drug Administration to discuss the NASH development strategy.

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[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).[3] 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, we 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 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 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. Therap Adv Gastroenterol. 2016, 9(1), 4-12
2. Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315
3. J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357

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