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

- **Phase 2 trial will include approximately 120 noncirrhotic biopsy-proven NASH patients and is 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**
- **The primary endpoint of DESTINY 1 will measure the relative change in the percentage of liver fat as measured by MRI-PDFF**
- **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**

LYON, France--(BUSINESS WIRE)-- POXEL SA (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), today announced the initiation of DESTINY 1 (Deuterium-stabilized R-pioglitazone (PXL065) Efficacy and Safety Trial In NASH), the single 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 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 approximately 120 noncirrhotic biopsy-proven NASH patients across multiple clinical sites in the US. 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 the first half of 2022.

“Based on the PXL065 results to-date and a wealth of available clinical trial results with pioglitazone treatment for NASH, we designed DESTINY 1, a streamlined Phase 2 trial, to evaluate the efficacy and safety profile of PXL065 with the goal of identifying the optimal dose or doses for a Phase 3 registration trial,” said Pascale Fouqueray, MD, PhD, EVP, Clinical Development and Regulatory Affairs at Poxel. “The doses that will be evaluated in the trial are 7.5 mg to 22.5 mg, a range that we believe has the potential to demonstrate an

improved therapeutic profile over 45 mg Actos®* (pioglitazone)."

"As a hepatologist, I participated in an early Phase 2 clinical trial with pioglitazone in biopsy-proven NASH patients. Although pioglitazone has achieved the most compelling treatment effects to-date for resolution of NASH without worsening of fibrosis, it is only prescribed by a small percentage of physicians, around 14%[1], for biopsy-proven NASH patients. The primary reason for this is pioglitazone's side effect of weight gain," said Stephen A. Harrison, MD, Director, Summit Clinical Research, a NASH trial site network, and Principal Investigator of DESTINY 1. "Based on pioglitazone's known efficacy and safety results in NASH and cardiovascular benefits combined with the exciting preclinical and clinical PXL065 results to-date, I believe PXL065 has the potential to produce compelling results in noncirrhotic biopsy-proven NASH patients."

"Pioglitazone and the larger class of drugs known as thiazolidinediones (TZDs) exert both genomic (PPAR) and non-genomic actions. PXL065, the deuterium-stabilized single R-stereoisomer of pioglitazone, has been shown to selectively mediate non-PPARγ effects of pioglitazone, such as inhibition of the mitochondrial pyruvate carrier that can ameliorate key components of NASH pathophysiology including steatosis, inflammation and fibrosis. This preclinical profile provides the potential for efficacy benefits in NASH that are similar to pioglitazone but with an improved side effect profile with respect to body weight gain and edema, which are observed with pioglitazone and other TZDs and PPARγ active agents," said David E. Moller, MD, EVP and CSO of Poxel.

PXL065 DESTINY 1 Trial Design
Based on results to-date as well as feedback from the U.S. Food and Drug Administration (FDA), the single Phase 2 36-week trial in approximately 120 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 505(b)(2) Regulatory Pathway
Poxel is advancing 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. A 505(b)(2) new drug application (NDA) contains full safety and efficacy reports but permits some of the information required for NDA approval, such as safety and efficacy information on the active ingredient (pioglitazone), to come from studies not conducted by or for the NDA applicant. Utilizing this regulatory pathway has the potential to result in a less expensive, lower risk development program and more expeditious route to approval compared to a traditional 505(b)(1) regulatory pathway.

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[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. Poxel has a strategic partnership with Sumitomo Dainippon Pharma for Imeglimin in Japan, China, South Korea, Taiwan and nine other Southeast Asian countries. A Japanese new drug application (J-NDA) is under review by the Pharmaceuticals and Medical Devices Agency (PMDA) to request approval for the manufacturing and marketing of Imeglimin for the treatment of type 2 diabetes. 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 MPC inhibitor, is in a single Phase 2 trial for the treatment of NASH. Poxel also has additional earlier-stage programs from its AMPK activator and deuterated TZD platforms targeting chronic and rare metabolic 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.

In the context of the COVID-19 outbreak, which was declared a pandemic by the World Health Organization (WHO) on March 12, 2020, the Company is regularly reviewing the impact of the outbreak on its business.

As of the date of this press release, and based on publicly available information, the Company has not identified the occurrence of any material negative effect on its business due to the COVID-19 pandemic, other than the delay in the initiation of the Phase 2 study enrollment for its drug candidate PXL065, which the Company initially planned during the second quarter of 2020 and was initiated on the date of this press release. However, the Company anticipates that the COVID-19 pandemic could have further material negative impact on its business operations. The worldwide impact of COVID-19 may notably affect the Company's internal organization and efficiency, particularly in countries where it operates and where confinement measures are implemented by the authorities. In addition, COVID-19 may impact market conditions and the Company's ability to seek additional funding or enter into partnerships. Particularly, delays in the supply of drug substance or drug products, in the initiation or the timing of results of preclinical and/or clinical trials, as well as delays linked to the responsiveness of regulatory authorities could occur, which could potentially have an impact on the Company's development programs and partnered programs. The Company will continue to actively monitor the situation.

All statements other than statements of historical fact included in this press release about future events are subject to (i) change without notice and (ii) factors beyond the Company's control. These statements may include, without limitation, any statements preceded by, followed by or including words such as "target," "believe," "expect," "aim," "intend," "may," "anticipate," "estimate," "plan," "project," "will," "can have," "likely," "should," "would," "could" and other words and terms of similar meaning or the negative thereof. Forward-looking statements are subject to inherent risks and uncertainties beyond the Company's control that could cause the Company's actual results or performance to be materially different from the expected results or performance expressed or implied by such forward-looking statements.

*Actos is the branded version of pioglitazone and a registered trademark of Takeda Chemical Industries, Ltd.

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[1] Therap Adv Gastroenterol. 2016, 9(1), 4-12

[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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