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Phase I trial results for Zealand's glucagon analogue, ZP4207 support its further development as a ready-to-use rescue treatment for severe hypoglycemia in diabetes patients on insulin therapy

- **Phase I data show that ZP4207 is safe and well tolerated after single-dose administration in both healthy volunteers and Type 1 diabetes patients**
- **ZP4207 also showed effects in raising blood glucose levels in Type 1 diabetes patients after an insulin-induced hypoglycemic event**
- **Zealand is also exploring a multiple-dose version of ZP4207 in a Phase Ib trial for mild to moderate hypoglycemia; trial enrolment has now been completed and results are expected in H2 2015**

Copenhagen, 26 June 2015 – Zealand announces results from a clinical Phase I trial with a single-dose version of its novel, stable glucagon analogue, ZP4207. ZP4207, invented and wholly-owned by Zealand, is suited for liquid formulation and has in preclinical studies shown promising potential as a more convenient ready-to-use rescue pen for the treatment of severe hypoglycemia. Severe hypoglycemia is an acute, life threatening condition affecting both Type 1 and Type 2 diabetes patients on insulin therapy when their blood sugar levels drop too low.

Zealand initiated the ZP4207 single-dose Phase I trial in November 2014 as a two-part study to evaluate safety and tolerability in both healthy volunteers and Type 1 diabetes patients. The enrollment and treatment of 64 healthy volunteers and 20 patients with Type 1 diabetes was completed ahead of schedule. Based on the results from the trial, Zealand will now progress the development of ZP4207 for severe hypoglycemia towards the next clinical phases.

In parallel with the development of ZP4207 as a single-dose rescue treatment, Zealand is also evaluating a multiple-dose version of ZP4207 in a clinical Phase IB trial for the treatment of mild to moderate hypoglycemia including its potential use in a dual-hormone artificial pancreas pump.

Commenting on the outcome of the Phase I study with single-dose ZP4207, **Britt Meelby Jensen, President and CEO of Zealand,** said:

"*We are very happy that the results of the Phase I trial support the potential we see for our proprietary stable glucagon product as a ready-to-use rescue pen for severe hypoglycemia. While existing treatments are effective, they are based on native glucagon as a lyophilized powder, which requires reconstitution in a multi-step handling process before use. We believe ZP4207 can offer diabetes patients on insulin therapy a much more convenient treatment option, and we now look forward to*

further advancing the development of our product. The progress we see in the development of our stable glucagon product is important in growing the value of our proprietary pipeline in line with our strategy, and it endorses our in-house peptide design expertise and clinical development capabilities."

Trial design and results: Phase I with single-dose ZP4207:

The first-in-man Phase I trial comprised two parts:

- In Part 1, Zealand enrolled 64 healthy volunteers who were treated with single-ascending doses of ZP4207 primarily to evaluate safety and tolerability and secondarily to evaluate various pharmacokinetic and pharmacodynamic measurements compared to a marketed glucagon hypoglycemia rescue treatment.

  Results showed that ZP4207 was safe and well tolerated across all doses evaluated (0.01 mg to 2.0 mg per subject). Furthermore, blood glucose levels were increased as expected across a broad dose range.

- In Part 2 of the trial, the same endpoints were evaluated for a selected single dose of ZP4207 in 20 patients with Type 1 diabetes. The patients were challenged with insulin into hypoglycemia before treatment with ZP4207 to get an indication of the efficacy of ZP4207 to release glucose stores and increase blood glucose levels in a cross-over design with a marketed glucagon rescue treatment as direct active comparator.

  Results showed that ZP4207 was also safe and well tolerated in patients with Type 1 diabetes. In addition, ZP4207 showed the expected effects on raising blood glucose levels after insulin induced hypoglycemia and similar to the effects of marketed glucagon.

Status of ZP4207 multiple-dose clinical Phase Ib trial

Zealand is also exploring a multiple-dose version of ZP4207 in a Phase Ib trial for the treatment of mild to moderate hypoglycemia. The ongoing development activities, including chronic toxicology studies, are supported by a USD 1.8 million grant from the Helmsley Charitable Trust. The enrolment into the Phase Ib trial has now been completed, and results are expected in H2 2015.

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About severe hypoglycemia

Severe hypoglycemia is an acute, life threatening condition resulting from a serious drop in blood sugar levels associated with insulin therapy in Type 1 and Type 2 diabetes patients. Hypoglycemia is also an issue to some extent for patients on sulfonylurea drugs. All patients with Type-1 diabetes and approximately 20% of Type-2 diabetes patients in the US are treated with insulin (Decision Resource, 2012). Type-1 diabetes patients are the most likely to experience episodes of hypoglycemia since they inject themselves with insulin several times per day or use an insulin pump.

Despite the availability of improved insulin products with reduced risk of severe hypoglycemia, the condition remains a major concern for patients. The American Diabetes Association (ADA) recommends that all patients with Type 1 diabetes and patients with Type 2 diabetes on insulin therapy carry a glucagon kit with them at all times (Center for Disease Control and Prevention 2011).

About glucagon and existing glucagon rescue treatments

Glucagon is a native peptide, which plays an important role in the control of blood sugar levels. The effects of glucagon are opposite to those of insulin – it helps to release stored glucose into the blood stream to increase blood sugar levels. The therapeutic use of native glucagon in cases of hypoglycemia is challenging due to the peptide's low solubility and very poor stability in liquid solution. Current glucagon treatments are therefore solely available in the form of a lyophilized powder, which requires reconstitution with sterile water in a multi-step process before use. In the case of an acute and severe hypoglycemia event, this can lead to handling errors, delay administration of glucagon and result in sub-optimal treatment.

About Zealand Pharma

Zealand Pharma A/S ("Zealand") (Nasdaq Copenhagen: ZEAL) is a biotechnology company based in Copenhagen, Denmark. Zealand has leading expertise in the discovery, design and development of novel peptide medicines and possesses in-house competences in clinical trial design and management with a therapeutic focus on metabolic diseases and acute care indications. The company is advancing a proprietary pipeline of novel medicines alongside a partnered product and development portfolio.

Zealand's first invented medicine, lixisenatide, a once-daily prandial GLP-1 agonist for the treatment of Type 2 diabetes, is marketed globally (ex-US) as Lyxumia® and is in Phase III development as a single-injection combination with Lantus® (LixiLan), both under a global license agreement with Sanofi. US regulatory filing for Lyxumia® is planned for Q3 2015 and filing for LixiLan is planned for Q4 2015 in the US and Q1 2016 in Europe.

Zealand's proprietary pipeline include danegaptide (prevention of Ischemic Reperfusion Injury) in Phase II and the stable glucagon analogue, ZP4207 in two Phase I trials as a single-use rescue pen (severe hypoglycemia) and a multiple-dose version (mild to moderate hypoglycemia) as well as several preclinical peptide therapeutics.

Partnering represents an important component of the strategy to leverage in-house expertise, share development risk in large clinical trials, provide funding and commercialize the company's products. Zealand currently has global license agreements and partnerships with Sanofi, Helsinn Healthcare and Boehringer Ingelheim.

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