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Zealand announces top-line results of Helsinn's Phase IIb trial with elsiglutide for the prevention of chemotherapy-induced diarrhea in colorectal cancer patients

- **In the trial, elsiglutide reduced the incidence of chemotherapy-induced diarrhea in colorectal cancer patients receiving 5-FU based chemotherapy regimens, but not sufficiently to meet the primary endpoint for statistical significance**
- **Elsiglutide was observed to be safe and well tolerated in this patient population**
- **Helsinn is working on potential development options for elsiglutide to be decided following a full evaluation of the Phase IIb data set**
- **The top-line results from the elsiglutide Phase IIb trial have no effect on Zealand's financial guidance for 2016**

Copenhagen, 4 May 2016 – Zealand announces that Helsinn has reported top-line results from its clinical Phase IIb dose-finding trial to assess the efficacy of elsiglutide in the prevention of diarrhea induced by chemotherapy in patients with colorectal cancer. The results showed a positive numerical but not statistically significant effect of elsiglutide on the primary endpoint, defined as the proportion of patients experiencing a maximum grade ≥ 2 diarrhea during the first cycle of chemotherapy. In the trial, elsiglutide demonstrated a favorable safety and tolerability profile.

Elsiglutide is a novel GLP-2 analogue invented by Zealand. Global development and commercialization rights to the compound are licensed to Helsinn for its therapeutic use in the field of cancer supportive care. Results from a previous clinical Phase IIa trial conducted by Helsinn have shown that elsiglutide reduces the severity of chemotherapy-induced diarrhea (CID) in colorectal cancer patients with a good safety profile. Diarrhea is one of the most debilitating side effects associated with cancer treatment and in particular chemotherapeutic agents containing 5-Fluorouracil (5-FU). No effective approved treatment for chemotherapy-induced diarrhea exists today.

Britt Meelby Jensen, President and Chief Executive Officer of Zealand, commented on the results: "*Diarrhea is a significant burden for many cancer patients receiving 5-FU based chemotherapy, and there is no effective approved treatment available. We are impressed by Helsinn's commitment to the clinical development program with elsiglutide to help improve life for these patients, and we will now wait to get full understanding of Helsinn's intended path forward for the program.*"

The Phase IIb trial with elsiglutide was conducted at 45 centers across five EU countries (Germany, Czech Republic, Hungary, Poland and Bulgaria), Belarus, Russia and Ukraine and included a total of 497 colorectal cancer patients treated with 5-FU based chemotherapy (FOLFOX or FOLFIRI). Of the total number of patients, 13 received additional treatment with a monoclonal antibody and were not

included in the primary trial population. All patients in the trial were randomized to treatment with one of three doses of elsiglutide (10 mg, 20 mg, or 40 mg) or placebo, administered subcutaneously once-daily over four consecutive days in the first two chemotherapy cycles. All patients were followed for three cycles.

Helsinn has indicated that it is working on potential options for the further development of elsiglutide. The company will evaluate the full set of data generated from the Phase IIb trial and discuss the results with medical experts with the objective of fully understanding the outcome for elsiglutide and evaluate next possible steps.

Zealand's financial guidance for 2016 unchanged

The outcome of Helsinn's clinical Phase IIb trial with elsiglutide has no effect on Zealand's financial guidance for 2016 as announced in the 2015 Annual Report and full year announcement on 16 March 2016.

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For further information, please contact:

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

About chemotherapy-induced diarrhea (CID)

Diarrhea is one of the most debilitating side effects associated with cancer treatment. CID is associated with weight loss, malnutrition, fatigue, loss of fluids and electrolytes imbalance that, in case of persistent and severe diarrhea, can result in life-threatening dehydration, renal insufficiency, and may contribute to cardiovascular morbidity. The incidence and severity of CID varies considerably with the nature and dose of the cytotoxic therapy and frequencies. A high incidence of diarrhea of any grade (between 30-80%) has been reported in colorectal cancer patients receiving chemotherapeutic agents containing 5- Fluorouracil (5-FU) alone or in combination with oxaliplatin or irinotecan. Other chemotherapeutic agents commonly administered to patients with lung, breast or neuroendocrine cancers may cause diarrhea to a lesser extent.

The occurrence of CID has a potential negative impact on the compliance of patients with their chemotherapy regimens and schedules, which can result in a delay in therapy, dosage reduction or discontinuation of therapy. Changes to chemotherapy treatment resulting from CID may ultimately affect the patient's clinical outcome, and impact on overall health care resource consumption. The occurrence of CID can significantly impair patients' quality of life.

About Elsiglutide

Elsiglutide is a novel, potent and selective GLP-2 analogue invented by Zealand for the prevention of chemotherapy-induced diarrhea (CID). GLP-2 is a native peptide, secreted upon ingestion. It plays a key role in intestinal growth and tissue formation by promoting regeneration of the epithelial surface of the digestive system.

Global development and commercial rights to elsiglutide for its use in cancer supportive care outside the Nordic countries are licensed to Helsinn (www.helsinn.com). Helsinn is developing elsiglutide as a potential first-ever therapy against chemotherapy-induced diarrhea.

About the Phase IIb dose-ranging trial with elsiglutide

The trial was a randomized, stratified, double-blind, double-dummy, parallel group, placebo-controlled, dose finding, multicenter, multinational, Phase IIb trial in patient with colorectal cancer receiving 5-fluorouracil (5-FU)-based chemotherapy (FOLFOX or FOLFIRI). Patients received, starting from the day of chemotherapy administration, a single daily dose subcutaneously of elsiglutide 10, 20 or 40 mg or placebo for four consecutive days. Each patient was in the study for three consecutive chemotherapy cycles. The treatment period for each patient was four consecutive days of the first two chemotherapy cycles.

Two populations were planned for this study. The population receiving FOLFOX or FOLFIRI without monoclonal antibody was defined as the Target population (at least 120 patients per treatment group, for a total 480 patients), while the population concomitantly receiving monoclonal antibody was defined as the Additional population (up to 30 patients per treatment group, total maximum of 120 patients). The primary endpoint was the proportion of patients with diarrhea of grade $\geq$ 2 or more during the first cycle of chemotherapy. The primary analysis took into consideration only the target population.

About the Helsinn Group

Helsinn is a privately-owned cancer supportive care pharmaceutical group with an extensive portfolio of marketed products and a broad development pipeline. Since 1976, Helsinn has been improving the everyday lives of patients, guided by core family values of respect, integrity and quality, through a unique integrated licensing business model working with long standing partners in pharmaceuticals, medical devices and nutritional supplement products. Helsinn is headquartered in Lugano, Switzerland, with operating subsidiaries in Ireland and the United States, a representative office in China, as well as a product presence in about 90 countries globally.

For more information, please visit www.helsinn.com

About Zealand Pharma A/S

Zealand Pharma A/S (Nasdaq Copenhagen: ZEAL) ("Zealand") is a biotech company with leading scientific expertise in turning peptides into medicines. Zealand has a growing proprietary pipeline of novel investigational medicines and a portfolio of products and projects 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 (ex-US) as Lyxumia® and has it under regulatory review in the US. The license agreement with Sanofi covers also a fixed-ratio combination of lixisenatide with basal insulin glargine (Lantus®) under regulatory review in both the US and Europe.

Zealand's proprietary pipeline of product candidates includes: *ZP4207 (single-dose rescue treatment*) for acute, 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