2nd Generation Insulins & management of Glycemic Variations

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Agenda

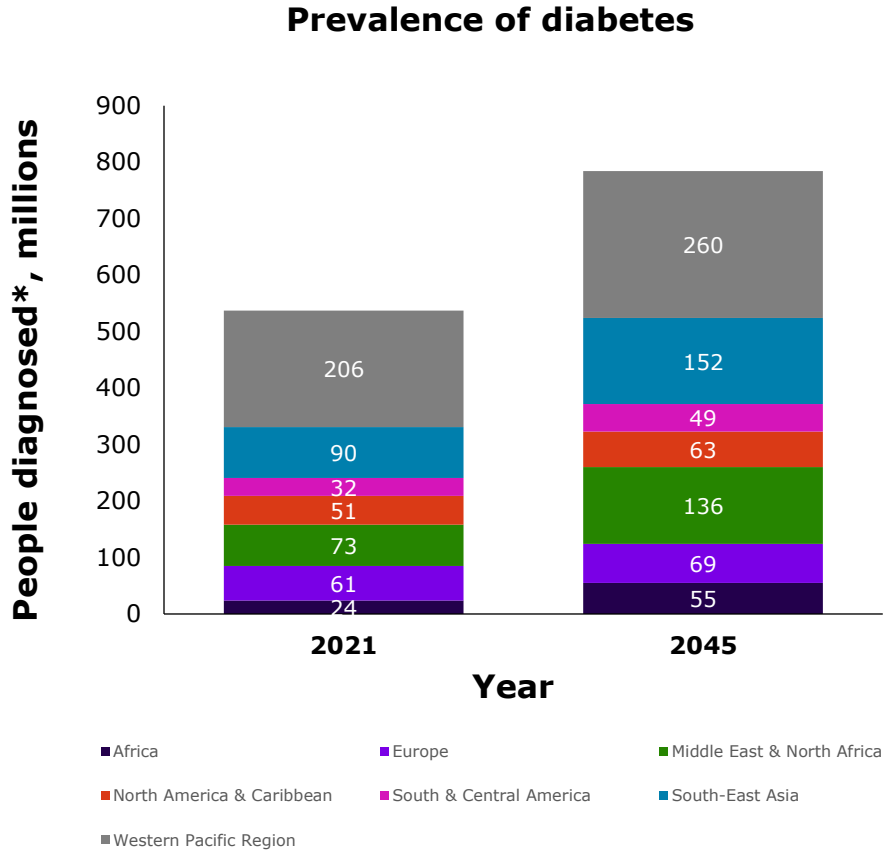
- Overview global picture of diabetes
- Highlight of problems with this epidemic & call to action
- 2nd generation basal insulins case scenario and the studies overview
- Cardio-Renal-Metabolic case scenario to FRC and studies overview
- Summary and take home points
- Q and As

Diabetes is one of the fastest growing global health emergencies of the 21st century

Diabetes affects 537 million global adult population*
- Overall, 9 in every 10 cases of diabetes is T2D

In 2021, diabetes care was estimated to cost $966 billion globally, a 316% increase over the last 15 years
- It is estimated that 50% of the people affected with diabetes are still undiagnosed

Estimates anticipate 783 million cases of diabetes globally by 2045, with a 46% increase from 2021*



*Aged 20–79 years.
T2D, Type 2 diabetes.
1. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. Last accessed: Nov 2024

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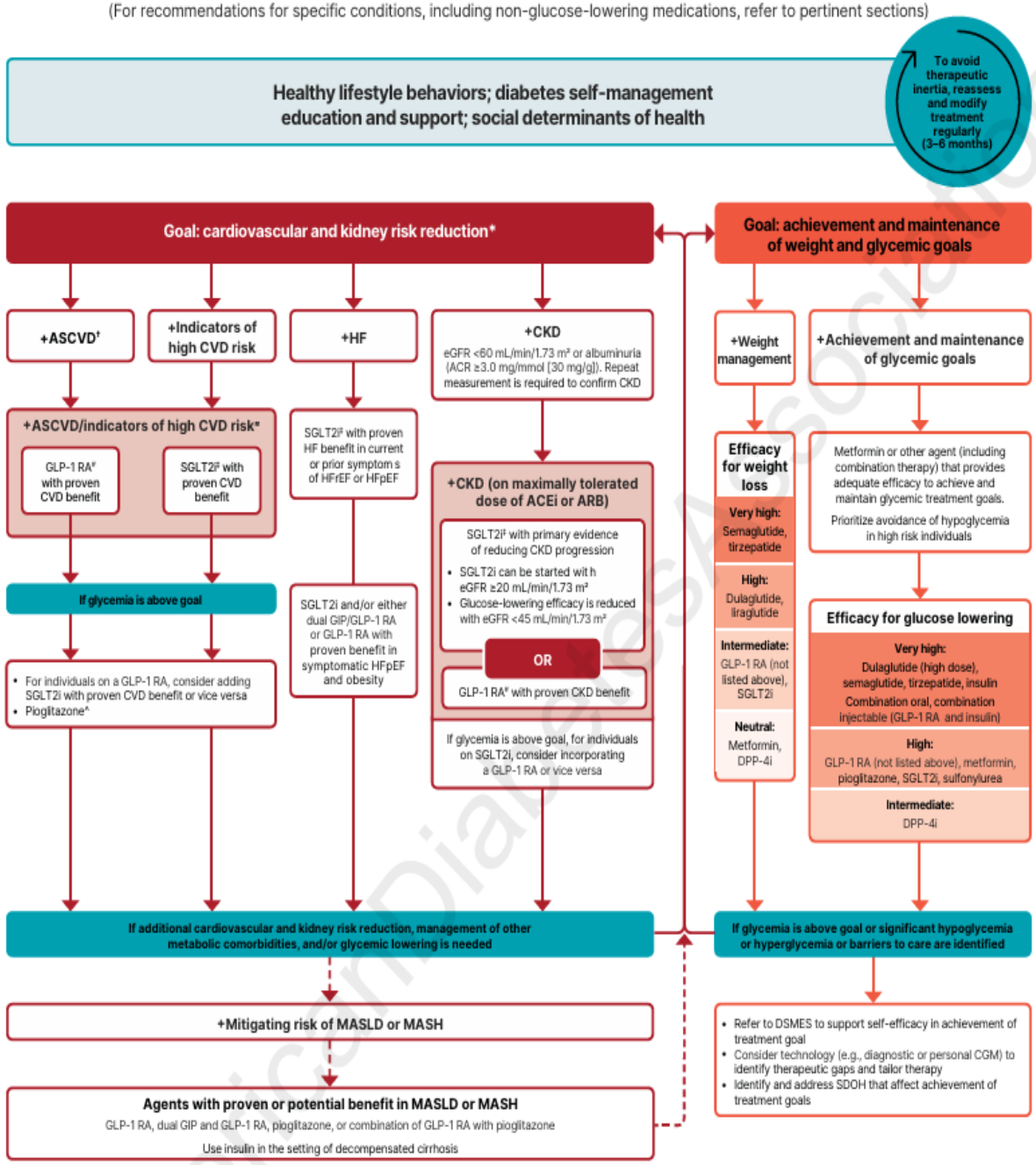
Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Diabetes Care Volume 49, Supplement 1, January 2026

Case1

Age: 62yr old male T2D
Weight: 85kg
Ht: 1.7
Occupation: Long distance bus driver
Duration of diabetes: 11 years
Current medications: Insulin Glargine U-100 48units once daily s/c, Metformin 1000mg bd
Controls: FBS = 11.8 mmol/l, HBA1c = 9.4%
Complaints: polyuria, fatigue, occasional night time hypoglycemia
Next step??? Which insulin and why?

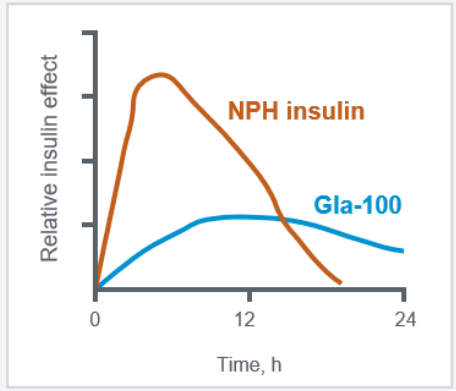
Evolution of basal insulin development from 1st to 2nd generation basal insulin analogs: overcoming limitations

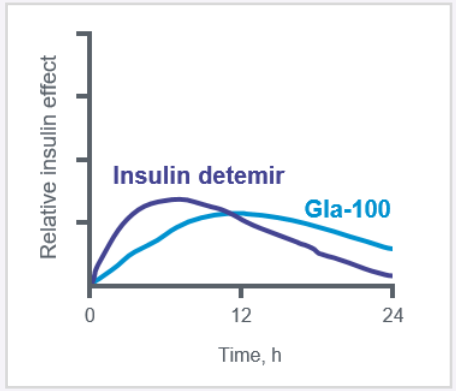
Insulin glargine 100 U/mL (Gla-100) and insulin detemir (IDet) were developed to overcome some limitations of early basal insulins such as NPH insulin, with less variable absorption and longer duration of action[1,2]

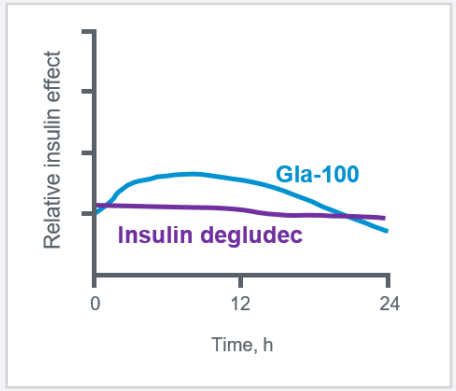
Longer-acting basal insulins, **insulin glargine 300 U/mL (Gla-300)** and insulin degludec (IDeg), have since been developed with less variability and more prolonged durations of action (>24 h)[1,2]

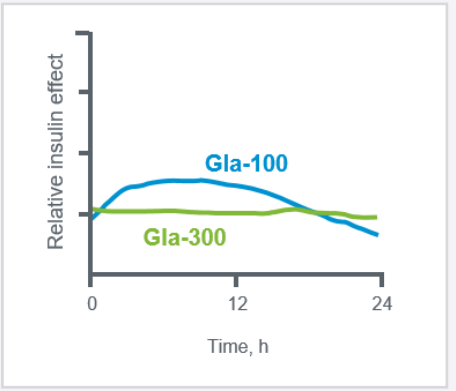
Timeline

Profile comparisons









Comparison of action after a single dose for NPH and Gla-100 and for Gla-100 and insulin detemir; Comparison at steady state for Gla-100 and Gla-300 and for Gla-100 and insulin degludec. NPH, neutral protamine Hagedorn. IDet, insulin detemir. IDeg, insulin degludec.

1. Eliaschewitz FG, Barreto T. Diabetol Metab Syndr. 2016;6;8:2; **2.** Pettus J et al. Diabetes Metab Res Rev. 2016;32(6):478–496.; **3.** HUMULIN N [PI] https://pi.lilly.com/us/HUMULIN-N-USPI.pdf; **4.** NOVOLIN N [PI] https://www.novo-pi.com/novolinn.pdf; **5.** LANTUS [PI] https://products.sanofi.us/lantus/lantus.html; **6.** LEVEMIR [PI] https://www.novo-pi.com/levemir.pdf; **7.** TRESIBA [PI] https://www.novo-pi.com/tresiba.pdf; **8.** TOUJEO [PI] https://products.sanofi.us/toujeo/toujeo.pdf

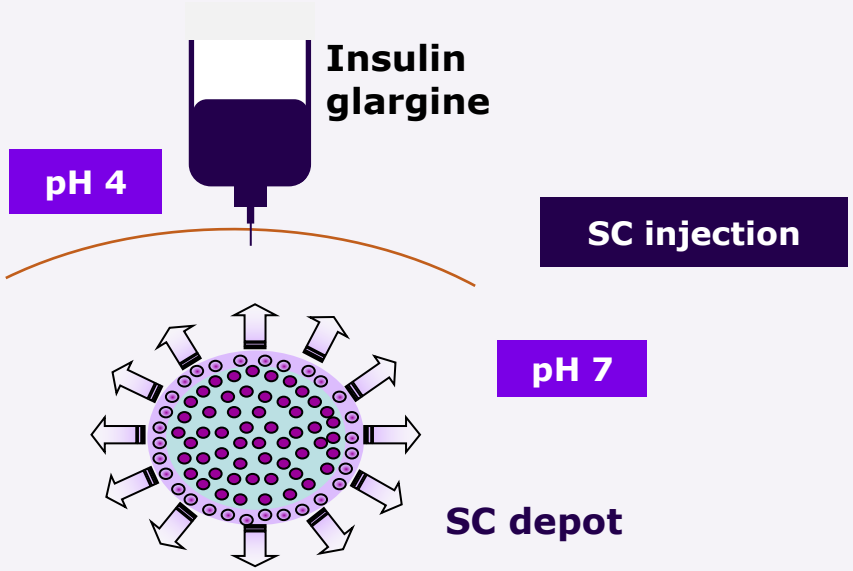
Mode of action: Mechanism of protraction via depot formation

Insulin glargine differs from human insulin by a glycine substitution at position A21 and the addition of two arginine residues to the B-chain

Insulin glargine is chemically stable and fully soluble in acid solution

Insulin glargine

21A-Gly-human insulin



For illustrative purposes only

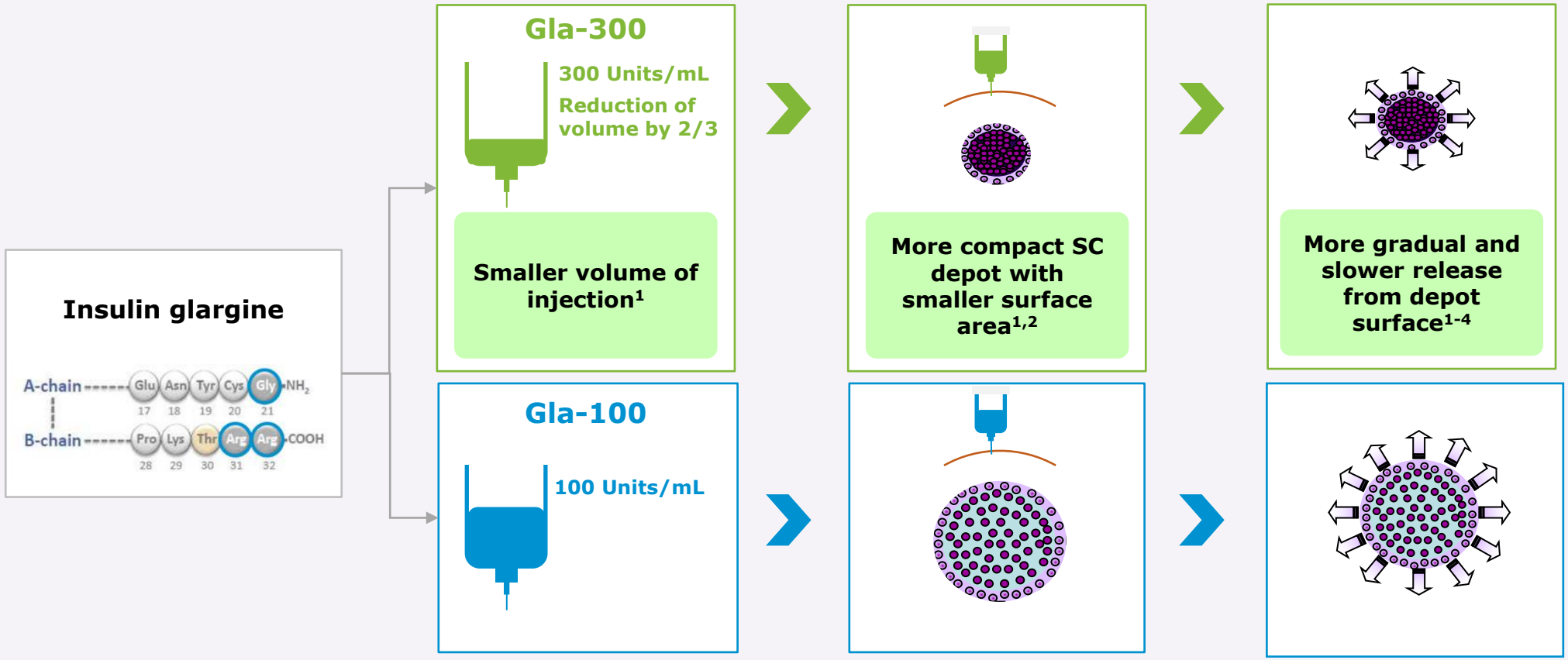
Following SC injection, insulin glargine precipitates amorphously creating a SC depot at physiological pH

Enzymatic maturation forms the active metabolite, 21A-Gly-human insulin, that is released slowly from the depot to the circulation

SC, subcutaneous.

Hedrington MS, et al. Diabetes Technol Ther. 2011;13(Suppl 1):S33–42; Becker RH et al. Diabetes Care. 2015;38(4):637–643.

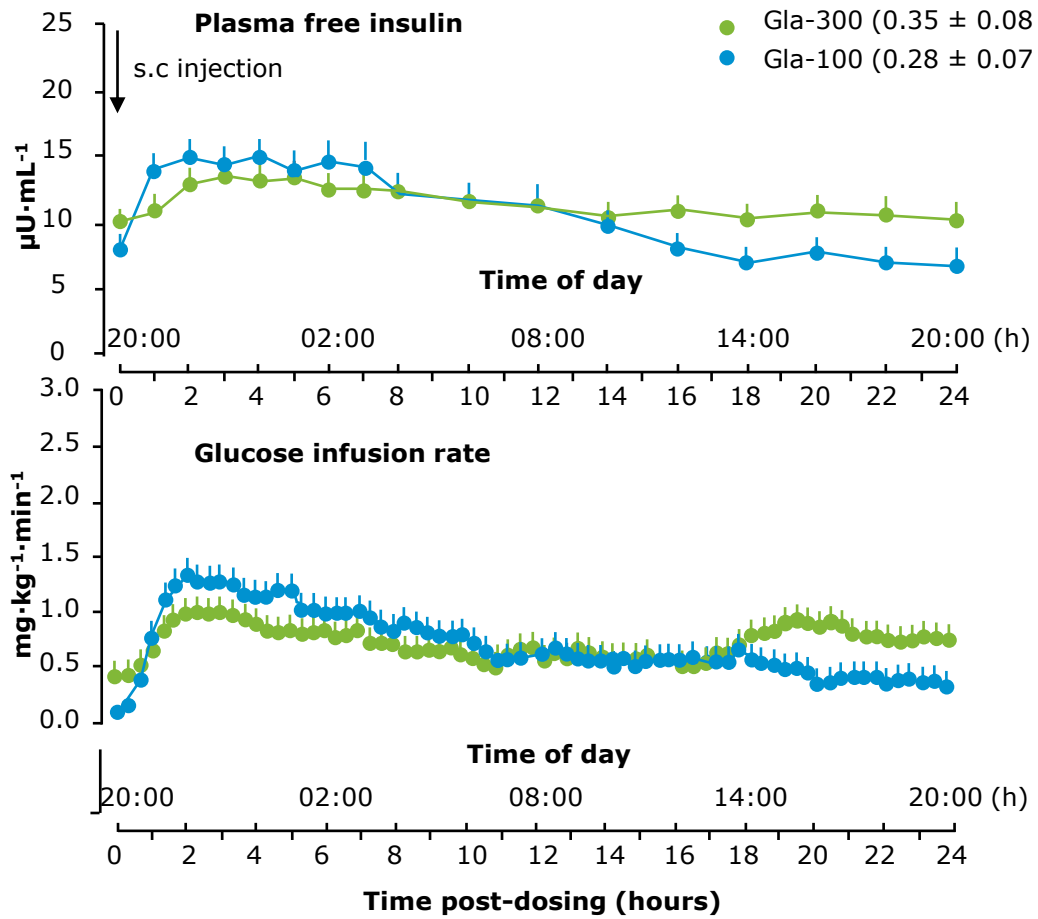
Compact depot formation results in more gradual insulin release with Gla-300 vs Gla-100



No differences in potency between Gla-100 and Gla-300 on a unit to unit base

For illustrative purposes only.
1. Pettus J, et al. Diabetes Metab Res Rev. 2016;32(6):478–496; **2.** Adapted from Sutton G, et al. Expert Opin Biol Ther. 2014;14(12):1849–1860;
3. Steinstraesser A, et al. Diabetes Obes Metab. 2014;16(9):873–876; **4.** Becker RH, et al. Diabetes Care. 2015;38(4):637–643.

Gla-300 exhibits a more stable profile with lower variability compared with Gla-100 after dose optimization in people with T1DM



PK and PD within-day variability was 50% and 17% lower with Gla-300

24-hr insulin profile for Gla-300 is flatter and more constant over 24 hrs compared with Gla-100

Glucose infusion rate was more consistent over 24 hr with Gla-300 vs Gla-100

After 3-month treatment period, BI dose was higher with Gla-300 vs Gla-100

BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; PD, pharmacodynamics; PK, pharmacokinetics; T1DM, type 1 diabetes mellitus.

Porcellati F, et al. Diabetes Care. 2019;42(1):85–92.

Conclusion: Gla-300 characteristics

- **Gla-300 forms a more compact and smaller depot vs Gla-100, which leads to:**
  - More gradual and slower release of insulin from the surface of the depot
  - More constant and prolonged glucose-lowering profile, maintaining tight blood glucose control for approximately 30 hours[1]
  - Low within-day fluctuation and between-day variability[2]
- **Gla-300 has more stable and more evenly distributed steady-state profile at 0.4 U/kg/day vs IDeg-100[3]**

Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL.

1. Becker RH, et al. Diabetes Care. 2015;38(4):637–643; **2.** Bailey TS, et al. Diabetes Metab. 2018;44(1):15–21; **3.** Becker et al. Diabetes Obes Metab. 2015;17(3):261–267.

Summary of key Gla-300 studies in T1D, T2D and special populations

T2D uncontrolled on

OADs

EDITION 3/JP2/AP
BRIGHT
TAKE CONTROL
REACH CONTROL
ACHIEVE CONTROL
DELIVER Naïve/Naive D
LIGHTNING
ATOS

OAD + GLP-1 RA

RESTORE-G
DELIVER-G

BOT

Switching from previous BI

EDITION 2
ARTEMIS-DM
LIGHTNING
REALI (NPH)

BB

Switching from previous BI

EDITION 1

DELIVER 2 & DELIVER D+, DELIVER-HR, TREGS

T1D

Adult

EDITION 4/JP
Bergenstal CGM
INRANGE CGM
OneCARE CGM
RESTORE-1
REALI T1
ULTRAFLEXI-1 CGM

Paediatric

EDITION JUNIOR

Special Populations

OLDER

SENIOR
DELIVER 3
ATOS Older
BRIGHT Older
REALI Older

CKD

BRIGHT Renal
ATOS Renal
DELIVER R
REALI CKD

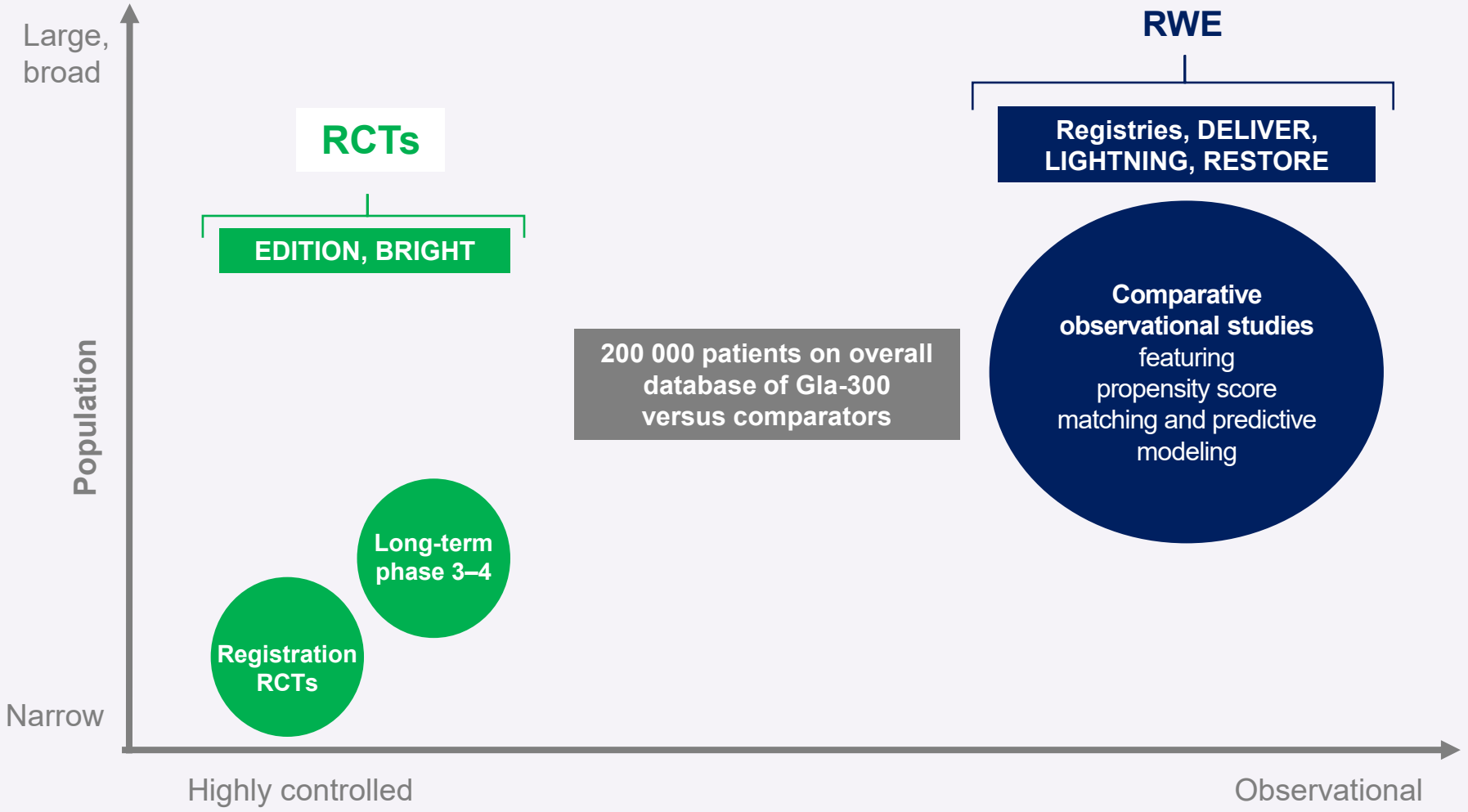
Other

ORION (Ramadan)
Gla-300 Pregnancy*

Interventional trial
Real-world evidence

Figure includes ongoing studies that are yet to be published. *Pharmacovigilance data

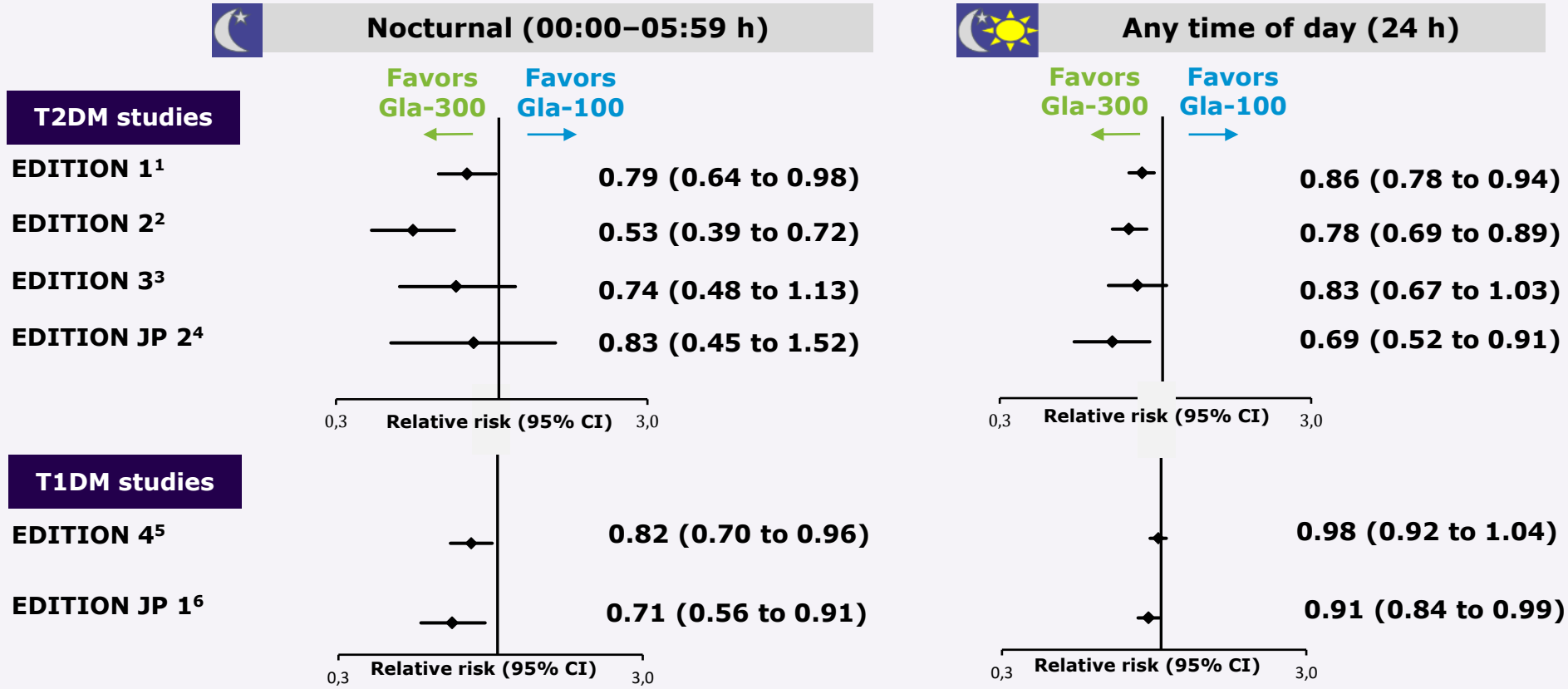
Evidence Generation for Gla-300 inT2DM



Gla-300, insulin glargine 300 U/mL; RCT, randomized controlled trial; RWE, real-world evidence; T2DM, type 2 diabetes mellitus.
Adapted from: Roche N et al. Ann Am Thorac Soc. 2014;11:99–104.

Gla-300 vs Gla-100 use may lead to reduced hypoglycemia during the titration period

Confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia vs Gla-100 from baseline to Week 8



Relative risk and 95% CI based on % of participants with ≥1 event of one confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia

1. Adapted from Riddle MC, et al. Diabetes Care. 2014;37(10):2755–2762; **2.** Yki-Järvinen H, et al. Diabetes Care. 2014;37(12):3235–3243; **3.** Bolli GB, et al. Diabetes Obes Metab. 2015;17(4):386–394; **4.**Terauchi Y, et al. Diabetes Obes Metab. 2016;18(4):366–374 (main article and Supplementary Table 4); **5.** Home PD, et al. Diabetes Care. 2015;38(12):2217–2225 (Supplementary Table 2); **6.** Matsuhisa M, et al. Diabetes Obes Metab. 2016;18(4):375–383 (Supplementary Table 3).

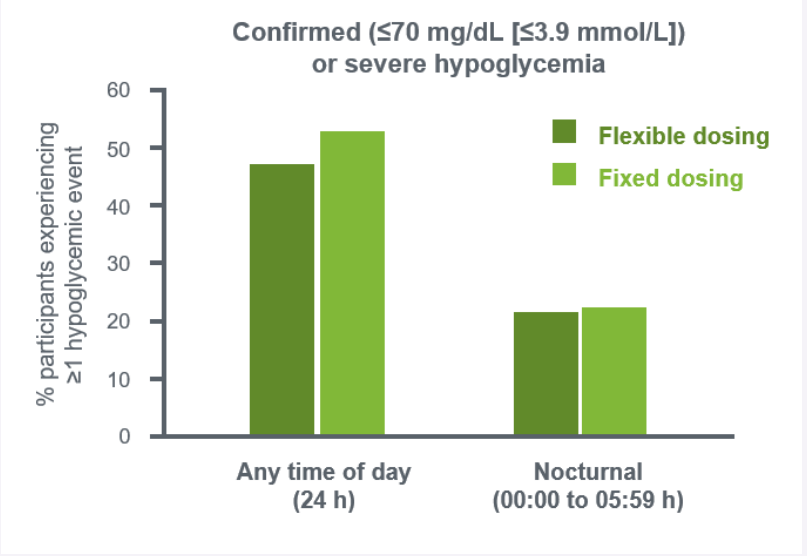
EDITION 1, 2

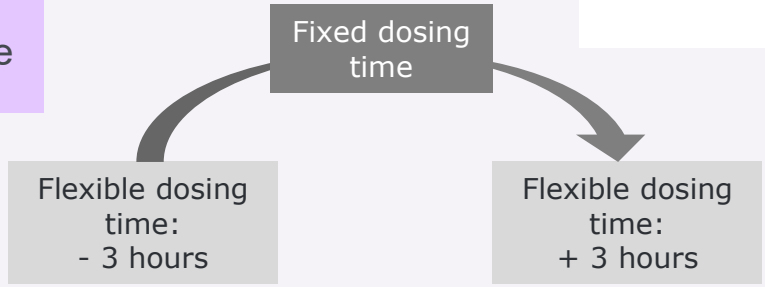
Flexible dosing time of Gla-300 had no effect on glycemic control and incidence of hypoglycemia vs fixed dosing time

Pooled EDITION 1 and 2 substudies in T2DM (Months 6–9)

HbA_{1C},%	Flexible dosing* n=99	Fixed dosing n=95
Month 6, mean (SD)	7.30 (0.93)	7.30 (0.96)
Month 6–9, LS mean change (SE)	0.05 (0.06)	0.00 (0.07)
LS mean difference (95% CI)	0.05 (–0.13 to 0.23)	

Gla-300 may allow some flexibility in timing injections to deal with the situational variability experienced in daily life



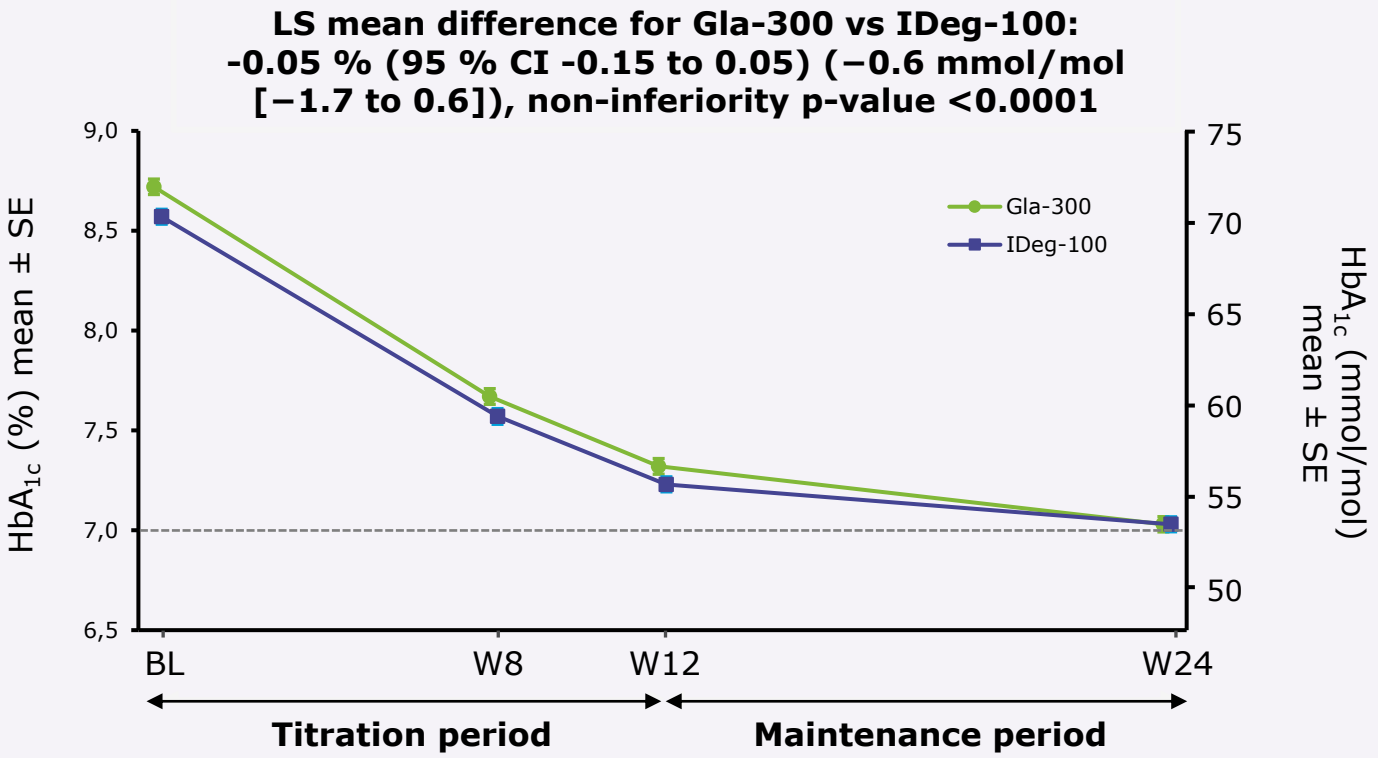


6-hour flexible dosing time window

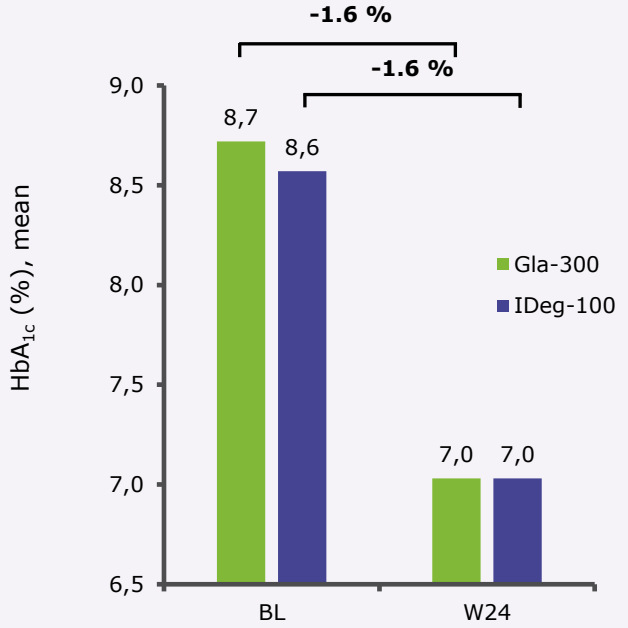
Sub studies design

*Flexible dosing time: Once-daily injection intervals of 24 ± 3 h
Adapted from Riddle M, et al. Diabetes Technol Ther. 2016;18(4):252–257.

BRIGHT: Non-inferiority of Gla-300 vs IDeg-100 in HbA_{1c} reduction at study end in T2DM patients



No. of participants	**Gla-300**	462	448	448	430
	IDeg	462	447	445	425



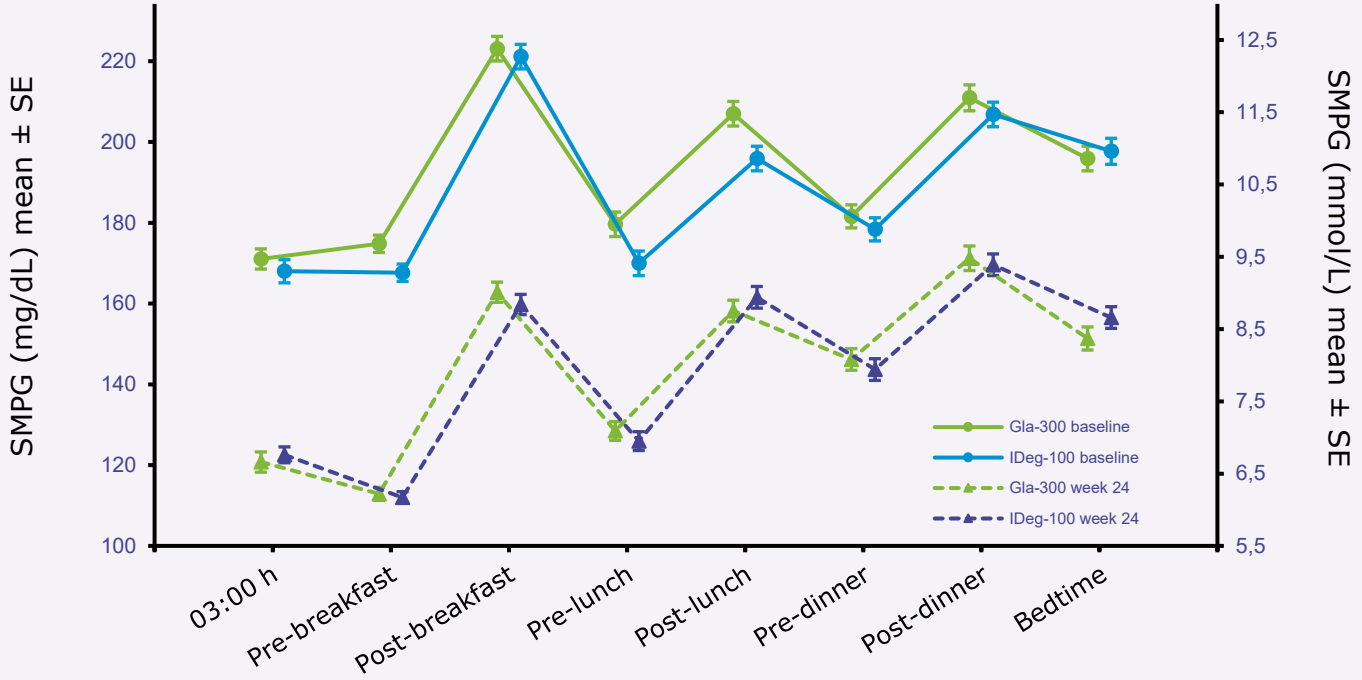
Change from BL to W24 displayed as LS mean values

ITT population; BL, baseline; ITT, intention-to-treat; LS, Least square; SE, standard error; W, week
Rosenstock J, et al. Diabetes Care 2018;41:2147–2154.

BRIGHT: Similar SMPG and variability profiles at baseline and study end vs IDeg

BRIGHT study: Trial designed to assess efficacy and safety of Gla-300 vs IDeg-100 in insulin-naïve people with type 2 diabetes (≥ 18 years) who were inadequately controlled with OADs, with/without GLP-1 RAs. The primary endpoint was change in HbA_{1c} from baseline to week 24, with other secondary endpoints, including: variability of 4-point and 8-point SMPG profiles

8-point SMPG profiles



Variability

	Gla-300	IDeg-100
24-h SMPG (Mean CV, %)		
Baseline	22.5	23.4
Week 24	27.6	28.0
Fasting SMPG (mg/dL)		
Baseline	177.85 ± 40.49	171.65 ± 38.16
Week 24	115.21 ± 23.66	113.29 ± 20.65
LS mean change[a]	−58.11 ± 1.21	−59.18 ± 1.22

ITT population

CV, coefficient of variation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; ITT, intention-to-treat; MMRM, mixed model for repeated measurements; SE, standard error; SMPG, self-monitored plasma glucose

1. Rosenstock J, et al. Diabetes Care. 2018;41(10):2147–2154; **2.** Cheng A, et al. Oral presentation at ADA 2018; 301-OR.

Key messages: Glycemic control and hypoglycemia in RCTs in adults with type 2 diabetes

Gla-300 vs Gla-100 EDITION studies	Gla-300 vs IDeg The BRIGHT study
Comparable HbA_{1c} reductions between Gla-100 and Gla-300[1–3]	**Similar glycemic control** with Gla-300 and IDeg for HbA_{1c} and FSMPG reduction in T2DM patients[5]
Lower risk of confirmed or severe **hypoglycemia** in T2DM with Gla-300 vs Gla-100[4]	**Incidence and rates** of anytime and nocturnal confirmed hypoglycemia comparable for Gla-300 and IDeg during full study and maintenance periods[5]
	Lower incidence and rates of confirmed hypoglycemia with Gla-300 vs IDeg at any time of day during the titration period[5]

FSMPG, fasting self-monitored plasma glucose

1. Riddle MC, et al. Diabetes Care. 2014;37(10):2755–2762; **2.** Yki-Järvinen H, et al. Diabetes Care. 2014;37(12):3235–3243; **3.** Bolli GB, et al. Diabetes Obes Metab. 2015;17(4):386–394; **4.** Roussel R, et al. Diabetes Metab. 2018;44(5):402–409; **5.** Rosenstock J, et al. Diabetes Care. 2018;41:2147–2154.

Conclusions: RESTORE-G study

Switch from GLP-1 RA to 2BI is a valuable option and Gla-300 vs. Deg-100 is associated with larger HbA_{1c} decrease[1]

Higher benefits on FBG control in free (Gla-300+GLP-1 RA) vs. fixed (iDegLira) combination has been found in people uncontrolled on GLP-1 RA with statistically significant larger BI dose increase in the free vs. FRC group, likely due to a better titration of the components in these patients[2]

BI, basal insulin; Deg-100, insulin degludec 100 U/mL; FBG, fasting blood glucose; FRC, fixed-ratio combination; Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; iDegLira, insulin degludec/liraglutide.

1. Napoli R et al. Presented at ADA 2023, June 23–26, 2023, San Diego, 779-P. 2. Candido R et al. Presented at ADA 2023, June 23–26, 2023, San Diego, 84-LB.

Gla-300 associated with similar glycemic improvements and less weight gain vs premix IDeg/Asp: Results from an ITC

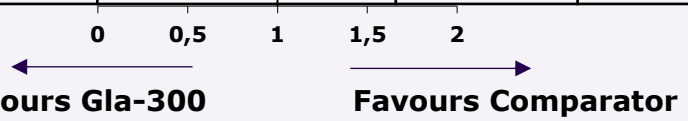
- There was no significant difference in change in HbA_{1c} or final insulin dose, although Gla-300 QD had significantly less weight gain than IDeg/Asp QD

Key outcomes	Treatment difference Gla-300 vs IDeg/Asp (95% CI)
Change in HbA_{1c}, %	0.10 (−0.20, 0.39) p=0.5
Final insulin dose, U/kg	0.03 (−0.05, 0.12) p=0.4
Weight gain, kg	−1.31 (−1.97, −0.65) p=0.0001

*Statistical significance
CI, confidence interval; Gla-300, insulin glargine 300 U/mL; IDeg/Asp, premixed insulin degludec and insulin aspart; ITC, indirect treatment comparison; OR; odds ratio; RR, risk ratio
Ritzel R et al, Diabetes Obes Metab. 2023;25(9):2495-2504

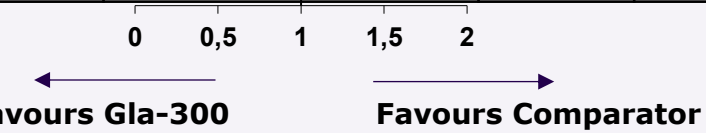
Safety findings for Gla-300 versus other basal insulins: a network meta-analysis

Risk of nocturnal hypoglycemia	RR	Lower CrI	Upper CrI
Gla-300 vs. DET	0.515	0.192	0.356
Gla-300 vs. NPH	0.176	0.051	0.548
Gla-300 vs. DEG	0.656	0.279	1.498
Gla-300 vs. PREMIX	0.361	0.135	0.944



Gla-300 was associated with a significantly lower nocturnal hypoglycaemia rate versus NPH and premixed insulin; no significant differences were noted in Gla-300 versus detemir and degludec

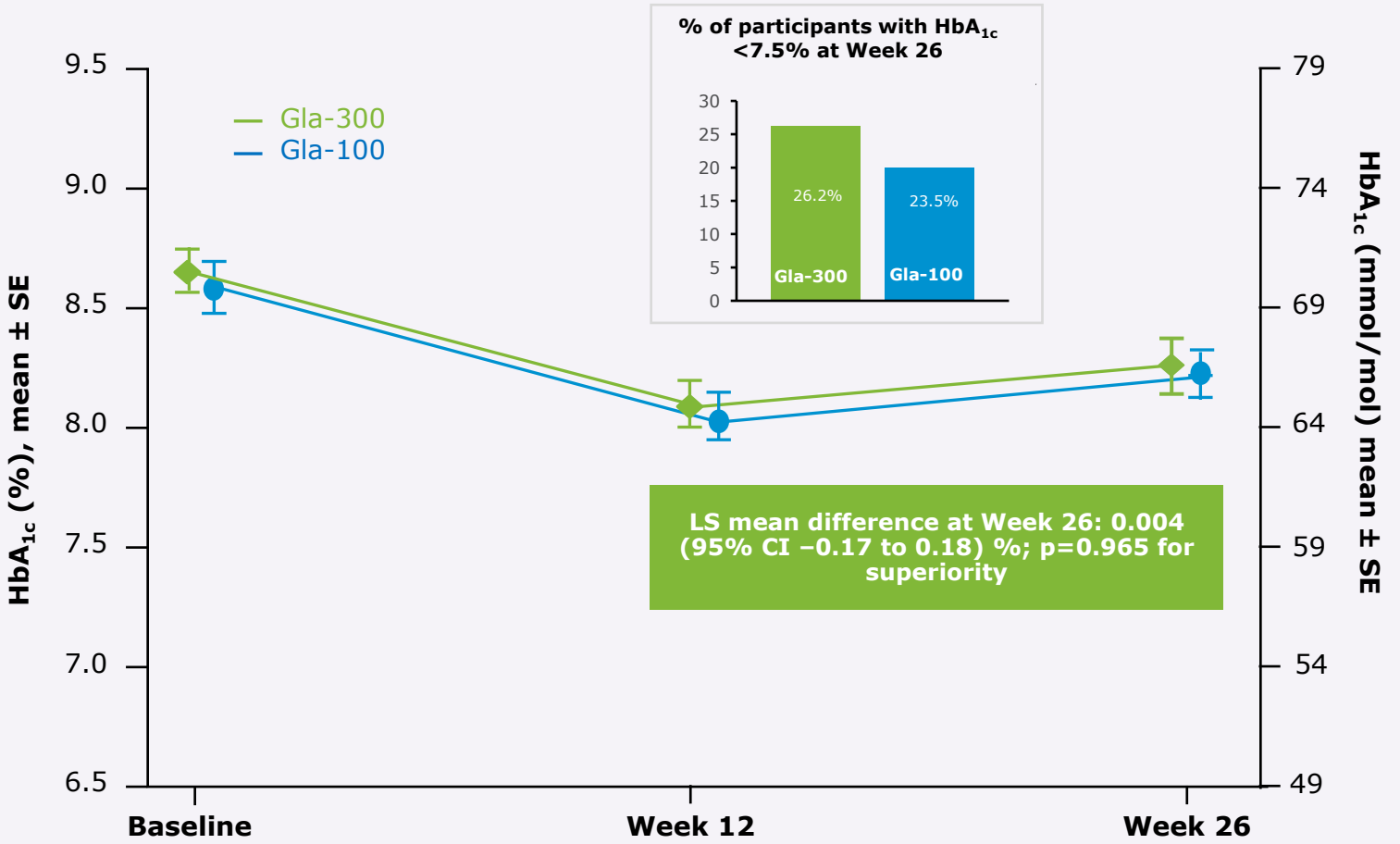
Risk of documented symptomatic hypoglycaemia	RR	Lower CrI	Upper CrI
Gla-300 vs. DET	0.625	0.193	2.000
Gla-300 vs. NPH	0.665	0.273	1.491
Gla-300 vs. DEG	0.552	0.231	1.344



Documented symptomatic hypoglycaemia rates of Gla-300 versus detemir, NPH and degludec were not significant

CrI, credible interval; DET, insulin detemir; DEG, insulin degludec; NPH, neutral protamine Hagedorn; PREMIX, premixed insulin; RR, relative risk
Freemantle N, et al. BMJ Open 2016;6:e009421.

EDITION JUNIOR: Gla-300 met the primary endpoint of non-inferiority to Gla-100 for reduction in HbA_{1c} at week 26 in children/adolescents† with T1D



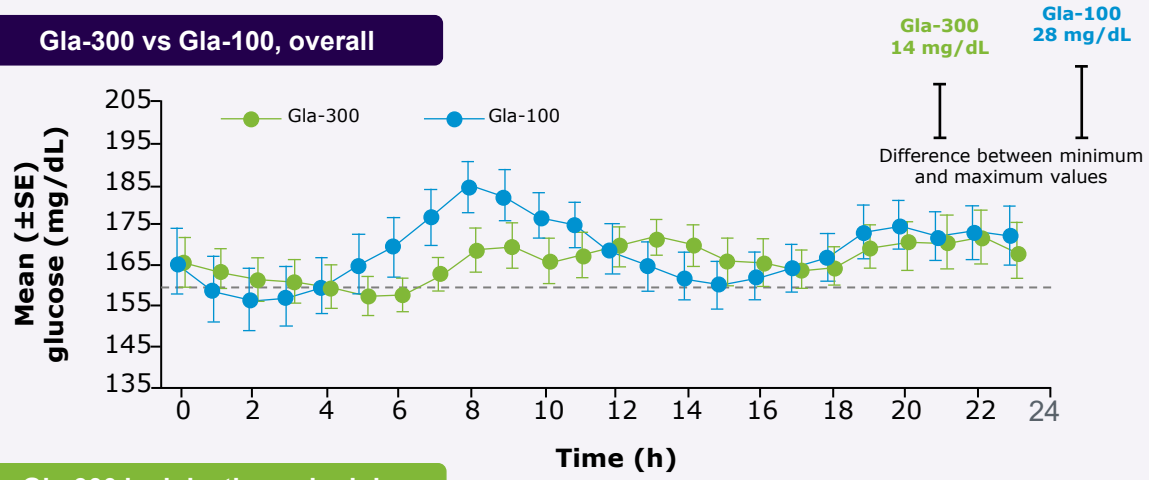
Gla-300 was non-inferior to Gla-100 in HbA_{1c} change from baseline to Week 26 (the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 0.3%)

HbA_{1c} (%)	Gla-300 n=233	Gla-100 n=230
Baseline mean (SD)	8.65 (0.88)	8.61 (0.87)
Change from baseline to Week 26		
Combined LS Mean (SE)	-0.40% (0.06%)	-0.40% (0.06%)
Combined LS Mean difference vs. Gla-100 (95% CI)	0.004 (-0.17 to 0.18)	
p-value for the superiority test	0.965	

Intent-to-treat population. *Multiple imputation analysis followed by analysis of covariance (ANCOVA) model (ITT population); †Aged 6–17 years. LS, least squares; SE, standard error.
Danne T et al. Diabetes Care 2020;43:1512–9;

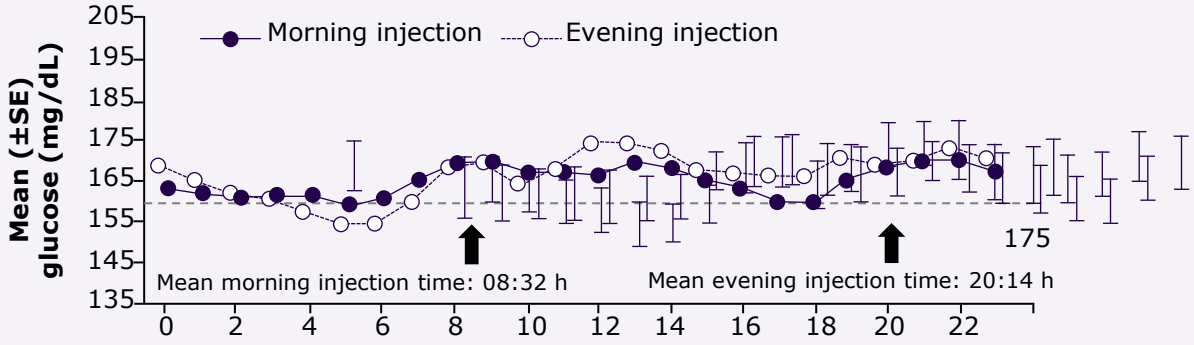
More stable glucose profile: Comparable time-in-range, less glycemic variability and reduced nocturnal hypoglycemia with Gla-300 vs Gla-100 in T1DM

Gla-300 vs Gla-100, overall

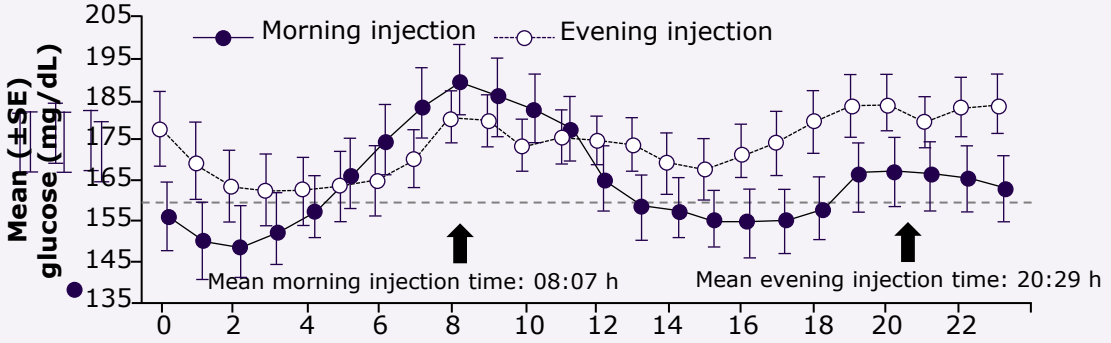


- Continuous glucose monitoring (CGM) confirms whether PK/PD differences translate to clinically relevant differences
- Gla-300 vs Gla-100:
  Improved glycemic control, with less fluctuation, independent of time of injection
- Reduced nocturnal confirmed* or severe hypoglycemia:
  4.0 vs 9.0 events/pt-year rate ratio 0.45; 95% CI 0.24–0.82

Gla-300 by injection schedule



Gla-100 by injection schedule



*<54 mg/dL by self-monitored plasma glucose
16-week, exploratory, open-label, parallel-group, two-period crossover study (clinicaltrials.gov identifier NCT01658579), 59 adults with type 1 diabetes were randomized (1:1:1:1) to once-daily Gla-300 or Gla-100 given in the morning or evening (with crossover in the injection schedule)Average 24-h glucose profiles during the last 2 weeks of each treatment period (CGM population; pooled data period A + B). The percentage of time within the target glucose range was comparable between the Gla-300 and Gla-100 groups. There was significantly less increase in CGM-based glucose during the last 4 h of the 24-h injection interval for Gla-300 compared with Gla-100 (least squares mean difference −14.7 mg/dL [95% CI −26.9 to −2.5]; P = 0.0192).
Bergenstal RM, et al. Diabetes Care. 2017;40(4):554–560.

Conclusion: Gla-300 in T1D

- Effective glycemic control as Gla-100 with
  - A lower risk of severe hypoglycemia[1]
  - A lower rate of nocturnal hypoglycemia during the first 8 weeks of treatment, when most of the up-titration of insulin would have occurred[2,3]
- Effective glycemic control as IDeg-100 with
  - similar TIR and glycemic variability[4]
  - Similar hypoglycemia risk and general safety profile[4]
  - better nocturnal glucose profile, in suboptimally controlled people with T1D, switching from first-generation BI in a real-world setting[5]
  - insulin dose adjustment of Gla-300 may not be necessary on days when spontaneous exercise is performed[6]
- Gla-300 provides similar glycemic control and comparable risk of hypoglycemia and lower incidence of severe hypoglycemia compared to Gla-100 in children and adolescents aged 6–17 years with T1D[7]

BI, basal insulin; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; T1D, type 1 diabetes; TIR, time in range

1. Danne T, et al. Diabetes Obes Metab. 2020;22:1880–7; **2.** Home PD, et al. Diabetes Care. 2015;38:221–-2225; **3.** Matsuhisa M, et al. Diabetes Obes Metab. 2016;18:375–383; **4.** Battelino T et al. Presented at ATTD 2022, 27–30 April 2022 Barcelona, Spain & virtual; **5.** Conget I et al. Diabetes Ther. 2021;12:2993-3009; **6.** Moser O, et al. Diabetes Technol Ther. 2023;25(3):161-168; **7.** Danne T, et al. Diabetes Care 2020;43:1512–9

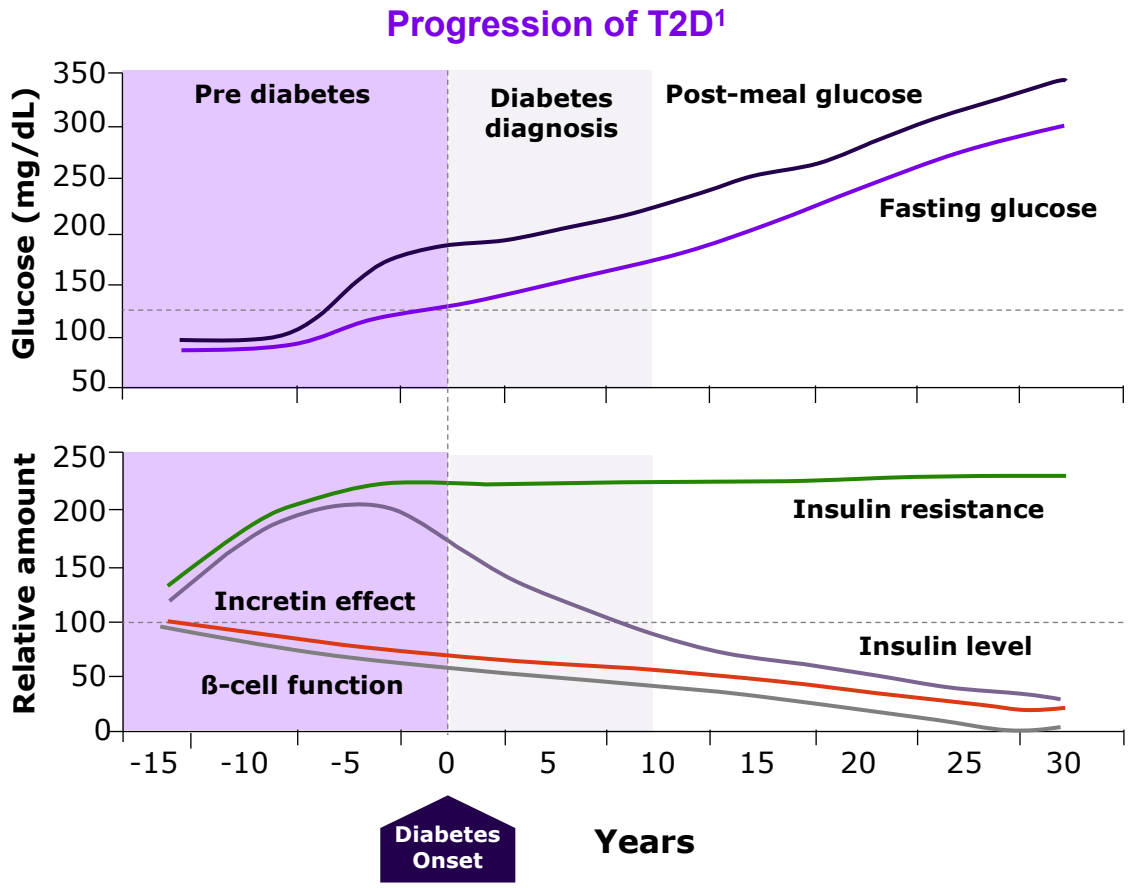
Conclusion: Gla-300 in T2D

- Consistently effective glycemic control, similar to Gla-100 and IDeg[1-5]
- **Lower risk** of confirmed or severe **hypoglycemia** in T2D with Gla-300 vs Gla-100[4]
- **Lower incidence and rates of confirmed hypoglycemia** with Gla-300 vs IDeg-100 at any time of day during the titration period[5]
- Intensification with Gla-300, when added to OAD +/- GLP-1RA, leads to
  - Lower nocturnal & symptomatic hypoglycemia versus NPH[6]
  - Significant reduction of HbA_{1c} when added to either weekly/daily GLP-1RA[7]
  - In people uncontrolled on GLP-1RA, switching to BI is a valuable intensification option[8] and Gla-300 vs. IDeg-100 is associated with larger HbA1c decrease[9]
  - Similar glycemic improvements with significantly less weight gain and a lower risk of clinically significant hypoglycemia compared with IDeg/Asp[10]
- Further improvement in HbA_{1c} in people with T2D uncontrolled on previous basal insulin[11,12]

Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; IDeg-100, insulin degludec 100 U/mL; IDeg/Asp, premixed insulin degludec and insulin aspart; OAD, oral antidiabetic drug; PG, plasma glucose; T2D, type 2 diabetes

1. Riddle MC, et al. Diabetes Care. 2014;37(10):2755–2762; **2.** Yki-Järvinen H, et al. Diabetes Care. 2014;37(12):3235–3243; **3.** Bolli GB, et al. Diabetes Obes Metab. 2015;17(4):386–394; **4.** Roussel R, et al. Diabetes Metab. 2018;44(5):402–409; **5.** Rosenstock J, et al. Diabetes Care. 2018;41:2147–2154; **6.** Freemantle N, et al. BMJ Open 2016;6:e009421; **7.** Bailey T et al. Diabetes Obes Metab 2022;24(8):1617-1622. **8.** Zheng L et al. Presented at ATTD 2022; 27–30 April 2022:P#753; **9.** Napoli R et al. Presented at ADA 2023, June 23–26, 2023, San Diego, 779-P; **10**. Candido R et al. *Nutr Metab Cardiovasc Dis*. 2023 [Epub ahead of print];; **11.** Müller-Wieland D, et al. Presented at ADA 2022, June 3–7, 2022, New Orleans, LA; **12.** Wolnik B et al. Journal of Diabetes Research. 2020

Due to the progressive nature of T2D, most individuals will require treatment advancement throughout the course of their lives



As T2D progresses, **advancement to injectable therapy** is required for many adults; many require basal insulin-based options[2–4]

ADA/EASD 2022 guidelines recommend the addition of a **mealtime insulin** when glycemic targets are no longer achieved with basal insulin[4]

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; T2D, type 2 diabetes.

1. Kendall D, et al. Am J Med. 2009;122(Suppl 6):S37–50; 2. American Diabetes Association. Diabetes Care. 2022;45(Suppl 1):S125–S143; 3. Buse J, et al. Diabetes Care. 2020;43:487–93;
4. Davies M, et al. Diabetes Care. 2022;45(11):2753–2786.

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FRC of basal insulin and GLP-1 RA in the management of T2D: A simplified approach

The complementary modes of action of basal insulin and GLP-1 RA provide rationale for a fixed-ratio combination for T2D

Case 2

Age: 62 yr old male
History: Morbid obesity (BMI 44), T2D poorly controlled, HPT and Stage3 CKD
C/o : progressive exertional dyspnea, bilateral pedal edema, orthopnea
Vitals: BP 155/98 mmHg, pulse 94, eGFR 45 ml/min/1.73 msq, UACR: 450mg/g (macroalbuminuria), HBA1c 10%
Current Rx: Insulin glargine 100 units/mL, Metformin 1000mg, Simvastatin 20mg dly, Furosemide 40mg dly, Perindopril (arginine) 5 mg / Indapamide 1.25 mg daily, Allopurinol 100 mg daily

What next and why??

Basal insulin + GLP-1 RA FRCs: Clinical rationale

Basal insulin[1]

⬇ FPG

- Inhibit hepatic glucose production
- Decrease adipocyte lipolysis

GLP-1 RA[1]

⬇PPG excursions

- Stimulate insulin secretion
- Suppress glucagon secretion
- Slow gastric emptying

Clinical benefits of basal insulin + GLP-1 RA FRCs

Target FPG and PPG[1,2]

Address multiple pathophysiological defects[1]

No additional risk of hypoglycemia (versus basal insulin)[3–6]

Weight neutrality or weight benefit (versus basal insulin)[4–6]

Reduced nausea versus monocomponents[5]

FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonists; PPG, postprandial plasma glucose.

1. Perreault L, et al. Adv Ther 2019;36:265-77; 2. Blonde L, et al. Curr Med Res Opin. 2019;35:793–804; 3. Gough S, et al. Lancet Diab Endocrinol. 2014;2:885–9; 4. Buse JB, et al. Diabetes Care. 2014;37:2926–33; 5. Rosenstock J, et al. Diabetes Care. 2016;39:2026–35; 6. Aroda VR, et al. Diabetes Care. 2016;39:1972–80.

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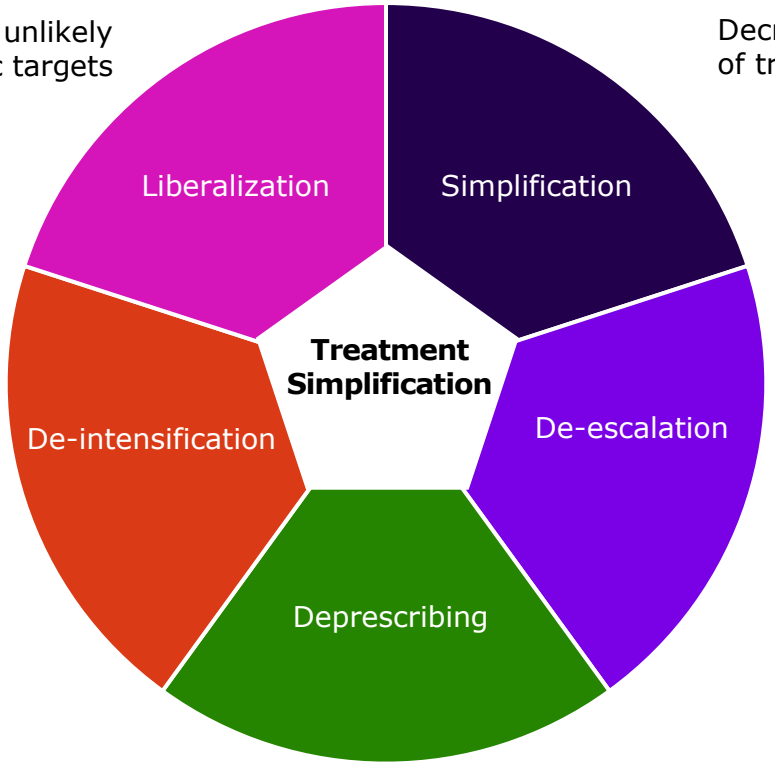
Treatment simplification is becoming increasingly recognized as an effective T2D management strategy…[1,2]

Relaxing of glycemic goals for people who are unlikely to benefit from their current glycemic targets

Decrease treatment complexity and burden of treatment, particularly insulin therapy



Medication is simplified, reduced or completely withdrawn (to prevent polypharmacy and associated adverse events)

Changing from more intensive to less intensive insulin regimens

Reducing medication without compromising safety

Expert panel guidance recommends that **treatment simplification** can be viewed as an attempt to decrease the complexity and thereby the burden of treatment for the individual

1. American Diabetes Association. Clinical Diabetes. 2022;40:10–38; 2. Jude E, et al. Diabetes Ther. 2022;13:619–34.

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ADA/EASD 2022 guidelines recommend to add a mealtime insulin in the form of basal plus, basal–bolus or premixed insulin

Consider adding insulin when personalized HbA1c target are not met with strategies described in previous slide

If advancement from basal insulin therapy is required to reduce HbA1c:

- Maintain cardio-renal protective agents
- Maintain metformin, SGLT2i and GLP-1 RA to avoid weight gain, limit insulin dose and hypoglycemia risk
- Consider using combination products of basal insulin/GLP-1 RA

Start using basal insulin analog (10 units or 0.1–0.2 units/kg/day) at bedtime; greater flexibility offered with longer-acting analogs

▼

Titrate to FPG but avoid over-basalization of insulin (consider introduction of CGM)

▼

When FPG is on target but HbA1c or TIR is not

▼

If not already on GLP-1 RA, consider use of GLP-1RA

▼

Add mealtime insulin in form of:

- Basal plus (progressive addition of boluses)
- MDI (multiple daily injections)
- Premixed insulins

Intensify along the way and preferably at each step

- Healthy behavior
- Nutritional therapy
- DSMES: with additional forces on injection technique, hypoglycemia and weight

CGM, continuous glucose monitoring; DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; MDI, multiple daily injection; SGLT2i, sodium/glucose cotransporter-2 inhibitor; TIR, time in range.

Davies MJ, et al. Diabetes Care 2022; 45(11):2753–2786.

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ADA/EASD 2022: Use of glucose-lowering medications in the management of T2D – Positioning of FRCs

Healthy lifestyle behaviors: Diabetes self-management, education and support (DSMES): social determinants of health (SDOH)

Goal: Cardiorenal risk reduction

ASCVD indicators	HF	CKD
Either /or GLP-1 RA with proven CV benefit SGLT2i with proven CV benefit	PREFERABLY SGLT2i with evidence of reducing HF	PREFERABLY SGLT2i with evidence of reducing CKD progression OR GLP-1 RA with proven CVD benefit

Combination injectable therapy (GLP-1 RA/insulin) is recommended as a **very high efficacy option to achieve glycemic goals**

Goal: Glycemic and weight management goals

GLYCEMIC MANAGEMENT: CHOOSE APPROACHES THAT PROVIDE THE EFFICACY TO ACHIEVE GOALS	ACHIEVEMENT AND MAINTENANCE OF WEIGHT MANAGEMENT GOALS:
Very high efficacy: Dulaglutide (high dose), Semaglutide, Tirzepatide, Insulin, Combination Oral, **Combination Injectable (GLP-1 RA/Insulin)**	**Consider regimen with high dual glucose and weight efficacy**
	Higher efficacy: Semaglutide, Tirzepatide
High efficacy GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD	**High efficacy:** Dulaglutide, Liraglutide
Intermediate efficacy DPP4-i	**Intermediate efficacy:** GLP-1 RA (not covered above), SGLT2i

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DPP4-i, dipeptidyl peptidase-4 inhibitor; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium glucose co-transporter-2 inhibitor; TZD, thiazolidinediones.

Davies M, et al. Diabetes Care 2022;45(11):2753–2786.

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Basal insulin + GLP-1 RA FRCs: A simplified treatment regimen from patients' perspective

Basal insulin[1]

⬇ FPG

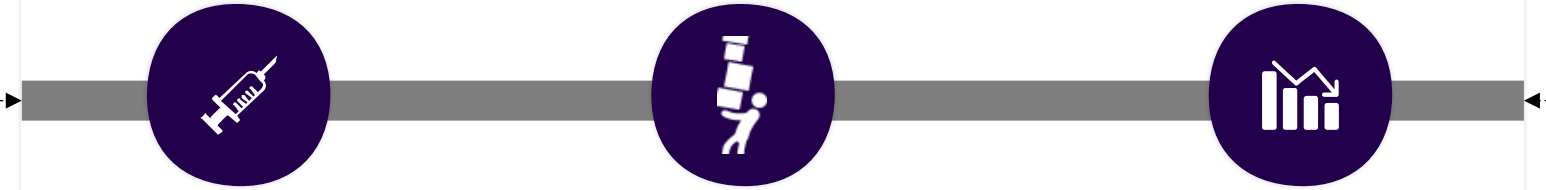
- Inhibit hepatic glucose production
- Decrease adipocyte lipolysis

GLP-1 RA[1]

⬇PPG excursions

- Stimulate insulin secretion
- Suppress glucagon secretion
- Slow gastric emptying

Reduced treatment burden with basal insulin + GLP-1 RA FRCs



Single daily injection[1,2]

Decreased treatment burden[3]

Reduced complexity[2]

1. Perreault L, et al. Adv Ther. 2019;36:265-77; 2. Blonde L, et al. Curr Med Res Opin. 2019;35:793–804; 3. Jude B, et al. Diabetes Ther. 2022;13:619–34.

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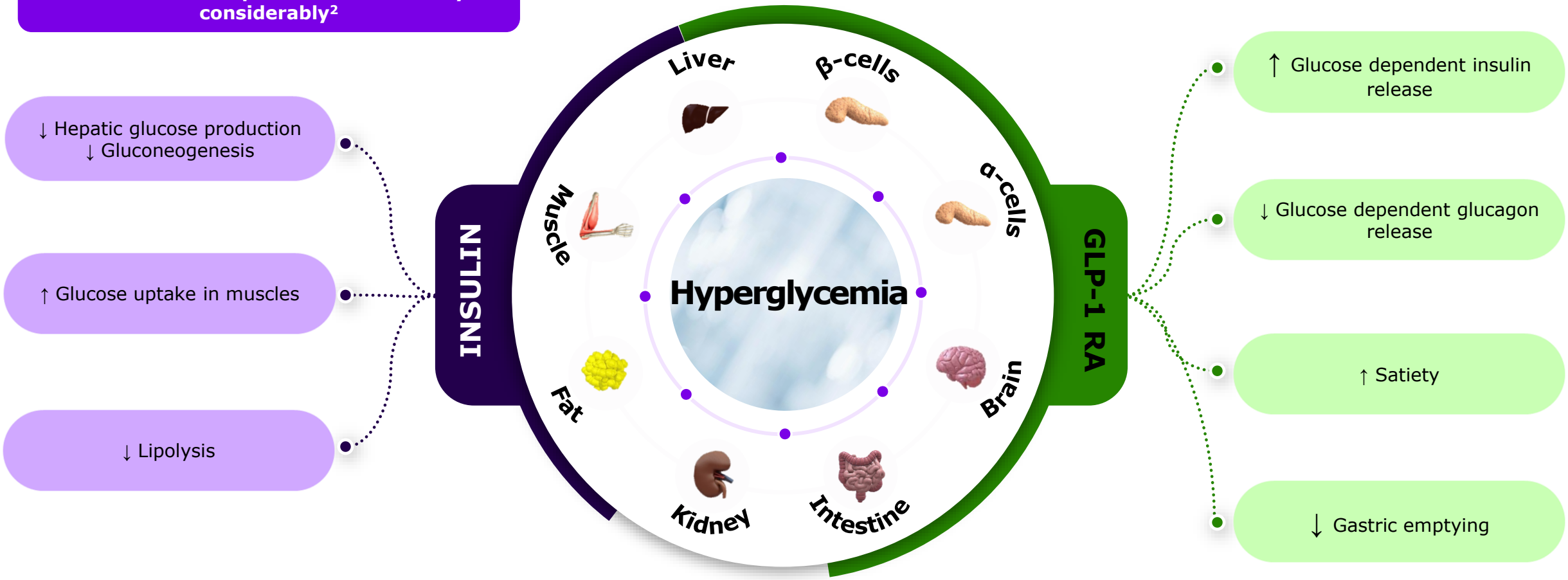
T2D pathophysiology: The ominous octet[1]

T2D is a heterogeneous, multifactorial disease in which clinical presentation can vary considerably[2]



GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; TZD, thiazolidinedione; T2D, type 2 diabetes.

1. DeFronzo RA, et al. Diabetes Care. 2013;36(Suppl 2):S127–S1; 2. American Diabetes Association. Diabetes Care. 2018;41(Suppl 1):S13–S27.

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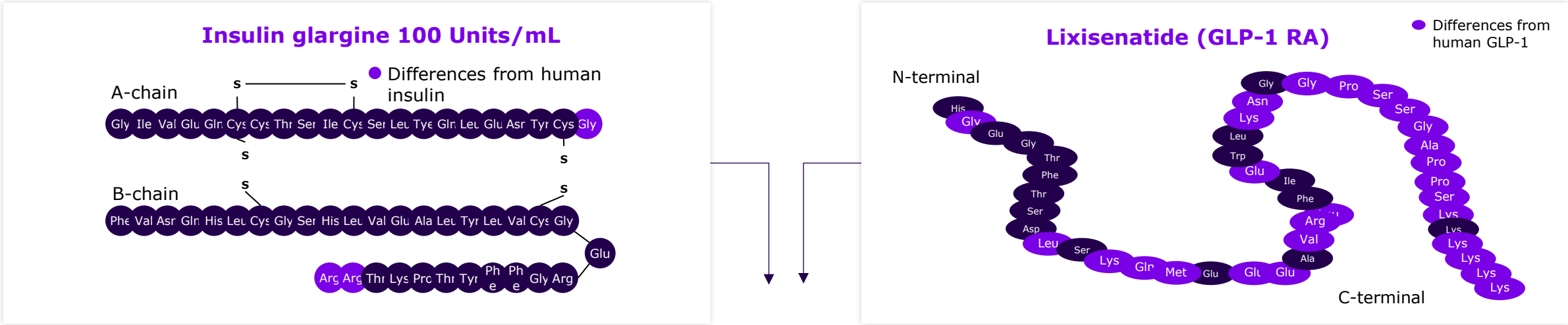
iGlarLixi: FRC of insulin glargine 100 U/mL and lixisenatide

Characteristics of combining insulin glargine 100 Units/mL and lixisenatide



- **Single daily injection** within the hour prior to the first meal of the day
- Greater **HbA1c reduction** versus its individual components
- Reduction in **FPG** and **PPG**
- More people **reach HbA1c goal** versus the individual components
- Mitigates the **weight gain** commonly experienced with basal insulin
- No additional risk of **hypoglycemia** vs basal insulin

Sanofi. Data on file. LixiLan-O CSR:87, 95, 97, 101, 103, 124, 125, 130

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Summary

The IDEAL study demonstrated that **de-intensification from MDI** to iGlarLixi resulted in **similar changes in HbA1c** levels, **significant reduction in body weight**, and fewer reported cases of hypoglycemia[1]

In the IDEAL study, insulin therapy de-intensification from MDI regimen into once-daily iGlarLixi showed **improvement in several CGM related outcomes**, namely increase in TIR, decrease in TAR, decrease in mean sensor glucose and improvement in overall quality of glycemia (**decrease in GRI**) in the iGlarLixi group with no changes in these metrics observed in the MDI group[2]

iGlarLixi is approved for treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to metformin with or without sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Sanofi does not advocate the use of medicinal product(s) outside of the recommendations within the prescribing information/product labelling. Please consult the latest prescribing information in your country of practice as information may vary from country to country.

CGM, continuous glucose monitoring; GRI, glycemia risk index; HbA1c, glycated hemoglobin; iGlarLixi, fixed-ratio combination of insulin glargine 100 U/mL and lixisenatide; MDI, multiple daily injection; TAR, time above range; TIR, time in range. 1. Peter Novodvorský et al. Diabetes 2024;73(Supplement_1):782-P; 2. Peter Novodvorský et al. Diabetes 2024;73(Supplement_1):747-P.

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Summary

- In people not achieving HbA1c <7% on maximum tolerated dose of daily or weekly GLP-1 RA and OADs, switching to iGlarLixi versus continuing the GLP-1 RA led to greater:
  - Reductions in HbA1c (LS mean difference –0.6%, p<0.0001), with a mean HbA1c at 26 weeks of 6.7% in the iGlarLixi group and 7.4% in the GLP-1 RA group
  - Proportion of people achieving HbA1c <7% (62% vs 26%; difference, 36%; p<0.0001)
  - Proportions of people achieving <7% HbA1c without documented symptomatic hypoglycemia, defined as either:
    - <54 mg/dL – 57% versus 25%, respectively
    - ≤70 mg/dL – 43% versus 25%, respectively
  - Reductions in FPG, PPG, and PPG excursions (p<0.0001 for all)
- Safety profile of iGlarLixi reflected those of its components, without new or unexpected findings

Switching to iGlarLixi is an efficacious option that may further improve glucose control in people insufficiently controlled with the maximum tolerated dose of daily or weekly GLP-1 RA and OAD(s), with a safety profile that reflects both components

FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; iGlarLixi, insulin glargine + lixisenatide; LS, least squares; OAD, oral antidiabetic drug; PPG, post prandial glucose; QW, once weekly.

Blonde L, et al. Diabetes Care. 2019;42:2108–16. DOI: https://doi.org/10.2337/dc19-1357.

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LixiLan-O: Summary

01

The primary objectives of the study were met as superiority of iGlarLixi in HbA1c change from baseline was shown versus both iGlar and Lixisenatide

02

iGlarLixi added to metformin:

- Improved HbA1c from 8.1% to 6.5%
- Reduced 2h-PPG and glucose excursions
- Prevented body weight gain seen at insulin introduction (–0.3 kg) with a significant difference of 1.4 kg versus iGlar ($p<0.0001$)
- Allowed 74% of patients to reach HbA1c <7%

03

Overall, iGlarLixi was well tolerated with a safety profile reflecting those of iGlar and Lixisenatide

- The incidence of documented (≤70 mg/dL) symptomatic hypoglycemia was similar in the iGlarLixi and iGlar treatment groups and lower in the Lixisenatide group
- Nausea and vomiting were reported considerably less frequently compared with Lixisenatide

HbA1c, glycated hemoglobin; iGlar, insulin glargine; iGlarLixi, insulin glargine + lixisenatide; PPG, post prandial glucose.

Rosenstock J, et al. Diabetes Care. 2016;39:2026–35. DOI: https://doi.org/10.2337/dc16-0917.

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Conclusion

In a real-world setting, people with T2D switching from a basal-bolus insulin regimen to a once-daily injection of iGlarLixi achieved a lower HbA1c with stable body weight, greater proportion of participants at target HbA1c (<7%) and a numerically lower hypoglycemic event rate

BBI, basal-bolus insulin; T2D, type 2 diabetes.

Giorgino F, et al. 84th American Diabetes Association Scientific Sessions, Orlando, June 21–24, 2024; Poster # 1867 LB.

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Summary

Efficacy of iGlarLixi:
iGlarLixi demonstrated significant improvements in TIR and other glycemic measures in people with HbA1c ≥9%–13% over 16 weeks

Safety Profile:
In line with earlier studies, iGlarLixi showed a low incidence of hypoglycemia, with no ADA level 3 events reported

Comparative Insights:
The study showed improved TIR, but comparisons are limited by differences in study design, population, and baseline characteristics, with target TIR harder to achieve in those with higher HbA1c and different monitoring conditions

Impact of SU Use:
Non-SU users demonstrated better glucose control than SU users, suggesting that concurrent secretagogue therapies may need reconsideration

The Soli-CGM study demonstrates that 16 weeks of treatment with iGlarLixi in people with T2D and high HbA1c, significantly improved TIR and reduced TAR without causing severe hypoglycemia. These findings add valuable insights enhancing the existing information on iGlarLixi, extending our understanding beyond just HbA1c levels.

ADA, American Diabetes Association; CGM, continuous glucose monitoring; FRC, fixed-ratio combination; HbA1c, glycated hemoglobin; iGlarLixi, fixed ratio of insulin glargine 100 U/mL and lixisenatide; SU, sulfonylurea; TAR, time above range; TIR, time in range; T2D, type 2 diabetes.

Frías JP, et al. *Diabetes Obes Metab*. Published online February 4, 2025.

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Thank you

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