**Company announcement – No. 4 / 2016**

# Zealand announces results of a Phase II Proof-of-Concept trial with danegaptide for cardiac reperfusion injuries

- **Danegaptide did not meet the primary efficacy endpoint of reducing ischemic reperfusion injuries, measured on the Myocardial Salvage Index, in patients with an ST-elevation myocardial infarction undergoing the standard treatment of PCI**
- **In the trial, danegaptide was shown to be safe and well tolerated**

*Copenhagen, 2 March 2016* – Zealand announces top-line results from its clinical Phase II Proof-of-Concept trial with danegaptide for the protection against cardiac reperfusion injuries in patients with an acute myocardial infarction (blood clot in the heart). Results show no effect of danegaptide on the primary endpoint of saving cardiac tissue from ischemic reperfusion injuries as measured on the Myocardial Salvage Index (MSI).

Danegaptide is a Zealand invented peptide and the first in a new class of gap junction modifiers. The compound has demonstrated cell protective and anti-arrhythmic properties and shown significant effect in established preclinical models of cardiac ischemic reperfusion injuries. Despite substantial improvements in the treatment of patients with ST-elevation myocardial infarction (STEMI), significant unmet medical needs remain in the field, primarily associated with reperfusion injuries.

**Britt Meelby Jensen, President and CEO of Zealand, said:** "*We had obviously hoped with this study to demonstrate a therapeutic benefit of danegaptide to patients. Cardiac damage remains a serious challenge following a heart attack, so in this sense, we are disappointed. Based also on the strong results seen with danegaptide in preclinical studies, we still think this was a relevant opportunity for us to explore despite the fact that this is a notoriously difficult therapeutic area, where many other drug candidates have failed. On behalf of Zealand, I would like to thank all patients and the study investigators at Rigshospitalet's Cardiac Center for their participation in this very well-conducted trial.*

**And she continued**: *"Internally, we will focus our resources on the many activities ongoing in our growing proprietary pipeline. This includes the two clinical Phase II programs, which we have initiated this year with our two investigational specialist medicines, ZP1848 for Short Bowel Syndrome and ZP4207 for hypoglycemia in diabetes, respectively."*

The clinical Phase II Proof-of-Concept trial was a randomized, double-blind, placebo-controlled trial conducted at one of the world's leading Cardiac Centers, situated at the Copenhagen University Hospital (Rigshospitalet). The trial enrolled patients with STEMI, who were randomized to treatment with danegaptide or placebo before undergoing the standard treatment of primary percutaneous coronary intervention (pPCI) to restore blood flow. The primary efficacy endpoint, Myocardial Salvage Index , was measured in a subgroup of patients, who qualified for magnetic resonance scanning (MRI) based on predefined criteria. MSI was measured three months after the myocardial infarction as the size of salvaged cardiac tissue relative to the cardiac tissue area at risk measured two days after pPCI.

The trial was appropriately powered and well-conducted, providing a clinical data set of high quality. Results from the trial showed no effect for danegaptide compared to placebo on the primary endpoint of MSI as a measure for cardiac tissue salvage, when added to the standard therapy provided. Data from secondary efficacy endpoints were consistent with the results on the primary endpoint. In the trial, danegaptide demonstrated to be safe and well tolerated.

Zealand will evaluate the complete data set and discuss with key medical experts to review all aspects of the trial outcome.


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### About the Phase II Clinical Proof-of-Concept trial with danegaptide

The trial was a conducted at Rigshospitalet in Copenhagen as a single center clinical Proof-of-Concept trial. A total of 585 patients (Intention to treat, ITT) with clinical signs and electrocardiographic (ECG) changes indicating ongoing ST-elevation myocardial infarction (STEMI) were enrolled in the trial. All patients were randomized to two different dose levels of danegaptide or placebo, administered at least 10 minutes prior to undergoing the standard treatment of primary percutaneous coronary intervention (pPCI) to restore blood flow.

The primary efficacy endpoint of the Phase II trial was the myocardial salvage index (MSI), measured in a subset of patients, fulfilling predefined criteria for undergoing cardiac magnetic resonance imaging (cMRI) (per protocol, N=169). MSI is defined as the absolute difference in size between myocardial tissue volume at risk, measured at day 2 (after PCI) and final infarct size, measured at day 90 (after PCI), relative to myocardial tissue volume at risk.

Secondary trial endpoints included cardiac biomarkers, ST-segment resolution and left ventricular ejection fraction, as well as evaluation of relevant safety parameters.

### About Ischemic Reperfusion Injuries

In case of an acute myocardial infarction (AMI), or a heart attack, a blood clot blocks the blood flow to important parts of the heart for a longer period of time (ST segment elevation myocardial infarction, STEMI). The standard treatment of AMI today is different types of interventions aimed at enabling the return of blood flow to the ischemic myocardium, thereby limiting the size of the infarct. Percutaneous coronary intervention (PCI), also called balloon dilatation, is the most common. In 2020, the incidence for STEMI is predicted to be 756.700 in US, EU and Japan combined, and approximately 80% of STEMI patients undergo PCI procedure.

Interventional treatment is the most effective method to restore blood flow or re-perfuse the heart, thereby reducing the infarct size and improving the outcome for patients with a STEMI. The process of myocardial reperfusion however, can paradoxically itself induce further cardiac tissue damage, a phenomenon known as myocardial reperfusion injury.

To date there are no marketed pharmacological treatments for the prevention of reperfusion injury.

### About danegaptide

Danegaptide is a therapeutic peptide invented by Zealand, exerting effect via activation of gap junction communication channels between cells, and demonstrating both anti-arrhythmic and cell protective properties.

In a pre-clinical dog model of acute myocardial infarction (AMI), i.e. an acute blood clot in the heart, danegaptide has shown dose-dependent significant reductions in infarct size after reperfusion. In another established pig model of reperfusion injury associated with an AMI, danegaptide significantly reduced infarct size compared to immediate full reperfusion. Results from an extensive Phase I program, including three (3) individual studies with a total of 153 subjects, showed that danegaptide was safe and well tolerated.

## About Zealand Pharma

Zealand Pharma A/S (Nasdaq Copenhagen: ZEAL) ("Zealand") is a biotech company with leading-edge scientific expertise in turning peptides into medicines. Zealand has a growing proprietary pipeline of novel investigational medicines and a mature portfolio of products and projects under license collaborations with Sanofi, Helsinn Healthcare 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 (ex-US) as Lyxumia® and has it under regulatory review in the US. The license agreement with Sanofi covers also LixiLan, which is the reference name for the fixed-ratio, single-product combination of lixisenatide and insulin glargine 100 Units/mL (Lantus®). LixiLan is under regulatory priority review by the US FDA and regulatory submission in the EU is planned by Sanofi for Q1 2016.

Zealand's proprietary pipeline includes: *ZP4207 (a stable glucagon rescue treatment*) for severe hypoglycemia (Phase II); *ZP1848* for Short Bowel Syndrome (Phase II); *ZP4207 (multiple-dose version)* for better hypoglycemia management in diabetes (Phase I); *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