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Poxel Announces Positive Update Following FDA Meeting for PXL065 for Treatment of NASH

- **FDA feedback supports plan to advance PXL065 using the 505(b)(2) regulatory pathway for NASH**
- **505(b)(2) process offers opportunity for a streamlined and efficient development plan**
- **Poxel provides update on PXL065 Phase 2 trial designed to identify optimal dose or doses for Phase 3 registration trial; initiation expected 2Q 2020**

LYON, France--(BUSINESS WIRE)-- POXEL S.A. (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), announced today an update for PXL065 following a positive meeting with the U.S. Food and Drug Administration (FDA) in the fourth quarter 2019. Based on feedback from the FDA, 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. NASH is a serious disease and PXL065 has the potential to address an unmet medical need, so the Company intends to seek Fast Track Designation. PXL065, the deuterium-stabilized R-stereoisomer of pioglitazone, is a mitochondrial pyruvate carrier (MPC) inhibitor being developed for the treatment of NASH.

“To my knowledge, PXL065 is in the unique position of being the first NASH clinical candidate being developed using a 505(b)(2) regulatory pathway with the potential to bridge to the vast amount of safety and efficacy data from pioglitazone studies,” 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.”

A 505(b)(2) 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 with a traditional development path.

“We are very pleased with the FDA feedback for the PXL065 development program. Using the 505(b)(2) regulatory process should enable reliance on relevant Actos® data, including the product label and published literature, which is anticipated to be used as part of the data

package for a future new drug application (NDA) for PXL065, pending successful completion of the Phase 2 and Phase 3 trials. The 505(b)(2) process in this context should provide the opportunity for an efficient and streamlined development plan with reduced financial and development risk," said Thomas Kuhn, CEO of Poxel. "We plan to initiate a Phase 2 trial for PXL065 for the treatment of NASH during the second quarter of 2020 in biopsy-proven NASH patients. The primary objective of this trial is to determine the optimal dose or doses to be tested in a Phase 3 registration trial."

In September 2019, a Phase 1b multiple ascending dose (MAD) trial, aiming to evaluate safety, tolerability and PK and support dose selection, was initiated. In this study three doses of PXL065 (7.5 mg, 15 mg and 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 on dose proportionality, which will support the Phase 2 and Phase 3 trials.

PXL065 Phase 2 Trial Design
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 to identify 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 different doses of PXL065 compared to placebo in biopsy-proven NASH patients using several efficacy endpoints 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.

Fast Track Designation
Poxel plans to submit a Fast Track designation request for PXL065. Fast Track designation is designed to facilitate the development and expedite the review of drugs that treat serious conditions and have the potential fill an unmet medical need. A drug that receives Fast Track designation is also eligible for more frequent meetings and communications with the FDA to discuss the drug's development plan[1].

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] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track.
[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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