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# Poxel Presents DESTINY-1 Phase 2 Results for PXL065 in NASH at AASLD The Liver Meeting® 2022

- **Late-breaking abstract selected by AASLD as one of the "Best of the Liver Meeting" for 2022**
- **Phase 2 for PXL065 in NASH achieved the primary efficacy endpoint for liver fat content reduction for all doses and showed strong improvement in fibrosis without worsening of NASH**
- **PXL065 is one of the most advanced therapies in development in NASH, for which there is no approved treatment**

LYON, France--(BUSINESS WIRE)-- POXEL SA (Euronext: POXEL - FR0012432516), a 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 that the results from its Phase 2 study of PXL065 in NASH (DESTINY-1) were presented during the late-breaking session at The Liver Meeting® 2022, hosted by the American Association for the Study of Liver Diseases (AASLD), being held in Washington, D.C. PXL065 is a novel, proprietary deuterium-stabilized

R-pioglitazone and one of the most advanced therapies in development in NASH, for which there is no approved treatment.

Stephen Harrison, MD, President, Summit Clinical Research, and principal investigator of this study, presented the results in the oral presentation titled, "*PXL065 (Deuterium-Stabilized R-enantiomer of pioglitazone) Reduces Liver Fat Content and Improves Liver Histology without PPARγ-mediated Side Effects in Patients with NASH: Analysis of a 36 Week Placebo-Controlled Phase 2 Trial (DESTINY-1).*"

Dr. Harrison noted: "*PXL065 lacks in vitro PPARγ activity whereas deuterium-stabilized (S)-pioglitazone accounts for all of the PPARγ agonism of racemic pioglitazone. Based on the established efficacy of pioglitazone in NASH and these findings with PXL065, we sought to test the hypothesis that a TZD which retains non-genomic mechanisms and reduced net in vivo PPARγ burden could be an effective and safe approach to the treatment of NASH. The DESTINY-1 efficacy results are aligned with prior studies showing similar benefits with pioglitazone. Importantly, PXL065 appears to have a clear PPARγ-sparing profile with respect to characteristic adverse effects of pioglitazone. From DESTINY-1 we conclude that PXL065 is a differentiated and novel oral agent with a new chemical structure, distinct*

*molecular pharmacology, a unique PK profile, reduced potential for PPARγ-driven adverse events and a very encouraging efficacy profile in patients with noncirrhotic NASH. Confirmation of histologic benefits by testing in a pivotal clinical trial is warranted*."

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

DESTINY-1 was 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.

Results presented today are as follows:

**Changes in Liver Fat and Key Markers of Fibrosis and Liver Injury**

- 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.
- Trend in least-square mean ALT decreases up to 18.4 IU/L vs. baseline. Subjects experiencing a decrease in ALT by more than -17U/L were numerically higher in the PXL065 groups (38% to 54%) versus placebo (26%).
- Statistically significant dose-dependent decreases in PIIINP (fibrogenesis biomarker, p=0.02 at 22.5 mg) and the NAFLD Fibrosis Score (p=0.04 at 22.5 mg) along with favorable trends for dose-dependent improvements in other markers of fibrogenesis/fibrosis risk (ProC3, ELF, Fib4) were observed.

Biopsy Endpoints

- 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.
- Worsening of fibrosis by ≥1 stage was observed in 9-12% of patients in PXL065 arms vs. 26% with placebo.
- A ≥2 point improvement in the NAFLD Activity Score (NAS) with no worsening of fibrosis was observed in 50% of PXL065 treated patients at the 15 and 22.5 mg dose levels vs. 30% with placebo.
- Across all PXL065 treatment arms (pooled data), 26% of patients achieved NASH resolution with ≥1 stage fibrosis improvement vs. 13% with placebo.

**Metabolic Parameters**

- A dose-dependent decrease in HbA1c (up to 0.41 % placebo-adjusted; p=0.003 at 22.5 mg) was observed; in patients with co-existing Type 2 diabetes, the placebo-adjusted change was up to -0.56%. Given baseline HbA1c values indicating good glucose control on existing Type 2 diabetes treatments (6.1-6.3% overall; 6.6-7.4% in T2D), these effects are potentially clinically meaningful.
- Modest plasma adiponectin level increase (p<0.0001 vs. placebo at 22.5 mg); consistent with limited degree of PPARg activation and observed safety profile with reduced potential for weight gain or peripheral edema.
- Improvements in insulin levels and insulin sensitivity indices (HOMA-IR, Adipo-IR, QUICKI) were also observed.

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.

- Low incidence of edema without 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. None were treatment related.

Pharmacokinetics

- 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.

**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.

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 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 now 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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**Investor relations / Media**

Aurélie Bozza
Investor Relations & Communication Senior Director
aurelie.bozza@poxelpharma.com
+33 6 99 81 08 36

Elizabeth Woo
Senior Vice President, Investor Relations & Communication
elizabeth.woo@poxelpharma.com

NewCap
Emmanuel Huynh or Arthur Rouillé
poxel@newcap.eu
+33 1 44 71 94 94

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