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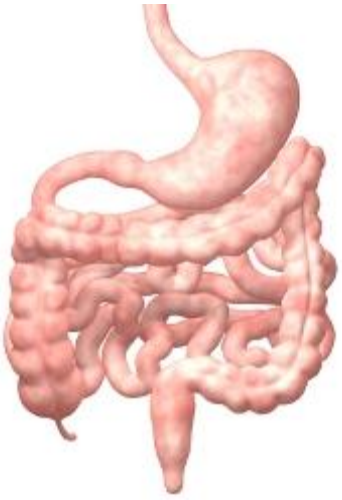
Elcelyx 'Guts' Conventional Thinking on Metformin



By Marie Powers
Staff Writer

A San Diego biotech with eight employees grabbed the spotlight at the American Diabetes Association (ADA) Scientific Sessions in Chicago with the revelation that Type II diabetes drug metformin acts in the lower bowel, not in the bloodstream.

Elcelyx Therapeutics Inc. is developing a delayed-release formulation of metformin, called NewMet, based on its gut sensory modulation (GSM) approach. At ADA, the company presented findings from a Phase IIa trial that compared NewMet with generic metformin in Type II diabetes, revealing the generic drug's mechanism of action. Contrary to popular belief, greater exposure in the plasma does not improve the efficacy of metformin – the most prescribed diabetes drug in the world – according to the study.

Using GSM, Elcelyx engineered NewMet to bypass the upper bowel, lowering systemic exposure and improving tolerability while maintaining metformin's glucose-lowering benefit.

Discovery of the mechanism of action was part intuition, part ingenuity. The company was formed in 2010 on the thesis of a weight loss approach involving the activation of taste receptors, explained Elcelyx CEO Alain Baron, a former senior vice president of research at Amylin Pharmaceuticals Inc. and former member of the Life Science Team at Morgenthaler Ventures.

"The idea was that we would activate these receptors of the gut with ingredients that were not absorbed into the bloodstream, because these receptors are actually there to sense nutrients," Baron told *BioWorld Today*. For example, when taste receptors on the tongue detect sweetness, those same receptors in the gut allow certain cells to sense that carbohydrates are being consumed.

The nutrient receptors are located on enteroendocrine cells located in the lining of the gut that produce key hormones, such as peptide YY (PYY), which signals satiety to the brain, and glucagon-like peptide-1 (GLP-1), which plays an important role in glucose regulation. One of the cells of special interest to Elcelyx, the L cell, became the basis for the company's name.

The company's early work proved that if those receptors were activated by ingredients that were not absorbed into the bloodstream, the cells could be activated and their contents – gut hormones – released, in an approach that became known as GSM.

Baron next theorized that certain existing drugs might work through the same mechanism. With his expertise in metabolic disorders, he quickly keyed on metformin, which is given in large doses and is poorly bioavailable but was shown to release GLP-1 . When coupled with literature suggesting metformin worked better orally than intravenously, Baron deduced that "maybe metformin works not by entering the bloodstream but by activating a receptor at the level of the gut."

To prove the hypothesis, the company formulated generic metformin with a pH-sensitive coating that made it less bioavailable until it reached the lower bowel.

"We were able to demonstrate the effect on the first try," Baron said. Although bioavailability was reduced by approximately half, efficacy was exactly the same.

"We reversed 52 years of dogma," he added.

'We're Looking for a Global Acquirer'

The breakthrough finding suggested a lower metformin plasma concentration might be used safely by patients with moderate and severe renal impairment – a population that is unable to use conventional metformin formulations due to the risk of lactic acidosis caused by high drug levels in the blood.

In the randomized, double-blind, three-way crossover Phase IIa study, 24 patients with Type II diabetes were randomized to twice-daily oral dosing of metformin HCl immediate release (1,000 mg), low-dose NewMet (500 mg) and high-dose NewMet (1,000 mg) for five days each, separated by a one-week washout. The treatments demonstrated similar reductions from baseline values in fasting plasma glucose (16 mg/dL to 22 mg/dL, $p < 0.01$ for all) and postprandial glucose (8 percent to 12 percent, $p < 0.001$ for all) despite a 45 percent to 57 percent reduction in circulating metformin in the high- and low-dose NewMet arms, respectively. Similarly, GLP-1 and PYY were increased by more than 50 percent across all treatments.

No safety concerns were noted for either NewMet or metformin, and NewMet had fewer gastrointestinal (GI) side effects than generic metformin.

A second, late-breaker ADA poster presented by Mark Fineman, Elcelyx's senior vice president of R&D, described a model designed to predict metformin plasma concentrations that would occur if patients with Type II diabetes and mild, moderate or severe renal impairment were to take NewMet. Results suggested that patients with renal impairment taking effective doses of NewMet would not have an increased risk of lactic acidosis. The company plans to initiate a pharmacokinetic study this summer in Type II diabetes patients with mild, moderate and severe renal impairment to confirm the predictions of the model.

In the meantime, Elcelyx launched a multicenter, double-blind dose-finding Phase IIb trial in May evaluating once-daily doses of 1,000 mg, 800 mg and 600 mg of NewMet to placebo. There are also two comparator arms with generic extended-release metformin dosed once-daily at 1,000 mg and 2,000 mg. The primary endpoint of the study is fasting plasma glucose at four weeks, with secondary endpoints through 12 weeks including changes in fasting plasma glucose, hemoglobin A1c, body weight and measures of safety and tolerability. The study has fully enrolled 240 patients with Type II diabetes. Top-line data are expected in late August, with the readout for long-term glucose lowering and weight benefits due in October, Baron said.

NewMet's market opportunity could be huge. Although metformin is the preferred first-line pharmacological treatment for Type II diabetes, 40 percent of U.S. patients with the condition do not take the drug, primarily due to GI issues or the contraindication of renal impairment, according to John Buse, professor of medicine and director of the Diabetes Care Center and chief of the division of endocrinology and executive associate dean for clinical research at University of North Carolina School of Medicine in Chapel Hill. Of the 60 percent who take metformin, only about 40 percent are able to titrate to fully effective doses, due to tolerability issues, added Buse, who served as an advisor on the Phase II NewMet study.

"There's an unmet need for metformin in this market," which comprises some 4 million individuals in the U.S. alone, Baron said. "We're not targeting the population that's doing well on current metformin. NewMet would allow more people to be on this foundational therapy and to stay on it throughout their lives, since renal impairment worsens with age."

Baron hopes a big pharma also will see that blockbuster opportunity. The plan is to sell the company – with the concurrent spin-out of a second product, a dietary supplement for weight management – following the Phase IIb study. Provided a pivotal trial begins next year and all goes well, NewMet could be on the market as early as 2016, Baron said.

"We're looking for a global acquirer, and we have no intention of keeping any rights," he said.

Since its inception, Elcelyx has raised $43 million in three financing rounds, with funding from Morgenthaler, Kleiner Perkins Caufield & Byers, Technology Partners and GSM Fund LLC, which was established this year to enable existing investors and insiders to participate in the company's Series C in February.

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