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Poxel Announces Publication of Positive Phase 2 Results from Phase 2 NASH Trial (DESTINY-1) for PXL065 in Journal of Hepatology

- **PXL065 Phase 2 trial for the treatment of NASH met its primary efficacy endpoint for liver fat content reduction at 36-weeks for all doses.**
- **Fibrosis improvement by >1 stage without worsening of NASH, an endpoint recognized by FDA for approval, occurred in 31-50% patients in the PXL065 study arms vs. 17% with placebo.**
- **Validation of PXL065 hypothesis - combining efficacy on liver and metabolic endpoints with reduced potential for PPARg side effects (weight gain and edema).**

LYON, France--(BUSINESS WIRE)-- Regulatory News:

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 publication in *Journal of Hepatology* of positive results for DESTINY-1 (Deuterium-stabilized R-pioglitazone [PXL065] Efficacy and Safety Trial In NASH), a 36-week dose-ranging Phase 2 trial. PXL065 is a novel, proprietary deuterium-stabilized R-stereoisomer of pioglitazone which has reduced PPARγ activity, but retains non-genomic pioglitazone actions.

To access the online publication from *Journal of Hepatology*, please use the following link: Evaluation of PXL065 – Deuterium-Stabilized (R)-Pioglitazone in NASH Patients: a Phase 2 randomized placebo-controlled trial (DESTINY-1) - Journal of Hepatology (journal-of-hepatology.eu)

Lead author, Stephen Harrison, MD, President, Summit Clinical Research, and principal investigator of the study, commented: "*Publication of these new clinical findings in such a prestigious journal is an important milestone in the field of new NASH therapeutics. With PXL065, an attractive and differentiated clinical profile has emerged, including reduced liver fat, fibrosis improvements and metabolic benefits along with very good safety and tolerability. PXL065 merits further study in a pivotal trial that could yield an important new oral medicine for NASH with additional potential for use in combination approaches*."

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.

117 subjects were randomized to one of 4 daily (QD) treatment arms (7.5 mg, 15 mg, 22.5 mg, placebo). Analysis of histologic changes was based on paired liver biopsies in PXL065 vs. placebo-treated NASH patients before and after the 36-week treatment period. This trial was not powered to detect statistically significant changes in histology endpoints.

Key Findings

- 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.
- Histology: Fibrosis improvement by ≥1 stage without worsening of NASH, an endpoint recognized by FDA for approval, occurred in 31-50% patients in the PXL065 study arms vs. 17% with placebo. Across all PXL065 treatment arms (pooled data), 39% of patients had fibrosis improvement by ≥1 stage without worsening NASH (%) vs. 17% with placebo.
- Safety & tolerability: 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. No increase in the incidence of peripheral edema vs. placebo.

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; in multiple prior trials, improvements in liver histology, including reductions in fibrosis, were demonstrated[1,2]. 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. PXL065 is a new chemical entity (NCE) where its further development will also be able to leverage the FDA 505(b)(2) regulatory pathway.

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 –mitochondrial pyruvate carrier (MPC) and acyl-CoA synthetase 4 (ACSL4) - each of which are implicated as NASH targets. In preclinical animal models, PXL065 exhibits the NASH efficacy associated with pioglitazone with no significant weight gain or fluid retention, side effects which are associated with the S-stereoisomer[4]. NASH Phase 2 (DESTINY 1 trial) results available to-date show statistically significant

effects of PXL065 on liver fat content, biomarkers related to liver fibrogenesis-fibrosis risk, as well as positive effects on fibrosis and other key parameters based on histology analysis. Relative to published data for pioglitazone, reduced potential for weight gain and edema was also evident. Based upon preclinical, Phase 1 and Phase 2 results, 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. For the treatment of NASH,**PXL065** (deuterium-stabilized *R*-pioglitazone) met its primary endpoint in a streamlined Phase 2 trial (DESTINY-1). In rare diseases, development of PXL770, a first-in-class direct adenosine monophosphate-activated protein kinase (AMPK) activator, is focused on the treatment of adrenoleukodystrophy (ALD) and autosomal dominant polycystic kidney disease (ADPKD). **TWYMEEG®** (Imeglimin), Poxel's first-in-class product that targets mitochondrial dysfunction, is marketed for the treatment of type 2 diabetes in Japan by Sumitomo Pharma and Poxel expects to receive royalties and sales-based payments. Poxel has a strategic partnership with Sumitomo Pharma for Imeglimin in Japan, China, and eleven other Asian countries. 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] Musso et al. Hepatology 2017; 65: 1058-1061.
[3] J Hepatol. 2016, 64:1388-402; Hepatology 2018, 67: 328-357.
[4] Jacques et al. Hepatol Comm 2021; 5:1412-1425.

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