InRange

Toujeo®
insulin glargine 300U/mL

It’s Time to discover
the InRange study results

InRange
NOW PUBLISHED
Jan 2023

First randomized controlled trial to compare 2nd-generation basal insulin analogues, Toujeo® and degludec 100 U/mL, in people with T1DM, using Time-in Range as the primary endpoint

For the treatment of Type 1 and Type 2 diabetes mellitus from the age of 6 years*[1]

Toujeo® is contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

The most common adverse events observed with Toujeo® are hypoglycemia, lipohypertrophy and injection site reactions.
Before prescribing the product always refer to the prescribing information in your country.
*Safety and efficacy in patients <6 years have not been established.
Degludec 100 U/mL, insulin degludec 100 U/mL; T1DM, type 1 diabetes mellitus.

sanofi

MAT-SE-2300047 v.1.0 DATE OF APPROVAL: January 2023

Beyond HbA_{1c}, glycemic variability and Time-in-Range are key metrics that are increasingly being used to support effective diabetes management

International guidelines recommend Time-in-Range and glycemic variability as key metrics to facilitate effective diabetes management[2,3]

> ***The consensus panel identified "time in range" as a metric of glycemic control that provides more actionable information than A1C alone[2]***
>
> Recommendations of the International Consensus on Time-in-Range, 2019

Glycemic variability is a common challenge for people with diabetes[4,5]

~56%

of people with T1DM were found to have excess GV (%CV of >36%)[4*]

~9 h/day

are spent outside target range† for an average person with T1DM[5]

Suboptimal Time-in-Range and excessive glycemic variability can have substantial negative impact on the lives of people with diabetes

Each 10% drop in TIR was associated with increased frequency of:

Different Studies

Retinopathy[6‡]	Microalbuminuria[6‡]	Neuropathy[7§]	Mortality[8¥]
+64% increased risk of retinopathy	**+40%** increased risk of microalbuminuria	**+25%** increased risk of peripheral neuropathy	**+5%** increased risk of CV mortality
In people with T1DM	In people with T1DM	In people with T2DM and CKD	**+8%** increased risk of all-cause mortality
			In people with T2DM

Time-in-Range and glycemic variability metrics have been linked to **emotions and overall mood[9-11]**

Fatigue ● Irritability ● Frustration

54%

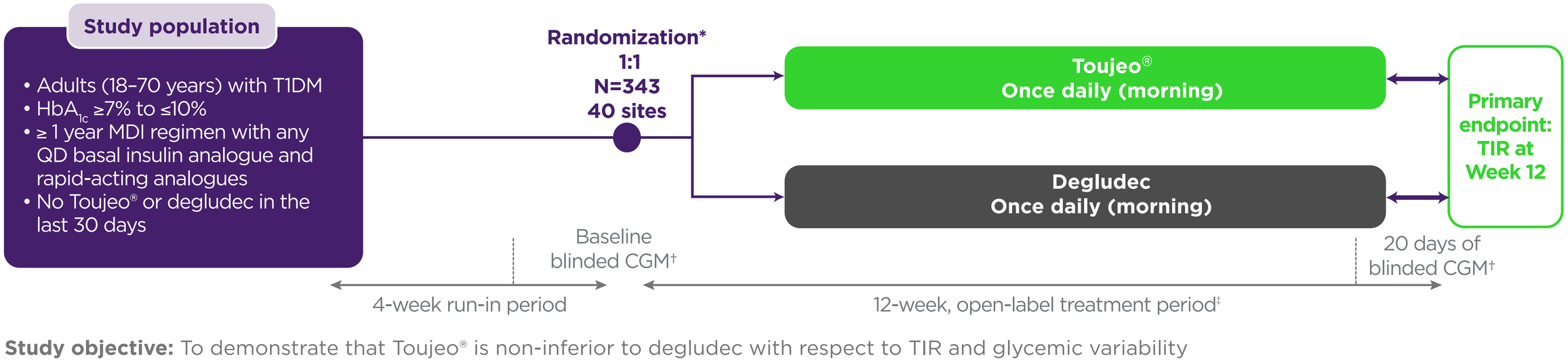
of people with T1DM ranked TIR as the **highest driver of a positive mindset[12¶]**

*Retrospective observational study of 376 persons with diabetes, 122 of whom had T1DM, and 79 had T2DM and were receiving insulin treatment. Subjects underwent CGM at the University Hospital of Montpellier between 2003 and 2012. %CV = [(SD of glucose)/(mean glucose)] x 100).[4] †In hyper- or hypoglycemia.[5] ‡Post hoc analysis using the DCCT dataset to evaluate the association of TIR of 70–180 mg/dL (3.9–10 mmol/L) with the development or progression of retinopathy and microalbuminuria to validate TIR as a metric. Criteria for the retinopathy outcome were met by n=271/1,440 (19%), and for the microalbuminuria outcome were met by n=116/1,283 (9%). Mean TIR for 7-point profiles for 1,440 people was 41 ± 16%.[6] §Data from a prospective observational cohort study which evaluated the association of TIR of 70–180 mg/dL (3.9–10 mmol/L) with microvascular diabetes outcomes, including peripheral neuropathy; 62 out of 105 participants with a total MNSI questionnaire score ≥2 were defined as having distal peripheral neuropathy.[7] ¥Prospective cohort study evaluating the link between TIR of 70–180 mg/dL (3.9–10 mmol/L) with all-cause and cardiovascular mortality, with the objective of validating TIR as surrogate marker of long-term adverse clinical outcomes.[8] ¶Online survey of 3,461 people with T1DM (n=1,026) or T2DM (n=1,154 on insulin; n=1,281 not on insulin). Respondents were presented with 25 questions. TIR emerged as the highest driver of a positive mindset.[12]

An innovative and robustly designed trial, providing new invaluable evidence for the management of T1DM using Time-in-Range

Robust study design

InRange is a robustly designed multi-center, randomized, active-controlled, parallel-group, 12-week, open-label phase 4 study[13-15]



Study objective: To demonstrate that Toujeo® is non-inferior to degludec with respect to TIR and glycemic variability

Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

Innovative trial approach

InRange is the first RCT to compare 2nd-generation basal insulin analogues **Toujeo® and degludec** in people with T1DM, **using Time-in-Range**, measured by CGM, **as the primary endpoint[13,14]**

Primary endpoint at Week 12

Percentage Time-in-Range ≥70 to ≤180 mg/dL (≥ 3.9 to ≤10 mmol/L)[15§]

Secondary endpoints

Main secondary endpoint: Glucose total coefficient of variation at Week 12[15]
Other secondary endpoints: Change from baseline to Week 12 in HbA_{1c}; percentage Time-above-Range; percentage Time-below-Range; within-day and between-day glucose coefficient of variation[15]

Safety endpoints

Incidence and event rates of hypoglycemia reported by the participant and based on SMPG readings from a glucometer;¥ incidence of adverse events; and daily insulin dose, assessed as an exploratory endpoint in the safety population[15]

*To be eligible for randomization, a minimum of 10 days (not necessarily consecutive) of useable CGM data generated during the run-in period was required. Randomization stratified by screening HbA_{1c} values of <8.0 vs ≥8.0%.[13,14] †Baseline CGM data collection was started in week -3 and stopped at randomization visit. CGM device was given to participants in week 9 and endpoint CGM data was collected over 20 consecutive days during weeks 10 to 12.[13-15] ‡The 12-week randomized treatment period included an insulin titration period (expected to be up to week 8). During this titration period, Toujeo® and degludec were titrated until participants achieved the target fasting SMPG of ≥70 to <100 mg/dL (≥3.9 to <5.6 mmol/L) while avoiding hypoglycemia. Initiation doses of Toujeo® and degludec corresponded to the previous BI dose.[13-15] §Assessed using blinded CGM.[13,14] ¥As a post hoc analysis, rates of hypoglycemia were also analyzed using CGM data.[15]

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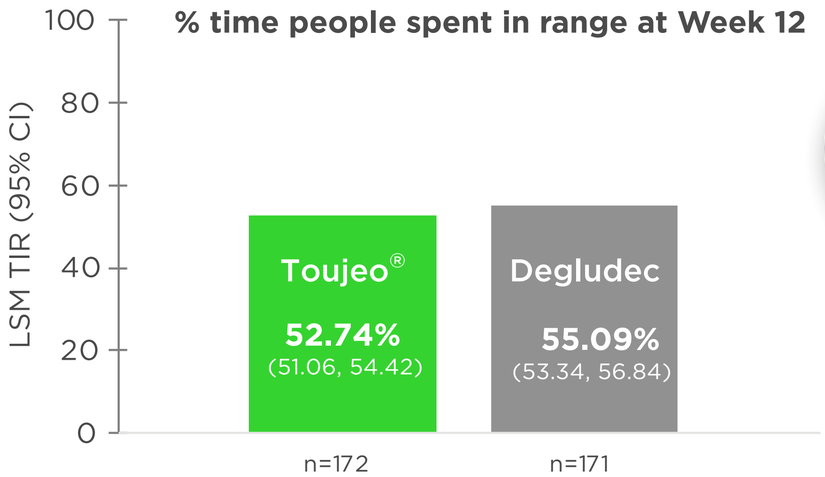
Toujeo® *vs* degludec 100 U/mL in T1DM:

Primary endpoint met

Main secondary endpoint met

Comparable Time-in-Range[15]

≤180 mg/dL
TIR
≥70 mg/dL



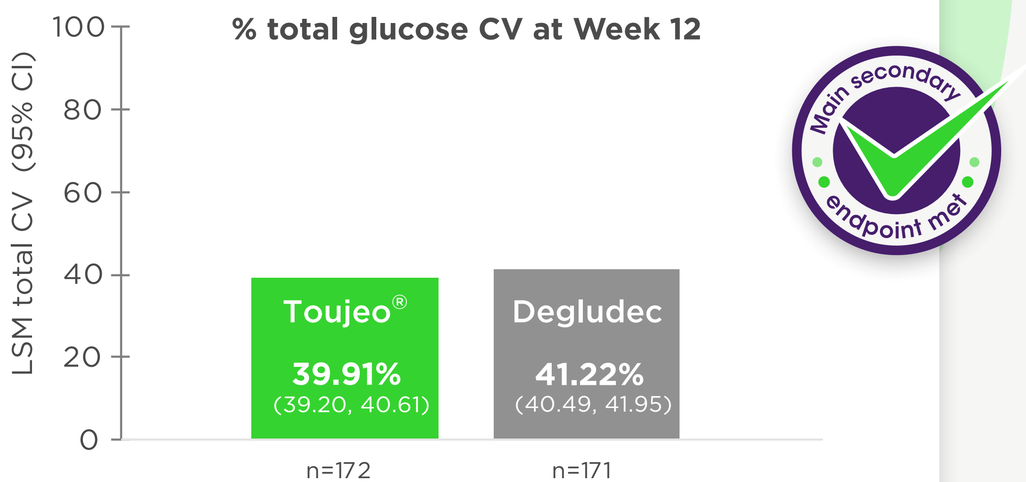
Primary endpoint met

LSM difference 3.16% (95% CI: 0.88, 5.44)
P=0.0067 for non-inferiority* of Toujeo®

With **similar Time-above-Range‡#** and **Time-below-Range§#** at Week 12[15]

Non-inferiority on glycemic variability[15]

Non-inferiority of Toujeo® vs degludec:
LSM difference in total glucose CV at week 12, adjusted for non-inferiority† testing
-5.44% (95% CI: -6.50, -4.38), P< 0.0001



Main secondary endpoint met

Variability difference of Toujeo® vs degludec
LSM difference in total glucose CV at week 12
-1.32% (95%CI: -2.32, -0.31)#

With **similar between-day¥#** and **within-day glycemic variability¶#** at Week 12[15]

To control the type I error, a hierarchical step-down testing procedure was applied for the primary endpoint and the main secondary endpoints. Superiority of Toujeo® with respect to degludec was not demonstrated on the primary efficacy endpoint (LSM difference -2.35% (95% CI: -4.75, 0.05); p= 0.0548).[13-15] Percent TIR and total glucose CV were both analyzed in the ITT population.[13-15] *Non-inferiority of the primary endpoint was demonstrated if the lower bound of the two-sided 95% CI of the adjusted difference estimate for m1 – 0.9*m0 (where m1 and m0 are the true means for Toujeo® and degludec groups respectively) was greater than 0.[13-15] †Non-inferiority of the main secondary endpoint was demonstrated if the upper bound of the two-sided 95% CI of the adjusted difference estimate of m1 – 1.1*m0 (m1= true mean of Toujeo® for the glucose total CV and m0= true mean of degludec) at Week 12 was <0.[13-15] #No multiplicity adjustments were made, and the 95% CIs are presented for descriptive purposes only.[15] ‡%TAR >180 mg/dL (>10 mmol/L) at Week 12, LSM: 41.52% with Toujeo® and 38.31% with degludec; LSM difference: 3.21% (95% CI: 0.49, 5.93).[15] §%TBR <70 mg/dL (<3.9 mmol/L) at Week 12: 5.55% with Toujeo® and 6.49% with degludec; LSM difference: -0.95 (95% CI:-1.93, 0.04).[15] ¥Glucose between-day CV: 17.23% with Toujeo® and 18.08% with degludec; LSM difference: -0.85% (95% CI: -1.98, 0.28).[15] ¶Glucose within-day CV at Week 12, LSM: 33.48% with Toujeo® and 34.37% with degludec; LSM difference: -0.89% (95% CI: -1.84, 0.07).[15]

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Toujeo® *vs* degludec 100 U/mL in T1DM:

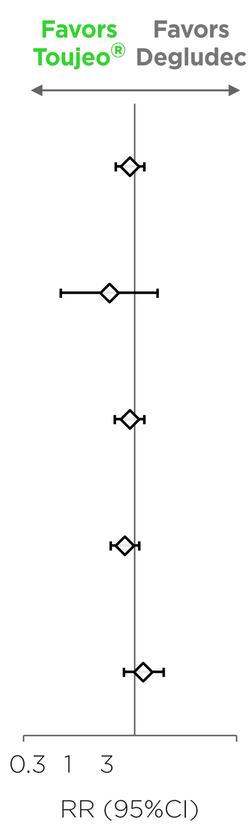
Comparable rates of hypoglycemia captured by SMPG from baseline to Week 12[15]

Comparable incidences of hypoglycemia, captured by SMPG, from baseline to Week 12[15]

Comparable rates of anytime (24 h) hypoglycemia

Event rate, events per patient-week

	Toujeo® N=172*	Degludec N=171*	RR (95%CI)
Any hypoglycemia	2.10	2.20	0.95 (0.82, 1.11)
Severe† hypoglycemia	0.004	0.006	0.76 (0.45, 1.28)
<70 mg/dL	2.01	2.11	0.95 (0.81, 1.11)
<70 mg/dL and ≥ 54 mg/dL (level 1)	1.43	1.59	0.90 (0.77, 1.05)
<54 mg/dL (level 2)	0.58	0.53	1.10 (0.89, 1.37)



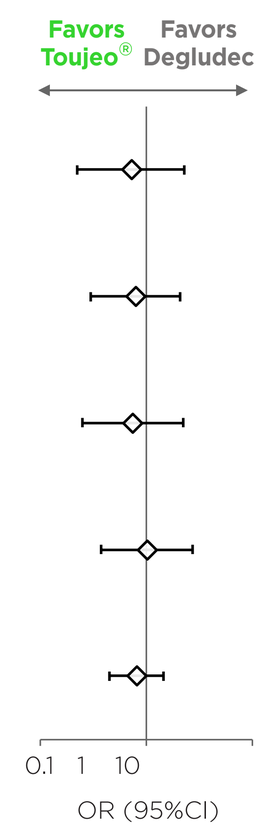
Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

With comparable rates of **nocturnal**‡ and **diurnal**§ **hypoglycemia, across all definitions**

Comparable incidences of anytime (24 h) hypoglycemia

Incidence, %

	Toujeo® N=172	Degludec N=171	OR (95%CI)
Any hypoglycemia	95.9%	97.1%	0.71 (0.22, 2.28)
Severe† hypoglycemia	4.7%	5.8%	0.79 (0.30, 2.05)
<70 mg/dL	95.3%	96.5%	0.74 (0.25, 2.19)
<70 mg/dL and ≥ 54 mg/dL (level 1)	95.3%	95.3%	1.01 (0.37, 2.74)
< 54 mg/dL (level 2)	83.1%	86.0%	0.80 (0.45, 1.45)



Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

With comparable incidences of **nocturnal**‡ and **diurnal**§ **hypoglycemia, across all definitions**

Incidence and event rates of hypoglycemia were assessed in the safety population (all randomized participants who received at least one dose of study drug) and analyzed according to the treatment received.[13-15] *Toujeo®: PW=2099.2, Degludec: PW=2113.8.[15] †Severe hypoglycemia is a level 3 hypoglycemia, as defined by the ADA: a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.[3] ‡00:00 to 05:59 hours[15] (data not shown in this leaflet). §06:00 to 11:59 hours[15] (data not shown in this leaflet).

InRange

Toujeo® *vs* degludec 100 U/mL in T1DM:

Comparable rates of hypoglycemia captured by SMPG were observed during Weeks 10 to 12[15]

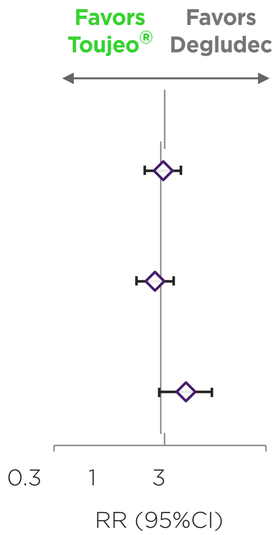
Comparable rates of hypoglycemia captured by CGM were observed during Weeks 10 to 12[15]

Comparable rates of SMPG-captured anytime (24 h) hypoglycemia (Weeks 10-12)

Post hoc analysis

Event rate, events per patient-week

	Toujeo® N=172*	Degludec N=171*	RR (95%CI)
<70 mg/dL	2.53	2.47	1.02 (0.84, 1.24)
<70 mg/dL and ≥ 54 mg/dL (level 1)	1.77	1.89	0.94 (0.77, 1.14)
<54 mg/dL (level 2)	0.76	0.58	1.30 (0.98, 1.73)



Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

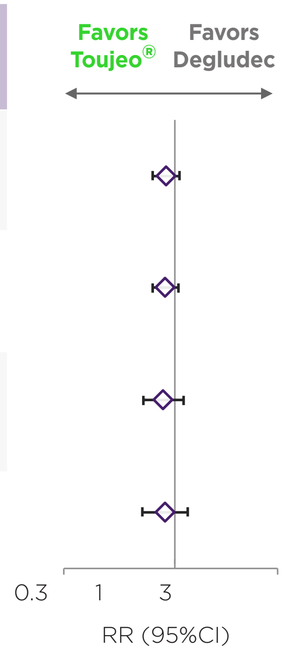
With comparable rates of SMPG-captured **nocturnal**# and **diurnal**** **hypoglycemia**

Comparable rates of CGM-captured anytime (24 h) hypoglycemia (Weeks 10-12)

Post hoc analysis

Event rate, events per patient-week

	Toujeo® N=172†	Degludec N=171†	RR (95%CI)
<70 mg/dL‡	7.34	8.19	0.91 (0.78, 1.05)
<70 mg/dL and ≥ 54 mg/dL§ (level 1)	4.53	5.10	0.90 (0.78, 1.03)
<54 mg/dL¥ (level 2)	2.63	2.86	0.88 (0.71, 1.09)
Prolonged <70 mg/dL¶	1.14	1.25	0.90 (0.70, 1.14)



Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

With comparable rates of CGM-captured **nocturnal**# and **diurnal**** **hypoglycemia**

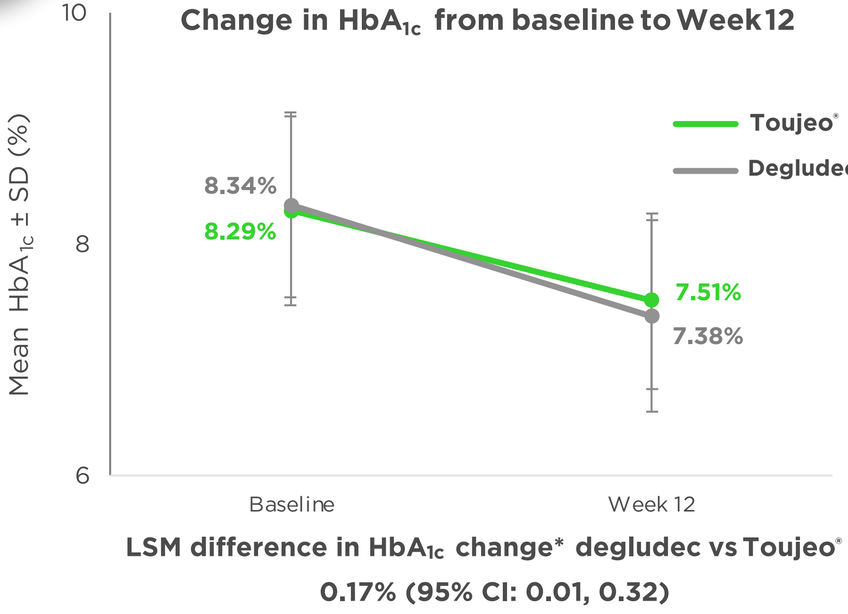
Event rates of hypoglycemia were assessed in the safety population (all randomized participants who received at least one dose of study drug) and analyzed according to the treatment received.[13-15] CGM-captured rates of hypoglycemia were 3–6-fold higher than SMPG-captured rates during the CGM data collection period.[15] *Toujeo®: PW=369.9, Degludec: PW=353.8.[15] †Toujeo®: PW=364.2 Degludec: PW=347.0.[15] ‡CGM: Number of periods with at least 15 minutes with sensor glucose <70 mg/dL. Event ends when glucose returns above 70 mg/dL for at least 15 minutes.[15] §CGM: Number of periods with at least 15 minutes with sensor glucose <70 mg/dL and ≥54 mg/dL (an event <70 mg/dL and ≥ 54 mg/dL was defined as a period < 70 mg/dL without a 15-minute excursion <54 mg/dL before the end of the event). Event ends when glucose returns above 70 mg/dL for at least 15 minutes.[15] ¥CGM: Number of periods with at least 15 minutes with sensor glucose <54 mg/dL. Event ends when glucose returns above 70 mg/dL for at least 15 minutes.[15] ¶Number of periods with at least 120 minutes with sensor glucose <70 mg/dL. Event ends when glucose returns above 70 mg/dL for at least 15 minutes.[15] #00:00 to 05:59 hours[15] (data not shown in this leaflet). **06:00 to 11:59 hours[15] (data not shown in this leaflet).

Toujeo® and degludec 100 U/mL in T1DM:

Additional efficacy data

Additional safety data

Second generation basal insulins brought clinically relevant HbA_{1c} reductions after switch from first generation analogues[15]



Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

Overall safety and tolerability profiles were consistent with the known safety profile of each product[15]

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)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	0
Patients with any treatment-related TEAE	4 (2.3)	7 (4.1)

Adapted from Battelino T, *et al. Diabetes Obes Metab* 2022.

*Changes in HbA_{1c} were analyzed using an ANCOVA model that included the fixed categorical effect of treatment group and the continuous fixed covariate of baseline HbA_{1c}. LSM change of Toujeo® was -0.75% vs -0.92% with degludec.[15] †Number and percentage of patients with at least one TEAE.[15] ‡No unexpected TEAEs were reported.[15]

First randomized controlled trial to compare 2nd-generation basal insulin analogues, Toujeo® and degludec 100 U/mL, in people with T1DM, using Time-in Range as the primary endpoint

InRange

Innovative and robustly designed trial providing new invaluable evidence for the management of T1DM using Time-in-Range

Toujeo® *vs* degludec in T1DM:

Primary endpoint met

Comparable Time-in-Range[15]
Non-inferiority on TIR met

Main secondary endpoint met

Non-inferiority on glycemic variability met[15]

Comparable rates and incidences of hypoglycemia[15]

Overall safety and tolerability profiles consistent with the known safety profile of each product[15]

InRange
NOW PUBLISHED
Jan 2023

A commitment from SANOFI to bring value to the care of people with T1DM

MAT-SE-2300047 v.1.0 January 2023

Abbreviations: ANCOVA, analysis of covariance; **BI**, basal insulin; **CGM,** continuous glucose monitoring; **CI**, confidence interval; **CKD**, chronic kidney disease; **CV,** cardiovascular; **%CV,** percentage coefficient of variation; **DCCT**, Diabetes Control and Complications Trial; **Degludec**, insulin degludec 100 U/mL; **GV**, glycemic variability; **HbA_{1c}**, hemoglobin A_{1c}; **ITT,** intention-to-treat; **LSM**, least squares mean; **MDI**, multiple dose injection; **MNSI**, Michigan Neuropathy Screening Instrument; **OR**, odds ratio; **PW**, patient-week; **QD**, once daily; **RCT,** randomized controlled trial; **RR**, rate ratio; **SAE**, serious adverse event; **SD**, standard deviation; **SMPG**, self-monitored plasma glucose; **T1DM**, type 1 diabetes mellitus; **T2DM**, type 2 diabetes mellitus; **TAR,** time-above-range; **TBR**, time-below-range; **TEAE**, treatment-emergent adverse event; **TIR**, time-in-range.

References: 1. Toujeo, European Summary of Product Characteristics; **2.** Battelino T, et al. Diabetes Care. 2019;42:1593–1603; **3**. ADA. Diabetes Care. 2022;45(Suppl 1); **4.** Monnier L, et al. Diabetes Care. 2017;40:832–838; **5**. Agiostratidou G, et al. Diabetes Care. 2017;40:1622–1630; **6.** Beck RW, et al. Diabetes Care. 2019;42:400–405; **7**. Mayeda L, et al. BMJ Open Diab Res Care. 2020;8:e000991; **8.** Lu J, et al. Diabetes Care. 2021;44:549–555; **9.** 57th EASD Annual Meeting of the European Association for the Study of Diabetes. Diabetologia;64:1–380 (2021)- Momentary assessment of type 1 diabetes patient's experiences in glucose variability and mood in real life (MERITS): first findings; **10**. Polonsky WH and Fortmann AL. J Diabetes Complications. 2020; 34(12):107746; **11**. Penckofer S, et al. Diabetes Technol Ther. 2012; 14(4):303-10; **12**. Runge AS, et al. Clin Diabetes. 2018;36:112–119; **13**. Battelino T, et al. Diabetes Ther 2020;11(4):1017-1027; **14**. Battelino T, et al. Diabetes Ther 2020;11(7):1907-1908; **15**. Battelino T, et al. Diabetes Obes Metab. 2022 Oct 20. doi: 10.1111/dom.14898.

Prescribing information

Toujeo® (insulin glargin), 300 enheter/ml injektionsvätska, lösning. Långverkande insulinanalog. Rx, (F), A10AE04. Indikation: Behandling av diabetes mellitus hos vuxna, ungdomar och barn från 6 års ålder. Varningar och försiktighet: Toujeo ska ej användas för behandling av diabetesketoacidos. För ytterligare information och prisuppgift, se **www.fass.se**. Kontaktuppgifter: Sanofi AB, Box 30052, 104 25 Stockholm, tel: +46 8 634 50 00, **www.sanofi.se.** Vid frågor kontakta: **infoavd@sanofi.com**. Datum för senaste översyn av produktresumén; november 2021.

Toujeo ingår i läkemedelsförmånen till alla patienter med typ 1-diabetes och till patienter med typ 2-diabetes där annan insulinbehandling inte räcker till för att nå behandlingsmålet på grund av upprepade hypoglykemier.

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