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Poxel Completes Enrollment in Phase 2 NASH Trial for PXL065 (DESTINY-1) in Biopsy-Proven Patients

- **PXL065 is a new chemical entity derived from pioglitazone, which has shown to retain NASH efficacy without triggering peroxisome proliferator-activated receptor (PPAR)-g-related side effects in preclinical studies**
- **Phase 2 trial of 123 noncirrhotic biopsy-proven NASH patients expected to report topline results in Q3 2022; trial designed to identify optimal dose or doses for Phase 3 registration trial**
- **Streamlined development with a single Phase 2 trial given knowledge of pioglitazone, including data in NASH, and 505(b)(2) regulatory pathway, which offers the opportunity for an efficient and lower risk development program**

LYON, France--(BUSINESS WIRE)-- POXEL SA (Euronext – POXEL - FR0012432516), a clinical stage biopharmaceutical company developing innovative treatments for chronic diseases with metabolic pathophysiology, including non-alcoholic steatohepatitis (NASH) and rare disorders, today announced the completion of enrollment in DESTINY-1 (Deuterium-stabilized R-pioglitazone (PXL065) Efficacy and Safety Trial In NASH), a dose-ranging Phase 2 trial evaluating PXL065 for the treatment of NASH. PXL065 is a novel, proprietary deuterium-stabilized R-stereoisomer of pioglitazone. DESTINY-1 enrolled 123 noncirrhotic biopsy-proven NASH patients across multiple clinical sites in the US in a 36-week, randomized, dose-ranging, double-blind, placebo-controlled, parallel group study designed to assess the efficacy and safety of PXL065. The primary endpoint of the study will measure the relative change in the percentage of liver fat content based on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF). The study will also assess the effects of PXL065 on liver histology and other metabolic and non-metabolic biomarkers. Results from the Phase 2 study are anticipated in Q3 2022.

“Pioglitazone – and other thiazolidinedione drugs - exert both genomic (PPARγ) and non-genomic actions. PXL065, the deuterium-stabilized single *R*-stereoisomer of pioglitazone, has been shown to selectively mediate non-genomic effects of pioglitazone that can ameliorate key components of NASH pathophysiology including steatosis, inflammation and fibrosis. This preclinical profile provides for potential benefits in NASH but with an improved side effect profile with respect to PPARγ - mediated body weight gain and edema,” said David E. Moller, MD, EVP and CSO of Poxel.

"In our Phase 1 development program, we first confirmed that PXL065 was safe and well-tolerated, and that substantially greater relative exposure to the preferred (low PPARγ) – R-

stereoisomer was achieved. By leveraging the 505(b)(2) regulatory path and with input from several top NASH advisors, DESTINY-1 was designed as a streamlined approach to validate that the efficacy of PXL065 in NASH is aligned with that established with pioglitazone. Results from this trial should allow us to select one (or potentially two) doses that could then be studied in a confirmatory pivotal trial," said Pascale Fouqueray, MD, PhD, Executive Vice President, Clinical Development and Regulatory Affairs at Poxel.

Stephen Harrison, MD, President, Summit Clinical Research, further commented: "Pioglitazone has a strong track record of efficacy in NASH with more than 5 trials showing substantial benefits on liver histology that match or exceed most contemporary efficacy results obtained with other oral molecules. Thus, testing the hypothesis behind DESTINY-1 is a worthy objective. As the principal investigator of this important trial, I am very excited to see that we will be positioned to receive results next year."

PXL065 DESTINY-1 Trial Design

The single Phase 2 36-week trial in 123 noncirrhotic biopsy-proven NASH patients will assess three doses of PXL065 (7.5, 15, 22.5 mg) compared to placebo. The primary endpoint of this trial will be the relative change in the percentage of liver fat content measured by MRI-PDFF at 36 weeks. The Phase 2 trial will also evaluate the efficacy on histological 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 Phase 3 registration trial for the treatment of noncirrhotic biopsy-proven NASH patients.

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 a novel, proprietary 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 non-genomic pathways including mitochondrial pyruvate carrier (MPC). 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[3]. 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 clinical stage biopharmaceutical company developing innovative treatments for chronic serious diseases with metabolic pathophysiology, including non-alcoholic steatohepatitis (NASH) and rare disorders. Poxel has clinical and earlier-stage programs from its adenosine monophosphate-activated protein kinase (AMPK) activator and deuterated TZD platforms targeting chronic and rare metabolic diseases. For the treatment of NASH, PXL065 (deuterium-stabilized *R*-pioglitazone) is in a streamlined Phase 2 trial (DESTINY1). PXL770, a first-in-class direct AMPK activator, has successfully completed a Phase 2a proof-of-concept trial for the treatment of NASH, which met its objectives. For the rare inherited metabolic disorder, adrenoleukodystrophy (ALD), the company intends to initiate Phase 2a proof of concept studies with PXL065 and PXL770 in patients with adrenomyeloneuropathy (AMN). TWYMEEG® (Imeglimin), Poxel's first-in-class lead product that targets mitochondrial dysfunction, has been approved and launched for the treatment of type 2 diabetes in Japan. Poxel expects to receive sales-based payments and royalties from Sumitomo Dainippon Pharma. Poxel has a strategic partnership with Sumitomo Dainippon Pharma for Imeglimin in Japan, China, South Korea, Taiwan and nine other Southeast Asian countries. 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] 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] Jacques et al. Deuterium-Stabilized (R)-Pioglitazone (PXL065) is responsible for pioglitazone efficacy in NASH yet exhibits little to no PPARγ activity

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