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Poxel Announces Detailed Imeglimin Phase 3 TIMES 1 Results Presented at 55th Annual Meeting of the European Association for the Study of Diabetes

- **Imeglimin results featured in symposium session with leading diabetes expert Ralph DeFronzo, M.D., discussing preclinical and clinical data supporting safety and efficacy of Imeglimin in various patient populations with type 2 diabetes**

LYON, France--(BUSINESS WIRE)-- POXEL S.A. (Euronext – POXEL – FR0012432516), a biopharmaceutical company dedicated to the development of innovative treatments for metabolic disorders, including type 2 diabetes and non-alcoholic steatohepatitis (NASH), announced today the presentation of detailed Phase 3 results from the TIMES 1 program, which evaluated the efficacy, safety and tolerability of Imeglimin in Japanese patients with type 2 diabetes as well as data supporting the safety and efficacy of Imeglimin in various patient populations. The data were featured in a symposium session at the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD), held at the Fira Barcelona Gran Via conference center in Barcelona, Spain from September 16 – 20, 2019.

The session was chaired by leading academic diabetes expert, Ralph DeFronzo, M.D., Professor of Medicine and Chief of the Diabetes Division at UT Health San Antonio and Deputy Director of the Texas Diabetes Institute, part of University Health System, San Antonio, Texas.

“In order to properly control type 2 diabetes, effective treatments need to correct both the defects in insulin secretion and insulin sensitivity,” said Prof. Ralph DeFronzo, M.D. “Imeglimin is a novel therapeutic approach with a unique mechanism of action that works at the level of the mitochondria. Through improving mitochondrial function, Imeglimin has been observed to increase muscle insulin sensitivity and insulin secretion and decrease hepatic glucose production, all of which play a critical role in the treatment of type 2 diabetes. This result has translated into safety and efficacy data that underscore Imeglimin’s potential to alter the landscape for oral treatment of patients with type 2 diabetes worldwide.”

The symposium included a specific focus on the patient population in Japan and the detailed Phase 3 TIMES 1 trial results. Asia is considered one of the most important geographic locations in treating the diabetes pandemic in the future, with Japan being the second largest single market after the U.S. Imeglimin Phase 3 TIMES 2 and TIMES 3 36-week open label results are expected around the end of 2019. A Japanese New Drug Application for

Imeglimin is targeted for 2020.

“Our vision as a company focused on developing drugs for metabolic diseases is to improve the therapeutic options available to patients. As such, Imeglimin’s effect on insulin secretion could be particularly well-suited for the treatment of type 2 diabetes patients, particularly in Japanese patients, because they may experience an early defect of insulin secretion,” said Christophe Arbet-Engels, M.D., Ph.D., Chief Medical Officer, Executive Vice President Late Development and Medical Affairs at Poxel. “Additionally, Imeglimin has the potential to significantly reduce HbA1c in patients inadequately controlled on insulin alone and could be a treatment option for sensitive patient populations, such as the elderly and those with impaired renal function because of its favorable safety profile.”

Imeglimin’s unique mechanism of action, coupled with its efficacy and safety profile, illustrates Imeglimin’s potential to be a candidate worldwide for the treatment of type 2 diabetes in almost all stages of the current anti-diabetic treatment paradigm, including monotherapy, or as an add-on to other glucose lowering therapies and in various populations of patients with type 2 diabetes.

Highlights from EASD Presentation of Imeglimin Results

Phase 3 TIMES 1 Data:
Data presented at the symposium included results from the Phase 3 TIMES 1 randomized, double-blind, placebo-controlled monotherapy trial. In this trial, Imeglimin was orally administered 1,000 mg twice daily versus placebo for 24 weeks in 213 Japanese patients. The TIMES 1 trial demonstrated robust efficacy and achieved statistical significance ($p<0.0001$) for its primary endpoint, defined as a change of glycated hemoglobin A1c (HbA1c) versus placebo at week 24, with an HbA1c placebo-corrected mean change from baseline of -0.87%.

For the TIMES 1 trial’s main secondary endpoint of a decrease from baseline in fasting plasma glucose (FPG), Imeglimin achieved statistical significance ($p<0.0001$) versus placebo at week 24, with an FPG placebo-corrected mean change from baseline of -19 mg/dL.

These data were also observed to be consistent in subpopulation patients with type 2 diabetes, such as the elderly and those with impaired renal function.

In this trial, the overall safety and tolerability of Imeglimin was similar to placebo and the adverse event profile was consistent with what was observed in the Phase 2b trial in Japan, and the U.S. and European Phase 1 and 2 programs.

In addition, Imeglimin data were shown to be in the high end of the HbA1c efficacy range when compared to data results in Japanese patients treated with SGLT2 and DPP4 inhibitors.

Mechanistic Data:
Further analysis of Imeglimin’s mode of action highlighted its ability to enhance insulin sensitivity and insulin secretion by improving mitochondrial function. In detail, Imeglimin improves mitochondrial function through three key mechanisms:

1. Imeglimin restores complex III activity and inhibits complex I activity, leading to increased mitochondrial oxidation of complex II substrates (lipids).
2. Imeglimin decreases reactive oxygen species (ROS) overproduction and protects mitochondria from excess oxidative stress, which is crucial since beta cells are especially sensitive to this.
3. Imeglimin increases PGC1a, the master regulator of mitochondrial biogenesis, and increases the number of mitochondria.

The improvement in mitochondrial function is associated with increased muscle insulin sensitivity and insulin secretion and decreased hepatic glucose production, all of which are important disease-modifying features.

The presentation is available on the EASD virtual meeting website, which can be accessed via the following link:
https://www.easd.org/virtualmeeting/home.html#!contentsessions/3117.

About the Phase 3 TIMES Program
TIMES (**T**rials of **Im**eglimin for **E**fficacy and **S**afety), the Phase 3 program for Imeglimin for the treatment of type 2 diabetes in Japan, consists of three pivotal trials involving over 1,100 patients. The TIMES program is a joint development effort between Poxel and Sumitomo Dainippon Pharma Co., Ltd. The companies entered into a strategic partnership in October 2017 for the development and commercialization of Imeglimin in Japan, China, South Korea, Taiwan and nine other Southeast and East Asian countries[1]. The TIMES program includes the following three trials that will be performed using the dose of 1,000 mg twice daily:

TIMES 1: A Phase 3, 24-week, double-blind, placebo-controlled, randomized, monotherapy trial to assess the efficacy, safety and tolerability of Imeglimin in Japanese patients with type 2 diabetes, using the change in HbA1c as the primary endpoint. Secondary endpoints of the trial include fasting plasma glucose, other standard glycemic and non-glycemic parameters. The TIMES 1 trial met its primary and secondary endpoints and the top-line data was reported on April 9, 2019.

TIMES 2: A Phase 3, 52-week, open-label, parallel-group trial to assess the long-term safety and efficacy of Imeglimin in Japanese patients with type 2 diabetes. In this trial, Imeglimin will be administrated orally as a monotherapy or combination therapy with existing hypoglycemic agents, including a DPP4 inhibitor, SGLT2 inhibitor, biguanide, sulphonylurea, glinide, alpha-glucosidase inhibitor, thiazolidine and GLP1 receptor agonist. The TIMES 2 results are expected around the end of 2019.

TIMES 3: A Phase 3, 16-week, double-blind, placebo-controlled, randomized trial with a 36-week open-label extension period to evaluate the efficacy and safety of Imeglimin in combination with insulin in Japanese patients with type 2 diabetes and inadequate glycemic control on insulin therapy. The TIMES 3 16-week portion of the trial met its primary endpoint with a favorable safety and tolerability profile observed and the top-line data was reported on June 25, 2019. The TIMES 3 36-week open label results are expected around the end of 2019.

About Imeglimin:
Imeglimin is the first clinical candidate in a new chemical class of oral agents called Glimins by the World Health Organization. Imeglimin has a unique mechanism of action (MOA) that

targets mitochondrial bioenergetics. Imeglimin acts on all three key organs which play an important role in the treatment of type 2 diabetes: the pancreas, muscles, and the liver, and it has demonstrated glucose lowering benefits by increasing insulin secretion in response to glucose, improving insulin sensitivity and suppressing gluconeogenesis. This MOA has the potential to prevent endothelial and diastolic dysfunction, which can provide protective effects on micro- and macro-vascular defects induced by diabetes. It also has the potential for protective effect on beta-cell survival and function. This unique MOA offers the potential opportunity for Imeglimin to be a candidate for the treatment of type 2 diabetes in almost all stages of the current anti-diabetic treatment paradigm, including monotherapy or as an add-on to other glucose lowering therapies.

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 **T**rials of **IM**eglimin for **E**fficacy and **S**afety (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 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 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)

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[1] including: Indonesia, Vietnam, Thailand, Malaysia, The Philippines, Singapore, Republic of the Union of Myanmar, Kingdom of Cambodia and Lao People's Democratic Republic.

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