



## **Poxel Presents Phase 1b Clinical Results for PXL065 and New Preclinical Data for PXL770 at AASLD The Liver Meeting® 2020**

- **Data support potential utility for treatment of NASH**
- **Analysis of results from the Phase 1b study of PXL065 (deuterium-stabilized R-pioglitazone) predicts efficacy at 15 mg once-daily is equivalent to 45 mg Actos®, with little to no PPARγ-related side effects, such as weight gain**
- **In a rodent NASH model, PXL770, a novel direct adenosine monophosphate-activated protein kinase (AMPK) activator, was observed to produce additional benefits when administered in combination with other NASH drug candidates vs. either agent alone**
- **PXL770 produced anti-inflammatory effects in mouse liver and adipose tissue and in human immune cells**
- **Specific biomarkers related to improvements involving mitochondria were observed in the livers of PXL770-treated NASH-model mice**
- **Poxel to host NASH KOL event focused on PXL770 results on December 14, 2020 featuring NASH expert, Kenneth Cusi, MD**
- **A detailed analysis of the type 2 diabetes subpopulation results from the PXL770 Phase 2a study as well as an update on the Phase 2b study design are expected within the coming weeks**

LYON, France--(BUSINESS WIRE)-- [POXEL SA](https://www.poxelpharma.com/en_us/product-pipeline/posters) (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 presentation of clinical data from the company's Phase 1b study of PXL065, which established a dose-proportional pharmacokinetic profile with a substantially altered ratio of R- and S-pioglitazone stereoisomers as predicted from preclinical and Phase 1a results. Additionally, several preclinical studies supporting the efficacy of PXL770 in NASH and other metabolic diseases were presented. The data were illustrated in four poster presentations at The Liver Meeting® Digital Experience 2020, held virtually from November 13-16, 2020, in association with the American Association for the Study of Liver Diseases (AASLD). The posters can be accessed on Poxel's website using the following link: [https://www.poxelpharma.com/en\\_us/product-pipeline/posters](https://www.poxelpharma.com/en_us/product-pipeline/posters).

"We are excited to present data that showcases the potential of our oral, first-in-class clinical candidates for NASH, PXL065 and PXL770, and which are complementary to the results observed to-date from both programs," said Thomas Kuhn, Chief Executive Officer of Poxel. "Further analysis from our Phase 1b clinical study highlights dose-equivalence for 15 mg of

PXL065 vs. 45 mg of Actos. This observation is particularly meaningful as it suggests that our product candidate could have an improved therapeutic profile compared to Actos, with equivalent or greater efficacy, while reducing or eliminating undesirable PPAR $\gamma$ -related side effects, including weight gain.”

“Additionally, as displayed across three PXL770 poster presentations, the preclinical data reveal the potential for direct effects on key components of NASH and demonstrate its potential as both a mono- and combination therapy,” continued Mr. Kuhn. “On the heels of positive, topline Phase 2a results, these additional data support the continued development of PXL770. We look forward to providing future updates on further analysis from the Phase 2a study and the Phase 2b trial design in biopsy-proven NASH patients.”

PXL065, the novel, proprietary deuterium-stabilized R-pioglitazone stereoisomer is currently being evaluated in DESTINY-I, a Phase 2 study in biopsy-proven NASH patients, which seeks to identify the optimal dose or doses for a Phase 3 registration trial. PXL770, a first-in-class direct adenosine monophosphate-activated protein kinase (AMPK) activator, will be advancing into a Phase 2b study for the treatment of noncirrhotic, biopsy-proven NASH. STAMP-NAFLD, the company’s Phase 2a proof-of-concept trial in nonalcoholic fatty liver disease (NAFLD) patients, recently met its primary endpoint and study objectives, demonstrating that PXL770 was observed to be safe, well-tolerated and that it achieved a statistically significant improvement in the relative decrease in liver fat mass as measured by MRI-PDFF at 12 weeks. Additionally, across several clinical parameters and preclinical studies, PXL770 has demonstrated broader potential in other chronic metabolic indications. Poxel is also evaluating earlier stage molecules from its AMPK activator and deuterated thiazolidinedione (TZD) platforms targeting other chronic and rare metabolic diseases.

### **Summary of PXL065 Clinical Phase 1b Results**

***Abstract Title: Phase 1b Study of PXL065 (Deuterium-Stabilized R-Pioglitazone), a Novel NASH Candidate, Predicts 15 mg Equivalent to 45 mg Actos®***

The double-blind, randomized, placebo-controlled Phase 1b study in healthy subjects evaluated PXL065 dosed at 7.5, 15 or 30 mg as compared to 45 mg of Actos over seven days, with a food effect assessment at 15 mg. Objectives of the study included assessing PXL065’s pharmacokinetic and pharmacodynamic (PK/PD) profile, specifically comparing relative exposures to R- and S-stereoisomers. The study also assessed intra-individual variability and exposure to the major metabolites of pioglitazone, M-III and M-IV.

The Phase 1b study met its endpoints and demonstrated a favorable safety and tolerability profile. Dose-proportionality was established at all doses. The 15 mg PXL065 dose resulted in plasma exposure to R-pioglitazone that was similar to Actos 45 mg. In contrast, exposure to S-pioglitazone (previously shown to be the only stereoisomer with PPAR $\gamma$  agonist activity) was five times lower after dosing PXL065 versus Actos. Together, these data indicate that deuterium at the chiral center of PXL065 results in consistent stabilization which delays interconversion to S-pioglitazone. Furthermore, analysis of metabolites showed that there is no change in the metabolism of PXL065 versus pioglitazone. Based on preclinical data and these Phase 1 human PK results, approximately 15 mg of PXL065 is predicted to yield similar chronic exposure to the desired stereoisomer, R-pioglitazone, and NASH efficacy as compared with 45 mg Actos, while reducing or eliminating PPAR $\gamma$ -related side effects such as weight gain.

“Our preclinical results have shown that Actos’ efficacy in NASH is mediated by R-pioglitazone, largely through non-genomic pathways, including inhibition of the mitochondrial pyruvate carrier, while S-pioglitazone is a potent PPAR $\gamma$  agonist, believed to be the driver of weight gain and fluid retention. Our goal in developing PXL065 as a deuterium-stabilized form of R-pioglitazone is to duplicate the efficacy of Actos, while reducing or eliminating the harmful PPAR $\gamma$ -related side effects,” said Pascale Fouqueray, MD, PhD, Executive Vice President Clinical Development and Regulatory Affairs at Poxel. “On further review, the full set of data from our Phase 1b study of PXL065 are in line with our topline analysis, which showed PXL065 was safe and well-tolerated, with improved bioavailability versus Actos. Furthermore, based on PK data from this study, as well as preclinical data, 15 mg of PXL065 is predicted to yield equivalent efficacy as 45 mg of Actos, with little to no PPAR $\gamma$ -related effects. Establishing dose-equivalence was a critical step and helped to enable our streamlined development approach. We look forward to supporting these projections with data from DESTINY-I, our Phase 2 study in biopsy-proven NASH patients, which seeks to identify the optimal dose or doses for a Phase 3 registration trial.”

### **Summary of PXL770 Preclinical Results**

Poxel presented three preclinical posters at The Liver Meeting related to PXL770. A summary of the data presented are as follows:

#### ***Abstract Title: PXL770, a Novel Direct AMP-activated Protein Kinase Activator Produces Greater Efficacy when Combined with Other Key Therapeutic Mechanisms Targeting NASH***

PXL770 was assessed in combination with other drug candidates for NASH, including a glucagon-like peptide receptor (GLP-1R) agonist (Semaglutide; SMG), a farnesoid x receptor (FXR) agonist (Obeticholic acid; OCA) and a thyroid hormone receptor (THR- $\beta$ ) agonist (Resmetirom; MGL) in a diet-induced obese (DIO) biopsy-proven mouse model of NASH. Data from these experiments demonstrated that combinations of PXL770 with either OCA, SMG or MGL improved selected NASH hallmarks to a greater extent than with the respective monotherapies, highlighting the potential benefit of combining PXL770 with FXR, GLP1-R and THR $\beta$  agonists to treat NASH.

“NASH is a complex disease with the need for treatments that address several core aspects of the pathophysiology. These preclinical results are supportive of the efficacy observed in our Phase 2a study and reinforce our thesis that PXL770 has the ability to effectively address multiple key drivers of this disease, including hepatic inflammation and hepatic steatosis. Moreover, these data highlight PXL770’s potential both as a monotherapy and in combination with other agents, showing additive benefits with the potential for greater efficacy than with monotherapy approaches alone,” said David E. Moller, MD, Executive Vice President and Chief Scientific Officer of Poxel. “Consistent data across clinical and preclinical studies have shown that AMPK plays a key role in cellular energy metabolism and appears to also directly reduce inflammation and improve mitochondrial health. Importantly, while these properties underscore the promise of PXL770 in NASH, they also reflect the therapeutic potential of this novel mechanism in other chronic and rare metabolic conditions.”

#### ***Abstract Title: PXL770, A New Direct AMP Kinase Activator and Potential NASH Therapeutic, Produces Anti-inflammatory Effects in Mouse Liver and Adipose Tissue***

## ***and in Human Immune Cells***

The effects of PXL770 on inflammation were assessed both *in vivo* and *in vitro* by examining anti-inflammatory effects on the livers of DIO NASH mice, ob/ob mouse adipose tissue and on human immune cells. PXL770 was found to exert anti-inflammatory effects in all three settings, including direct effects when assessed *in vitro*. In DIO-NASH mice, PXL770 improved NAFLD activity score (NAS) by decreasing liver steatosis, hepatic ballooning and liver inflammation, all common disease characteristics of NASH. In mouse adipose tissue explants, PXL770 prevented the nuclear activation of NF- $\kappa$ B and concomitantly reduced secretion of several inflammatory cytokines. In human dendritic cells from two donors, PXL770 reduced IL-6, IL-12 and TNF $_{\alpha}$  release and promoted an increase in T<sub>regs</sub> cells. The demonstrated effects of AMPK activation with PXL770 on inflammation extend beyond metabolic modulation and are promising for the treatment of NASH, as well as other inflammatory and metabolic diseases.

### ***Abstract Title: PXL770, a Novel Direct AMP-activated Protein Kinase Activator, Improves Hepatic Mitochondrial Function in a Rodent NASH Model***

Hepatic mitochondria play a critical role in the development and pathogenesis of steatosis and NASH. AMPK has been reported to enhance mitochondrial health by regulating various aspects of mitochondrial homeostasis. The potential effects of PXL770 on mitochondria were evaluated in a DIO biopsy-proven mouse model of NASH. Data demonstrated that PXL770 had a positive effect on mitochondrial health, specifically through improvements in markers of mitochondrial biogenesis, network-structure, oxidative stress and apoptosis mediated by mitochondria. These results may underlie subsequent improvements in NAS across all hallmarks of NASH, in particular hepatic steatosis and cell death.

**Poxel will discuss these preclinical data for PXL770 as well as present a more detailed analysis of its Phase 2a trial during a KOL event featuring NASH expert, Kenneth Cusi, MD, Chief of the Division of Endocrinology, Diabetes & Metabolism in the Department of Medicine at the University of Florida, on December 14, 2020. Further details about the event will be available in the Events section on Poxel's website under the following link: [https://www.poxelpharma.com/en\\_us/news-media/events](https://www.poxelpharma.com/en_us/news-media/events).**

## **About NASH**

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 PXL770**

PXL770 is a first-in-class AMPK activator. AMPK is a central regulator of multiple metabolic pathways leading to the control of lipid metabolism, glucose homeostasis and inflammation. Based on its central metabolic role, targeting AMPK offers the opportunity to pursue a wide range of indications to treat chronic metabolic diseases, including diseases that affect the

liver, such as NASH.

### 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<sup>1</sup>. Pioglitazone is the only drug recommended for biopsy-proven NASH patients by the Practice Guidelines published by the AASLD and the European Association for the Study of the Liver (EASL)<sup>2</sup>. 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, has successfully completed a Phase 2a proof-of-concept trial for the treatment of NASH. The Phase 2a trial met its primary endpoint and study objectives. PXL770 could also have the potential to treat additional metabolic diseases. **PXL065** (deuterium-stabilized R-pioglitazone), a MPC inhibitor, is in a streamlined 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](http://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 that remains unresolved. 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.

---

<sup>1</sup> Cusi, et al., Ann Intern Med. 2016, 165(5), 305-315).

<sup>2</sup> J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357.

View source version on businesswire.com:

<https://www.businesswire.com/news/home/20201116005739/en/>

**Poxel SA**

Jonae R. Barnes

Senior Vice President, Investor Relations, Corporate Communication and Public Relations

[jonae.barnes@poxelpharma.com](mailto:jonae.barnes@poxelpharma.com)

+1 617 818 2985

Aurélie Bozza

Investor Relations and Communication Director

[aurelie.bozza@poxelpharma.com](mailto:aurelie.bozza@poxelpharma.com)

+33 6 99 81 08 36

**Investor relations / Media - EU/US**

Trophic Communications

Stephanie May or Joanne Tudorica  
[may@trophic.eu](mailto:may@trophic.eu) or [tudorica@trophic.eu](mailto:tudorica@trophic.eu)  
+49 171 185 56 82 or +49 175 804 1816

**Investor relations / Media - France**

NewCap

Emmanuel Huynh / Arthur Rouillé

[poxel@newcap.eu](mailto:poxel@newcap.eu)

+33 1 44 71 94 94

Source: Poxel SA