



New Imeglimin Data Demonstrating Pancreatic Beta-Cell Protection Presented at the American Diabetes Association 78th Scientific Sessions

- **Imeglimin was observed to protect and preserve human beta-cells from cell death from fructose- and glucose-induced toxicity by inhibiting mitochondrial Permeability Transition Pore opening (mPTP)**
- **Preclinical data highlights Imeglimin's potential to delay type 2 diabetes disease onset and progression through the preservation of beta-cell mass**

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 an oral presentation was made at the American Diabetes Association (ADA) 78th Scientific Sessions showing important new benefits relating to Imeglimin's unique mechanism of action in a preclinical model. The abstract titled, "Imeglimin Protects Ins-1 Cells and Human Islets Against High Glucose and High Fructose-induced Cell Death by Inhibiting the Mitochondrial PTP Opening" was presented in a scientific session.

"Loss of insulin-producing beta-cells contributes to type 2 diabetes and its progression. These preclinical data demonstrate Imeglimin's ability to prevent beta-cell death by fructose- and glucose-induced toxicity through its unique mechanism of action of inhibiting the mPTP opening, a mitochondrial channel involved in cell death," said Professor Eric Fontaine, MD, PhD, Grenoble Alpes University, an author of the presentation who managed this study. "These data, combined with previously reported data demonstrating Imeglimin's beneficial effects on beta-cell preservation and function in several different clinical and preclinical studies, are striking and highlight Imeglimin's potential not only to treat type 2 diabetes disease, but also delay its progression."

"We are continuing to generate further differentiating data that are additive to Imeglimin's strong and consistent clinical results. The potential of Imeglimin to preserve beta-cells from cell death could be particularly important for patients who experience an early beta-cell failure, such as Japanese patients. These results are particularly interesting given the improvement of beta-cell function observed in the Phase 2b clinical study," said Thomas Kuhn, CEO of Poxel. "Working with our partner Sumitomo Dainippon Pharma, we have made significant progress advancing the Phase 3 Trials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) program for Imeglimin in Japan with the initiation of all three pivotal Phase 3 trials,

and we are on track for the TIMES 1 efficacy data in the first half of 2019. In addition, we are working closely with our partner Roivant Sciences to advance Imeglimin into a Phase 3 program in the US and Europe.”

Imeglimin is an orally-available drug candidate with a novel mechanism of action that has been observed in clinical studies to demonstrate glucose lowering benefits by simultaneously targeting all three key organs which play an important role in the treatment of type 2 diabetes: the liver, muscles and the pancreas. Imeglimin has demonstrated in preclinical studies the potential to address mitochondrial dysfunction, which is believed to be at the core of type 2 diabetes pathophysiology. Imeglimin has completed Phase 1 and Phase 2 development in over 1,200 subjects in the US, EU and Japan.

About the Study

In a preclinical model of human pancreatic islet cells, researchers investigated if Imeglimin could prevent mPTP opening and cell death induced by high glucose or fructose concentrations in INS-1 cells and human pancreatic islets. mPTP status in intact cells was assessed by confocal microscopy by measuring mitochondrial membrane potential (TMRM) and NAD(P)H (autofluorescence). Cell viability was measured by flow cytometry. In INS-1 cells and human islets, 30 mM glucose or 2.5 mM fructose for 24 hours led to PTP opening (increase in the NAD(P)H/TMRM ratio), this phenomenon being prevented by 100µM Imeglimin. Compared to normal glucose concentration (100%), cell viability significantly decreased ($p < 0.05$) in cells exposed to 30 mM glucose ($76 \pm 5\%$ and $47 \pm 18\%$ in INS-1 cells and human islets, respectively) and to 2.5 mM fructose for 72 hours ($78 \pm 3\%$ and $35 \pm 11\%$ in INS-1 cells and human islets, respectively), but remained unchanged when these cells were preincubated with 100µM Imeglimin (in 30mM glucose: $94 \pm 3\%$ and $98 \pm 3\%$ / in 2.5mM fructose: $96 \pm 4\%$ and $79 \pm 6\%$ in INS-1 cells and human islets, respectively).

Together, these results demonstrate that Imeglimin is able to prevent high glucose and fructose-triggered cell death through the inhibition of an mPTP opening and that an mPTP-targeted strategy can prevent beta-cell death. These data show that in addition to its beneficial effect on beta-cell function, Imeglimin may also have the potential to preserve beta-cell mass in a dysmetabolic environment.

The presentation at the ADA is available on the Company's website under “Scientific Publications” or by using the following link <http://poxel.com/our-science/scientific-publications.php>.

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 liver, muscles and the pancreas, 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 Trials of **IM**eglimin for **E**fficacy and **S**afety (TIMES) program for the treatment of type 2 diabetes in Japan. Our partner Roivant Sciences will be responsible for Imeglimin's development and commercialization in countries outside of Poxel's partnership with Sumitomo Dainippon Pharma, including the U.S. and Europe. Our second program, PXL770, a first in class direct adenosine monophosphate-activated protein kinase (AMPK) activator, is in Phase 1 and we plan on developing it for the treatment of NASH. PXL770 could also have the potential to treat additional metabolic diseases. We intend to generate further growth through strategic partnerships and pipeline development. (Euronext: POXEL, www.poxelpharma.com)

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