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Poxel Initiates Phase 1b Multiple Ascending Dose (MAD) Trial for NASH Drug Candidate, PXL065

- **Phase 1b MAD trial is designed to evaluate safety, tolerability and pharmacokinetics (PK) and support dose selection for a pivotal study; topline results expected in Q4 2019**
- **Results from Phase 1a single ascending dose (SAD) study of PXL065 to be presented at American Association for the Study of Liver Diseases (AASLD) Annual Meeting, November 8-12, 2019 in Boston, MA**
- **Poxel will meet with U.S. Food and Drug Administration (FDA) in early Q4 2019 to discuss the registration program and 505(b)(2) regulatory pathway, which has the potential for expedited development and accelerated regulatory approval**

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 the initiation of a Phase 1b double-blind, randomized, placebo-controlled study in healthy subjects to evaluate the safety, tolerability and pharmacokinetics (PK) as well as support dose selection for a pivotal study of PXL065. This study aims to confirm the predicted relative exposure and dose proportionality of PXL065.

PXL065, the deuterium-stabilized R-stereoisomer of pioglitazone, targets mitochondrial pyruvate carrier (MPC) inhibition. PXL065 is being developed for the treatment of noncirrhotic NASH patients and has the potential to provide an improved therapeutic profile over 45 mg of Actos®* (pioglitazone). Pioglitazone has been extensively studied in NASH with demonstrated efficacy[1,2], but its use is limited due to its side effect profile, including weight gain and fluid retention, which appear to be associated with the S-stereoisomer.

“Our in-depth understanding of the cellular energy regulation pathways related to metabolic diseases, such as NASH, has helped to facilitate the rapid advancement of a diverse pipeline with two promising clinical programs for this chronic metabolic disease,” said Thomas Kuhn, CEO of Poxel. “Based on preclinical and Phase 1 results to-date, we believe PXL065 has the potential to exhibit an improved therapeutic profile compared to pioglitazone for noncirrhotic NASH patients. We continue to believe strongly in the role of mitochondrial metabolism for the treatment of NASH and anticipate topline data from this Phase 1b study in the fourth quarter of this year. In addition, PXL065 has the potential for expedited development through the 505(b)(2) regulatory pathway, and we will be meeting with the FDA early in the fourth quarter to discuss the registration program.”

The Phase 1b trial is a double-blind, randomized, placebo-controlled MAD study that will assess the safety, tolerability and PK in approximately 30 healthy subjects, following seven days of receiving three doses (7.5 mg, 15 mg and 30 mg) of PXL065 versus 45 mg Actos®. The study has opened sites and has initiated recruitment of subjects. Topline results from this study are expected in the fourth quarter of 2019.

The Phase 1b trial initiation follows topline positive results from the Company’s Phase 1a single ascending dose (SAD) study of PXL065, reported in April 2019. The Phase 1a study evaluated the safety, tolerability and PK of three 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. Furthermore, stabilization of R-pioglitazone with deuterium was confirmed at all doses tested. Data from this study will be presented at the AASLD Annual Meeting, held November 8-12, 2019 in Boston, MA.

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 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[3]. 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)[4]. 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 targets mitochondrial pyruvate carrier (MPC) inhibition. 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 noncirrhotic NASH patients.

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), targets mitochondrial pyruvate carrier (MPC) inhibition, 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)

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*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.
[3] Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315).
[4] J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357.

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