

The focus of this review is insulin glargine [rDNA origin] injection 300 U/ml (Gla-300, Toujeo®). Gla-300 is a next generation basal insulin with a novel formulation of insulin glargin delivering the same amount [as glargine 100 U/ml, Gla-100, Lantus®] in 1/3 volume.

Toujeo® (Gla-300) is an investigational basal insulin, which has the potential to provide as effective blood sugar control as Lantus® with better tolerated titration-to-target by reducing low blood sugar events (especially nocturnal hypoglycaemia), particularly during the first 8-week initiation phase (post hoc analysis) and possible 3-hour flexibility in dosing regimen. Pharmacokinetic and pharmacodynamic studies have demonstrated a smoother and more prolonged profile for Gla-300 compared with Lantus®, which is expected to lead to effective blood sugar control that lasts beyond 24 hours, with a favorable safety profile and low within-individual, within-day blood sugar variability. Toujeo® demonstrated lower glucose variability compared with Lantus® in people with type 1 diabetes. By comparing morning and evening injections using 24-hour continuous glucose monitoring, Toujeo® demonstrated comparable overall blood sugar control compared with Lantus®, but with a more constant 24-hour blood sugar profile.

The EDITION program is a worldwide and extensive series of six Phase 3a studies demonstrating the efficacy and safety of Gla-300 in broad and diverse populations of people with diabetes. The EDITION program included over 3,500 people with diabetes who were uncontrolled on their current therapy; all studies met their primary endpoints by demonstrating Gla-300 can provide comparable glycemic control (measured by HbA<sub>1C</sub> reduction) compared with Lantus® in various type 1 and type 2 diabetes populations: people with type 2 diabetes who were uncontrolled on basal plus mealtime insulin or basal insulin plus oral glucose-lowering agents – clinically challenging population (EDITION 1 - basal plus mealtime insulin, n=807; EDITION 2 - basal insulin plus oral glucose-lowering agents, n=811); people with type 2 diabetes who were uncontrolled on anti-diabetic therapies other than insulin (basal insulin initiation) (EDITION 3, n=878); type 1 diabetes patients (EDITION 4, n=549); Japanese diabetes population (EDITION JP1, type 1 diabetes, n=243; EDITION JP2, type 2 diabetes, n=240).

In people with type 2 diabetes, EDITION 1 and 2 demonstrated significantly fewer patients experienced severe or confirmed night-time low blood sugar hypoglycaemia from week 9 to month 6 (EDITION 1: 21% fewer patients, p=0.0045; EDITION 2: 23% fewer patients, p=0.038). EDITION 3 included people with less severely progressed type 2 diabetes and showed significantly fewer people who were new to insulin therapy experienced low blood sugar events during the night over the study period (post-hoc analysis), when treated with Gla-300, compared with Lantus® (relative risk reduction of 24%).

In a pooled analysis of EDITION 1, 2, 3 Gla-300 consistently showed significantly fewer hypoglycaemic events at any time of day, including night-time events, compared with Lantus<sup>®</sup> across studies and differing type 2 patient populations (rate ratio [per participant-year] reduced by 14%; p=0.0116), particularly during the first 8-week titration phase (when comparing -23% at any time of the day and -42% during the night). Documented symptomatic low blood sugar events were also reduced at any time of day (-12%) and during the night (-25%). In Japanese people with type 2 diabetes uncontrolled on basal insulin and oral anti-diabetics (EDITION JP2), incidence of hypoglycaemia at night-time was also reduced, with 38% fewer patients experiencing  $\geq 1$  event over the 6-month study period.

EDITION 4, an international study of people with type 1 diabetes, showed that those randomized to Gla-300 showed similar night-time and any-time of the day low blood sugar event rates compared with Lantus<sup>®</sup>. But EDITION 4 indicated a 31% relative risk reduction (significant; per participant-year) in confirmed or severe night-time low blood sugar events in the first 8 weeks (post-hoc analysis) for Gla-300 vs. Lantus<sup>®</sup>. EDITION 4 also demonstrated neither glycemic control nor hypoglycaemia events differed between morning and evening Gla-300 injection groups, as well as at least comparable efficacy and safety. In a study including only Japanese people with type 1 diabetes (EDITION JP1-basal plus mealtime insulin), night-time low blood sugar event rates were 15% lower with Gla-300 as compared to Lantus<sup>®</sup> over the 6-month study period. In EDITION JP1, 29% fewer patients experienced night-time low blood sugar with Gla-300 compared with Lantus<sup>®</sup> during the first 8 weeks of treatment (post-hoc analysis).

In all EDITION studies, Gla-300 demonstrated weight neutrality (less than 1 kg gain). Furthermore, in EDITION 2, 4 and JP1, weight gain was significantly less with Gla-300 treatment compared with Lantus<sup>®</sup> treatment. In EDITION JP2, the patients treated with Gla-300 lost weight, compared with a slight increase in the Lantus<sup>®</sup> group (-0.6 kg vs. 0.4 kg respectively).