SWITCH 1: Reduced Hypoglycemia with Insulin Degludec (IDeg) vs. Insulin Glargine (IGlar), Both U100, in Patients with T1D at High Risk of Hypoglycemia: A Randomized, Double-Blind, Crossover Trial

The long duration of action of insulin degludec (IDeg) (>42 hours), a new generation basal insulin approved last year, offers a distinct advantage over the standard insulin glargine. The longer duration of action with reduced peak to trough variations in insulin concentration at steady state, reduces risks of hypoglycemia. “Hypoglycemia,” said Wendy S. Lane, MD, Mountain Diabetes and Endocrine Center, Asheville, NC, lead investigator for the SWITCHT trial at her 2016 American Diabetes Association poster, “is the most dangerous complication for the management of type 1 diabetes.”

In the phase 3a development program, IDeg demonstrated non-inferiority to insulin glargine U100 (IGlar) with respect to HbA1c, with lower rates of nocturnal confirmed hypoglycemia. The phase 3 data, however, had potential limitations based on the lack of study blinding, inclusion of non-symptomatic hypoglycemia, exclusion of patients with at least one risk factor for hypoglycemia and insufficient tracking of IGlar administration timing.

SWITCH 1 was designed to show non-inferiority for IDeg + insulin aspart (IAsp) versus IGlar + IAsp in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycemia episodes during a maintenance period commencing after 16 weeks of treatment. Severe episodes were defined as those requiring external intervention, and a confirmed symptomatic episode was defined as one confirmed by finger stick with BG <56 mg/dL with symptoms. Patients with type 1 diabetes (n=501, 53.7% male, mean age 45.9 years) were randomized 1:1 to either IDeg OD + IAsp or IGlar U100 OD + IAsp, titrated for 16 weeks, followed by a 16-week maintenance period. Subsequently, all patients were switched over to the other regimen (titration and maintenance) for another 32 weeks. IAsp was given 2- to 4-times per day as part of a full mealtime basal-bolus regimen.
Dr. Lane underscored that the mean duration of diabetes in the cohort was 23.4 years and that baseline mean fasting glucose was 169.8 mg/dL. “These are the types of patients typically excluded from clinical trials,” she observed.

All patients included in SWITCHT 1 had at least one hypoglycemia risk factor; they were treated to a strict target of 71–90 mg/dL (lowest of three consecutive measurements).

The primary endpoint of non-inferiority and superiority in rates of severe or BG-confirmed symptomatic hypoglycemia with IDeg versus IGlar in the maintenance periods was achieved, with an 11% lower rate (estimated rate ratio [ERR] [95% CI] 0.89 [0.85; 0.94], p<0.0001). For the same measure looking specifically at rates of nocturnal hypoglycemia, a secondary endpoint which Dr. Lane described as “the most dangerous and most worrisome,” the reduction was 36% (ERR 0.65 [0.56; 0.73], p<0.0001). Severe hypoglycemia was reduced by 26% in the maintenance period (0.74 [0.61; 0.90], p<0.05). Similarly significant rate reductions were reported for the full treatment period for IDeg versus IGlar across these same measures.

The pre-requisite of achieving HbA1c non-inferiority in both treatment periods was also met. At the end of treatment period 1 (before crossover) mean HbA1c was 6.92% for IDeg versus 6.78% for IGlar; the mean HbA1c rates at the end of treatment period 2 (post-crossover) were 6.95% for IDeg and 6.97% for IGlar. Baseline HbA1c was 7.6% in both treatment arms.

Weight changes were comparable between groups for both treatment periods. Also, adverse event and serious adverse event rates were similar between groups.

Dr. Lane concluded, “SWITCH 1 demonstrates a significant hypoglycemia benefit with IDeg versus IGlar and provides reassurance that in a type 1 diabetes population, there were no safety concerns in switching to IDeg from any other basal insulin regimen, or from continuous subcutaneous insulin infusion.” She commented further, “Patients have a flat, peakless basal insulin for the first time...This is progress in basal insulin therapy that we can offer to our patients with type 1 diabetes.”