Toujeo®
insulin glargine 300U/mL

InRange: comparison of the second-generation basal insulin analogues glargine 300 U/mL and degludec 100 U/mL in persons with type 1 diabetes using continuous glucose monitoring

Toujeo® (insulin glargine) is a long-acting, second-generation, basal insulin indicated for the treatment of diabetes mellitus in adults, adolescents and children from the age of six years.[1]

Key takeaway

In adults with type 1 diabetes mellitus (T1DM), Toujeo® demonstrated noninferiority with respect to insulin degludec 100 U/mL for percentage Time-In-Range at 12 weeks.[2]

Background

The InRange clinical trial is the first study to use Time-In-Range (TIR) as the primary endpoint, measured by continuous glucose monitoring (CGM), to compare the second-generation basal insulin analogues Toujeo® and insulin degludec 100 U/mL in adults with T1DM.[3]

Why this matters

Historically, HbA_{1c} is used as a metric to monitor blood glucose in those with T1DM, and studies show that a target of 7% is important in reducing long-term microvascular risks of diabetes. However, hypoglycaemia and the fear it causes remain barriers to maintaining low blood glucose levels and many people with T1DM struggle to achieve this recommended target.[3] In recent years, CGM has become more commonly used as it allows measurements every 5–15 minutes. This means data can be used in real time to immediately guide lifestyle and therapeutic decisions, helping to improve glycaemic control.[3]

A key metric obtained by CGM is TIR, defined as the time spent within the target glucose range of 3.9 to 10 mmol/L. TIR profiles can be used to determine the frequency of glycaemic excursions and can help healthcare professionals to establish personalised glycaemic targets.[3]

sanofi

MAT-IE-2200283 (v2.0) | November 2022

Ambulatory glucose profile

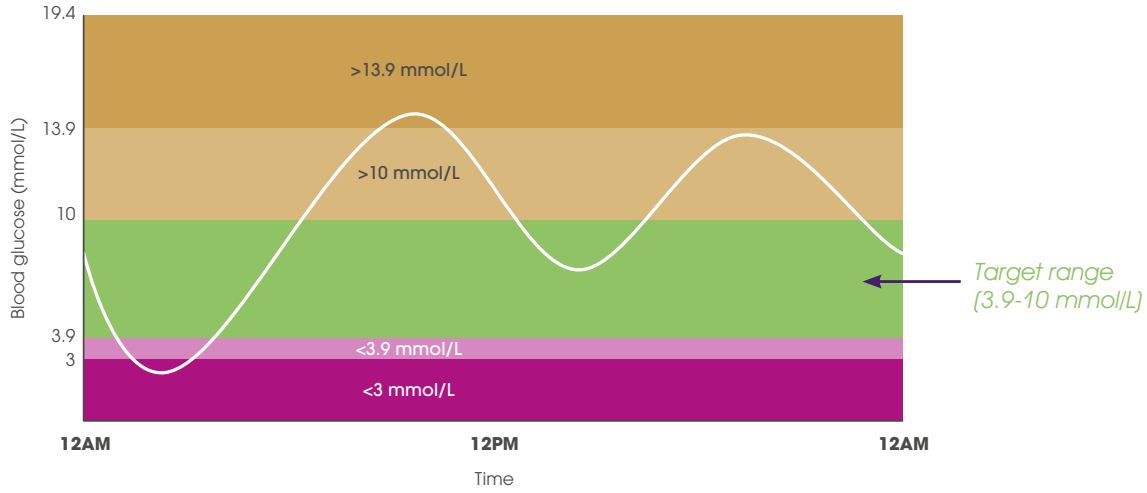


Image adapted from Battelino T, et al. 2019.[4]

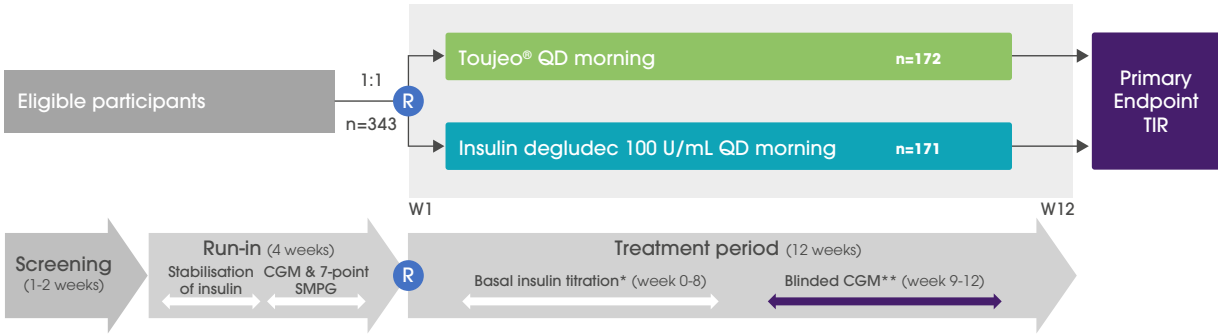
Study aims and design

Study objective

To demonstrate that Toujeo® is noninferior to insulin degludec 100 U/mL in terms of glycaemic control, measured by TIR and variability, as assessed using CGM, in adults with T1DM.[3]

Study design

A multicentre, randomised, active-controlled, parallel-group, 12-week, open-label, Phase IV study collected blinded CGM data over 20 consecutive days from adults with T1DM. Participants were randomised to receive Toujeo® or insulin degludec 100 U/mL once per day.[3]



CGM: continuous glucose monitoring; QD: daily; SMPG: self-measured plasma glucose; TIR: Time-in-Range.

*Basal insulin dose titrated at least weekly (but no more often than every three days) until participants achieve the target fasting self-measured plasma glucose (SMPG) of ≥3.9 to <5.6 mmol/L while avoiding hypoglycaemia episodes; **Over 20 consecutive days during weeks 9–12.

Image adapted from Battelino T, et al. 2020.[3]

Eligibility criteria included:[3]

- Adults with T1DM aged 18–70
- HbA_{1c} ≥7% to ≤10%
- Multiple daily injection (MDI) regime with any once-daily basal insulin and rapid acting analogues for at least one year
- No Toujeo® or insulin degludec 100 U/mL in the last 30 days

It is important to note that blinded CGM allows the capture of CGM parameters without the participant's behaviour being influenced by their own CGM-derived glucose readings. This is particularly relevant in open-label treatment trials where knowledge of both the treatment and the measured outcome could lead to bias in the results.[5] CGM data did not guide insulin titration. Instead, basal insulin was titrated to achieve the target fasting SMPG of ≥3.9 to <5.6 mmol/L while avoiding hypoglycaemic episodes.[3]

Study endpoints

Primary endpoint:

To demonstrate that Toujeo® is noninferior to insulin degludec 100 U/mL measured by time spent in the glucose range of 3.9 to 10 mmol/L at Week 12, assessed using 20 days of blinded CGM data generated during the randomised period.[3]

Main secondary endpoints:

- Noninferiority of Toujeo® with respect to insulin degludec 100 U/mL for glucose total coefficient of variability (CV) at Week 12.[3]
- Superiority of Toujeo® with respect to insulin degludec 100 U/mL for percentage TIR at Week 12.[3]

Other secondary endpoints:

- Glucose within-day and between-day CV at Week 12.[3]
- Change from baseline to Week 12 in HbA_{1c} and central laboratory fasting plasma glucose.[3]
- Percentage time and mean hours per day spent in target range (anytime and during the night (00:00 to 05:59 hours)).[3]

Safety endpoints:

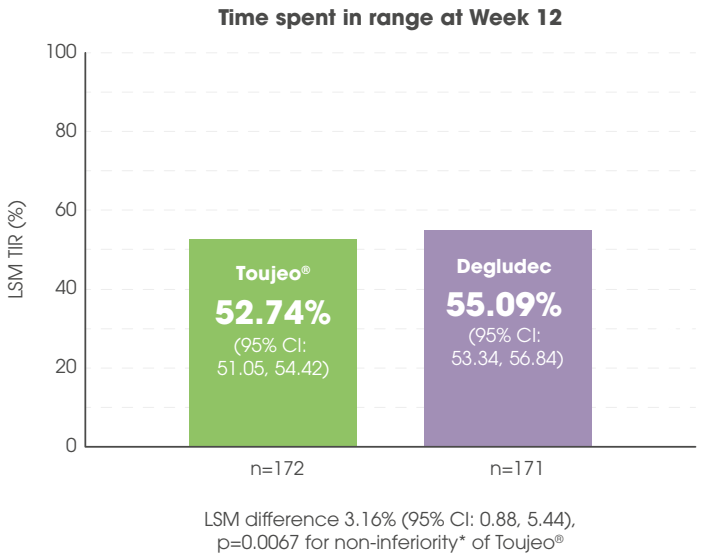
- Number of patients with adverse events (AEs).[3]
- Number of patients with ≥1 hypoglycaemic event from baseline to Week 12.[3]
- Number of hypoglycaemic events per participant-year from baseline to Week 12.[3]

A hierarchical step-down testing procedure has been applied to the primary efficacy endpoint (noninferiority for percentage TIR) and main secondary endpoints (noninferiority (10% margin) for glucose total CV, and superiority for percentage TIR) to control for type I error. For other secondary endpoints and other efficacy variables, no multiplicity adjustments have been made, and any 95% CI and p values have been presented for descriptive purposes only.[3]

Key findings

Primary endpoint

Toujeo® demonstrated noninferiority with respect to insulin degludec 100 U/mL for percentage TIR. Both treatments led to similar results of 52.74% and 55.09%, respectively (p=0.0067 for noninferiority of Toujeo®).[2]



CI: confidence interval; Degludec: insulin degludec 100 U/mL; LSM: least squares mean; TIR: Time-in-Range.

*Non-inferiority was assessed in the intent-to-treat population (ITT). Non-inferiority of the primary endpoint was demonstrated if the lower bound of the two-sided 95% CI of the adjusted difference estimate for $m_1 - 0.9*m_0$ (where m_1 and m_0 are the true means for Toujeo® and degludec groups respectively) was greater than 0.

Image adapted from Battelino T, et al. 2022.[2]

Main secondary endpoints

The first main secondary endpoint was met. **Toujeo® demonstrated noninferiority for glucose total CV** at Week 12 with respect to insulin degludec 100 U/mL.[2]

	Toujeo®	Degludec
LS mean (95% CI)	**39.91%** (39.20, 40.61)	**41.22%** (40.49, 41.95)
Non-inferiority LS mean difference (95% CI)	**-5.44%** (-6.50, -4.38) p< 0.0001	

Degludec: insulin degludec 100 U/mL; LS: least squares; TIR: Time-in-Range.

Image adapted from Battelino T, et al. 2022.[2]

Main secondary endpoints

The second main secondary endpoint, superiority of Toujeo® for percentage TIR at Week 12 with respect to insulin degludec 100 U/mL, was **not demonstrated** (LSM difference -2.35% (-4.75, 0.05), p=0.0548).[2]

Safety endpoints

Overall safety and tolerability profiles were consistent with the known safety profile of each product and there were no unexpected safety findings.[2]

Treatment emergent adverse events

n (%)	Toujeo® (n=172)	Degludec (n=171)
Patients with any TEAE	50 (29.1)	35 (20.5)
Patients with any treatment emergent SAE	7 (4.1)	8 (4.7)

Degludec: insulin degludec 100 U/mL; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Table adapted from Battelino T, et al. 2022.[2]

Rates (events per patient-year) and incidence of anytime hypoglycaemia were comparable between each group.[2]

Comparable rates of anytime documented hypoglycaemia (24 h)

	Toujeo® (n=172)	Degludec (n=171)	RR (95%CI)
<3.9 mmol/L and ≥3 mmol/L	74.4	82.8	**0.90 (0.77, 1.05)**
<3 mmol/L	30.3	27.5	**1.10 (0.89, 1.37)**

Comparable incidences of anytime documented hypoglycaemia (24 h)

	Toujeo® (n=172)	Degludec (n=171)	OR (95%CI)
<3.9 mmol/L and ≥3 mmol/L	95.3%	95.3%	**1.01 (0.37, 2.74)**
<3 mmol/L	83.1%	86.0%	**0.80 (0.45, 1.45)**

CI: confidence interval; Degludec: insulin degludec 100 U/mL; OR: odds ratio; RR: rate ratio.

Tables adapted from Battelino T, et al. 2022.[2]

Study limitations

Blinded CGM methodology may not reflect real life use of CGM technology and may not capture the additional benefit of CGM as an intervention.[6]

Conclusions

- InRange is the first clinical trial to use TIR as a primary endpoint to compare the second-generation insulin analogues Toujeo® and insulin degludec 100 U/mL.[3]
- Toujeo® demonstrated noninferiority to insulin degludec 100 U/mL for percentage TIR and percentage CV at Week 12.[2]
- Superiority of Toujeo® vs insulin degludec 100 U/mL was not demonstrated for TIR.[2]
- Overall safety and tolerability profiles were consistent with the known safety profile of each product.[2]

References

1. Toujeo 300 units/ml DoubleStar, solution for injection in a pre-filled pen. Summary of Product Characteristics. January 2021.
2. Battelino et al., CGM-based Time-in-Range Using Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Type 1 Diabetes: The Head-to-Head Randomized Controlled InRange Trial. Diabetes Obes Metab. (2022) doi: 10.1111/dom.14898
3. Battelino T, Bosnyak Z, Danne T, et al. InRange: comparison of the second-generation basal insulin analogues glargine 300 U/mL and degludec 100 U/mL in persons with type 1 diabetes using continuous glucose monitoring – study design. Diabetes Ther. 2020;11:1017–1027.
4. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593–1603.
5. Muchmore D, Sharp M & Vaughn D. Benefits of blinded continuous glucose monitoring during a randomised clinical trial. J Diabet Sci Tech. 2011;5:676–680.
6. Ahn D, Pettus J & Edelman S. Unblinded CGM should replace blinded CGM in the clinical management of diabetes. J Diabet Sci Tech. 2016;10:793–798.

Prescribing Information

Prescribing Information: Toujeo® (insulin glargine 300 units/ml)

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Toujeo SoloStar and DoubleStar pre-filled pens. Each ml contains 300 units of insulin glargine. SoloStar pen contains 1.5ml (450 units) of solution for injection. DoubleStar pen contains 3ml (900 units) of solution for injection. **Indication:** Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years. **Dosage and Administration:** Toujeo is administered subcutaneously, by injection into the abdominal wall, the deltoid or the thigh, once daily, at any time of the day, preferably at the same time every day. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. The dose regimen (dose and timing) should be adjusted according to individual response. Do not administer intravenously. In type 1 diabetes mellitus, Toujeo must be combined with short-/rapidacting insulin to cover mealtime insulin requirements. In patients with type 2 diabetes mellitus, recommended daily starting dose is 0.2 units/kg followed by individual dose adjustments. Toujeo can also be given together with other anti-hyperglycaemic medicinal products. *Switch between insulin glargine 100 units/ml and Toujeo:* Insulin glargine 100 units/ml and Toujeo are not bioequivalent and are not directly interchangeable. When switching from insulin glargine 100 units/ml to Toujeo, this can be done on a unit-to-unit basis, but a higher Toujeo dose (approximately 10-18%) may be needed to achieve target ranges for plasma glucose levels. When switching from Toujeo to insulin glargine 100 units/ml, the dose should be reduced (approximately by 20%). *Switching from other basal insulins to Toujeo:* A change of dose and/or timing of the basal insulin and concomitant anti-hyperglycaemic treatment may be required. Dose adjustments may also be required if the patient's weight or lifestyle changes, the timing of insulin dose is changed, or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia. Toujeo must not be mixed or diluted with any other insulin or other medicinal products. Close metabolic monitoring is recommended during a switch and in the initial weeks thereafter. SoloStar 1-80 units per single injection in steps of 1 unit and DoubleStar 2-160 units in steps of 2 units. When changing from Toujeo SoloStar to Toujeo DoubleStar, if the patient's previous dose was an odd number, then the dose must be increased or decreased by 1 unit. Toujeo DoubleStar prefilled pen is recommended for patients requiring at least 20 units per day. **Special Populations:** Insulin requirements may be diminished in the elderly or patients with renal or hepatic impairment. *Paediatric:* When switching basal insulin to Toujeo, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia. The safety and efficacy of Toujeo in children and adolescents below 6 years of age have not been established. **Contraindications:** Hypersensitivity to insulin glargine or any excipients. **Precautions and Warnings:** *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Toujeo is not the insulin of choice for treatment of diabetic ketoacidosis. Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered. *Hypoglycaemia:* In case of insufficient glucose control or a tendency to hyper/hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered. Particular caution should be exercised, and intensified blood glucose monitoring is advisable for patients in whom hypoglycaemic episodes might be of clinical relevance and in those where dose adjustments may be required. Warning signs of hypoglycaemia may be changed, less pronounced or absent in certain risk groups, potentially resulting in severe hypoglycaemia and loss of consciousness. Risk groups include patients in whom glycaemic control is markedly improved, hypoglycaemia develops gradually, an autonomic neuropathy is present, or who are elderly. The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia. *Intercurrent illness:* Requires intensified metabolic monitoring and often it is necessary to adjust the insulin dose. *Insulin antibodies:* administration may cause insulin antibodies to form. *Use with pioglitazone:* Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. *Medication errors:* Insulin labels must always be checked before each injection to avoid errors between Toujeo and other insulins. Patients must be instructed to never use a syringe to remove Toujeo from the SoloStar or DoubleStar prefilled pen, A new sterile needle must be attached before each injection. Needles must not be re-used. *Pregnancy and lactation:* There are no data from exposed pregnancies in controlled clinical trials. However, there is a large amount of data on use of insulin glargine 100 units/ml in pregnant women indicating no specific adverse effects on pregnancy and no specific malformative nor feto/neonatal toxicity. The use of Toujeo may be considered during pregnancy, if clinically needed. Careful monitoring of glucose control is essential. It is unknown if insulin glargine is excreted in breast milk. **Interactions:** Substances that affect glucose metabolism may require adjustment of insulin glargine. **Adverse Reactions:** *Very common:* Hypoglycaemia. Prolonged or severe hypoglycaemia may be life-threatening. *Common:* Lipohypertrophy, injection site reactions, including redness, pain, itching, hives, swelling, or inflammation. *Prescribers should consult the SmPC in relation to other adverse reactions.* **Legal Category:** POM. **Marketing Authorisation Number:** SoloStar 5 pen pack: EU/1/00/133/035; DoubleStar 5 pen pack: EU/1/00/133/038. **Marketing Authorisation Holder:** Sanofi Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany. **Further information is available from:** Medical Information, Sanofi, 18 Riverwalk, Citywest Business Campus, Dublin 24 or contact IEmedinfo@sanofi.com.

Date of preparation: July 2022. MAT-IE-2200355 (V1.0)

Adverse events should be reported. Reporting forms and information can be found at **www.hpra.ie**; email: **medsafety@hpra.ie** Adverse events should also be reported to Sanofi Ireland Ltd. Tel: 01 403 5600. Alternatively, send via email to **IEPharmacovigilance@sanofi.com**