Press Release
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Zealand advances its proprietary stable glucagon analogue for severe hypoglycemia in diabetes into clinical development

- **Novel glucagon analogue ZP4207 has unique potential as a ready-to-use rescue pen to offer diabetes patients on insulin therapy a more effective and convenient treatment of severe hypoglycemia episodes**
- **First human subjects successfully dosed in a clinical Phase I trial to evaluate safety and efficacy. Trial results are expected mid-2015**
- **The trial start marks an important milestone in the advance of Zealand's pipeline of proprietary medications**

Copenhagen, 17 November 2014 – Zealand Pharma A/S ("Zealand") (Nasdaq Copenhagen: ZEAL) announces that the company has dosed the first human subjects in a clinical Phase I trial with ZP4207, its novel stable glucagon analogue. The objectives of the trial are to evaluate the safety and human efficacy of ZP4207 as a novel approach to offer better and more convenient treatment of 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.

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 and increase blood sugar levels. The therapeutic use of native glucagon in cases of hypoglycemia is made difficult by the peptide's very poor stability and low solubility. Current glucagon treatments are available in the form of 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.

In preclinical studies, ZP4207 has demonstrated a strong stability profile and a good solubility, supporting the potential use of this glucagon analogue in a liquid dosage form as a ready-to-use rescue pen. Data from these studies suggest further that ZP4207 is comparable to native glucagon in its effect on releasing glucose stores into the blood stream to restore blood sugar levels, while being suitable for long term storage. Zealand currently retains all rights to ZP4207.

In a comment to the advance of ZP4207 into clinical development, **David H. Solomon, President and Chief Executive Officer of Zealand,** said: *"We are extremely pleased to announce the first human dosing's of our glucagon analogue as a potential ready-to-use rescue pen to treat hypoglycemia. This important milestone is a result of Zealand's patient-centric approach to*

innovation and our core expertise in the design of novel peptide medicines. ZP4207 represents the second program in Zealand's proprietary pipeline of acute care medication, and we believe the product has the potential to offer significant benefits to diabetes patients as it addresses one of the most challenging and most feared acute problems associated with the disease."

In the first part of the Phase I clinical trial, conducted at a selected diabetes centre in Germany, Zealand expects to enroll up to 64 healthy volunteers who will be treated with single-ascending doses of ZP4207. The trial objectives are primarily to evaluate safety and tolerability and secondarily to evaluate various pharmacokinetic and pharmacodynamic measurements, as compared to native glucagon. In a second part of the trial, the same endpoints will be evaluated in 20 patients with Type 1 diabetes, who will be made hypoglycemic before treatment to get an indication of the efficacy of ZP4207 to release glucose stores and increase blood sugar levels in a cross-over design with native glucagon as active comparator. Zealand expects to complete the Phase I trial in H1 2015 with results available mid 2015.

The clinical development of ZP4207 as a better and more convenient treatment of severe episodes of hypoglycemia has the potential to follow an expedited plan, which could lead to first regulatory filing of this Zealand therapeutic as soon as early 2018.

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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 primarily an issue for diabetes patients treated with insulin and, to some extent, 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 insulin with reduced risk of hypoglycemia such as insulin glargine and insulin degludec, severe hypoglycemia remains a serious concern for patients, and 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 ZP4207

ZP4207 is a novel analogue of human glucagon, invented by Zealand to demonstrate a strong stability profile in liquid solution, supporting its potential use as a ready-to-use rescue pen for the treatment of severe hypoglycemia. Data from preclinical studies with ZP4207 suggest that it is comparable to native glucagon in releasing glucose stores into the blood stream, while being suitable for long-term storage in a ready-to use pen at room temperature. Following insulin-induced hypoglycemia in rats, ZP4207 demonstrated its ability to rapidly and dose-dependently restore blood glucose to baseline levels or above. Furthermore, this novel glucagon analogue has shown both a pharmacokinetic profile and an effect on blood glucose overall similar to native glucagon in dogs.

The features of ZP4207 leaves the potential also for its use as a component in a insulin-glucagon hormone pump, a so-called 'artificial pancreas' which could represent an important advance in the treatment of patients with type 1 diabetes.

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 also 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 in Phase III development as a single-injection combination with Lantus® (LixiLan), both under a global license agreement with Sanofi. US regulatory filing of Lyxumia® is planned for summer 2015 and of LixiLan as early as end 2015.

Zealand proprietary pipeline includes danegaptide (prevention of ischemic reperfusion injury) and the stable glucagon product, ZP4207 (treatment of severe hypoglycemia) as well as several preclinical peptide therapeutics. Partnering represents an important component of 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, Boehringer Ingelheim and Eli Lilly.

For further information: **www.zealandpharma.com** Follow us on Twitter @ZealandPharma