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Poxel Announces Presentation of PXL065 Phase 1a Results at the Liver Meeting® 2019

- **PXL065 observed to have a favorable safety, tolerability and pharmacokinetic (PK) profile in the Phase 1a trial**
- **PXL065 intends to utilize the 505(b)(2) regulatory pathway, which offers the opportunity for a streamlined and efficient development plan**
- **Poxel plans to advance PXL065 in a Phase 2 trial in biopsy-proven NASH patients designed to identify the optimal dose or doses for a Phase 3 registration trial; initiation expected 2Q 2020**

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 presentation of PXL065 Phase 1a results during a poster presentation session at the Liver Meeting® 2019 hosted by the American Association for the Study of Liver Diseases (AASLD). In the poster presentation, PXL065 was observed to have a favorable safety, tolerability and PK profile in the Phase 1a trial. 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 in combination with the preclinical studies and PK modelling suggests that 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 eagerly awaiting the results from the Phase 1b multiple ascending dose trial, which should support dose selection for the Phase 2 and 3 trials. 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.”

“As a hepatologist, I participated in early Phase 2 clinical trials with pioglitazone in biopsy-proven NASH patients. To-date, pioglitazone has achieved compelling treatment outcomes for the resolution of NASH without the worsening of fibrosis. However, it is only prescribed by a small percentage of physicians, around 14%[1], for biopsy-proved NASH patients due to its common side effect of weight gain,” said Stephen A. Harrison, MD, Visiting Professor of Hepatology, Radcliffe Department of Medicine, University of Oxford, UK. “Based on preclinical and clinical results, I am excited about the potential for an improved therapeutic profile for PXL065 compared to pioglitazone.”

PXL065 Phase 1a Study Results
The Phase 1a study evaluated the safety, tolerability and pharmacokinetics (PK) of three doses of PXL065 (7.5, 22.5, 30 mg) 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 (C_{max} and AUC) increased in a dose-proportional manner following oral administration with moderate inter-individual variability. Furthermore, stabilization of R-pioglitazone with deuterium was observed at all doses tested and was shown to be dose-independent.

The poster presented at the AASLD meeting titled, "Phase 1 study of PXL065 confirms dose proportionality & stabilization of the preferred stereoisomer (R-pioglitazone) for the treatment of NASH," is available on the Company's website under Product Pipeline/Posters and by using the link here.

PXL065 Phase 2 Clinical Plan
Poxel plans to advance 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 effectiveness reports but has some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, 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 development path.

In September 2019, Poxel announced the initiation of a Phase 1b multiple ascending dose (MAD) trial, aiming to evaluate the safety, tolerability and PK and support dose selection. In this study, three doses of PXL065 (7.5, 15, 30 mg) versus 45 mg Actos® are administered to approximately 30 healthy subjects. Results of this study are expected in the fourth quarter of 2019. The data from this study should provide important information regarding dose proportionality, which will support the Phase 2 and Phase 3 trials.

Following the FDA meeting and review of the Phase 1b MAD trial results, Poxel plans to initiate a Phase 2 trial in the second quarter of 2020 with the primary objective of identifying the optimal dose or doses to be evaluated in a Phase 3 registration trial. The Phase 2 design will take into account the knowledge available related to the clinical use of pioglitazone. The Company anticipates evaluating three doses of PXL065 compared to placebo in biopsy-proven NASH patients and using several endpoints, which may include non-invasive biomarkers such as alanine aminotransferase (ALT) and MRI-PDFF, histology (biopsy to assess measures of NASH efficacy in the liver) and body weight gain assessment**.** Poxel is currently finalizing the design of the Phase 2 clinical development plan with input from scientific experts, advisors and key opinion leaders, and the Company will provide an update once this plan is formalized.

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[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 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 in Phase 1 clinical testing and being developed 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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[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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