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Zealand and Beta Bionics to collaborate on the development of a first-in-class dual-hormonal bionic pancreas system for treatment of people with type 1 diabetes

- **Synergistic match of Beta Bionics's dual-hormonal, artificial, or *bionic*, pancreas device platform, the iLet, and Zealand's novel liquid stable glucagon analog, ZP4207**
- **An automated insulin + glucagon delivery system with integrated continuous blood glucose monitoring and mathematical dosing algorithms offers the potential for a paradigm shift in the treatment of diabetes**
- **Expected next step under the collaboration is the initiation of clinical trials in H2 2016**
- **Zealand's financial guidance for 2016 remains unchanged**

Copenhagen, Denmark and Boston, Massachusetts, 10 June 2016 – Zealand Pharma, or Zealand, a peptide drug discovery, design and development company, and Beta Bionics, a medical technology company, jointly announced today that they have engaged in a collaboration. The objective of the collaboration is to combine essential proprietary product rights from each party to advance a new dual-hormonal artificial, or *bionic,* pancreas system to the next step in its clinical development. Such a system has the ultimate potential to offer people with diabetes on insulin therapy more efficacious, safer, and easier blood sugar control for better long-term disease management and outcomes.

The new system under the collaboration is based on an advanced bionic pancreas platform technology, developed at Boston University and Beta Bionics, which has been integrated into a pocket-sized wearable medical device, called *the iLet*. Boston University has granted an exclusive worldwide license of the iLet technology to Beta Bionics. The bionic pancreas technology in the iLet is designed for automated delivery of both insulin and glucagon analogs and has been tested and refined in nearly 10 years of clinical trials. All of these trials used recombinant human glucagon, which necessitated daily reconstitution at the point of care.

In future trials, Zealand will evaluate a multiple-dose version of its proprietary novel glucagon analog, ZP4207, with the iLet. ZP4207 is invented and developed by Zealand and has been shown to have a unique stability profile for use in liquid formulation.

Britt Meelby Jensen, President and Chief Executive Officer of Zealand: "*We are truly excited about our collaboration with Beta Bionics. It allows us to evaluate our novel liquid glucagon, ZP4207, in the clinic for use in the state-of-the-art iLet device developed by Beta Bionics and Boston University. I believe we stand in front of a unique opportunity to develop a system for automated delivery of both insulin and glucagon and with the potential to offer a paradigm shift in the treatment of diabetes. Together with Beta Bionics, we have a vision of making the iLet device and our novel liquid formulation glucagon available for people with diabetes as soon as development timelines allow, and we look forward to starting our first joint clinical trials in people with type 1 diabetes later this year.*"

Professor Ed Damiano, co-developer of the iLet technology, Professor of Biomedical Engineering at Boston University, and President and Chief Executive Officer of Beta Bionics, added: "*We have long awaited and eagerly anticipated the development of a stable pumpable glucagon analog suitable for chronic use in our dual-hormone bionic pancreas. This has proven to be a challenging task. We are therefore very pleased that Beta Bionics now has access to Zealand's novel investigational glucagon analog, and that Zealand now has our bionic pancreas platform to administer it. We at Beta Bionics and Zealand share a deep appreciation for the synergy that comes from combining our two complementary technologies. Our collaboration is fueled by a common commitment to bring about a paradigm shift in diabetes management, and to fulfill the promise and potential that our partnership holds for the health and well-being of people with type 1 diabetes and their families.*"

People with type 1 diabetes have impaired pancreatic function. They suffer from insulin deficiency and inappropriate and inadequate glucagon secretion – both endogenous hormones are essential to ensure stable and healthy blood glucose metabolism. People with type 1 diabetes depend on a complicated daily insulin regimen to control hyperglycemia (high blood glucose levels) and carbohydrates to manage hypoglycemia (low blood glucose levels). They must constantly track and adjust their blood sugar levels to remain healthy and reduce the chronic and acute risks associated with hypo- and hyperglycemia. Today, many people with type 1 diabetes are on insulin pump therapy to control their blood sugar levels. A dual-hormone bionic pancreas, which automatically determines both insulin and glucagon doses and then delivers insulin and glucagon analogs, can much more faithfully mimic the function of a healthy pancreas and significantly improve diabetes management, relative to insulin pump therapy. A fully automated system would at the same time offer a significant relief to people with type 1 diabetes. A scalable commercial dual-hormone system has so far remained elusive, due to the lack of a stable, pumpable, liquid formulation of either glucagon or a glucagon analog product.

In out-patient and home-use randomized cross-over trials, the bionic pancreas technology that has been integrated into the iLet, has shown significant reductions in blood glucose levels, reductions in hypoglycemia, and reductions in intersubject as well as intrasubject glycemic variability in adults, adolescents, and pre-adolescents with type 1 diabetes (*New England Journal of Medicine*. 2014, 371:313–25; *Lancet Diabetes and Endocrinology*. 2016, 4:233–43). These trials have been conducted in collaboration with endocrinologists at the Massachusetts General Hospital, Stanford University, the University of Massachusetts Medical Center, and the University of North Carolina.

Zealand has evaluated ZP4207 in Phase Ia and Phase Ib single and multiple ascending dose trials. In these trials, ZP4207 was observed to be safe and well tolerated with the ability to provide a clinically relevant blood glucose response.

Zealand and Beta Bionics expect as a next step in their collaboration to initiate a Phase IIa clinical trial to test safety and efficacy of ZP4207 when used in the iLet. The trial is expected to enroll the first patients with type 1 diabetes in H2 2016.

Zealand retains its financial guidance for 2016

The collaboration with Beta Bionics and the clinical activities expected to be initiated in H2 2016 for ZP4207 when used in the iLet will not change Zealand's financial guidance for 2016.

For further information, please contact

At Zealand:

Britt Meelby Jensen, President and Chief Executive Officer
Tel: +45 51 67 61 28, email: bmj@zealandpharma.com.

Hanne Leth Hillman, Senior Vice President, Investor Relations and Communications
Tel: +45 50 60 36 89, email: hlh@zealandpharma.com.

At Beta Bionics:

Edward R. Damiano, President and Chief Executive Officer
Tel: +1 617-358-5632, email: edamiano@betabionics.com.

Edward B. Raskin, Vice President Public Benefit Development & Corporate Strategy
Tel: +1 949-293-2076, email: eraskin@betabionics.com.

About type 1 diabetes

Type 1 diabetes results from a loss of the ability to produce insulin. Insulin is a hormone produced by the pancreas that has a number of important functions in the human body, particularly in the control of blood glucose levels and preventing hyperglycemia (high blood sugar levels). Type 1 diabetes is a complex, chronic and progressive disorder, which, when poorly managed, can lead to long-term health complications and a shortened life expectancy. Chronic high blood glucose levels increase the risk of cardiovascular diseases such as high blood pressure, heart disease and stroke. Prolonged and widely varying blood glucose levels can lead to microvascular complications, resulting in permanent damage to the kidneys, the eyes, the sensory, motor, and autonomous nerves, as well as the extremities. Both high blood glucose levels (hyperglycemia) and low blood glucose levels (hypoglycemia) are undesirable and present serious health hazards.

According to the International Diabetes Federation, in 2015 an estimated 40 million people between the ages of 20 and 79 were affected by type 1 diabetes globally.

About hypoglycemia

Hypoglycemia is a condition in which blood glucose drops to unsafe levels. It is most frequently associated with diabetes and primarily arises in people with type 1 diabetes and those with type 2 diabetes who are on insulin therapy. According to Decision Resources, all people with type 1 diabetes and approximately 20% of people with type 2 diabetes in the United States are treated with insulin. People with 1 diabetes are the most likely to experience episodes of hypoglycemia since they often inject themselves with insulin up to six times per day or use an insulin pump.

Symptoms of a hypoglycemic episode include anxiety, sweating, tremors, palpitations, nausea, and pallor. In severe cases, hypoglycemia can lead to loss of consciousness, seizures, coma, and death. Severe hypoglycemia or “insulin shock” occurs when blood glucose levels become so low that the assistance of another person is required to treat the condition, which typically involves administration of intravenous glucose or glucagon injection. Severe hypoglycemia is classed as a diabetic emergency. According to the American Diabetes Association, hypoglycemia occurs frequently and the fear of another episode often leads to conservative insulin administration and poor glucose control (i.e., allowing blood glucose to remain higher than desired), which, in turn, increases risk of micro- and macrovascular complications (*Diabetes Care.* 2013, 36:1384–95).

It is also clear that people with type 1 diabetes who experience frequent hypoglycemia become unaware of the symptoms and are then predisposed to most severe expression of the condition because they do not feel the more, subtle impending signs. Many people with type 1 diabetes have hypoglycemia for several hours overnight, which, in itself, is dangerous, but which can also lead to hypoglycemic unawareness in the daytime. (*Acta Diabetologica.* 1998, 35:183–93) Furthermore, hypoglycemia is considered especially unsafe for children with type 1 diabetes under the age 6, who’s developing brains can be adversely affected by low blood sugars at a level which might not cause harm for the more mature brain. (*Journal of Pediatrics.* 1999, 134:492–98).

About Beta Bionics, Inc.

Beta Bionics, Inc. was established in 2015 as a Massachusetts public benefit corporation. In carrying out its general public benefit mission, Beta Bionics has established the following four guiding principles:

- To provide and to protect the company's turnkey solutions for safe and effective autonomous glycemic control;
- To bring the company's technology to as many people with T1D as possible as expeditiously and responsibly as possible;
- To continue to innovate and to offer the latest advances as expeditiously and responsibly as possible; and
- To act in the best possible interest of the T1D community.

The company's bionic pancreas platform, referred to as the iLet, is a pocket-sized wearable medical device that autonomously manages blood sugar levels in people with diabetes. The bionic pancreas technology integrated into the iLet, which was licensed by Beta Bionics from Boston University, has demonstrated dramatic improvements in clinical outcomes, including significant reductions in blood glucose levels, reductions in hypoglycemia, and reductions in intersubject and intrasubject glycemic variability in adults, adolescents, and pre-adolescents with type 1 diabetes (*New England Journal of Medicine. 2014, 371:313–25; Lancet Diabetes and Endocrinology. 2016, 4:233–43*). The company received an initial investment of USD 5 million from Eli Lilly & Company at the end of 2015.

Beta Bionics is based in Boston, Massachusetts. For further information about Beta Bionics, please visit www.betabionics.org or follow us on Twitter @betabionics.

About Zealand Pharma A/S

Zealand Pharma A/S (Nasdaq Copenhagen: ZEAL) ("Zealand") is a biotechnology company with leading scientific expertise in turning peptides into medicines. Zealand has a pipeline of proprietary drug candidates which target specialty disease areas with significant unmet medical needs and a portfolio of medicines and product candidates under license collaborations with Sanofi, Helsinn and Boehringer Ingelheim.

The company's first invented medicine, lixisenatide, a once-daily prandial GLP-1 analogue for the treatment of type 2 diabetes, is licensed to Sanofi who markets the product globally outside the US as Lyxumia®. The fixed-ratio combination of basal insulin glargine (Lantus®) and lixisenatide, referred to as iGlarLixi, is under regulatory review in the US and Europe.

Zealand's proprietary pipeline of drug candidates includes: *ZP4207* (single-dose rescue treatment) for acute, severe hypoglycemia (Phase II); *ZP1848* for Short Bowel Syndrome (Phase II); *ZP4207* (multiple-dose version) intended for use in a dual-hormone artificial pancreas system for better hypoglycemia management in diabetes (in preparation for Phase II); *ZP2929* for diabetes/obesity (Phase I); and several preclinical peptide therapeutics.

The company is based in Copenhagen (Glostrup), Denmark. For further information about Zealand's business and activities, please visit www.zealandpharma.com or follow us on Twitter @ZealandPharma.