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Poxel Presents Promising Data for PXL770 and PXL065 for the Treatment of NASH at the American Association for the Study of Liver Diseases Meeting

- **PXL770 was shown to have a beneficial effect on both the adipose tissue and liver through direct activation of AMPK in a DIO-NASH model**
- **PXL065 data suggests the potential for similar efficacy with a reduced side effect profile from pioglitazone for NASH**

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 that poster presentations for PXL770 and PXL065 (formerly DRX-065; acquired from DeuteRx LLC) showing promising data for the treatment of NASH were made on November 10-11, 2018, at the American Association for the Study of Liver Diseases (AASLD) meeting in San Francisco, California.

In the first poster presentation, PXL770 was shown to have a beneficial effect on the two key pathways involved in non-alcoholic fatty liver disease (NAFLD), the lipolysis in the adipose tissue (AT) and *de novo* lipogenesis in the liver, through direct activation of adenosine monophosphate-activated protein kinase (AMPK) in a diet-induced obesity non-alcoholic steatohepatitis (DIO-NASH) model. NAFLD is characterized by hepatic lipid accumulation resulting primarily from AT lipolysis (70%), and *de novo* lipogenesis (20%), highlighting the key role of AT in the development of NAFLD.

“AMPK is a key target acting on steatosis, inflammation and hepatic fibrogenesis,” said Sophie Bozec, PhD, Senior Vice President, Research and Development Pharmacology at Poxel. “Supported by positive preclinical mechanistic and efficacy results in a DIO-NASH model, we believe that PXL770 is uniquely positioned to treat the underlying root causes of NASH, including liver steatosis, inflammation and fibrosis, which are driven by the accumulation of free fatty acids in the liver coming from the AT and from their endogenous synthesis in the liver.”

In the second poster presentation, PXL065 Phase 1 results demonstrated that PXL065 was shown to be safe and well-tolerated with no adverse events. Based on the pharmacokinetic (PK) results, modeling predicts that a 15 mg dose of PXL065, a

deuterium-stabilized R-stereoisomer of pioglitazone, is expected to yield similar efficacy as 45 mg of the parent drug, pioglitazone (Actos®*) with an improved side effect profile, including reduced weight gain and fluid retention.

“Pioglitazone has demonstrated therapeutic efficacy for NASH, even in patients with advanced fibrosis. However, its PPARγ-related side effects of weight gain, bone fractures and fluid retention have limited its therapeutic potential and use,” said Pascale Fouqeray, MD, PhD, EVP, Early Development and Translational Medicine at Poxel. “PXL065 has the potential to preserve the pharmacological benefits of pioglitazone required for the treatment of NASH, such as a reduction of hepatic steatosis, inflammation, ballooning and fibrosis and could reduce PPARγ agonism and the associated side effects that are thought to be related to S-pioglitazone.”

“We are looking forward to advancing both PXL770 and PXL065 into proof-of-concept studies in 2019,” said Thomas Kuhn, CEO of Poxel. “With the recent acquisition of DeuteRx’s drug candidate, PXL065, we are rapidly expanding our presence in NASH and are one of only a few biotech companies with two clinical programs in development in this therapeutic area. The underlying pathophysiological mechanisms that contribute to the development and progression of NAFLD and NASH are highly complex and support the need for the development of novel therapies acting on different targets. Both of our programs have the potential to be developed as a monotherapy or in combination together or with other agents.”

PXL770 Results

In the poster presentation, PXL770 was shown to have a beneficial effect on the liver and AT metabolism in a DIO-NASH mouse model. After 41 weeks, only DIO-NASH mice with biopsy-confirmed steatosis (score ≥2) and fibrosis (stage ≥1) were included (n=12) and received orally vehicle (control) or PXL770 35 or 75 mg/kg twice-daily for eight weeks.

The DIO-NASH mouse model showed that DIO-NASH mice compared to normal chow diet mice exhibited characteristics of NASH, including steatohepatitis (NAFLD Activity Score, NAS=7), liver fibrosis (score=2), elevated liver triglycerides (TG, x26) as well as inflammation. In this model, PXL770 at both doses, increased AMPK activity in the liver (P-AMPK/AMPK, +128%; $p<0.05$, +143%, $p<0.001$) and improved liver health. Compared to the control group, PXL770 at both doses decreased liver weight (-23%, $p<0.01$; -33%, $p<0.01$). PXL770 reduced NAS (-32%; -44% $p<0.01$) decreasing steatosis, this was also confirmed by the reduction of liver TG content (-36%; -42%, $p<0.01$), inflammation and hepatocellular ballooning. The benefit of PXL770 on fibrosis was measured by a strong down-regulation in the expression of fibrogenesis genes (e.g. type I collagen, -65%; -68%, $p<0.01$) and a decrease in hepatic stellate cell activation (aSMA positive staining -34%; -39%, $p<0.01$).

In addition to showing a beneficial effect on the liver, PXL770 improved AT metabolism. PXL770 activated AMPK (P-AMPK/AMPK, +130% ns; +152%, $p<0.01$) in visceral AT and reduced fat pad mass at both doses (-25%; -37%, $p<0.01$). PXL770 decreased the activity of hormone-sensitive lipase (P-HSLser565 +416%; +425%, $p<0.01$), consistent with the decrease in plasma free fatty acid level (-37%; -38%, $p<0.01$). PXL770 reduced AT

inflammation, decreasing MCP-1 gene expression (-55% $p<0.05$ at 75 mg/kg) and increased AT mitochondrial biogenesis, increasing PGC1-α protein expression (+321%; +409%, $p<0.01$).

Based on these and other preclinical findings, PXL770 appears to be a promising drug candidate for the treatment of NASH.

PXL065 Results

In the poster presentation for PXL065, a Phase 1 open-label study was presented, which evaluated the safety, tolerability and pharmacokinetics (PK) of a single dose of PXL065 compared to Actos®, in healthy subjects. Twelve healthy subjects received a single oral dose of 45 mg Actos or 22.5 mg PXL065. Subjects remained in the clinic for 36 hours post-dose and returned as out-patients on Days 4 and 7 for follow-up assessments. Based on these results, a PK model was generated to predict the dose of PXL065 that gives the same exposure to R-pioglitazone as a 45 mg dose of Actos and the number of dosing days required to reach steady state. In addition, exposure to PPARγ active species was compared between equivalent doses of PXL065 and Actos.

The Phase 1 study indicated PXL065 was safe and well-tolerated. No adverse effects were reported. After a single dose of PXL065, the relative exposure to R-pioglitazone increased >3-fold compared to Actos. Total exposure to the PPARγ active metabolites, M-III and M-IV, decreased by 50% compared to Actos.

Based on modeling, a 15 mg dose of PXL065 is predicted to yield the same exposure to R-pioglitazone as a 45 mg dose of Actos. The human PK results and simulations, combined with preclinical animal studies, suggest that PXL065, has the potential to offer similar efficacy for NASH compared to pioglitazone with a reduction of the undesired PPARγ-related side effects of weight gain and fluid retention.

The posters titled “PXL770, a New Direct AMP Kinase Activator, Acting on the Adipose Tissue and the Liver, Demonstrates Promising Effects for Treatment of Non-Alcoholic Steatohepatitis” and “Safety, Tolerability and Pharmacokinetics of PXL065, the Stabilized, R-Stereoisomer of Pioglitazone: A Mitochondrial Function Modulator for Nonalcoholic Steatohepatitis (NASH) without the PPARγ Agonism and Related Side Effects” are available on the Company’s website under “Posters” or by using the following link http://www.poxelpharma.com/en_us/product-pipeline/posters.

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 diabetes. Currently no curative or specific therapies are available.

About PXL770

PXL770 is a first-in-class direct adenosine monophosphate-activated protein kinase (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 non-alcoholic steatohepatitis (NASH)[1].

About PXL065 (formerly DRX-065)

PXL065 is deuterium-stabilized R-pioglitazone developed by DeuteRx LLC. Pioglitazone 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 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 (stereoisomers) that interconvert *in vivo*. Using deuterium, DeuteRx stabilized each stereoisomer and characterized their dramatically different pharmacological properties. In *in vitro* studies, PXL065 has been shown to target MPC as an inhibitor. In preclinical models, PXL065 exhibits the anti-inflammatory activity and NASH efficacy 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, PXL065 is expected to exhibit a better therapeutic profile than pioglitazone for NASH.

About Poxel SA

Poxel uses its development expertise in metabolism to advance a pipeline of drug candidates focused on the treatment of metabolic disorders, including type 2 diabetes and non-alcoholic steatohepatitis (NASH). We have successfully completed the Phase 2 clinical program for our first-in-class lead product, Imeglimin, which targets mitochondrial dysfunction, in the U.S., Europe and Japan. Together, with our partner Sumitomo Dainippon Pharma, we are conducting the Phase 3 Trials of IMeglimin for Efficacy and Safety (TIMES) program for the treatment of type 2 diabetes in Japan. Our partner Roivant Sciences is responsible for Imeglimin's development and commercialization in countries outside of Poxel's 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 advancing into 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 mitochondrial pyruvate carrier (MPC) inhibitor, is in Phase 1 and being developed for the treatment of NASH. Poxel also has additional earlier-stage programs, including deuterated drug candidates for metabolic, specialty and rare diseases. We intend to generate further growth through strategic partnerships and pipeline development. (Euronext: POXEL, www.poxelpharma.com)

*Actos is a registered trademark of Takeda Chemical Industries, Ltd.

1. Source: Smith B. K et al., (2016) Am J Physiol Endocrinol Metab 311, E730 – E740
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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