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Poxel Announces Positive Results for PXL065 Phase 1b Trial and Provides Program Update

- **PXL065 Phase 1b multiple ascending dose trial was observed to demonstrate a dose-proportional pharmacokinetic profile and consistent stabilization of R-pioglitazone at all doses tested**
- **In 2Q 2020, Poxel plans to initiate a Phase 2 36-week trial in biopsy-proven NASH patients designed to identify optimal dose or doses for Phase 3 registration trial**
- **13-week repeated-dose toxicity study in dogs was observed to show an improved safety margin over pioglitazone**
- **PXL065 is being developed using the 505(b)(2) regulatory pathway, which offers the opportunity for a streamlined and efficient development program**

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 positive results from a Phase 1b multiple ascending dose (MAD) trial evaluating safety, tolerability and the pharmacokinetic (PK) profile of PXL065 in healthy subjects after repeated administration and provided further details for the Phase 2 clinical trial design. In addition, the Company highlighted new preclinical data in which PXL065 was observed to show an improved safety margin over pioglitazone. PXL065, the deuterium-stabilized R-stereoisomer of pioglitazone, is a mitochondrial pyruvate carrier (MPC) inhibitor being developed for the treatment of NASH.

“The outcome of the PXL065 Phase 1b study is positive and provides us with important data regarding the benefits of the R-stereoisomer of pioglitazone in terms of tolerability and PK, showing consistent exposure to the preferred R-stereoisomer and dose proportionality at all doses tested. With these results, combined with other clinical and preclinical data, we are able to identify the dosing range of 7.5 mg to 22.5 mg that will be evaluated in the Phase 2 trial, a range we believe has the potential to provide an improved therapeutic profile over 45 mg Actos®*,” said Thomas Kuhn, CEO of Poxel. “Based on the encouraging results to-date, we plan to initiate a Phase 2 trial for PXL065 in biopsy-proven NASH patients during the second quarter of 2020 with the primary objective to determine the optimal dose or doses to be tested in a Phase 3 registration trial.”

“NASH is a major public health concern and is a growing contributor to the burden of end-stage liver disease. There remains an urgent need to develop effective therapeutics for NASH,” said Arun Sanyal, MD, Professor of Medicine, Physiology and Molecular Pathology

at Virginia Commonwealth University School of Medicine, Richmond, Virginia. “Pioglitazone has been shown in multiple studies to improve NASH with a trend for improvement in hepatic fibrosis. However, its use is limited by its side effects, especially weight gain. PXL065 is an exciting innovation with the potential to preserve the beneficial effects of pioglitazone on NASH while limiting the associated side effects. The current study provides a strong rationale for more advanced histology-based clinical trials to test this concept.”

PXL065 Phase 1b Results

The Phase 1b double-blind, randomized, placebo-controlled MAD trial evaluated the safety, tolerability and PK in 30 healthy subjects, following seven days of receiving three doses (7.5, 15 and 30 mg) of PXL065 versus 45 mg Actos®. The PK assessment showed that PXL065 plasma exposure (C_{max} and AUC) increased in a dose-proportional manner up to 30 mg, the highest dose tested, when using a tablet formulation. Stabilization of R-pioglitazone with deuterium was observed at all doses tested, which is consistent with results observed in the Phase 1a single dose trial. Furthermore, an assessment of food effect on the PK of PXL065 in fed versus fasted conditions did not demonstrate a clinically meaningful difference.

PXL065 Phase 2 Trial Design

Based on the Phase 1b MAD results, preclinical results as well as feedback from the U.S. Food and Drug Administration (FDA), Poxel plans to initiate a Phase 2 36-week trial in noncirrhotic biopsy-proven NASH patients that will assess three doses of PXL065 (7.5, 15, 22.5 mg) compared to placebo in at least 120 patients in the second quarter of 2020. The primary endpoint of this trial will be the reduction of liver fat mass measured by MRI-PDFF. The Phase 2 trial will also evaluate efficacy on histology endpoints assessed by liver biopsy, assessment of other non-invasive tests and assessment of body weight changes. The goal of this trial is to identify the optimal dose or doses of PXL065 to advance into a pivotal registration trial for the treatment of noncirrhotic biopsy-proven NASH patients.

13-Week Dog Toxicity Results

Poxel recently completed a 13-week repeated-dose toxicity study in dogs comparing PXL065 to pioglitazone. PXL065 was observed to show an improved safety profile over pioglitazone. The study also supports that S-pioglitazone is driving the toxicity effects seen in dogs with pioglitazone at the highest dose tested, which translates into at least a four-fold increase in predicted safety margin (dog vs human) of PXL065 compared to pioglitazone. Under the 505(b)(2) regulatory process and the FDA Guidance on the Development of New Stereoisomeric Drugs, repeated-dose toxicity studies can be limited to one mammalian species instead of two mammalian species.

Poxel is advancing PXL065 using a 505(b)(2) regulatory pathway, which will in part reference and rely on the Actos® (pioglitazone) product label and relevant published literature. A 505(b)(2) new drug application (NDA) contains full safety and efficacy reports but permits some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the NDA applicant. Utilizing this regulatory pathway has the potential to result in a less expensive and faster route to approval compared to a traditional 505(b)(1) development path.

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. Although pioglitazone is not approved by the FDA for the treatment of NASH, it 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 off-label 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 different pharmacological properties. In *in vitro* studies, PXL065 has been shown to target mitochondrial pyruvate carrier (MPC) as an inhibitor. In preclinical animal models, PXL065 exhibits the anti-inflammatory and NASH activity 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, Poxel believes that PXL065 may have a better therapeutic profile than pioglitazone for NASH.

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 is conducting 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 Phase 2 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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*Actos is the branded version of pioglitazone and a registered trademark of Takeda Chemical Industries, Ltd.

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[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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