The Dual Hormonal Artificial Pancreas in Diabetes Management

- Medical Innovation Day Challenge
Background for the challenge
A paradigm shift in treating diabetes

- Zealand Pharma is a Danish biotech company and a leader with a strong track record in peptide drug development

- The company is currently developing dasiglucagon – a novel analogue of human glucagon – for the use in a dual hormone artificial pancreas for treatment of patients with diabetes

- In the world of diabetes, the development of an artificial pancreas has been a matter of discussion since the 1970’ies – however the necessary technology has not been available until now

- In recent years, the technology has advanced a lot in Constant Glucose Monitors (CGM), insulin pumps, fast acting insulins, and algorithms to define what to do with insulin dispense based on CGM data

- In 2017, the first integrated insulin pump system, where insulin suspense will automatically be stopped based on an algorithm of CGM data and patient input was launched by Medtronics (Minimed 670G)

- The missing link to an artificial pancreas is the liquid glucagon. In a matter of years this will be available and will open up for a paradigm shift in the way you treat patients with diabetes
Zealand is advancing a portfolio of metabolic and gastrointestinal medicines

A leader with a strong track record in peptide drug development

- 5,000 peptides synthesized
- 10 projects advanced to clinical development
- > 500 patents registered

Focus on speciality gastrointestinal and metabolic diseases

- > 180 gastrointestinal (GI) diseases
- 60 million people in the U.S. suffer from GI diseases

Zealand Pharma A/S

Founded in 1998

Listed on Nasdaq
- Copenhagen: ZEAL.CO
- New York: ZEAL

Market cap 3 July ‘17: DKK 3.5 bn / USD 0.52 bn

~ 130 employees, mainly in R&D

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1 Total of 556 registered, of which 276 published.

## Important milestones in 2017 for our product candidates

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<tr>
<th>Product candidate</th>
<th>Indication</th>
<th>Development stage</th>
<th>2017 milestone</th>
<th>Status</th>
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<tr>
<td>Glepaglutide*1 GLP-2 analog</td>
<td>Short bowel syndrome</td>
<td>Preclinical, Phase 2, Phase 1, Phase 2, Phase 3, Registration</td>
<td>Phase 2 results</td>
<td>Achieved</td>
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<tr>
<td>Dasiglugacon*1 Rescue pen</td>
<td>Acute, severe hypoglycemia (insulin shock)</td>
<td>Phase 3</td>
<td>Phase 3 initiation</td>
<td>Commenced</td>
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<tr>
<td>Dasiglucagon*1 Pump therapy</td>
<td>Type 1 diabetes management</td>
<td>Phase 2a</td>
<td>Phase 2a results</td>
<td>Achieved</td>
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<td>Dasiglucagon*1 Rare diseases</td>
<td>Congenital Hyperinsulinism</td>
<td>Phase 1</td>
<td>Phase 2 initiation</td>
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<tr>
<td>GLP1-GLU2 dual agonist</td>
<td>Obesity/type 2 diabetes</td>
<td>Preclinical</td>
<td>Phase 1 initiation</td>
<td></td>
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<tr>
<td>Amylin analog*2</td>
<td>Obesity/type 2 diabetes</td>
<td>Preclinical</td>
<td>Phase 1 initiation</td>
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* Glepaglutide and dasiglucagon are proposed International Nonproprietary Names (pINN).
1 Fully owned by Zealand.
2 Global development and commercial rights are owned by Boehringer Ingelheim.
Tight glucose control remains a significant challenge with current T1D treatment options

Production of both insulin and glucagon are dysregulated in T1D

Insulin only therapy does not restore glucose control and carries the risk of hypoglycemia

A dual hormone pump system incorporating insulin and glucagon has the potential to

- Gain more effective and stable glucose control
- Eliminate the fear of hypoglycemia
- Reduce concerns about living with diabetes

Dasiglucagon and a breakthrough pump solution may offer a paradigm shift in diabetes treatment
Glucagon market potential in dual hormone setting is a significant product opportunity

U.S. insulin pump market is expected to grow

No. of type 1 diabetes patients on pump in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
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<tbody>
<tr>
<td>2015</td>
<td>400,000¹</td>
</tr>
<tr>
<td>2020</td>
<td>560,000²</td>
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</tbody>
</table>

Growth drivers:

- Increased prevalence
- Improved technology / fully automated pumps
- Broader patient segment

¹ American Association of Diabetes Educators.

Zealand partners with Beta Bions

“"A dual-hormone pump has the potential to significantly improve glucose control in diabetes and enable a paradigm shift."”

Edward Damiano
President and CEO, Beta Bions

iLet™
from Beta Bions
Automated diabetes management with a dual-hormone pump therapy would enable a paradigm shift

Treatment with both insulin and glucagon in a dual-hormone system has shown improved glucose control over insulin-only treatment:\(^1\):

### Treatment with insulin only in a pump:
*Daily Continuous Glucose Monitoring glucose level*

### Treatment with both insulin and glucagon in a dual-hormone pump system:
*Daily Continuous Glucose Monitoring glucose level*

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The challenge: How to make the technology available to patients

With a fully functional Dual Hormone Artificial Pancreas along liquid stable glucagon and insulins available we are on the verge of a paradigm shift in how to treat patients suffering from diabetes.

The challenge is:

- How can this technology best be made accessible to benefit patients in an established diabetes treatment market like the U.S. or Denmark?

- What are the key drivers/stakeholders to make this happen?

- How can Zealand Pharma help to make the paradigm shift happen?
Details and parameters for the challenge

The diabetes market constitute of:
- Drug: pharmaceutical products to manage blood glucose levels (insulin, GLP-1, glucagon etc.)
- Glucose monitoring: manual devices (finger prick testing) and constant glucose monitors (e.g. Dexcom)
- Insulin pumps: various levels of automation in pumps (Medtronic Minimed series, Insulet Corp patch pump systems, etc.)

Typically, a patient with an insulin pump would have various levels of reimbursement for all the various parts. However, cost of treatment is an issue.
- Adding a pump, glucose meter, and glucagon to a patient on insulin treatment is a significant cost increase in the direct cost of treatment

Treatment data on an unprecedented level will be available with the a fully automated system
- You will have real-time data on blood glucose level, activity and use of insulin and glucagon. Much more data on activity and outcome to be expected to be available for patients, healthcare providers, and academia/industry
Background information
Diabetes: epidemiology and cost of disease

Epidemiology
According to the International Diabetes Federation, or IDF, in 2015 an estimated 415 million people between the ages of 20 and 79 were affected by diabetes globally, with up to 91% of adults with the disease in high-income countries having type 2 diabetes. The IDF also estimated that as of 2015, 29.3 million individuals in the United States, or 9.2% of the population, had diabetes. The IDF estimates that globally 642 million adults will be affected by diabetes by 2040.

Cost of disease
According to the IDF, diabetes-related expenditures in 2015 totaled $521 billion in North America, the Caribbean and Europe. Further, according to the IDF, aggregate diabetes-related expenditures in the United States, China and Germany, the three countries that spend the most on healthcare, amounted to 60% of the total global expenditures on diabetes, even though these countries only accounted for 35.1% of the global diabetes population. In addition, the IDF estimates the aggregate diabetes-related expenditures in the three highest spending regions of Western Pacific, Middle East and North Africa and South and Central America amounted to $157.7 billion in 2015 and expects these expenditures to increase by 39% by 2040 as a result of aging populations, people leading increasingly unhealthy lifestyles and an expected increase in life expectancy.
Diabetes: glycemic control measure

Treatments for type 2 diabetes are intended to reestablish glucose homeostasis, or a condition of balance or equilibrium of glucose levels since widely varying glucose levels can lead to long term health complications for patients.

HbA1c is the generally accepted measure of glycemic (glucose level) control, and the most validated measure of how well a patient has been able to control its type 2 diabetes. It is a blood test that checks the amount of glucose bound to hemoglobin, a protein found inside red blood cells responsible for carrying oxygen coming from the lungs to the different parts of the body. When hemoglobin bonds with glucose, a coat of sugar forms on the hemoglobin, and that coat gets thicker when there is more glucose in the blood. HbA1c tests measure how thick that coat has been over the past approximate three months, which is how long a typical red blood cell lives. People who have type 2 diabetes have higher HbA1c levels than normal. As a result, an HbA1c test can be used to diagnose and monitor the progression of type 2 diabetes.

A consensus statement adopted by the American Diabetes Association, or the ADA, and the European Association for the Study of Diabetes, or the EASD, in 2012 and updated in 2015, in light of the results of controlled clinical trials, provided that in order to reduce the risk of the most common complications of diabetes, an HbA1c level equal to or greater than 7.0% should trigger initiation of therapy (or a change in prior therapy) with the goal of achieving an HbA1c level of less than 7.0%.
Diabetes: general disease types and risk

Diabetes is a group of diseases characterized by high blood glucose levels that result from deficiencies in the body's ability to produce, use or respond to insulin. Glucose is the type of sugar that the cells of the body use for energy. Insulin is a hormone produced in the beta cells of the pancreas that plays a central role in transporting glucose from the blood stream into cells.

There are two forms of diabetes, type 1 and type 2:
• Type 1 diabetes results from a loss of the ability to produce insulin. Type 1 diabetes is treated generally with injections of insulin or modified forms of insulin (insulin analogs); and

• Type 2 diabetes is a chronic disease, which begins when the body cannot produce adequate levels of insulin or loses the ability to respond to insulin (insulin resistance). The key to effective management of type 2 diabetes is to control high blood glucose levels (hyperglycemia).

Both type 1 and type 2 diabetes are complex, chronic and progressive disorders that, left untreated, can lead to long-term health complications and shortened life expectancy. 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.

Of the various risk factors involved in contracting type 2 diabetes, including lifestyle and age, one of the most important is obesity. Obesity plays a central role in insulin resistance and the progression of type 2 diabetes. Body weight loss is associated with substantial reductions in diabetes-related mortality in overweight individuals while also improving other health parameters, such as blood pressure and cholesterol levels.
Artificial Pancreas and Insulin Pumps

The pancreas is the organ in the body that secretes the hormones insulin and glucagon. In a healthy pancreas, insulin and glucagon are secreted in a manner that maintains blood glucose levels within an acceptable range. An artificial pancreas is intended to achieve control of blood glucose levels if a diseased natural organ cannot.

At present, most of the marketed artificial pancreas systems serve simply as insulin pumps, automatically injecting insulin when needed. In these single-hormone systems, glucagon, if also required, must be administered manually by the patient or a third party.

According to the American Association of Diabetes Educators, in 2016 insulin pumps were used by 400,000 patients, or approximately 35% of type 1 diabetes patients in the United States. Informa Pharma Intelligence’s Meddevicetracker database reports that the U.S. market for insulin pumps (consisting of both the pumps and the accompanying consumable products (e.g., infusion sets, or the plastic tubing that delivers insulin from the pump into the body) but excluding insulin itself) was valued at $1.7 billion in 2015 and is expected to reach $2.5 billion by 2020, representing a growth rate of over 40%, as a result of the introduction of superior and less invasive pumps and integrated systems being adopted for use by a broader group of patients in a growing diabetes population. With technological innovation likely driving this trend, assuming the same growth rate reported by Meddevicetracker moving forward, the market for insulin pumps will be double in 2025 what it was in 2015.
Dasiglucagon: a novel analogue of human glucagon that is stable in a water based formulation

Zealand Pharma is developing dasiglucagon, a novel analog of human glucagon, a hormone that increases the level of blood glucose in the body. In pre-clinical trials, dasiglucagon has shown a favorable stability and solubility profile in a liquid formulation, as compared to native glucagon, and is being investigated for use as a rescue treatment for severe hypoglycemia, in a dual-hormone artificial pancreas system for insulin-dependent diabetes patients, and in a single-hormone pump for subcutaneous infusion as a treatment for CHI. We are currently exploring two different formulations for these opportunities in parallel.

A multiple-dose version intended for use in a dual-hormone artificial pancreas system for insulin-dependent diabetes patients and use in a single-hormone pump for subcutaneous infusion for the treatment of CHI.

Third party clinical studies have demonstrated that adding a glucagon component to an artificial pancreas system (insulin pump) significantly limits the risk of hypoglycemia, while ensuring better glucose management for patients with type 1 diabetes.
The iLet: a dual hormone pocket-sized wearable medical device

We initiated a collaboration with Beta Bionics, Inc., or Beta Bionics, a medical device company, to investigate the use of our multiple-dose version of dasiglucagon with Beta Bionics' iLet investigational bionic pancreas platform technology in June 2016, and formalized our collaboration with Beta Bionics in a February 2017 co-development agreement.

iLet is a dual-hormone pocket-sized wearable medical device that Beta Bionics believes will be able to autonomously manage blood sugar levels in diabetes patients. We have submitted an IND for this use of dasiglucagon to the FDA. We retain all proprietary rights to dasiglucagon under this collaboration arrangement.

In December 2016, we initiated a Phase 2a clinical trial in adult patients with type 1 diabetes to test the safety, tolerability and efficacy in improving glycemic control of dasiglucagon as compared to a recombinant glucagon marketed by Eli Lilly, when administered by a test-version of the iLet bionic pancreas in which an iPhone is used to control dosing using an algorithm developed by Beta Bionics for use in the iLet bionic pancreas.

The test conditions were chosen to optimize the opportunity to evaluate the ability of dasiglucagon (and comparator) to maintain blood glucose in the desired target glycemic range. Results from this single-center, open-label randomized cross-over trial were reported in June 2017. The trial provided evidence that dasiglucagon was able to maintain blood glucose in the target glycemic range in a manner comparable to human recombinant glucagon when administered automatically via the iLet controlled pump system. We also initiated, in December 2016, a Phase 2a clinical trial in adult type 1 diabetes patients treated with continuous subcutaneous insulin infusion, or insulin pumps, to assess pharmaconkinetic responses after micro-doses of dasiglucagon under euglycemic and hypoglycemic conditions and compared to a recombinant glucagon marketed by Eli Lilly. Results from this trial, in which dasiglucagon was observed to be safe and well tolerated across all tested dose levels and to provide clinically relevant increases in blood glucose under both euglycemic and hypoglycemic settings, were released in May 2017.