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Poxel Announces Positive Results from Phase 2 NASH Trial (DESTINY-1) for PXL065, A Novel, Proprietary Deuterium-Stabilized R-Stereoisomer of Pioglitazone

- **The Phase 2 trial for the treatment of NASH met its primary efficacy endpoint; PXL065-treated patients achieved statistically significant improvements in the relative decrease in liver fat content measured by magnetic resonance imaging estimated proton density fat fraction (MRI-PDFF) at 36-weeks for all doses.**
- **Key secondary measures in PXL065-treated patients included a statistically significant improvement in Pro-C3, a biomarker of fibrogenesis.**
- **PXL065 was observed to be safe and well tolerated with no dose dependent increase in body weight and no increased lower extremity edema vs. placebo. Safety profile is consistent with reduced PPARg-mediated side effects vs. published results of pioglitazone.**
- **Histology results pending in September, along with the positive initial readout, will inform the next steps of PXL065 in NASH, including the potential for Phase 3 development.**

LYON, France--(BUSINESS WIRE)-- POXEL SA (Euronext : POXEL - FR0012432516), clinical stage biopharmaceutical company developing innovative treatments for chronic serious diseases with metabolic pathophysiology, including non-alcoholic steatohepatitis (NASH) and rare metabolic disorders, today announced positive top-line results for DESTINY-1 (Deuterium-stabilized R-pioglitazone [PXL065] Efficacy and Safety Trial In NASH), the dose-ranging Phase 2 trial of PXL065 for the treatment of NASH. PXL065 is a novel, proprietary deuterium-stabilized R-stereoisomer of pioglitazone which has reduced PPARγ activity but retains non-genomic thiazolidinedione (TZD) actions.

"Pioglitazone has a good record of efficacy in NASH with 6 clinical trials in NASH patients to-date having demonstrated substantial benefits on liver histology that compare favorably to other oral molecules in development," said Stephen Harrison, MD, President, Summit Clinical Research. *"DESTINY-1 was designed to show that PXL065 could achieve a similar efficacy profile as PPARγ targets, but with reduced adverse effects of body weight increase and edema. As the principal investigator of this important trial, I am pleased by the data we've seen so far and am looking forward to reviewing the pending histology results soon."*

"The data we've seen to-date support our hypothesis – that deuterium modification of the pioglitazone R-enantiomer produces differentiated pharmacology – by reducing PPARγ

activity and related adverse effects while retaining aspects of pioglitazone-like efficacy," said Pascale Fouqueray, MD, PhD, Executive Vice President, Clinical Development and Regulatory Affairs at Poxel. *"Positive effects on liver fat content and a well-recognized biomarker of fibrogenesis are reassuring. We are excited to soon review the histology results from this study."*

"These Phase 2 results in NASH are an important milestone for Poxel and add to our track record of executing successful clinical trials. With the addition of the histology data from the DESTINY-1 trial, PXL065 could be advanced into a pivotal Phase 3 program for NASH – representing a large unmet need and market opportunity," stated Thomas Kuhn, Chief Executive Officer of Poxel. *"Today's results also validate the concept of the d-TZD platform, which could be utilized in additional diseases such as ALD. We remain fully committed to improve the health and well-being of patients through the development of innovative treatments for serious chronic metabolic diseases."*

Summary of Phase 2 NASH (DESTINY-1) PXL065 Study Results

DESTINY-1 is a Phase 2, 36-week, randomized, dose-ranging, double-blind, placebo-controlled, parallel group study designed to assess the efficacy and safety of PXL065 in patients with noncirrhotic biopsy-proven NASH across multiple clinical sites in the US. The primary endpoint of the study measured the relative change in the percentage of liver fat content based on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF). The study also assessed the effects of PXL065 on liver histology and other metabolic and non-metabolic biomarkers. Histology results are expected in September.

Top-line results available at present include:

- 117 subjects were randomized to one of 4 daily (QD) treatment arms (7.5 mg, 15 mg, 22.5 mg, placebo).
- The primary efficacy endpoint was achieved: a statistically significant (p=0.024 to p=0.008) mean relative decrease vs. placebo of 21% to 25% in liver fat content from baseline to 36 weeks was observed at all PXL065 doses. 40% of patients who received PXL065 at the 22.5 mg dose achieved a >30% relative reduction in liver fat content.
- Non-invasive biomarker results to-date included: dose-dependent decreases in fibrogenesis markers Pro-C3 (significant vs. placebo at the 22.5 mg dose; p=0.02) and enhanced liver fibrosis (ELF) index. Trends in least-square mean ALT decreases up to 18.4 IU/L vs. baseline were observed. However, this parameter did not reach statistical significance. Further data analysis is ongoing.
- There was no dose dependent increase in body weight: a minimal least-square mean increase of 0.68 kg was observed at the top dose of 22.5 mg vs. placebo. The incidence of edema did not show an observed treatment or dose relation when compared to placebo. With respect to other safety measures, PXL065 was observed to be generally safe and well tolerated; the number of patients presenting with treatment-emergent serious adverse events (TESAEs) were similar among all groups including placebo without dose effect.
- As predicted, pharmacokinetic measurements showed dose-proportional drug levels with the desired degree of higher exposure to the pioglitazone R-stereoisomer and reduced exposure to the (PPARg active) S-stereoisomer.

Additional data from histology results are expected in September. The full Phase 2 results will be submitted for presentation at an upcoming scientific meeting.

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, Poxel 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) and acyl-CoA synthetase 4 (ACSL4). 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]. NASH Phase 2 (DESTINY 1 trial) results available to-date show statistically significant effects of PXL065 on liver fat content and a biomarker of liver fibrogenesis. Relative to published data for pioglitazone, reduced potential for weight gain and edema was also evident. Based upon preclinical, Phase 1 and preliminary Phase 2 results to date, Poxel believes that PXL065 may have a better therapeutic profile than pioglitazone for NASH and may also have suitable properties for further development in other indications including adrenoleukodystrophy (ALD).

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 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) met its primary endpoint in a streamlined Phase 2 trial (DESTINY-1). **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, is approved and marketed for the treatment of type 2 diabetes in Japan. Poxel expects to receive from Sumitomo Pharma royalties and sales-based payments. Poxel has a strategic partnership with Sumitomo 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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