For medical journalists outside U.S. only

Toujeo®
(insulin glargine [rDNA origin] injection, 300U/mL)

Key points
- In diabetes management, insulin initiation is often delayed in type 2 diabetes, partly due to the fear of low blood sugar events (hypoglycemia) and its consequences, or weight gain.
- Hypoglycemia is one of the most frequent adverse events experienced by insulin users. Hypoglycemia and fear of it can restrict titration of insulin dose and could lead to early discontinuation of therapy.
- Toujeo® (insulin glargine [rDNA origin] injection, 300U/mL) is a next-generation basal insulin that offers a steady and prolonged activity profile that lasts a full 24 hours and beyond compared with Lantus®, with low within-individual, within-day blood sugar variability, in pharmacokinetic and pharmacodynamic studies.
- Toujeo® has demonstrated similar blood sugar control to Lantus® in all Phase III EDITION program studies (primary efficacy endpoint), conducted in a broad and diverse range of people with diabetes, which was maintained at one year in EDITION I and II (people with type 2 diabetes).
- In type 2 diabetes patients Toujeo® has a lower risk of confirmed hypoglycemia vs. Lantus®, demonstrating significantly fewer patients experiencing night-time low blood sugar compared with Lantus® (Phase III data: EDITION I,13 II;14 and EDITION I–III meta-analysis21), which was maintained at one year (EDITION I15 and II16). This effect was already seen during the first eight weeks of the studies, when most of the insulin dose changes occurred (EDITION I–III meta-analysis27).

Addressing unmet needs in diabetes
Persistent high blood glucose levels (hyperglycemia) can cause long-term complications, including cardiovascular disease, blindness, kidney failure and amputation. In addition, long-term effects of episodes of low blood sugar (hypoglycemia) include weight gain, increased risk of cardiovascular disease, reduced mental function and dementia. These life-limiting complications also add to the substantial burden on the healthcare economy represented by diabetes.

Hypoglycemia is one of the most frequent adverse events experienced by insulin users and all types of hypoglycemia, at any time of the day or night, are inconvenient, frightening and important to address.

Despite escalating regimens of medications, many patients may eventually require insulin therapy to achieve adequate glycemic control. However, in diabetes management insulin initiation is often delayed and, despite proven efficacy, insulin has been resisted by patients and physicians partly due to the fear of hypoglycemia and weight gain. Hypoglycemia, and fear of it, can restrict titration insulin dose and could lead to early discontinuation of therapy.

Toujeo®
Toujeo® is a next-generation basal insulin that offers a steady and prolonged activity profile that lasts a full 24 hours and beyond compared with Lantus®, with low within-individual, within-day blood sugar variability, in pharmacokinetic and pharmacodynamic studies. Toujeo® shows proven HbA1c control with a well-tolerated titration-to-target by reducing low blood sugar events, particularly during the first 8-week initiation phase, but also, in people with type 2 diabetes, during the maintenance phase (weeks 9 to 26) and, when needed by the patient, an occasional 3-hour flexibility in dosing regimen.

Pharmacokinetic and pharmacodynamic (PK/PD) studies
PK/PD studies aim to understand the biochemical and physiological effects of a drug on the body; the mechanism(s) of action of the drug; and the relationship between drug concentration and its effects. PK/PD studies have demonstrated a steady and prolonged activity profile for Toujeo® that lasts a full 24 hours and beyond compared with Lantus®, with 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 similar overall blood sugar control compared with Lantus®, but with a more stable 24-hour blood sugar profile.
• **Toujeo** reduces low blood sugar events throughout the day, including the night-time (EDITION I–III meta-analysis).21
• In all EDITION studies, Toujeo® demonstrated weight neutrality vs. baseline (less than 1kg weight gain).13–18,23,24
• In type 1 diabetes, Toujeo® demonstrated minimal glycemic variability.25
• Similar safety profile with Toujeo® compared with Lantus® demonstrated in the EDITION studies.13–18
• Toujeo® has been approved by the U.S. Food and Drug Administration, the European Commission and Health Canada. Toujeo® was launched in the U.S. in March 2015 and Germany in May 2015. Further regulatory decisions and product launches are anticipated throughout 2015.

**Toujeo® demonstrates comparable blood sugar control compared with Lantus®**

The EDITION program is a worldwide and extensive series of six Phase III studies (4 global and 2 Japanese studies) demonstrating the efficacy and safety of Toujeo® in broad and diverse populations of people with diabetes, in comparison to Lantus®.

**Lower risk of hypoglycemia with Toujeo® compared with Lantus® in type 2 diabetes**

In people experiencing challenges in managing their type 2 diabetes, EDITION I (basal plus mealtime insulin) and EDITION II (basal insulin plus oral glucose-lowering agents [except sulfonylureas]) demonstrated that significantly fewer patients experienced severe or confirmed (≤70 mg/dL [3.9 mmol/L] night-time low blood sugar from week 9 to month 6 (EDITION I: 21% fewer patients, p=0.0045; EDITION II: 23% fewer patients, p=0.038),13,14 which was maintained at one year (from baseline to month 12–15% fewer patients for EDITION I: relative risk [RR] 0.84 [95% CI: 0.75 to 0.94]; and 16% fewer for EDITION II: RR 0.84 [0.71 to 0.99]).19,20

EDITION III included people with less severely progressed type 2 diabetes (those who were new to basal insulin therapy, also treated with oral glucose-lowering agents [except sulfonylureas] and/or GLP-1 receptor agonists). Results showed similar numbers of people in the Toujeo® and Lantus® groups experienced severe or confirmed low blood sugar events during the night from week 9 to month 6 (RR 0.90 [95% CI 0.67 to 1.22]).15 Significantly fewer people experienced severe or confirmed (≤70 mg/dL [3.9 mmol/L]) low blood sugar events during the night over the six-month study period (post-hoc analysis) when treated with Toujeo®, compared with Lantus® (relative risk reduction of 24%, RR 0.76 [95% CI 0.59 to 0.99]).

In a pooled analysis of EDITION I–III, Toujeo® consistently showed significantly fewer severe or confirmed (≤70 mg/dL [3.9 mmol/L]) low blood sugar events at any time of day, including night-time events, over the six-month study period compared with Lantus® across studies and differing type 2 patient populations (rate ratio [per participant-year] reduced by 14% 0.86 [95% CI: 0.77 to 0.97] at any time of day; reduced by 31% 0.69 [95% CI: 0.57 to 0.84] at night-time).21 This effect was already seen during the first eight weeks of the studies, when most of the insulin dose changes occurred (see below).

In addition, the relative risks of experiencing ≥1 severe or confirmed (≤70 mg/dL [3.9 mmol/L]) low blood sugar event at any time of day (-9% RR 0.91 [95% CI: 0.87 to 0.96]) and during the night (-25% RR 0.75 [95% CI: 0.68 to 0.83]) were also reduced with Toujeo® compared with Lantus®.21

In Japanese people with type 2 diabetes uncontrolled on basal insulin and oral glucose-lowering agents (EDITION JP II), incidence of severe or confirmed (≤70 mg/dL [3.9 mmol/L]) low blood sugar events at night-time was also reduced, with 38% fewer patients experiencing ≥1 event over the 6-month study period (RR 0.62 [95% CI: 0.44 to 0.88]).18

**Reduction in hypoglycemic events with Toujeo® in type 1 diabetes**

EDITION IV (basal plus mealtime insulin), an international study of people with type 1 diabetes, showed that those randomized to Toujeo® experienced similar night-time and any time of the day low blood sugar event rates compared with Lantus®. EDITION IV also investigated the timing of administration of Toujeo® vs. Lantus® by comparing outcomes in people with diabetes that injected their basal insulin either in the morning or in the evening.
Meta-analysis 1-year data

An updated meta-analysis including one-year data from the EDITION I, II and III studies in people with type 2 diabetes showed a more sustained reduction in blood sugar for Toujeo® (insulin glargine [rDNA origin] injection, 300 U/mL) compared with Lantus®. Toujeo® also demonstrated a reduced risk of hypoglycemia at any time of day and at night, in addition to a beneficial effect on weight gain.$^37$

EDITION I, II and III assessed Toujeo® versus Lantus® in a diverse population of people with type 2 diabetes. A patient-level meta-analysis of one-year data was conducted. Blood sugar control was sustained in both groups, with more sustained HbA1c reduction for Toujeo® at one year (LS mean difference [95% confidence interval (CI)] between groups in HbA1c change from baseline -0.10 [-0.18 to -0.02]; p=0.0174). There was a reduced risk of confirmed (≤70 mg/dL) or severe hypoglycemia at any time (24 hours) (percentage of people ≥1 event, relative risk [95% CI] 0.94 [0.90 to 0.98]) and during the night (RR 0.85 [0.77 to 0.92]) versus Lantus®.

Weight neutrality with Toujeo®

In all EDITION studies, Toujeo® demonstrated weight neutrality vs. baseline (less than 1 kg gain after 6 months).$^{13–18}$ In EDITION I and III, weight gain was similar between Toujeo® and Lantus® (EDITION I: increased by 0.9 kg in both groups;$^{15}$ EDITION III: difference at month 6: -0.22 kg; p=0.378).$^{35}$ Furthermore, weight gain was significantly less with Toujeo® treatment compared with Lantus® treatment in EDITION II (difference in weight gain at month 6: -0.58 kg; p=0.015);$^{14}$ EDITION IV (difference at month 6: -0.56 kg, p=0.037)$^{16}$ and EDITION JP I (difference at month 6: -0.6 kg; p=0.0347).$^{24}$ In EDITION JP II, the patients treated with Toujeo® lost weight, compared with a slight increase in the Lantus® group (-0.6 kg vs. 0.4 kg respectively; difference at month 6: -1.0 kg; p=0.0003).$^{36}$

Potential improved safety profile supporting titration-to-target

In type 2 diabetes people, in addition to reduced night-time low blood sugar events during the maintenance phase (month 3–6), Toujeo® has also demonstrated reduced night-time low blood sugar events during the first eight weeks of treatment (post-hoc analysis), potentially offering safer titration-to-target compared with Lantus®.$^{16,17,22}$

In EDITION I and II, the incidence of any severe or confirmed night-time low blood sugar event (% of people with at least one event) was lower for Toujeo® during the first eight weeks, when most of the insulin dose changes occurred, compared with the Lantus® group (EDITION I: RR 0.79 [0.64 to 0.98]; EDITION II: RR 0.53 [0.39 to 0.72]).$^{13,14}$

In a pooled analysis of EDITION I–III, a more pronounced, significant reduction in the percentage of participants experiencing ≥1 low blood sugar event was observed during the first eight weeks (when most of the insulin dose changes occurred; -17% at any time of the day and -31% during the night) when comparing Toujeo® with Lantus® (post-hoc analysis).$^{32}$

EDITION I and II also showed a reduction in the incidence of any severe or confirmed low blood sugar event, including symptomatic at any time of the day (over a 24 hour period) over the 6-month treatment period (EDITION I: RR 0.93 [0.88 to 0.99]; EDITION II: RR 0.90 [0.83 to 0.98]), particularly during the first eight weeks (EDITION I: RR 0.86 [0.78 to 0.94]; EDITION II: RR 0.78 [0.69 to 0.89]).$^{13,14}$
Over the 12-month study period, in Japanese people with type 1 and type 2 diabetes respectively, Toujeo® (insulin glargine [rDNA origin] injection, 300 U/mL) maintained similar blood sugar control, with fewer people experiencing night-time low blood sugar events (blood sugar levels ≤ 54 mg/dL in the study with people with type 1 diabetes, and ≤ 70 mg/dL in the study with people with type 2 people), compared with Lantus®.

In Japanese people with uncontrolled type 1 diabetes (EDITION JP 1), confirmed night-time low blood sugar (≤70 mg/dL) event rates and percentage of participants experiencing ≥1 event over the 12-month study period were comparable in both groups. However, hypoglycemic events at the lower threshold (<54 mg/dL) were 38% lower with Toujeo®. Risk reduction of nighttime low blood sugar events compared with Lantus® at this threshold showed that 21% fewer patients experienced nighttime low blood sugar events with Toujeo®.

In Japanese people with type 2 diabetes uncontrolled on basal insulin and oral anti-diabetics (EDITION JP 2), incidence of low blood sugar events at nighttime (blood sugar levels ≤ 70mg/dL) was also reduced (27% fewer patients experiencing ≥1 event over 12-month study period). Event rates (per patient-year) of low blood sugar at night-time were consistently lower with Toujeo® compared with Lantus® over 12-month study period with 59% fewer severe hypoglycemic events. Over the course of the study, people with type 2 diabetes treated with Toujeo® also saw a reduction in weight, in comparison to those treated with Lantus® who saw a slight increase.

Minimal glycemic variability with Toujeo®

In a PK/PD study including 50 people with type 1 diabetes, Toujeo® demonstrated low within-day fluctuation of blood sugar levels and high between-day reproducibility in terms of exposure and activity of Toujeo®, when using therapeutic doses.

Toujeo® regulatory decisions and launches

Toujeo® has been approved by the U.S. Food and Drug Administration (FDA), the European Commission and Health Canada, and is under review by other regulatory authorities around the world.

Toujeo® was launched in the U.S. in March 2015 and Germany in May 2015. Further regulatory decisions and product launches are anticipated throughout 2015.