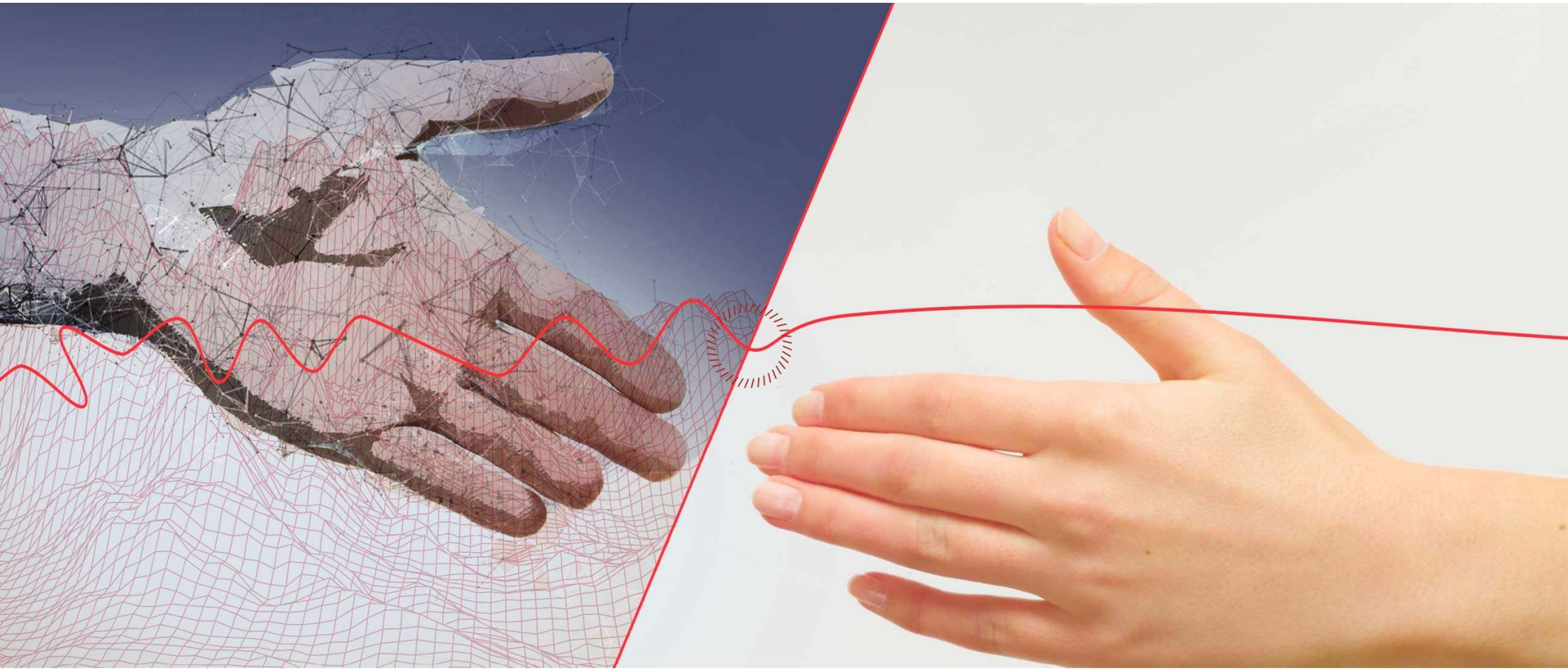


The outcome of studies using Toujeo (insulin glargine 300 units/mL) in patients with Type 1 and Type 2 Diabetes: expanding the evidence base

SANOFI DIABETES & CARDIOVASCULAR

This symposium has been organised and funded by Sanofi.
Prescribing information is available at this meeting.

SAGB.TJO.18.10.1688a DoP Oct 2018

Agenda

09.15 – 09.20	**Introduction**	Professor Mike Baxter, Sanofi
09.20 – 09.35	**BRIGHT study** Results of the first head-to-head randomised clinical trial comparing the efficacy and safety of Toujeo (Insulin Glargine 300units/ml) vs insulin degludec in T2 Diabetes	Professor Vinod Patel, Nuneaton
09.35 – 09.50	**SPARTA study** Real World Evidence in adults in the UK with T1 Diabetes switching to Toujeo (Insulin Glargine 300units/ml)	Dr Terence Pang, Dudley
09.50 – 10.00	**Q&A session**	Professor Mike Baxter, Sanofi

More similarities than differences testing Toujeo® (insulin glargine 300 units/mL) versus insulin degludec 100 units/mL in insulin-naïve type 2 diabetes: the randomised head-to-head BRIGHT trial[1]

BRIGHT

Professor Vinod Patel

This symposium has been organised and funded by Sanofi.
Prescribing information can be found at the end of the presentation and is available at this meeting.

SAGB.TJO.18.10.1688b DoP Nov 2018

Disclosures

I have worked most of the larger pharmaceutical industries in relation to educational events in Diabetes Care. This includes:

- Sanofi, Eli Lily, Novo Nordisk. BI, MSD, Merck, Napp and AZ
- There is occasional Advisory Board work.

BRIGHT Study
Introduction[1]

- Long-acting BI analogues, such as Lantus® (insulin glargine 100 units/mL), provide longer duration of action, flatter action-profiles, and less day-to-day variability than NPH insulin, with lower risk of hypoglycaemia
- Further PK/PD improvements have been made with the even longer-acting second-generation BI analogues, Toujeo® and insulin degludec 100 units/mL, which have **smoother PK/PD profiles than the first-generation Lantus® with less glycaemic variability**
- Toujeo® and insulin degludec 100 units/mL both provide **similar HbA_{1c} reductions to Lantus® but with less hypoglycaemia** in people with T2DM
- However, direct clinical comparisons between these two second-generation BI analogues have been unavailable until now

The BRIGHT study was the first head-to-head randomised clinical trial designed compare the efficacy and safety of Toujeo® with insulin degludec 100 units/mL in insulin-naïve patients with Type 2 diabetes who were inadequately controlled with oral antihyperglycaemic medication, with or without GLP-1 receptor agonists

BI: basal insulin; NPH: Neutral Protamine Hagedorn; PK/PD: pharmacokinetic/pharmacodynamic; T2DM: type 2 diabetes mellitus; GLP-1: glucagon-like peptide-1

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

Meet our patient !

58-year-old, diabetes 4 years

Small company roof repairs and renovations

Putting on weight- BMI 32.5

Taking:

- **Simvastatin 40mg**
- Ramipril 5mg od
- Metformin 850mg tds
- Glargine 24 units nocte- fasting glucose levels variable, headaches

BP: **146/84,** T-Chol 5.2 mmol/l, LDL 2.7, HDL 1.0

HbA1c 68mmol/mol = 8.4%

Creatinine 118 umol/l, eGFR 64ml/min, UACR 4.0 (NR < 2,0)

Previous laser Rx for Diabetic Maculopathy

What shall we do ?

What is the evidence-base for our decisions?

BRIGHT Study
Study endpoints and assessments[1]

- **Primary endpoint**
  - Change in HbA_{1c} from baseline to study end at week 24
- **Secondary efficacy endpoints included:**
  - Change in fasting SMPG and variability of 24-hour SMPG from baseline to week 24
- **Secondary safety endpoints included:**
  - Incidence and event rates of anytime (24hr) and nocturnal (00:00-05:59hr) confirmed hypoglycaemia, during the 24-week, on-treatment period, the active titration period (0–12 weeks), and the maintenance period (13–24 weeks)
  - Treatment-emergent AEs, including serious AEs
  - Body weight
- **Other assessments (not pre-specified endpoint):**
  - Change in basal insulin dose

HbA_{1c}: glycated haemoglobin; SMPG: self-monitored plasma glucose; AEs: adverse events

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study
A multicentre, open-label, 24-week, non-inferiority study[1,2]

Titration target: fasting SMPG 4.4–5.6 mmol/L [80–100 mg/dL] without hypoglycaemia

1:1 randomisation

- Adults with T2DM
- Insulin naïve
- Treated with OAD ± GLP-1 RA
- HbA_{1c} ≥7.5 (≥58 mmol/mol) and ≤10.5 % (≤91 mmol/mol)
- BMI >25 or <40 kg/m²

Stratification by:

- HbA_{1c} at screening (<8.0/≥8.0 % [<64/≥64 mmol/mol])
- Use of SU or glinide use at screening (Yes/No)

Toujeo® once daily (PM), N=466§

Recommended starting dose: 0.2 units/kg*

Titration period (0–12 weeks) → *Maintenance period* (13–24 weeks)

Insulin degludec 100 units/mL once daily (PM), N=463§

Recommended starting dose: 10 units/day*

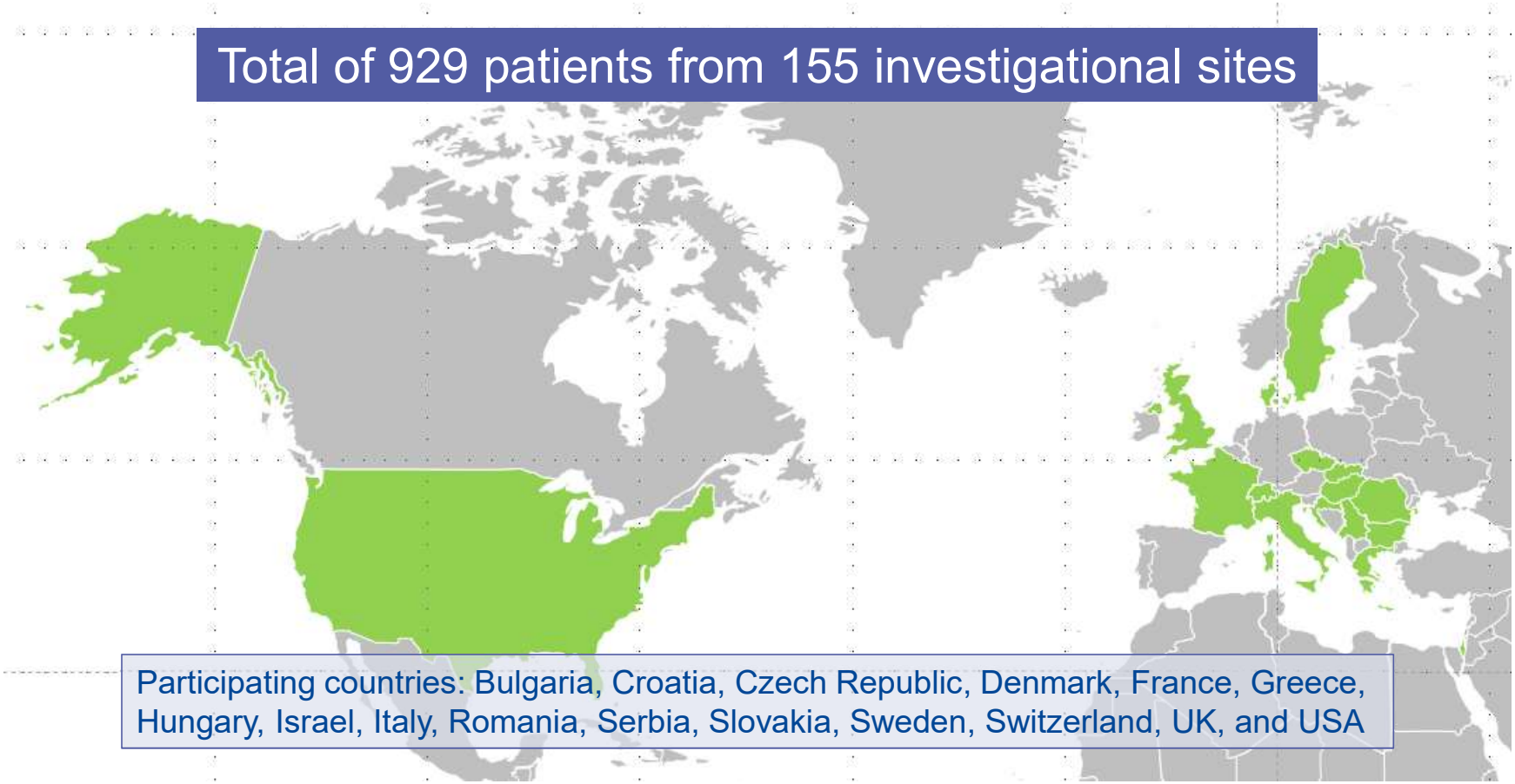
Adapted from: Rosenstock JR, et al. Diabetes Care 2018; Rosenstock JR, et al. Diabetes Care 2018 supplementary data

SMPG: self-monitored plasma glucose; T2DM: type 2 diabetes mellitus; OAD: oral antihyperglycaemic drug; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated haemoglobin; BMI: body mass index *Once daily subcutaneous self-injection, between 18:00hr and 20:00hr. Titrated to fasting self-measured plasma glucose of 4.4-5.6mmol/L [80-100mg/dL]. Background therapies were not changed unless safety concerns necessitated dose reduction or discontuination. § Randomised population

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]
2. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print] supplementary data

Patients and participating countries

Total of 929 patients from 155 investigational sites



Participating countries: Bulgaria, Croatia, Czech Republic, Denmark, France, Greece, Hungary, Israel, Italy, Romania, Serbia, Slovakia, Sweden, Switzerland, UK, and USA

BRIGHT Study
Baseline patient characteristics[1]

Baseline patient characteristics		Toujeo® (N=466)*	Insulin degludec 100 units/mL (N=463)*
Patient profile	Age, years	60.6 ± 9.6	60.5 ± 9.8
	Sex, % (male/female)	53/47	54/46
	BMI: kg/m^2	31.7 ± 4.3	31.3 ± 4.4
Known T2DM duration, years		10.5 ± 6.1	10.7 ± 6.5
Clinical characteristics	HbA_{1c} %	8.71 ± 0.83	8.57 ± 0.80
	HbA_{1c} <8.0% (<64mmol/mol)	86 (18.5)	85 (18.4)
	HbA_{1c} ≥8.0% (≥64mmol/mol)	380 (81.5)	378 (81.6)
	FPG, mg/dL	191 ± 49	182 ± 51
	Fasting SMPG, mg/dL	178 ± 40	172 ± 38

Adapted from: Rosenstock JR, et al. Diabetes Care 2018

Baseline demographic and clinical characteristics were similar across the two treatment groups.

BMI: body mass index; T2DM: type 2 diabetes mellitus; HbA_{1c}: glycated haemoglobin; FPG: fasting plasma glucose; SMPG: self-monitored plasma glucose. *Randomised population. Data expressed as mean ± standard deviation unless stated otherwise.

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study
Background therapy use[1]

Background therapy use		Toujeo® (N=466)*	Insulin degludec 100 units/mL (N=463)*
Number of prior non-insulin antihyperglycaemic agents used, n (%)	0	0 (0.0)	1 (0.2)
	1	70 (15.0)	65 (14.0)
	2	179 (38.4)	187 (40.4)
	>2	217 (46.6)	210 (45.4)
Prior non-insulin antihyperglycaemic treatments, %	Metformin	91.8	91.1
	Sulfonylureas	64.6	66.7
	Glinides	2.6	1.9
	Thiazolidinediones	4.5	5.2
	DPP-4 inhibitors	26.0	22.9
	SGLT-2 inhibitors	13.3	13.4
	GLP-1 RAs	9.9	14.0
	Alpha-glucosidase inhibitors	1.9	1.5
	Other	0.2	0.2

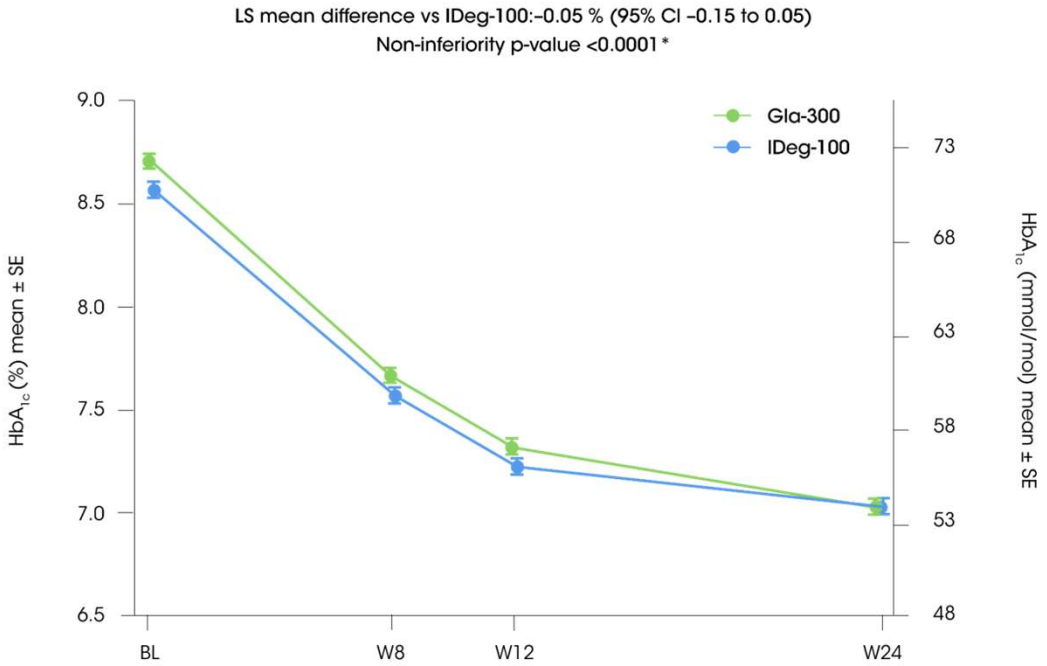
Adapted from: Rosenstock JR, et al. Diabetes Care 2018

DPP-4: dipeptidyl peptidase 4; SGLT-2: sodium-glucose co-transporter-2; GLP-1 RA: glucagon-like peptide-1 receptor agonist.
*Randomised population. Data expressed as mean ± standard deviation unless stated otherwise

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study – primary endpoint
Change in HbA_{1c} from baseline to week 24[1]

- **Comparable and effective HbA_{1c} reduction at 24 weeks**
  - ✓ Non-inferiority of HbA_{1c} reduction with Toujeo® vs. insulin degludec 100 units/mL (~1.6%*)



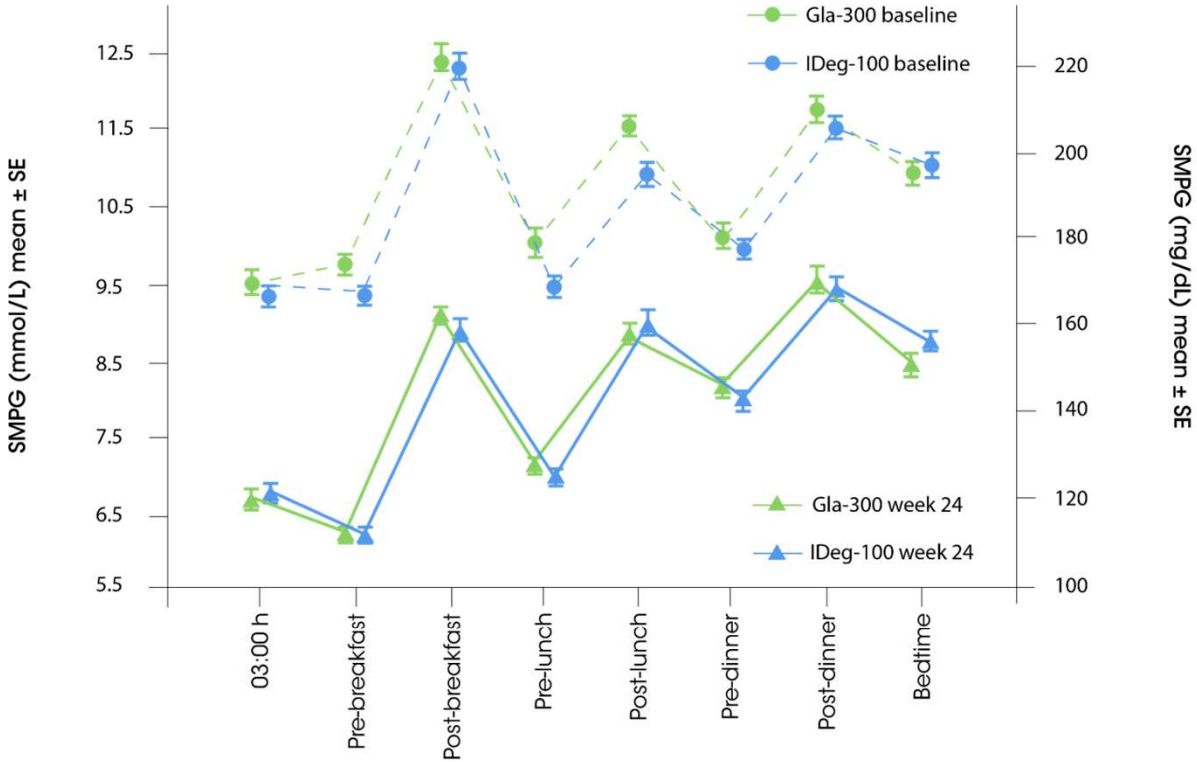
Adapted from: Rosenstock JR, et al. Diabetes Care 2018.
Gla-300: Toujeo®; IDeg-100: insulin degludec 100 units/mL; Intention to treat population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

LS: least squares; CI: confidence interval; SE: standard error. BL: baseline. W: week.
*Primary endpoint p<0.0001 for non-inferiority; **LS mean change from baseline to week 24 ± SE for Toujeo® of -1.64 ± 0.04 vs. insulin degludec 100 units/mL of -1.59 ± 0.04. LS mean difference for Toujeo® vs. insulin degludec 100 units/mL of -0.05%; 95% CI: -0.15 to 0.05

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study – secondary endpoint
Within-day variability of 24hr SMPG[1]

- ✓ Similar within-day variability of 24hr SMPG (based on 8-point SMPG profiles) was observed with Toujeo® and insulin degludec 100 units/mL at baseline and week 24[1]



Adapted from: Rosenstock JR, et al. Diabetes Care 2018.
Gla-300: Toujeo®; IDeg-100: insulin degludec 100 units/mL; Intention to treat population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

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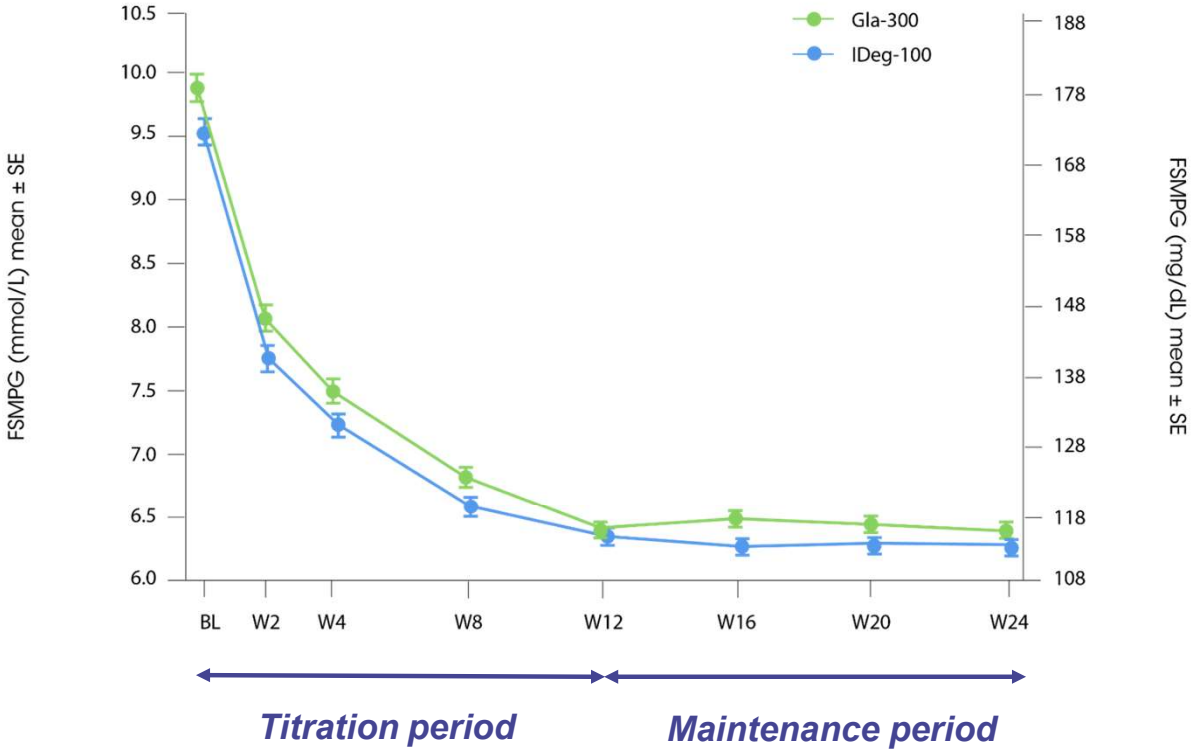
SMPG: self-monitored plasma glucose; SE: standard error

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study – secondary endpoint
Fasting SMPG profiles[1]

- ✓ Similar fasting SMPG profiles were observed with Toujeo® and insulin degludec 100 units/mL by week 24[1]



Adapted from: Rosenstock JR, et al. Diabetes Care 2018.
Gla-300: Toujeo®; IDeg-100: insulin degludec 100 units/mL; Intention to treat population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

SANOFI DIABETES & CARDIOVASCULAR

FSMPG: fasting self-monitored plasma glucose; SE: standard error; BL: baseline; W: week

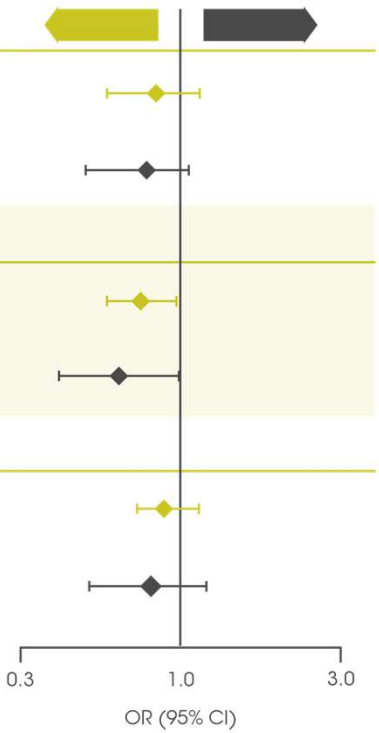
1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study – secondary endpoint
Anytime confirmed hypoglycaemia incidence[1]

Incidence

Incidence %

	Toujeo®	Insulin degludec 100 U/mL	OR (95% CI)	p-value*
Full study period (0–24 weeks)				
Confirmed (≤3.9mmol/L)	66.5	69.0	0.88 (0.66 to 1.17)	0.371
Confirmed (<3.0mmol/L)	14.7	18.4	0.76 (0.53 to 1.08)	0.123
Titration period (0-12 weeks)				
Confirmed (≤3.9mmol/L)	47.4	54.3	0.74 (0.57 to 0.97	0.030
Confirmed (<3.0mmol/L)	7.8	11.7	0.63 (0.40 to 0.99)	0.044
Maintenance period (13–24 weeks)				
Confirmed (≤3.9mmol/L)	54.1	55.8	0.93 (0.72 to 1.22)	0.618
Confirmed (<3.0mmol/L)	9.8	11.2	0.86 (0.56 to 1.33)	0.505



Adapted from: Rosenstock JR, et al. Diabetes Care 2018

CI: confidence interval; OR: odds ratio. Safety population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462) ***All p-values are analysed as nominal***

*Only 1 participant experienced severe hypoglycaemia (1 event), in the Toujeo® group, due to a skipped evening meal and not reducing her insulin dose after a previous non-severe event; **Active titration period: 0-12 weeks; ARR: absolute risk reduction; § Anytime (24hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); ¥ Maintenance period: 13-24 weeks

- ✓ Toujeo® demonstrated **lower incidence of anytime (24hr) confirmed hypoglycaemia** (≤3.9mmol/L and <3.0mmol/L) vs. insulin degludec 100 units/mL **during the titration period****
  - ↓ **26% relative risk reduction** (≤3.9mmol/L) (ARR=-6.9%)
  - ↓ **37% relative risk reduction** (<3.0mmol/L) (ARR=-3.9%)
- ✓ Comparable incidence of anytime§ confirmed hypoglycaemia in the maintenance¥ period and 24-week on-treatment study period

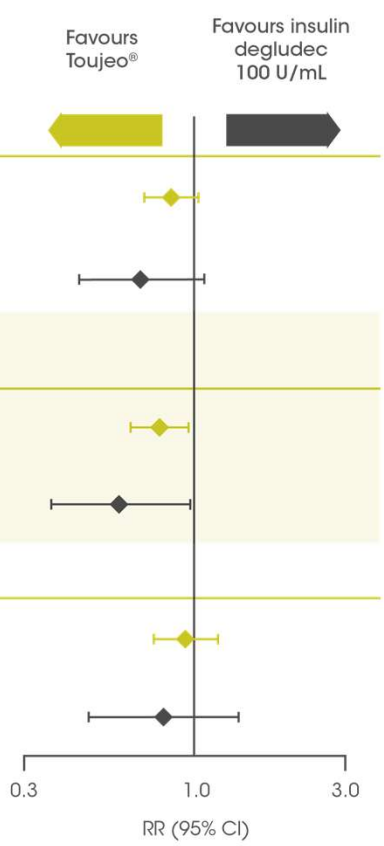
1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study – secondary endpoint
Anytime confirmed hypoglycaemic events[1]

Event rates

Events per patient-year

	Toujeo®	Insulin degludec 100 U/mL	RR (95% CI)	p-value*
Full study period (0–24 weeks)				
Confirmed (≤3.9mmol/L)	9.34	10.83	0.86 (0.71 to 1.04)	0.130
Confirmed (<3.0mmol/L)	0.61	0.88	0.69 (0.45 to 1.08)	0.104
Titration period (0-12 weeks)				
Confirmed (≤3.9mmol/L)	8.08	10.47	0.77 (0.62 to 0.96)	0.023
Confirmed (<3.0mmol/L)	0.49	0.86	0.57 (0.34 to 0.97)	0.038
Maintenance period (13–24 weeks)				
Confirmed (≤3.9mmol/L)	10.64	11.21	0.95 (0.76 to 1.19)	0.650
Confirmed (<3.0mmol/L)	0.73	0.91	0.81 (0.48 to 1.39)	0.448



Adapted from: Rosenstock JR, et al. Diabetes Care 2018

CI: confidence interval; RR: rate ratio. Safety population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462) ***All p-values are analysed as nominal**

One participant experienced severe hypoglycaemia (1 event), in the Toujeo® group, due to a skipped evening meal and not reducing her insulin dose after a previous non-severe event; **Active titration period: 0-12 weeks; ARR: absolute risk reduction; § Anytime (24hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); ¥ Maintenance period: 13-24 weeks

- ✓ Toujeo® demonstrated **lower event rates of anytime (24hr) confirmed hypoglycaemia** (≤3.9mmol/L and <3.0mmol/L) vs. insulin degludec 100 units/mL **during the titration period****
  - ↓ **23% relative risk reduction** (≤3.9mmol/L) (ARR=-2.4%)
  - ↓ **43% relative risk reduction** (<3.0mmol/L) (ARR=-0.4%)
- ✓ Comparable event rates of anytime§ confirmed hypoglycaemia in the maintenance¥ period and 24-week on-treatment study period

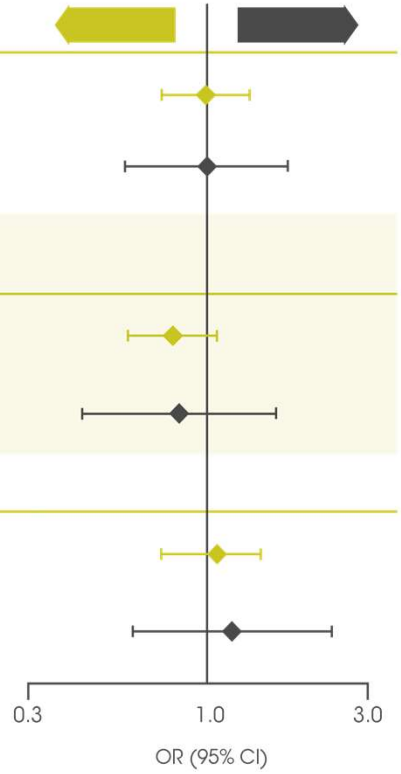
1. **Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]**

BRIGHT Study – secondary endpoint
Nocturnal confirmed hypoglycaemia incidence[1]

Incidence

Incidence %

	Toujeo®	Insulin degludec 100 U/mL	OR (95% CI)	p-value*
Full study period (0–24 weeks)				
Confirmed (≤3.9mmol/L)	28.6	28.8	0.99 (0.74 to 1.32)	0.931
Confirmed (<3.0mmol/L)	6.1	6.1	1.00 (0.58 to 1.72)	0.991
Titration period (0-12 weeks)				
Confirmed (≤3.9mmol/L)	15.2	18.8	0.77 (0.54 to 1.08)	0.133
Confirmed (<3.0mmol/L)	2.8	3.5	0.80 (0.38 to 1.69)	0.564
Maintenance period (13–24 weeks)				
Confirmed (≤3.9mmol/L)	21.4	21.0	1.03 (0.74 to 1.42)	0.881
Confirmed (<3.0mmol/L)	4.5	3.8	1.18 (0.61 to 2.29)	0.620



- ✓ Comparable incidence of nocturnal§ confirmed hypoglycaemia in the maintenance¥ period and 24-week on-treatment study period

Adapted from: Rosenstock JR, et al. Diabetes Care 2018.
CI: confidence interval; OR: odds ratio. Safety population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462) ***All p-values are analysed as nominal**

§ Nocturnal (00:00-05:59hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); ¥ Maintenance period: 13-24 weeks

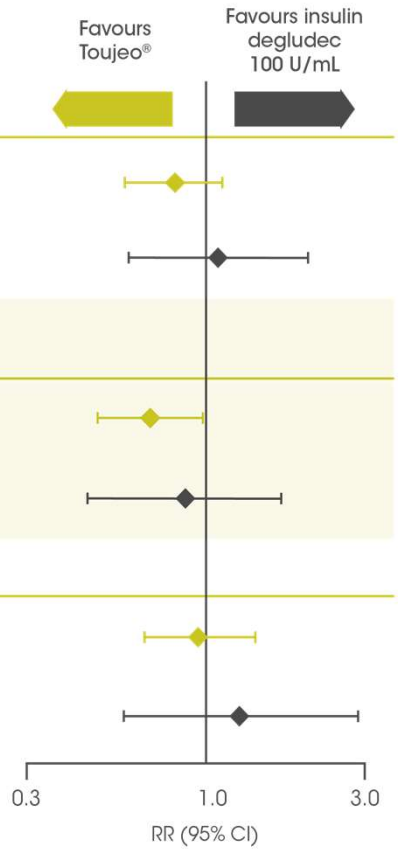
1. **Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]**

BRIGHT Study – secondary endpoint
Nocturnal confirmed hypoglycaemic events[1]

Event rates

Events per patient-year

	Toujeo®	Insulin degludec 100 U/mL	RR (95% CI)	p-value*
Full study period (0–24 weeks)				
Confirmed (≤3.9mmol/L)	1.83	2.26	0.81 (0.58 to 1.12)	0.204
Confirmed (<3.0mmol/L)	0.24	0.22	1.09 (0.60 to 2.00)	0.777
Titration period (0-12 weeks)				
Confirmed (≤3.9mmol/L)	1.42	2.20	0.65 (0.43 to 0.98)	0.040
Confirmed (<3.0mmol/L)	0.16	0.19	0.85 (0.40 to 1.79)	0.662
Maintenance period (13–24 weeks)				
Confirmed (≤3.9mmol/L)	2.24	2.33	0.96 (0.66 to 1.40)	0.839
Confirmed (<3.0mmol/L)	0.33	0.26	1.27 (0.57 to 2.83)	0.555



Adapted from: Rosenstock JR, et al. Diabetes Care 2018

CI: confidence interval; RR: rate ratio. Safety population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462) ***All p-values are analysed as nominal**

**Active titration period: 0-12 weeks; ARR: absolute risk reduction; § Nocturnal (00:00-05:59hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); ¥ Maintenance period: 13-24 weeks

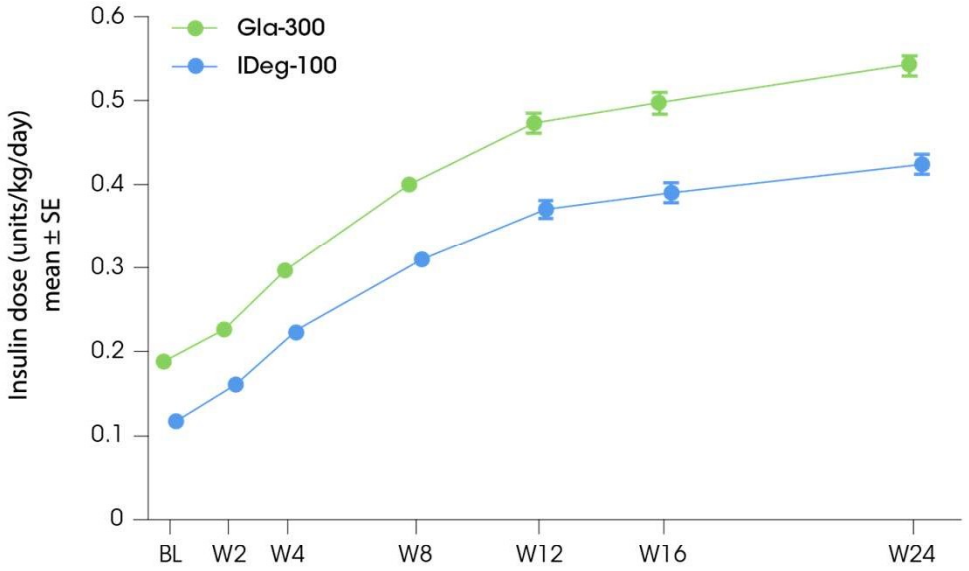
- ✓ Toujeo® demonstrated **lower event rates of nocturnal (00:00-05:59hr) confirmed hypoglycaemia (≤3.9mmol/L)** vs. insulin degludec 100 units/mL **during the titration period****
  - ↓ **35% relative risk reduction** (≤3.9mmol/L) (ARR=-0.8%)
- ✓ Comparable event rates of nocturnal§ confirmed hypoglycaemia in the maintenance¥ period and 24-week on-treatment study period

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

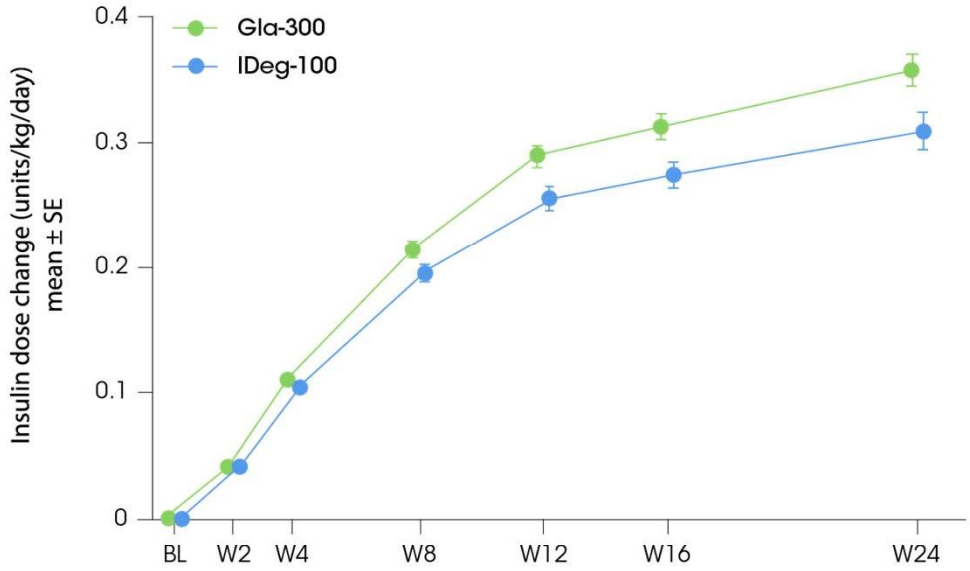
BRIGHT Study
Basal insulin dose increase over 24 weeks[1,2]

- Slightly higher mean daily insulin dose for Toujeo® than insulin degludec 100 units/mL at study start and end[1]

Average daily insulin dose[2]



Change in average insulin dose[2]



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Gla-300: Toujeo®; IDeg-100: insulin degludec 100 units/mL; Intention to treat population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

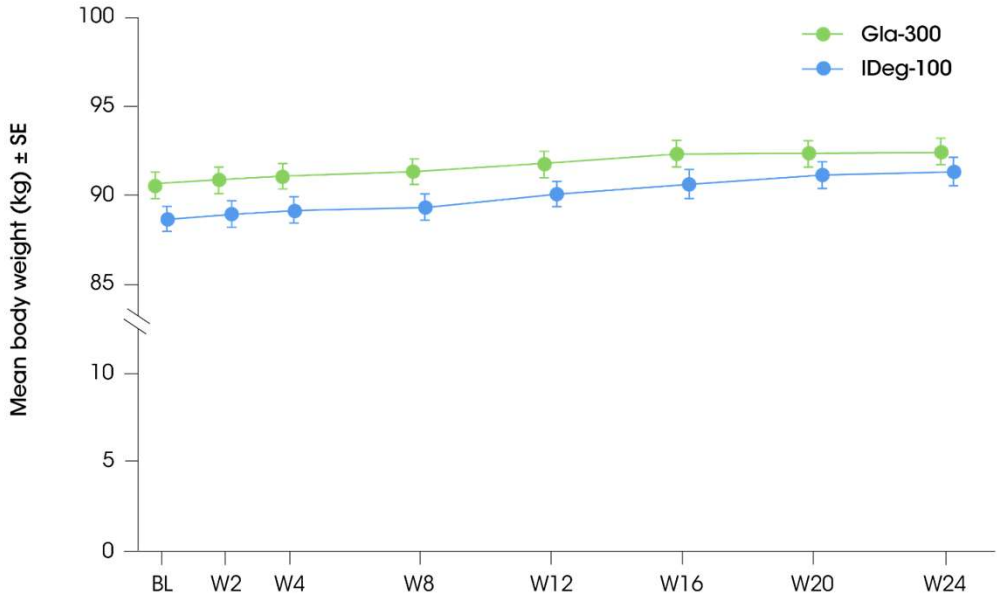
SANOFI DIABETES & CARDIOVASCULAR
SE: standard error; BL: baseline; W: week

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]
2. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print] supplementary data

BRIGHT Study
Body weight change over 24 weeks[1,2]

- Comparable weight gain with both treatments[1]

Body weight change over 24 weeks[2]



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Gla-300: Toujeo®; IDeg-100: insulin degludec 100 units/mL; Intention to treat population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

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SE: standard error; BL: baseline; W: week

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]
2. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print] supplementary data

BRIGHT Study
Treatment-emergent adverse events[1]

- No specific safety concerns were reported
- **Only 1 participant experienced severe hypoglycaemia during the entire study**
  - A single event occurring in the Toujeo® group due to a skipped evening meal and not reducing her insulin dose after a previous non-severe event 2 days earlier

N(%)	Toujeo® (N=462*)	Insulin degludec 100 units/mL (N=462*)
Patients with any treatment-emergent AE	202 (43.7)	221 (47.8)
Patients with any treatment-emergent serious AE	21 (4.5)	20 (4.3)
Patients with any treatment-emergent AE leading to death	1 (0.2)*	0 (0.0)
Patients with any treatment-emergent AE leading to permanent treatment discontinuation	4 (0.9)	5 (1.1)

*One death in the Toujeo® group, due to adenocarcinoma of the colon (deemed unrelated to study treatment)
AE: adverse event. * Safety population (Toujeo®, N=462; insulin degludec 100 units/mL, N=462)

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

Meet our patient !

58-year-old, diabetes 4 years

Small company roof repairs and renovations

Putting on weight- BMI 32.5

Taking:

- **Simvastatin 40mg**
- Ramipril 5mg od
- Metformin 850mg tds
- Glargine 24 units nocte- fasting glucose levels variable, headaches

BP: **146/84,** T-Chol 5.2 mmol/l, LDL 2.7, HDL 1.0

HbA1c 68mmol/mol = 8.4%

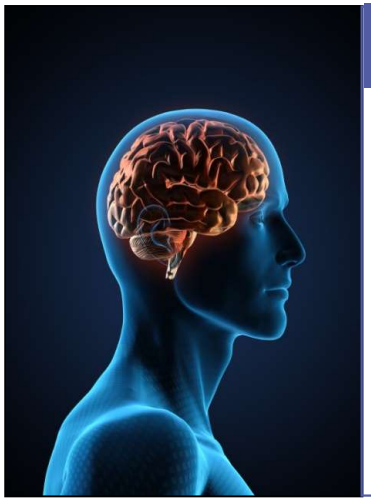
Creatinine 118 umol/l, eGFR 64ml/min, UACR 4.0 (NR < 2,0)

Previous laser Rx for Diabetic Maculopathy

What shall we do ?

What is the evidence-base for our decisions?

Morbidity of hypoglycaemia in diabetes



Brain

Blackouts, seizures, coma, death

Cognitive dysfunction

Psychological effects

Musculoskeletal

Falls, accidents

eg driving

Fractures, Dislocations

Cardiovascular

Myocardial ischaemia (angina and infarction)

Cardiac arrhythmia

Abnormal prolonged cardiac repolarisation

↑ QTc

Sudden death

ABC of Diabetes. Holt and Kumar 2015. BMJ Books

BRIGHT Study
Summary[1]

- **BRIGHT is the first head-to-head study comparing the efficacy and safety of Toujeo® vs. insulin degludec 100 units/mL in insulin-naïve patients with Type 2 diabetes and showed:**
  - **Comparable** (~1.6%*) **and effective HbA_{1c} reduction** between Toujeo® and insulin degludec 100 units/mL
  - Similar variability in 24hr SMPG and fasting SMPG profiles with both treatments
    - **Despite comparable variability in 24hr SMPG and fasting SMPG profiles, Toujeo® provided lower incidence and rates of anytime§ (24hr) hypoglycaemia during the active titration period****
  - Comparable weight gain with both treatments, despite a slightly higher mean daily insulin dose for Toujeo® than insulin degludec 100 units/mL at study end
    - **Slightly higher Toujeo® dose in BRIGHT did not translate into increased hypoglycaemia risk nor greater weight gain**

SMPG: self-monitored plasma glucose; *Primary endpoint p<0.0001 for non-inferiority; LS mean change from baseline to week 24 ± SE for Toujeo® of -1.64 ± 0.04 vs. insulin degludec 100 units/mL of -1.59 ± 0.04. LS mean difference for Toujeo® vs. insulin degludec 100 units/mL of -0.05%; 95% confidence interval: -0.15 to 0.05; § Anytime (24hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); **Active titration period: 0-12 weeks

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

BRIGHT Study
Summary[1]

- During the on-treatment, 24-week study and maintenance periods¥, the incidence and event rate of anytime (24hr) and nocturnal (00:00-05:59hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) were comparable between treatment groups

- During the titration period (0-12 weeks):

  – The incidence and event rate of anytime (24hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) and the event rate of nocturnal (00:00–05:59hr) confirmed hypoglycaemia (≤3.9mmol/L) were lower with Toujeo®

    ↓ 26% relative risk reduction (≤3.9mmol/L) in anytime (24hr) hypoglycaemia incidence (ARR=-6.9%)
    ↓ 23% relative risk reduction (≤3.9mmol/L) in anytime (24hr) hypoglycaemic event rate (ARR=-2.4%)
    ↓ 35% relative risk reduction (≤3.9mmol/L) in nocturnal (00:00-05:59hr) hypoglycaemic event rate (ARR=-0.8%)

  – The incidence of nocturnal (00:00-05:59hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L) and the event rate of nocturnal (00:00-05:59hr) confirmed hypoglycaemia (<3.0mmol/L) were comparable between treatment groups

- **Less hypoglycaemia during week 0 to 12 – the time of more intensive insulin titration – could be important as it may help build patient confidence to initiate and properly titrate their basal insulin with less fear of hypoglycaemia[2]**

SANOFI DIABETES & CARDIOVASCULAR

¥ Maintenance period: 13-24 weeks

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]
2. Mehul R. Dalal. et al. DOI 10.1007/s12325-017-0592-x, Published online: August 4, 2017

BRIGHT Study
Conclusion[1]

In previously insulin-naïve patients with inadequately controlled T2DM, Toujeo® and insulin degludec 100 units/mL provided **comparable glycaemic control***, accompanied by **comparable hypoglycaemia** during the full study period and maintenance period¥, and **less anytime hypoglycaemia§ during the titration period** with Toujeo®**

T2DM: type 2 diabetes mellitus; *Primary endpoint p<0.0001 for non-inferiority; LS mean change from baseline to week 24 ± SE for Toujeo® of -1.64 ± 0.04 vs. insulin degludec 100 units/mL of -1.59 ± 0.04. LS mean difference for Toujeo® vs. insulin degludec 100 units/mL of -0.05%; 95% confidence interval: -0.15 to 0.05; ¥Maintenance period: 13-24 weeks; § Anytime (24hr) confirmed hypoglycaemia (≤3.9mmol/L and <3.0mmol/L); **Active titration period: 0-12 weeks

1. Rosenstock JR, et al. Diabetes Care 2018. DOI:10.2337/dc18-0559 [epub ahead of print]

Important safety information[1]

Toujeo® and Lantus® (insulin glargine 100 units/mL) are not bioequivalent and therefore are not interchangeable

Medication error prevention

Patients should check they have the correct insulin before injecting, and never withdraw insulin from the pen with a needle and syringe

Hypoglycaemia

Patient adherence to dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia

Drug interactions

Caution when pioglitazone is used with insulin

Pregnancy/Lactation

There is no clinical experience of Toujeo® use in pregnant women

Adverse drug reactions (ADRs)

Hypoglycaemia, in general, is the most frequent adverse reaction of insulin therapy and may occur if the insulin dose is too high in relation to the insulin requirement

1. Toujeo® Summary of Product Characteristics.

Toujeo® Prescribing Information

Toujeo® (insulin glargine 300 units/ml)
Please refer to Summary of Product Characteristics prior to use of Toujeo. Presentation: Toujeo Solostar pre-filled pens each contain 450 Units of insulin glargine in 1.5 ml of solution for injection, equivalent to 10.91 mg/ml.
Indication: Treatment of diabetes mellitus in adults.
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. 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-/rapid-acting 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.
Special populations: Insulin requirements may be diminished in the elderly or patients with renal or hepatic impairment. *Paediatric:* No data available.

Contraindications: Hypersensitivity to insulin glargine or any excipients.
Precautions and warnings: Toujeo is not the insulin of choice for treatment of diabetic ketoacidosis. *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 pre-filled pen, A new sterile needle must be attached before each injection. Needles must not be re-used. *Pregnancy and lactation:* There is 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.
Adverse reactions: *Very common (≥1/10):* Hypoglycaemia. Prolonged or severe hypoglycaemia may be life-threatening. *Common (≥1/100 to <1/10):* Lipohypertrophy, injection site reactions, including redness, pain, itching, hives, swelling, or inflammation. *Uncommon (≥1/1,000 to <1/100):* Lipoatrophy. *Rare (≥1/10,000 to <1/1,000):* Allergic reactions; which may be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock and may be life threatening; visual impairment, retinopathy and oedema. *Very rare (<1/10,000):* Dysgeusia, myalgia. Overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.
Please consult SmPC for full details of the adverse reactions.
NHS price: £33.13 for pack of x3 1.5ml pens.
Legal category: POM.
Marketing Authorisation (MA) holder: Sanofi Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.
MA Number: SoloStar 3 Pen pack: EU/1/00/133/034.
Full prescribing information is available from: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS. Tel: 01483 505515 or the Sanofi Diabetes Care Line 08000 352 525.
Date of preparation: April 2018

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Sanofi Tel: 0800 0902314.
Alternatively, send via E-mail to UK-drugsafety@sanofi.com

Lantus® Prescribing Information

Lantus® (insulin glargine 100 units/ml)
Please refer to Summary of Product Characteristics prior to use of Lantus.
Presentations: Lantus 100 units/ml solution for injection in a vial or in a cartridge. Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen. Lantus cartridges and Solostar pre-filled pens each contain 3 ml of solution for injection, equivalent to 300 units insulin glargine. Each vial contains 10 ml of solution for injection, equivalent to 1000 units.
Indications: Treatment of diabetes mellitus in adults, adolescents and children of 2 years or above.
Dosage and administration: Lantus is administered subcutaneously once daily, at any time but at the same time each day. Injection sites must be rotated within a given injection area from one injection to the next. Do not administer intravenously. Lantus dosage should be individually adjusted. In type 2 diabetes mellitus, Lantus can also be used in combination with orally active antidiabetic medicinal products. Lantus must not be mixed with other insulins or diluted. *Switch from twice daily NPH insulin to Lantus:* To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Lantus should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment. *Switch from Toujeo (insulin glargine) 300 units/ml to Lantus:* Lantus and Toujeo are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily Toujeo to a once daily regimen with Lantus should reduce their dose by approximately 20%. *Switching from other insulins to Lantus:* When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Lantus, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products). Close metabolic monitoring is recommended during, and for a period after, transition from other insulins to Lantus. 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. *Elderly population (≥65 years old), patients with renal or hepatic impairment:* Insulin requirements may be diminished. *Children (<2 years of age):* No data are available.
Contraindications: Hypersensitivity to insulin glargine or any excipients.
Precautions and warnings: Lantus is not the insulin of choice for treatment of diabetic ketoacidosis. In case of insufficient glucose control or a tendency to hypo/hyperglycaemic episodes all relevant factors must be reviewed before dose adjustment is considered. Transferring a patient to another type or brand of insulin should be done under strict medical supervision. *Hypoglycaemia:* Particular caution should be exercised, and intensified blood 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. The prolonged effect of subcutaneous Lantus may delay recovery from hypoglycaemia. Due to more sustained basal insulin supply with Lantus, less nocturnal but earlier morning hypoglycaemia can be expected. *Intercurrent illness:* requires intensified metabolic monitoring. *Insulin antibodies:* administration may cause insulin antibodies to form. Rarely, this may necessitate dose adjustment. *Pioglitazone:* Cases of cardiac failure have been reported, especially in patients with risk factors for development of cardiac heart failure. Patients on this combination should be observed and 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 Lantus and other insulins. Lantus Solostar is only suitable for subcutaneous injections from its pre-filled pen. Lantus cartridges are only suitable for subcutaneous injections from a reusable pen (JuniorSTAR which delivers Lantus in 0.5 unit dose increments and Autopen 24, AllStar and AllStar PRO which all deliver Lantus in 1 unit dose increments). If administration by syringe is necessary, a vial should be used. *Interactions:* A number of substances affect glucose metabolism and may require dose adjustment of Lantus. *Pregnancy and lactation:* No clinical data on exposed pregnancies from controlled clinical trials are available. A large amount of post-marketing data indicates no specific adverse effects of Lantus in pregnancy. Use of Lantus in pregnancy can be considered if clinically needed. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential. It is unknown if Lantus is excreted in breast milk.
Adverse reactions: *Very common (≥1/10):* Hypoglycaemia. Prolonged or severe hypoglycaemia may be life-threatening. *Common (≥1/100 to <1/10):* Lipohypertrophy, injection site reactions. *Uncommon (≥1/1,000 to <1/100):* Lipoatrophy. *Rare (≥1/10,000 to <1/1,000):* Allergic reactions, visual impairment, retinopathy and oedema. *Very rare (<1/10,000):* Dysgeusia, myalgia. Overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.
Please consult SmPC for full details of the adverse reactions.
NHS list price: 1 x 10ml Lantus vial: £27.92; 5 x 3ml Lantus cartridge: £37.77; 5 x 3ml Lantus SoloStar: £37.77.
Legal category: POM.
Marketing Authorisation (MA) holder: Sanofi Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany. **MA Numbers:** Vial: EU/1/00/134/012, Cartridge: EU/1/00/134/006, SoloStar: EU/1/00/134/033.
Full prescribing information is available from: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS. Tel: 01483 505 515 or the Sanofi Diabetes Care Line 08000 352 525.
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SPARTA study: Real World Evidence in adults in the UK with T1 Diabetes switching to Toujeo (insulin glargine 300 units/mL)

Terence Pang PhD FRCP Edin, Medical Service Head Diabetes,
Dudley Group of Hospitals NHS FT

SANOFI DIABETES & CARDIOVASCULAR

This symposium has been organised and funded by Sanofi.

Prescribing information can be found at the end of the presentation and is available at this meeting.

SAGB.TJO.18.10.1688 DoP Oct 2018

Disclosures

- Institutional investigator fees: Novo Nordisk, Sanofi
- Research Fellowship: Novo Nordisk
- Advisory Board: Novo Nordisk
- Speakers Bureau: Sanofi, Eli Lilly, Napp Pharmaceuticals, Janssen

A multicentred, UK, retrospective observational study to assess the effectiveness of insulin glargine 300 units/mL in treating people with Type 1 diabetes mellitus in routine clinical practice (SPARTA)

Terence Pang[1], Steve C. Bain[2], R. Neil A. Black[3], James G. Boyle[4], Jackie Elliott[5], Adele Holcombe[6], Keni C.S. Lee[7], Ciara Mulligan[8], Luke Saunders[9], Ahmed Yousseif[10], and Mike Baxter[7]

[1]The Dudley Group NHS Foundation Trust, Russells Hall Hospital, Dudley, UK
[2]Institute of Life Science, Swansea University Medical School, Swansea, UK
[3]Department of Endocrinology & Diabetes, Altnagelvin Hospital, Derry, Northern Ireland
[4]Glasgow Royal Infirmary, School of Medicine, University of Glasgow, Glasgow, UK
[5]Diabetes and Endocrine Department, Sheffield Teaching Hospitals, Sheffield, UK
[6]North East Essex Diabetes Service, Suffolk GP Federation, Colchester, UK
[7]Sanofi, Guildford, UK
[8]Ulster Hospital, SE Trust, Belfast, Northern Ireland
[9]pH Associates, Marlow, UK
[10]Diabetes and Endocrine Department, Royal Free London NHS Foundation Trust, London, UK

onlinelibrary.wiley.com/doi/epdf/10.1111/dme.13847

Plan

Toujeo®: basic pharmacology

Toujeo® mimics endogenous insulin

Toujeo® clinical efficacy and safety profile

Applicability to our practice?

SPARTA study: Real World Evidence

Toujeo® in summary

"Will a switch of insulin to Toujeo help my patient?"

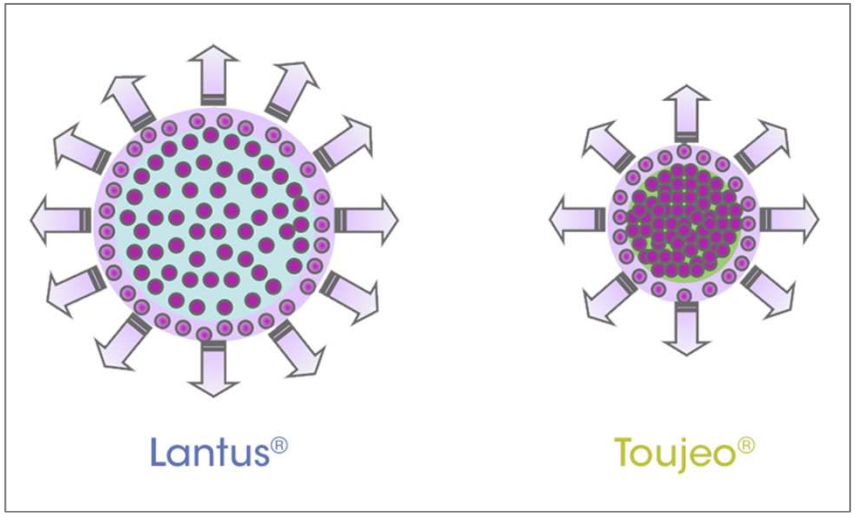
Toujeo®
The next-generation formulation of insulin glargine

Toujeo®: basic pharmacology

Toujeo®: mimics endogenous insulin

Compared with Lantus® (insulin glargine 100 units/mL),

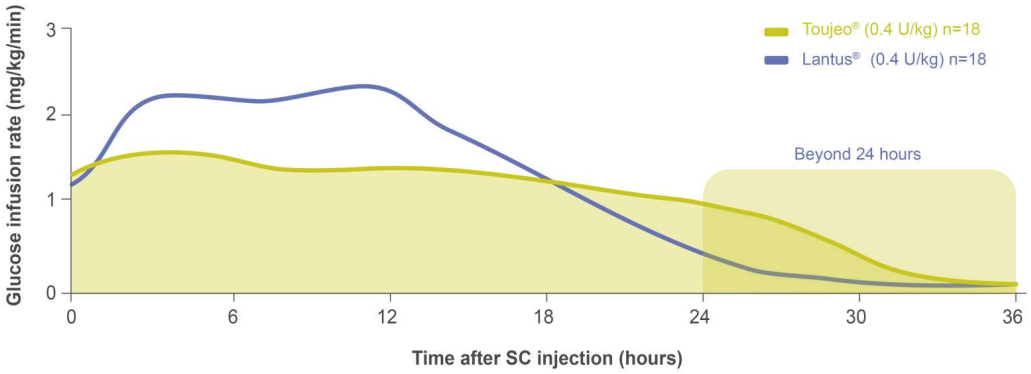
✓ Toujeo® offers[1–4] a **reduced subcutaneous precipitate size**



Adapted from Sutton et al, 2014

✓ Toujeo® demonstrated a **more stable and prolonged activity profile for a full 24 hours and beyond[1,4]**

Glucose infusion rate following Toujeo® or Lantus® administration[1,4]



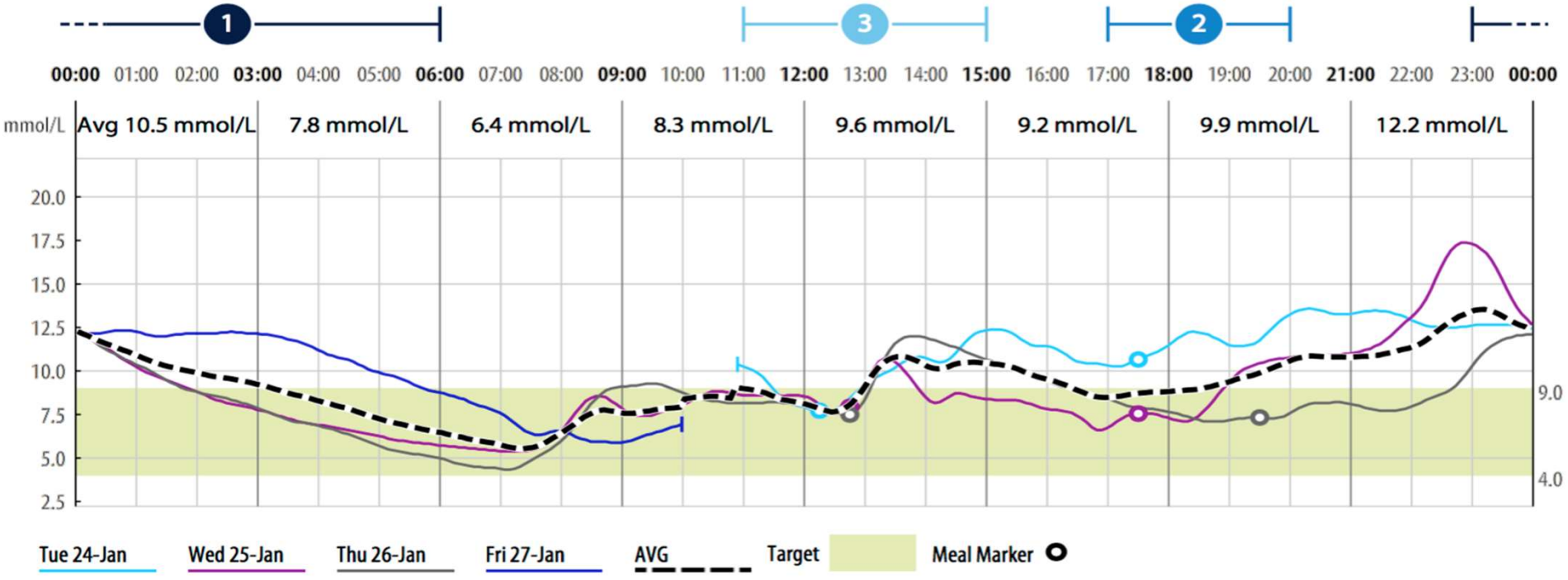
PK/PD study in people with T1DM using euglycaemic-clamp technique at steady state.
The results of euglycaemic clamp studies do not necessarily predict clinical outcomes in all patients.
PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

1. Toujeo® Summary of Product Characteristics. **2.** Sutton G *et al*, Expert Opin Biol Ther 2014;14(12): 1849–60. **3.** Owens DR, *et al*. Diabetes Metab Res Rev 2014;30(2):104–19. **4.** Becker RH, *et al*. Diabetes Care 2015;38(4):637–43.

PD, pharmacodynamics; PK, pharmacodynamics; T1DM, type 1 diabetes mellitus

Toujeo®
The next-generation formulation of insulin glargine

Example patient on Lantus



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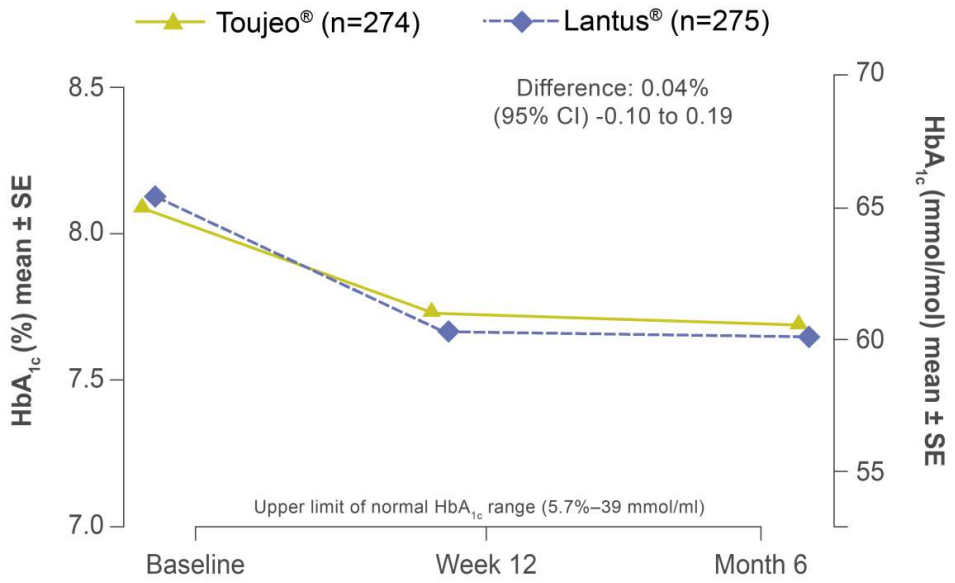
Clinical efficacy and safety profile

HbA1c

EDITION 4
Effective HbA1c reduction in people with T1DM vs. Lantus® (insulin glargine 100 units/mL) [1]

- Compared with Lantus®, Toujeo® demonstrated:
  - ✓ **Similar long-term HbA_{1c} reduction**

HbA_{1c} change during treatment in the modified intent-to-treat population



Adapted from Home PD et al, 2015

CI, confidence interval; HbA_{1C}, haemoglobin A_{1C}; SE, standard error; T1DM, type 1 diabetes mellitus

1. Home PD *et al*. Diabetes Care 2015;38(12):2234–37.

Toujeo®
Clinical efficacy and safety profile

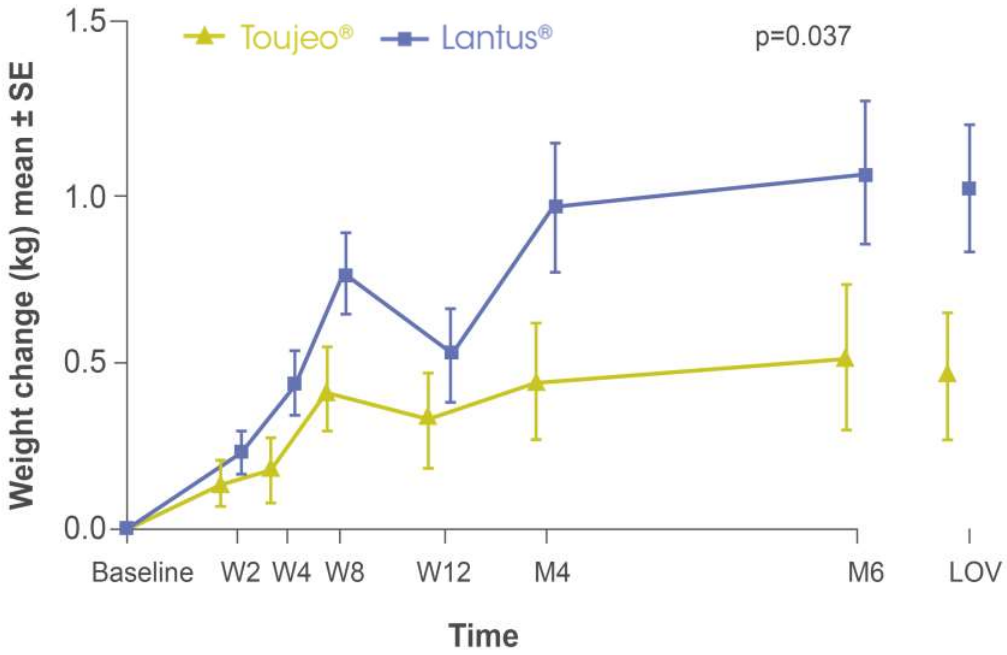
HbA$_{1c}$

kg

EDITION 4
Weight data in T1DM on basal bolus regimen

- After 6 months of treatment, Toujeo® compared with Lantus® (insulin glargine 100 units/mL) demonstrated:
  - ✓ **Less body weight gain** [1]

Time course of body weight change in EDITION 4



Adapted from Home PD et al, 2015

LOV, last on-treatment value; SE, standard error; T1DM, type 1 diabetes mellitus

1. Home PD *et al*. Diabetes Care 2015;38(12):2234–37.

Toujeo®
Clinical efficacy and safety profile

HbA$_{1c}$

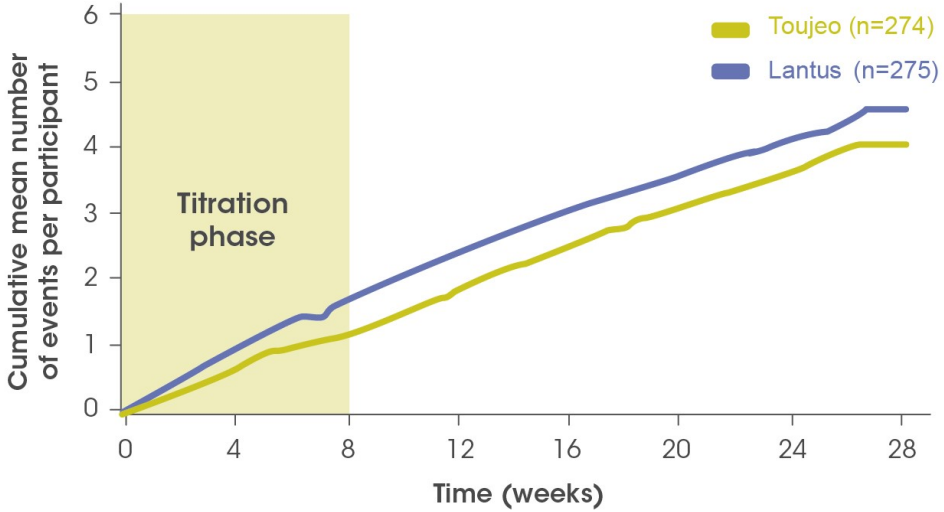
kg

EDITION 4

Cumulative mean numbers of confirmed (<3.9 mmol/L) or severe nocturnal hypoglycaemic events in people with T1DM[1]

- Compared to Lantus®, Toujeo® demonstrated:
  - ✓ **A 31% lower** (RR 0.69 [95% CI 0.53-0.9]) **rate of nocturnal hypoglycaemic events** (events/person-year) **during the titration phase** (baseline to week 8)
  - ✓ **Similar rate of nocturnal hypoglycaemic events** (events/person-year) **during the maintenance phase** (week 9 to month 6)

Cumulative mean numbers of confirmed (<3.9 mmol/L) or severe nocturnal hypoglycaemic events in people with T1DM[9]



Adapted from Home PD et al, 2015 & supplementary data

Absolute rate reduction:
11.20 (Lantus®) – 7.75 (Toujeo®) = 3.45 events/person-year

RR, relative risk; CI, confidence interval; T1DM, type 1 diabetes mellitus
Nocturnal = 0000h -0559hrs

1. Home PD *et al*. Diabetes Care 2015;38(12):2234–37. **2.** Home PD *et al*. Diabetes Care 2015;38(12): 2234–37 and supplementary data.

Toujeo®
The next-generation formulation of insulin glargine

Compared with Lantus® (insulin glargine 100 units/mL), Toujeo® demonstrated

- ✓ **A more stable and prolonged activity profile for a full 24 hours and beyond**[1,2]
- ✓ **Similar long-term HbA_{1c} reduction**
- ✓ **Less body weight gain** [1]after 6 months of treatment
- ✓ **A 31% lower** (RR 0.69 [95% CI 0.53-0.9]) **rate of nocturnal hypoglycaemic events** (events/person-year) **during the titration phase** (baseline to week 8)
- ✓ **Similar rate of nocturnal hypoglycaemic events** (events/person-year) **during the maintenance phase** (week 9 to month 6)

Plan

Toujeo®: basic pharmacology

Toujeo® mimics endogenous insulin

Toujeo® clinical efficacy and safety profile

Applicability to our practice?

SPARTA study: Real World Evidence

Toujeo® in summary

"Will a switch of insulin to Toujeo help my patient?"

Applicability to our practice?

- Usual HbA1C in clinics ≥ 9%
  Study excludes patients HbA1C ≥ 10%
- Did not include patients from UK
- Toujeo delivered in Tactipen (1.5 unit increments)
- Difficulties in targeting pre-breakfast SMBG 4.4-7.2 mmol

Toujeo®: basic pharmacology

Toujeo® mimics endogenous insulin

Toujeo® clinical efficacy and safety profile

Applicability to our practice?

SPARTA study: Real World Evidence

Toujeo® in summary

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SPARTA study: Real World Evidence

Comparing RCT vs RWE studies

Randomised Controlled Trial		Real-World Evidence
Set-up and running takes time		Routinely collected clinical data: (SPARTA: planning to publication = 1 year)
Selected participants (volunteers)		Broader group from clinical practice
Trial Protocol		Usual care
Relatively free of bias		Risk of residual confounding; Bias (selection, ascertainment, classification)
Establish causality – will it work?		Correlation – can it work in my clinic?

SPARTA study: Real World Evidence

Aims

- Assess effectiveness of Toujeo (Gla-300) in patients with T1D treated in UK clinical setting

- “Will a switch of insulin to Toujeo help my patient?”

SPARTA study: Real World Evidence

Methodology and study design[1,2]

- **Objective**
  - To describe real-world outcomes of switching from basal insulin to Toujeo® (insulin glargine 300 units/mL) in patients with T1D regarding effectiveness, demographics, treatment patterns, and hypoglycaemia occurrence
- **Design**
  - Retrospective, observational, descriptive study
  - 8 participating centres across the UK with defined minimum (n=10) and maximum (n=100) patients enrolled in each centre
  - In total, 299 patients with T1D recruited aged ≥18 to <75 years
  - Anonymised patient-level data collected from electronic medical notes and paper charts by members of the direct care team
- **Data Collection (Sept-Dec 2017)**
  - At baseline (6 months prior to Toujeo® initiation, except for HbA_{1c} that was collected 3 months prior to Toujeo® initiation)
  - At 6 months following Toujeo® initiation (plus 3 months for HbA_{1c})
- **Inclusion criteria**
  - Patients with T1D
  - Aged ≥18 to <75 years
  - Prescribed Toujeo® ≥6 months before data collection
  - HbA_{1c} levels recorded within 3 months before initiating Toujeo®

HbA_{1C}, haemoglobin A_{1C} ; T1D, type 1 diabetes

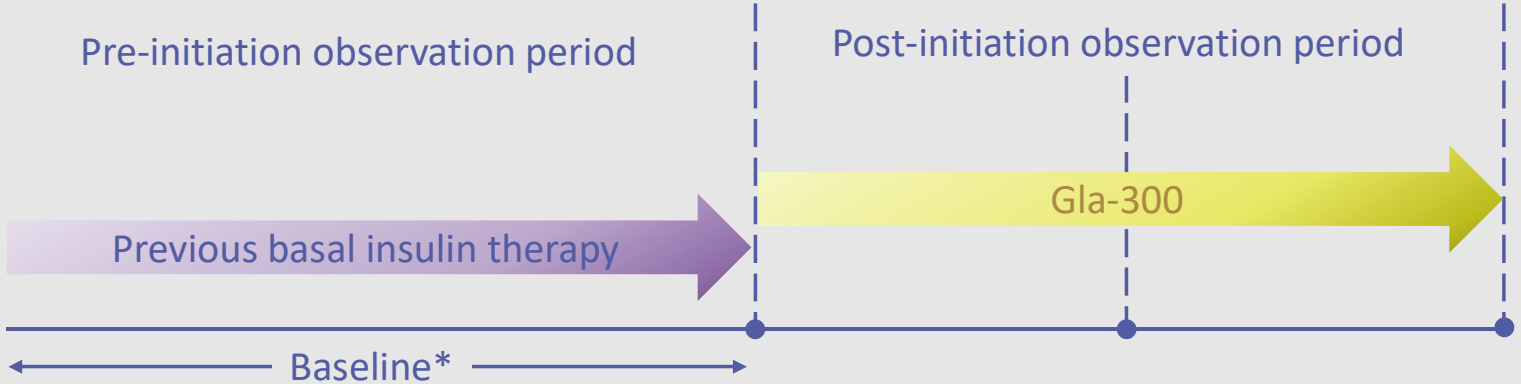
GEOGRAPHICAL DISTRIBUTION OF THE EIGHT PARTICIPATING CENTRES

1. T. Pang, *et al.* Poster MON-173-LB presented at ENDO, 2018.
2. T. Pang, et al. Poster P513B presented at DUK, 2018.

SPARTA study: Real World Evidence

Trial design[1]

Primary end point: Change in HbA1C (6 months after Toujeo initiation vs baseline)



0 month	3 months¥	6 months†
HbA1C**	HbA1C¥	HbA1C†
Weight		Weight
Insulin dose		Insulin dose
DKA		DKA
Hypos		Hypos
Structured Education		Structured Education
** -3 to 0 mths	¥2-4 mths	† 5-9 mths

*Collection of data in the "baseline" period is defined as the most recent observation within the 6 months prior to initiation of Gla-300, with the exception of HbA1c, which will be collected within 3 months prior to initiation of Gla-300

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

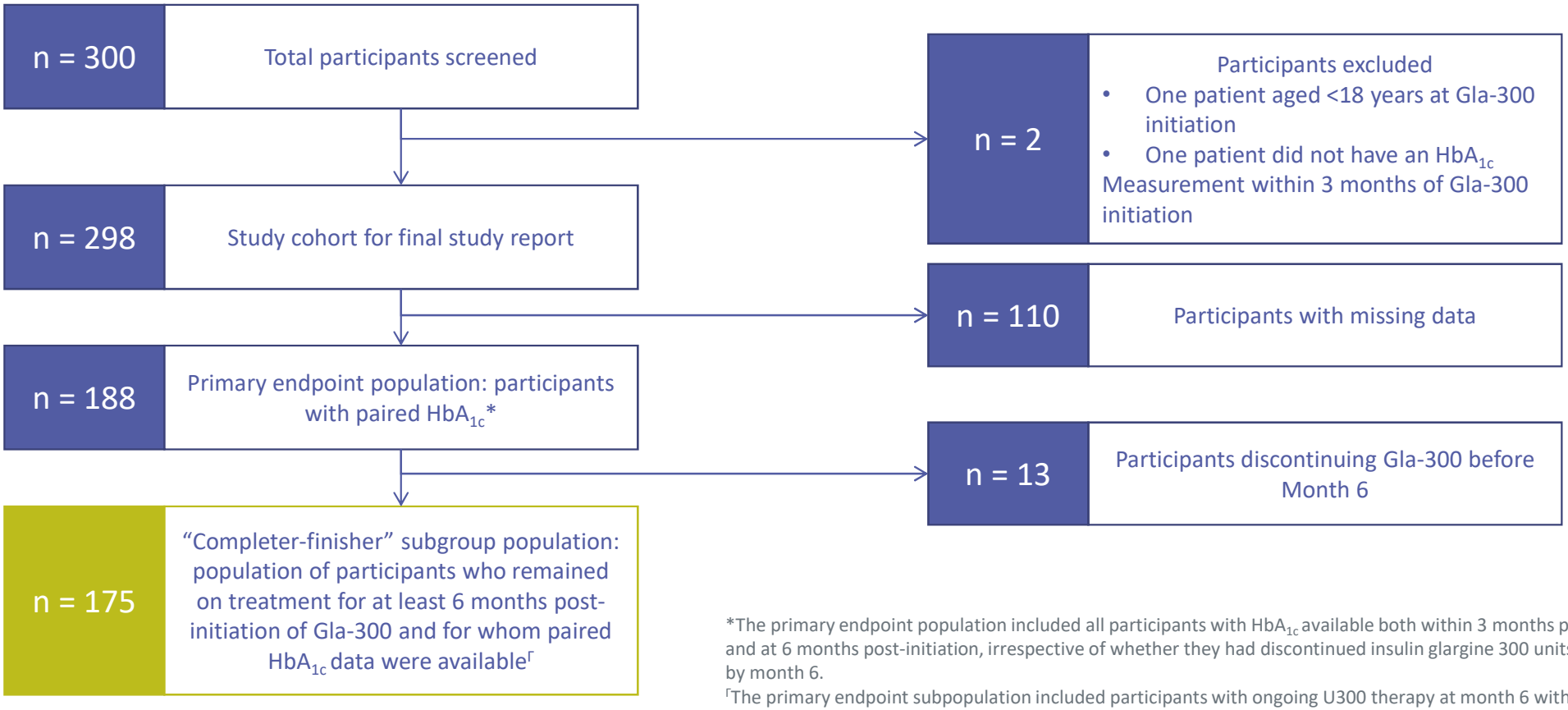
Controls applied to study[1]

Limitations	Adjustment
Inadequate power	Reliability estimates indicate sample size of 200 would have 99% confidence in detecting a -0.3 mmol/mol of primary outcome
Selection bias	Multi-centre (geography, practice setting, enrollment limits) Reverse consecutive recruitment Post hoc tests for data heterogeneity
Ascertainment	Source data verification by site visit
Confounding	Collecting data on: prandial insulin dose / CHO ratio changes structured education uptake

Uncontrolled limitations: incomplete records; medication compliance
patient recall bias (hypos); residual confounding

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Participant screening and eligibility[1]



*The primary endpoint population included all participants with HbA_{1c} available both within 3 months pre-initiation and at 6 months post-initiation, irrespective of whether they had discontinued insulin glargine 300 units/ml (U300) by month 6.

「The primary endpoint subpopulation included participants with ongoing U300 therapy at month 6 with HbA1c available both within 3 months pre-initiation and at 6 months post-initiation if they remained on U300 at month 6.

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Baseline patient characteristics

Baseline patient demographic and clinical characteristics[1]		Value	Number of patients (n)
Overall		-	299
Patient Profile	Age: mean (SD), years	42.2 (14.0)	299
	Gender: Male, n (%)	153 (51)	299
	Ethnicity: White, n (%)	217 (73)	299
	Body Weight: mean (SD), kg	80.2 (20.1)	106*
	BMI: mean (SD), kg/m	28.3 (6.7)	161*
Time since diagnosis	Mean time: mean (SD), years	20.4 (12.8)	271
	Median time: median (IQR), years	18.1 (10.6 – 29.7)	271
Clinical characteristics	HbA_{1c}: mean (SD), %	9.3 (1.7)	173*
	Number of patients with severe hypoglycaemic episodes in last 6 months, n (%)	6 (2)	299
	DKA in last 6 months, n (%)	4 (1)	299

* Paired values recorded at baseline and 6 months.

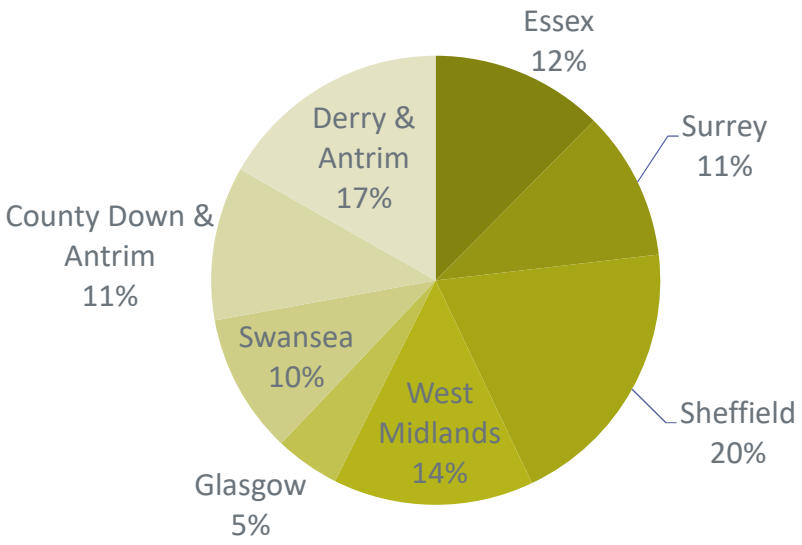
BMI: body mass index; DKA: diabetic ketoacidosis; IQR: interquartile range; SD: standard deviation; HbA_{1c}: glycated haemoglobin

1. T. Pang, *et al.* Poster MON-173-LB presented at ENDO, 2018.

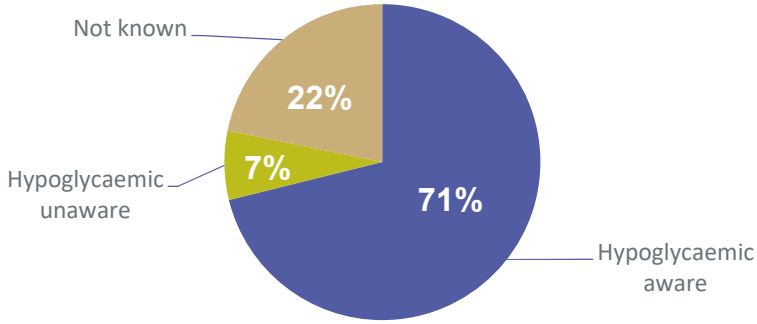
SPARTA study: Real World Evidence

Baseline patient characteristics[1]

Proportion of participants by county



Hypoglycaemic awareness status at baseline



Diabetes-related comorbidities, n (%)	
Obesity	43 (14)
Dyslipidaemia	70 (23)
Hypertension	54 (18)
Cardiovascular disease	21 (7)
Depression	53 (18)
Kidney disease (nephropathy)	22 (7)
Retinopathy	99 (33)
Neuropathy	28 (9)
Coeliac disease	9 (3)
Thyroid disease	32 (11)
None recorded	97 (33)

Comorbidities not mutually exclusive.

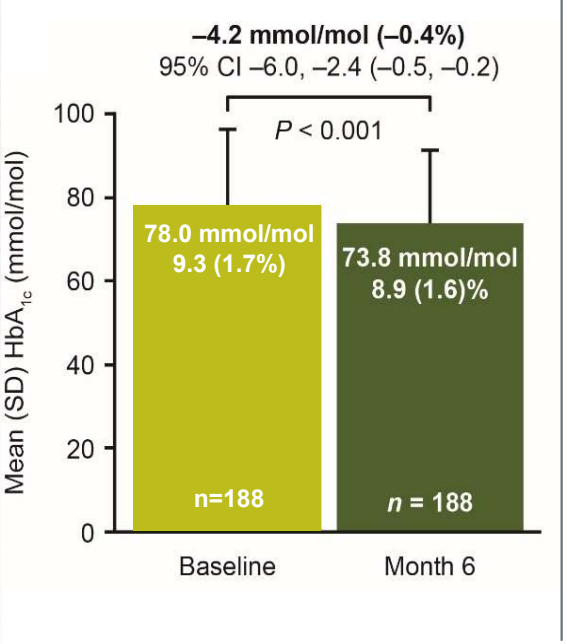
1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

SPARTA study: Real World Evidence

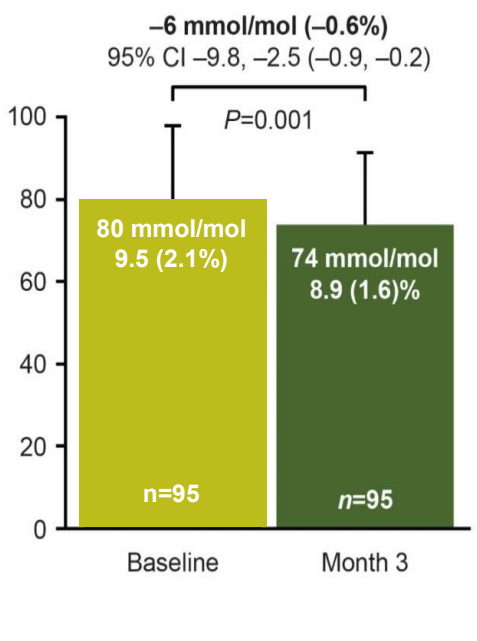
Change in HbA_{1C}

For overall population

from baseline to month 6

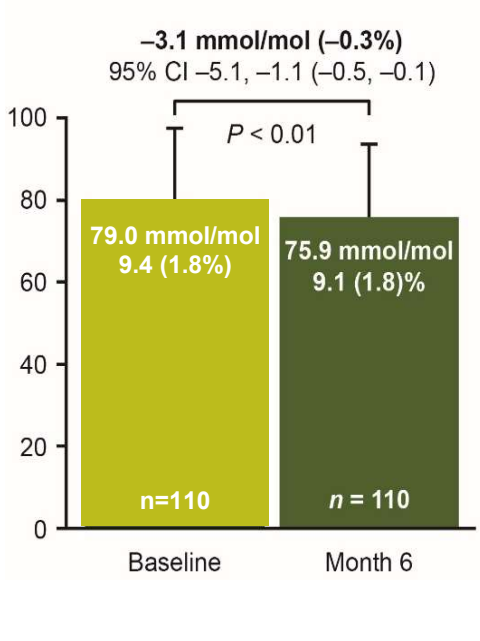


from baseline to month 3

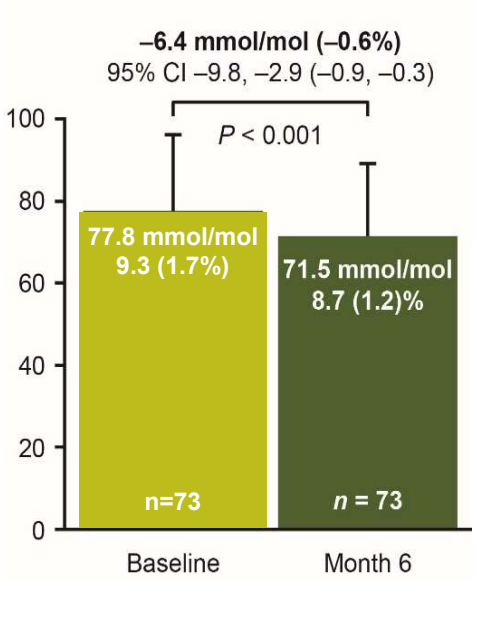


From baseline to month 6 for subgroup of participants previously on

once-daily basal insulin



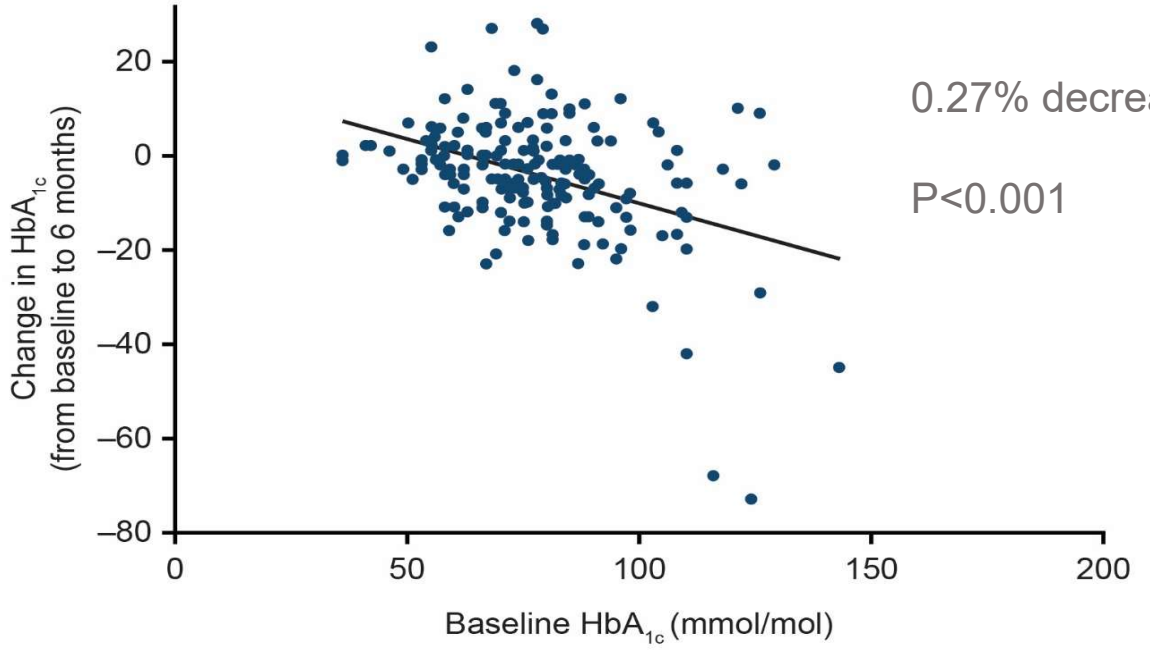
twice-daily basal insulin



1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

HbA1C

Linear model comparing change in HbA_{1C}* to baseline HbA_{1C}



0.27% decrease for every 1% higher baseline HbA_{1C}

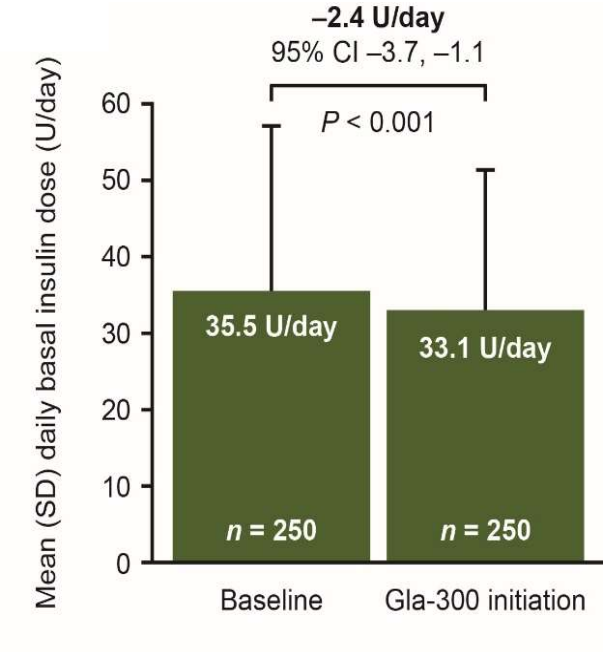
P<0.001

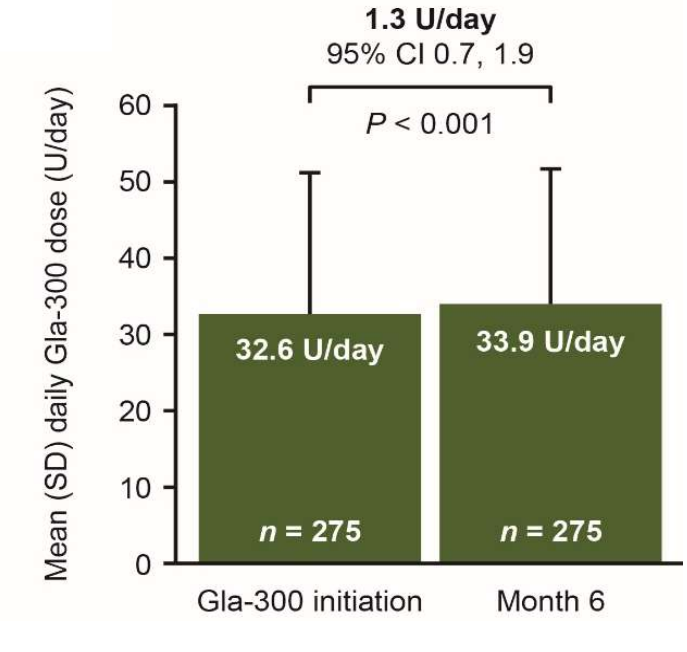
*from baseline to month 6 post-initiation of U300

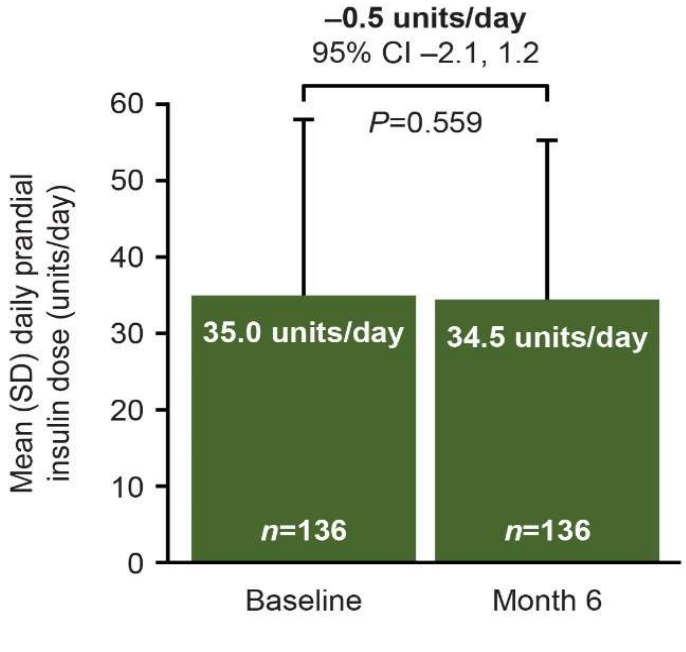
1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Daily dose of basal insulin

- ✓ **No significant difference in total daily prandial insulin dose or total daily insulin dose between previous insulin therapy (baseline) and month 6 or U300 initiation and month 6[1]**





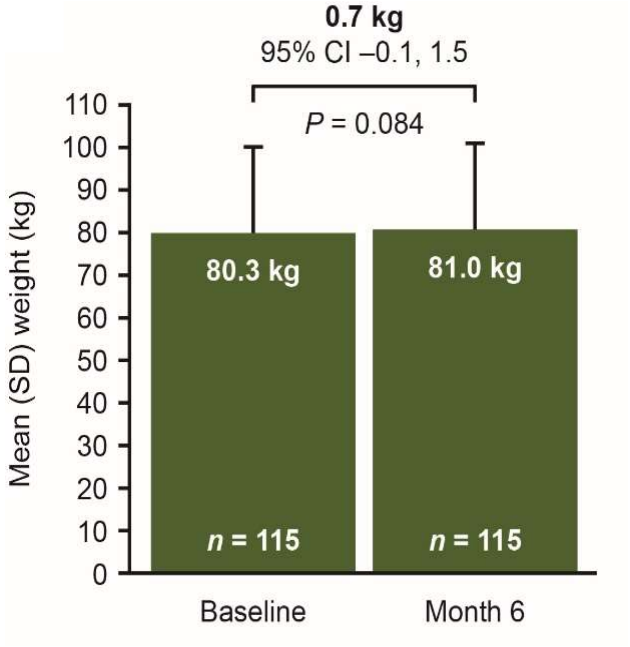


1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Change in weight

✓ **There was no clinically significant difference in weight between baseline and month 6[1]**

Change in body weight from baseline to month 6 post-initiation of insulin glargine 300units/ml (U300)



1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Diabetes education

Proportion of participants who attended structured diabetes education at baseline and within 6 months after the initiation of U300 and the types of education used[1]

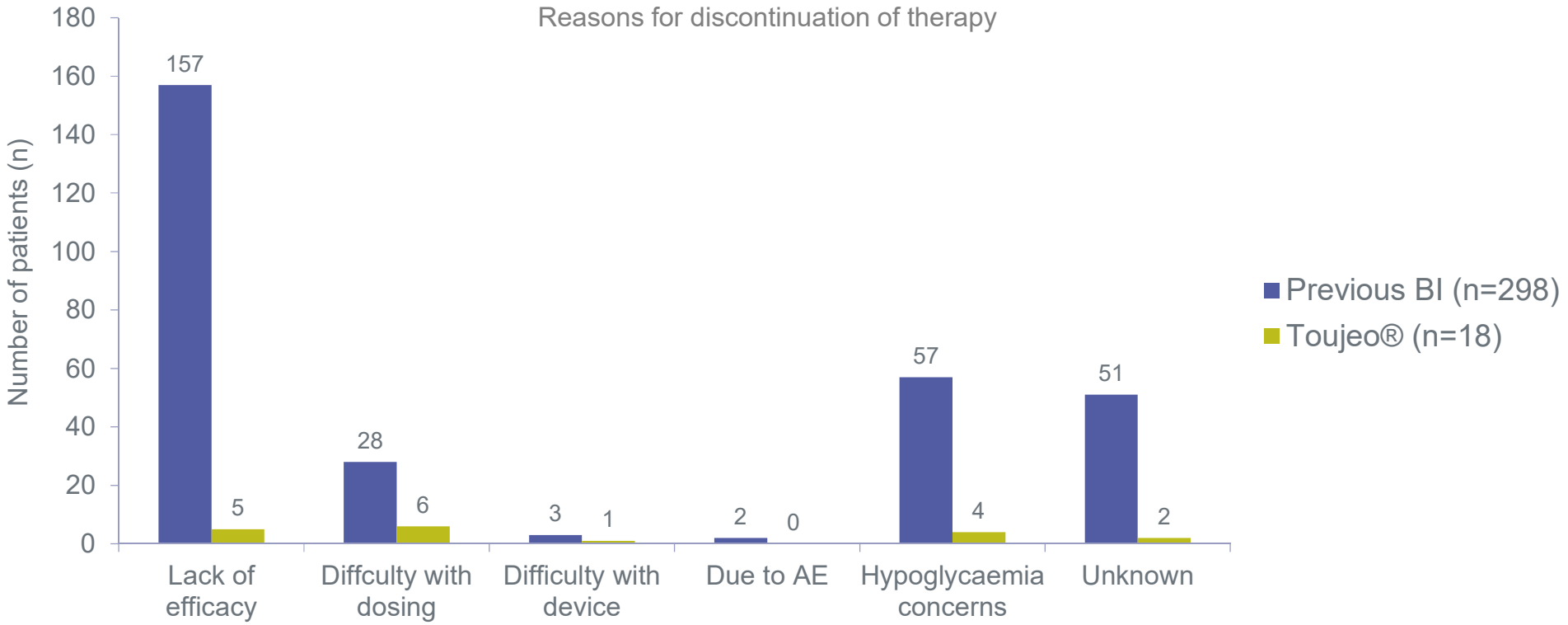
	Prior to U300 initiation *n* (%)	**Following U300 initiation *n* (%)**
Structured diabetes education	***n*=298**	***n*=298**
Yes	17 (6)	19 (6)
No	268 (90)	265 (89)
Not known	13 (4)	14 (5)
Type of education	***n*=17**	***n*=19**
DAFNE	5 (29)	9 (47)
BERTIE/CHOICE*	4 (24)	4 (21)
WICKED	0	0
STEPH	4 (24)	2 (11)
DAFYDD	2 (12)	2 (11)
One-to-one with dietitian	1 (6)	
3-h carbohydrate counting course		2 (11)
Not recorded	1 (6)	

*BERTIE and CHOICE are combined patient numbers

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

Reasons for discontinuation of BI therapy

✓ **Lack of efficacy is the most common reason for discontinuation of previous BI (53% patients)[1]**



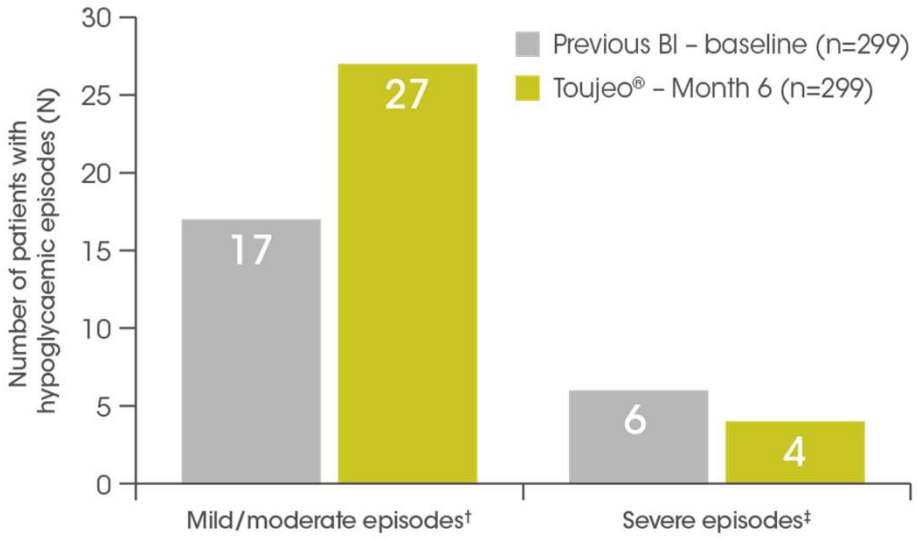
BI: basal insulin; AE: adverse events

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

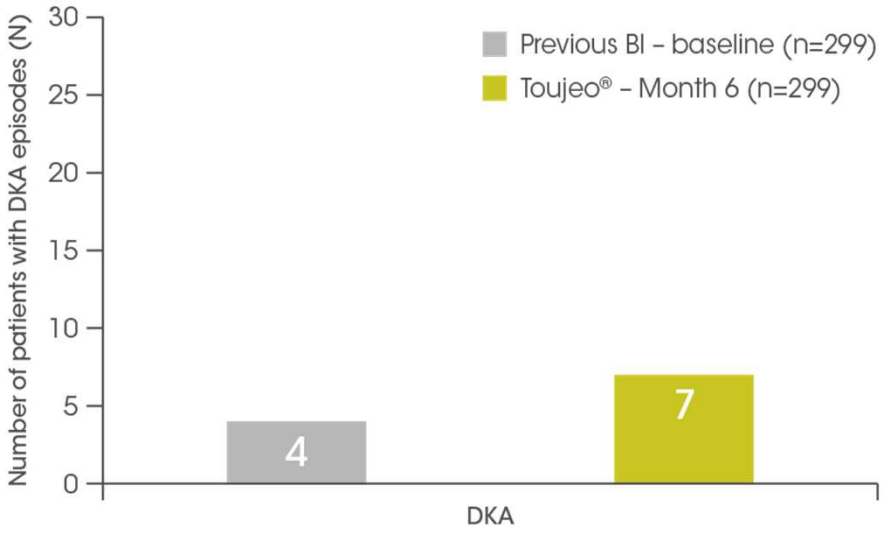
Patients with hypoglycaemic and DKA episodes

- Compared to previous BI[1], Toujeo® was associated with:
  - ✓ **No significant difference on the number of patients reporting episodes of severe hypoglycaemia**
  - ✓ **No significant difference on the number of patients reporting episodes of DKA**

Distribution of the patients with hypoglycaemic* episodes



Distribution of the patients with DKA episodes



Adapted from T. Pang, et al. Poster presented at ENDO 2018

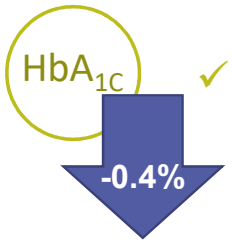
*Mild/moderate and severe categories not mutually exclusive. †Under-reporting of mild/moderate hypoglycaemic episodes occurs within the community; this means that the data here should be interpreted with caution. ‡Requiring third-party assistance.

BI: basal insulin; DKA: diabetic ketoacidosis

1. T. Pang, *et al.* Poster MON-173-LB presented at ENDO, 2018.

Summary of findings

- SPARTA represents the real-world experience of using Toujeo® in patients with T1D in the UK[1]
- **Switching from previous basal insulin to Toujeo® in people with T1D is associated with:[1]**



✓ **0.4% reduction in HbA_{1C}** at 6 months

- ✓ Greatest benefit in those switching from twice daily basal insulin
- ✓ Higher baseline HbA_{1C}

✓ **No clinically relevant changes in BI dose***

✓**No significant difference** in the number of patients reporting either episodes of **severe hypoglycaemia or DKA***

✓**No significant change in body weight** *†

*Results observed for reported patients.

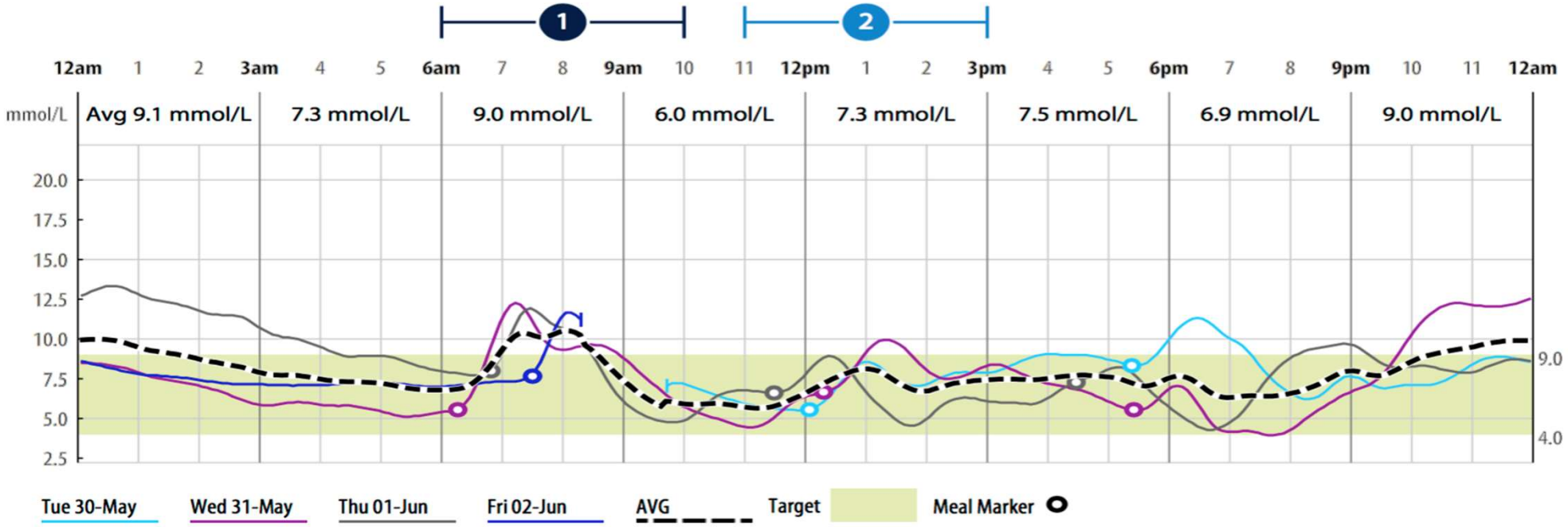
†No significant change in body weight for patients for whom data were available (n=106, Δ 0.7kg, p=0.09)

BI: basal insulin

1. T. Pang, *et al.* Research Article, DME-2018-00425 published on Diabetic Medicine, 2018

SPARTA study: Real World Evidence

- Point estimate for ↓HbA_{1C} in line with RCT
- Risk of selection bias from 60% clinic attenders
- Suboptimal titration may lead to under-estimate
- Correlation of baseline HbA_{1C} vs change in HbA_{1C} against “placebo” effect



Time in range: from 50 to 79%
? PK / PD effect
? Compliance
? ⬇Pre-emptive snacking

Plan

Toujeo®: basic pharmacology

Toujeo® mimics endogenous insulin

Toujeo® clinical efficacy and safety profile

Applicability to our practice?

SPARTA study: Real World Evidence

Toujeo® in summary

"Will a switch of insulin to Toujeo help my patient?"

Conclusions

- Efficacy of Toujeo in T1D in RCT translatable to routine UK clinical practice
- Well conducted RWE study using routinely collected clinical data can:
  - complement RCT in clinical decision making
  - generate hypotheses for further research

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Toujeo, a change of the dose of the basal insulin may be required and the concomitant anti-hyperglycaemic treatment may need to be adjusted.
Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

Acknowledgments

- Sanofi UK
- pH Associates
- Minal Lawrence
- Research DSN

Toujeo® Prescribing Information

Toujeo® (insulin glargine 300 units/ml)
Please refer to Summary of Product Characteristics prior to use of Toujeo. Presentation: Toujeo Solostar pre-filled pens each contain 450 Units of insulin glargine in 1.5 ml of solution for injection, equivalent to 10.91 mg/ml.
Indication: Treatment of diabetes mellitus in adults.
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. 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-/rapid-acting 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.
Special populations: Insulin requirements may be diminished in the elderly or patients with renal or hepatic impairment. *Paediatric:* No data available.

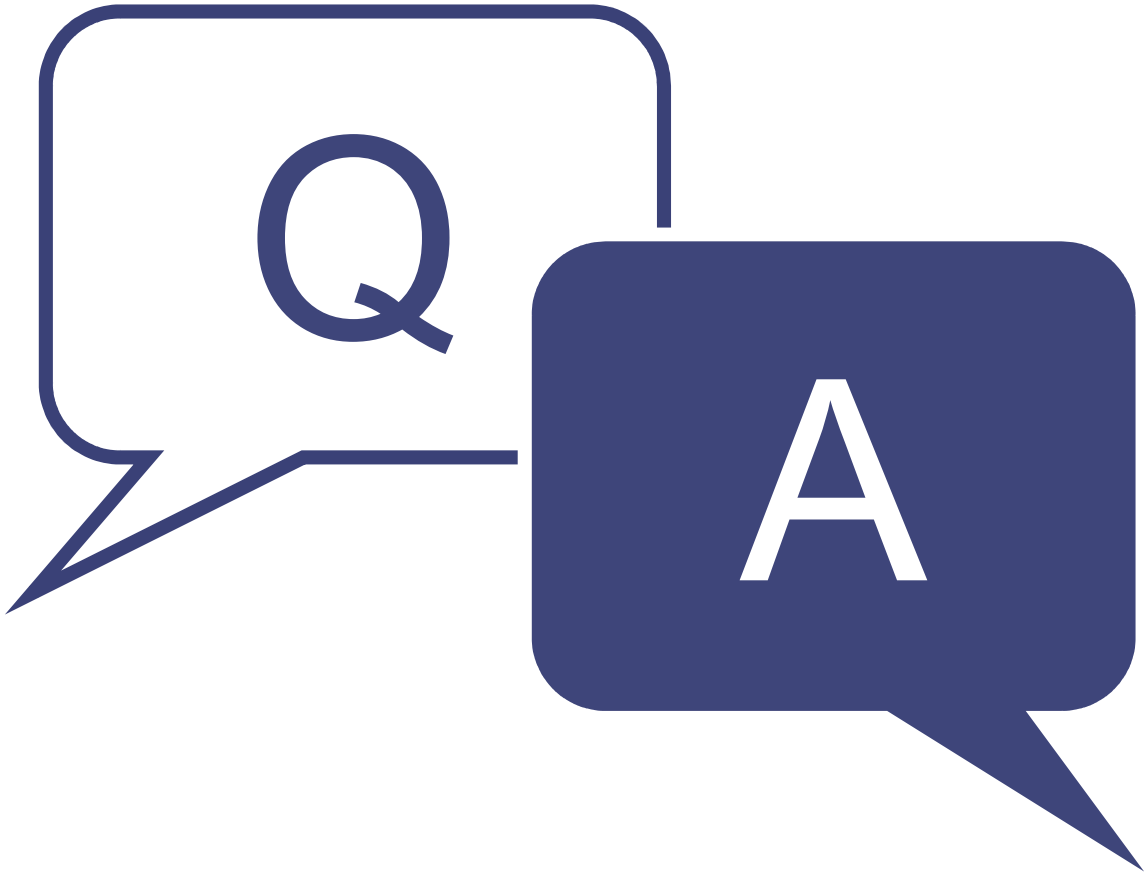
Contraindications: Hypersensitivity to insulin glargine or any excipients.
Precautions and warnings: Toujeo is not the insulin of choice for treatment of diabetic ketoacidosis. *Hypoglycaemia:* In case of insufficient glucose control or a tendency to hyper/hypoglycaemic episodes, the patient's adherence 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 pre-filled pen, A new sterile needle must be attached before each injection. Needles must not be re-used. *Pregnancy and lactation:* There is 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.
Adverse reactions: *Very common (≥1/10):* Hypoglycaemia. Prolonged or severe hypoglycaemia may be life-threatening. *Common (≥1/100 to <1/10):* Lipohypertrophy, injection site reactions, including redness, pain, itching, hives, swelling, or inflammation. *Uncommon (≥1/1,000 to <1/100):* Lipoatrophy. *Rare (≥1/10,000 to <1/1,000):* Allergic reactions; which may be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock and may be life threatening; visual impairment, retinopathy and oedema. *Very rare (<1/10,000):* Dysgeusia, myalgia. Overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.
Please consult SmPC for full details of the adverse reactions.
NHS price: £33.13 for pack of x3 1.5ml pens.
Legal category: POM.
Marketing Authorisation (MA) holder: Sanofi Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.
MA Number: SoloStar 3 Pen pack: EU/1/00/133/034.
Full prescribing information is available from: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS. Tel: 01483 505515 or the Sanofi Diabetes Care Line 08000 352 525.
Date of preparation: April 2018

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Sanofi Tel: 0800 0902314.
Alternatively, send via E-mail to UK-drugsafety@sanofi.com

Lantus® Prescribing Information

Lantus® (insulin glargine 100 units/ml)
Please refer to Summary of Product Characteristics prior to use of Lantus.
Presentations: Lantus 100 units/ml solution for injection in a vial or in a cartridge. Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen. Lantus cartridges and Solostar pre-filled pens each contain 3 ml of solution for injection, equivalent to 300 units insulin glargine. Each vial contains 10 ml of solution for injection, equivalent to 1000 units.
Indications: Treatment of diabetes mellitus in adults, adolescents and children of 2 years or above.
Dosage and administration: Lantus is administered subcutaneously once daily, at any time but at the same time each day. Injection sites must be rotated within a given injection area from one injection to the next. Do not administer intravenously. Lantus dosage should be individually adjusted. In type 2 diabetes mellitus, Lantus can also be used in combination with orally active antidiabetic medicinal products. Lantus must not be mixed with other insulins or diluted. *Switch from twice daily NPH insulin to Lantus:* To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Lantus should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment. *Switch from Toujeo (insulin glargine) 300 units/ml to Lantus:* Lantus and Toujeo are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily Toujeo to a once daily regimen with Lantus should reduce their dose by approximately 20%. *Switching from other insulins to Lantus:* When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Lantus, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products). Close metabolic monitoring is recommended during, and for a period after, transition from other insulins to Lantus. 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. *Elderly population (≥65 years old), patients with renal or hepatic impairment:* Insulin requirements may be diminished. *Children (<2 years of age):* No data are available.
Contraindications: Hypersensitivity to insulin glargine or any excipients.
Precautions and warnings: Lantus is not the insulin of choice for treatment of diabetic ketoacidosis. In case of insufficient glucose control or a tendency to hypo/hyperglycaemic episodes all relevant factors must be reviewed before dose adjustment is considered. Transferring a patient to another type or brand of insulin should be done under strict medical supervision. *Hypoglycaemia:* Particular caution should be exercised, and intensified blood 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. The prolonged effect of subcutaneous Lantus may delay recovery from hypoglycaemia. Due to more sustained basal insulin supply with Lantus, less nocturnal but earlier morning hypoglycaemia can be expected. *Intercurrent illness:* requires intensified metabolic monitoring. *Insulin antibodies:* administration may cause insulin antibodies to form. Rarely, this may necessitate dose adjustment. *Pioglitazone:* Cases of cardiac failure have been reported, especially in patients with risk factors for development of cardiac heart failure. Patients on this combination should be observed and 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 Lantus and other insulins. Lantus Solostar is only suitable for subcutaneous injections from its pre-filled pen. Lantus cartridges are only suitable for subcutaneous injections from a reusable pen (JuniorSTAR which delivers Lantus in 0.5 unit dose increments and Autopen 24, AllStar and AllStar PRO which all deliver Lantus in 1 unit dose increments). If administration by syringe is necessary, a vial should be used. *Interactions:* A number of substances affect glucose metabolism and may require dose adjustment of Lantus. *Pregnancy and lactation:* No clinical data on exposed pregnancies from controlled clinical trials are available. A large amount of post-marketing data indicates no specific adverse effects of Lantus in pregnancy. Use of Lantus in pregnancy can be considered if clinically needed. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential. It is unknown if Lantus is excreted in breast milk.
Adverse reactions: *Very common (≥1/10):* Hypoglycaemia. Prolonged or severe hypoglycaemia may be life-threatening. *Common (≥1/100 to <1/10):* Lipohypertrophy, injection site reactions. *Uncommon (≥1/1,000 to <1/100):* Lipoatrophy. *Rare (≥1/10,000 to <1/1,000):* Allergic reactions, visual impairment, retinopathy and oedema. *Very rare (<1/10,000):* Dysgeusia, myalgia. Overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.
Please consult SmPC for full details of the adverse reactions.
NHS list price: 1 x 10ml Lantus vial: £27.92; 5 x 3ml Lantus cartridge: £37.77; 5 x 3ml Lantus SoloStar: £37.77.
Legal category: POM.
Marketing Authorisation (MA) holder: Sanofi Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany. **MA Numbers:** Vial: EU/1/00/134/012, Cartridge: EU/1/00/134/006, SoloStar: EU/1/00/134/033.
Full prescribing information is available from: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS. Tel: 01483 505 515 or the Sanofi Diabetes Care Line 08000 352 525.
Date of preparation: April 2018

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Sanofi Tel: 0800 0902314.
Alternatively, send via E-mail to UK-drugsafety@sanofi.com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