Hypoglycaemia Frequency and Physiological Response to Double or Triple Doses of Once-weekly Insulin Icodec Versus Once-daily Insulin Glargine in Type 2 Diabetes

Thomas R Pieber1; Kristine Niss Arfela; Roman Calleitzen; Karen Margrete Due Thomsen; Shannon O’Hara; Marlies Hart; Ines Musrlic; Eva Sekhlikova; Martina Urschitz; Hanne Haahr2; 1Medical University of Graz, Graz, Austria; 2Novo Nordisk, Aalborg, Denmark; 3Novo Nordisk, Aalborg, Denmark; 4Novo Nordisk, Inc, Plainsboro, NJ.

Aim
- To compare insulin insulin (icodec) and insulin glargine U100 (glargine) in individuals with type 2 diabetes in terms of the frequency of hypoglycaemia after double or triple doses - the physiological response to hypoglycaemia after a triple dose in individuals with plasma glucose (PG) <54 mg/dL and/or for hypoglycaemia symptoms.

Introduction
- Icodec is a basal insulin being developed for once-weekly (OW) dosing. After subcutaneous injection and absorption into the circulation, icodec binds strongly to albumin, creating an inactive depot, from which icodec is slowly and continuously released, resulting in a half-life appropriate for OW dosing.
- Icodec has an efficacy and safety profile similar to that of daily (DS) glargine, as demonstrated in phase 2 clinical trials - phase 3a (ONWARDS) trials are ongoing.
- Owing to icodec being a novel basal insulin, the glucodynamics during hypoglycaemia development as well as the symptomatic and counterregulatory response to hypoglycaemia for this insulin require thorough investigation.

Methods
- The study was a randomized, open-label, two-period crossover trial (Figure 1A).
- Eighty-three individuals with type 2 diabetes receiving basal insulin with or without oral antidiabetic drugs received i codec for 4 weeks or DS glargine for 11 days.
- Total weekly doses were equimolar based on the individual daily run-in dose of glargine.
- A 100 mg/dL PG nadir was used to define the time to steady state.
- Second, triple and doses of insulin on glargine were administered and hypoglycaemia was induced 4 hours (i.e. day 0) and 7 hours (i.e. day 1) after insulin injection. This corresponded to the expected time of maximum glucagon lowering effect for each insulin.

Results
- Eighty-three individuals with type 2 diabetes received i codec or glargine. The i codec group was 50% male, had a mean age of 57 years, a mean body weight of 87.1 kg and a mean body mass index (BMI) of 27.8 kg/m².
- 43 individuals with type 2 diabetes receiving basal insulin with or without oral antidiabetic drugs were included in the analysis of the physiological response to hypoglycaemia.
- There were no severe hypoglycaemic episodes (other than those induced) during the i codec titration period and all episodes during the glargine period.

Conclusions
- Double or triple doses of i codec versus DS glargine do not lead to increased risk of hypoglycaemia.
- During hypoglycaemia, comparable symptomatic and moderately greater counterregulatory responses were seen with i codec versus glargine.

References:

All regulatory hormone levels increased during hypoglycaemic development (Figure 4). Concentrations of adrenaline at PG ≤45 mg/dL, and cortisol at PG ≤45 mg/dL were greater for i codec than for glargine.

Figure 2: Change in regulatory hormone concentration on development of hypoglycaemia following a triple dose of insulin i codec or insulin glargine U100.