ADA 2021

June 25-29

Poster #109-LB

To view or download the poster book and/or to listen to the author summary of this e-poster scan the QR code.

Summary

Poster book

Comparative effectiveness of insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (iDeg-100) in insulin naïve type 2 diabetes adults: RESTORE-2 real world study

GIAN PAOLO FADINI[1], RAFFAELLA BUZZETTI[2], ANTONIO NICOLUCCI[3], MARIA CHIARA ROSSI[3], MONICA LAROSA[4], DOMENICO CUCINOTTA[5], ON BEHALF OF RESTORE-2 STUDY GROUP

[1]Department of Medicine, University of Padova, Via Giustiniani 2, 35128, Padova, Italy. gianpaolo.fadini@unipd.it.

[2]Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185, Rome, RM, Italy.

[3]CORESEARCH, Center for Outcome Research and Clinical Epidemiology, Pescara, Italy.

[4] Sanofi, Milan, Italy.

[5]University of Messina, Piazza Pugliatti, 1, 98122, Messina, Italy.

Aknowledgments, Disclosures, source of fundings

Gian Paolo Fadini has received grants, lecture fees or honoraria from the following companies:

- Abbott
- AstraZeneca
- Boehringer
- Lilly
- Mundipharma
- Novo Nordisk
- Sanofi

Supported by: Sanofi

Introduction and aim

- **Second generation basal insulins (2BI) provide similar/improved efficacy with better safety compared to 1st generation BI (1BI)**. These results have been widely proved in RCTs: both EDITION (Gla-300 vs Gla-100) and BEGIN trials (iDeg-100 vs Gla-100) have highlighted a similar glycemic control but less hypoglycemia in type 2 diabetes (T2D) patients versus Gla-100 (1).

- These results are sustained by their smoother, less variable and more prolonged PK/PD profile vs 1BI (2). Recently, **the BRIGHT study,** a RCT in naïve patients withT2D**, has shown that Gla-300 and iDeg-100 provided similar glycemic control improvements with relatively low hypoglycemia risk**. Hypoglycemia incidence and rates were comparable with both basal insulins during the full study period but lower in favor of Gla-300 during the dose titration period (3).

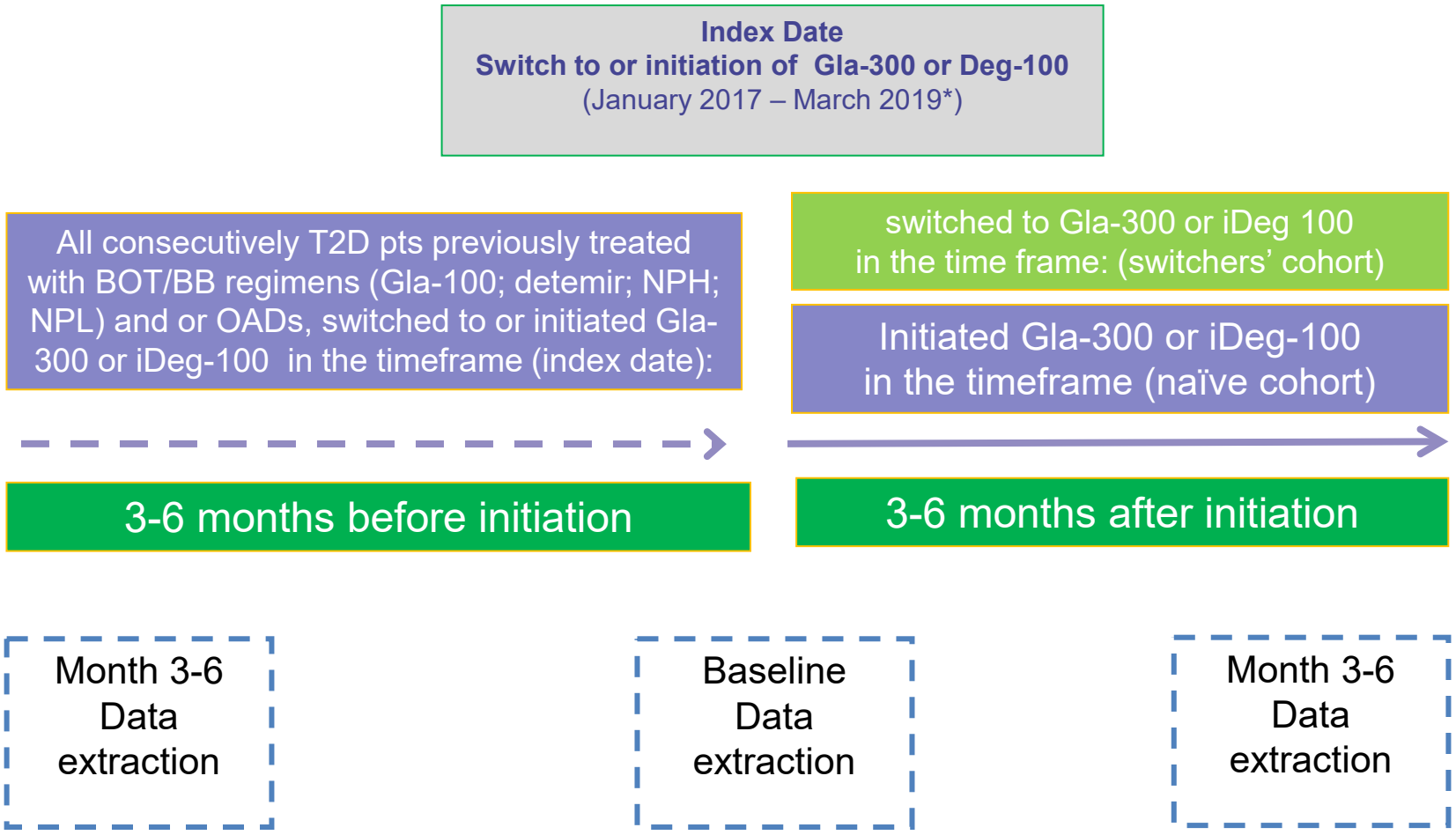
- In **the DELIVER Naïve D real world study, initiation of Gla-300 or iDeg-100 resulted in similar improvements in glycemic control and comparable hypoglycemia outcomes** and discontinuation rates **in a clinical US setting**, consistently with the BRIGHT (4). Real-world data on 2BI in patients with T2D are essential to fully confirm the RCTs outcomes, but they are still limited.

- The study aimed to **compare effectiveness of 2BI (**Gla-300 vs. iDeg-100) **in insulin-naïve T2D in a real-life Italian** setting.

RESTORE

1. R.Roussel , et al Diabetes & Metabolism Volume 44, Issue 5, November 2018, Pages 402-409 . 2. Reinhard H.A. Becker, et al. Diabetes Care Apr 2015, 38 (4) 637-643; DOI: 10.2337/dc14-0006; 3 . J. Rosenstock et al. Diabetes Care 2018; https://doi.org/10.2337/dc18-0559. 4. S.D. Sullivan et al. Diabetes Obes Metab 2019 Sep;21(9):2123-2132.

Study Flowchart



**Estimated extraction data end. A longer time-frame could be evaluated on the basis of the actual start-up date of the retrospective data extraction*

- This was a retrospective, non-inferiority, multicenter study, from electronic medical records.
- All patients initiating Gla-300 or iDeg-100 in January 2017- 2020 were 1:1 propensity score matched

RESTORE

Patients' disposition

19 centers provided data on 357 patients in each PSM cohort.

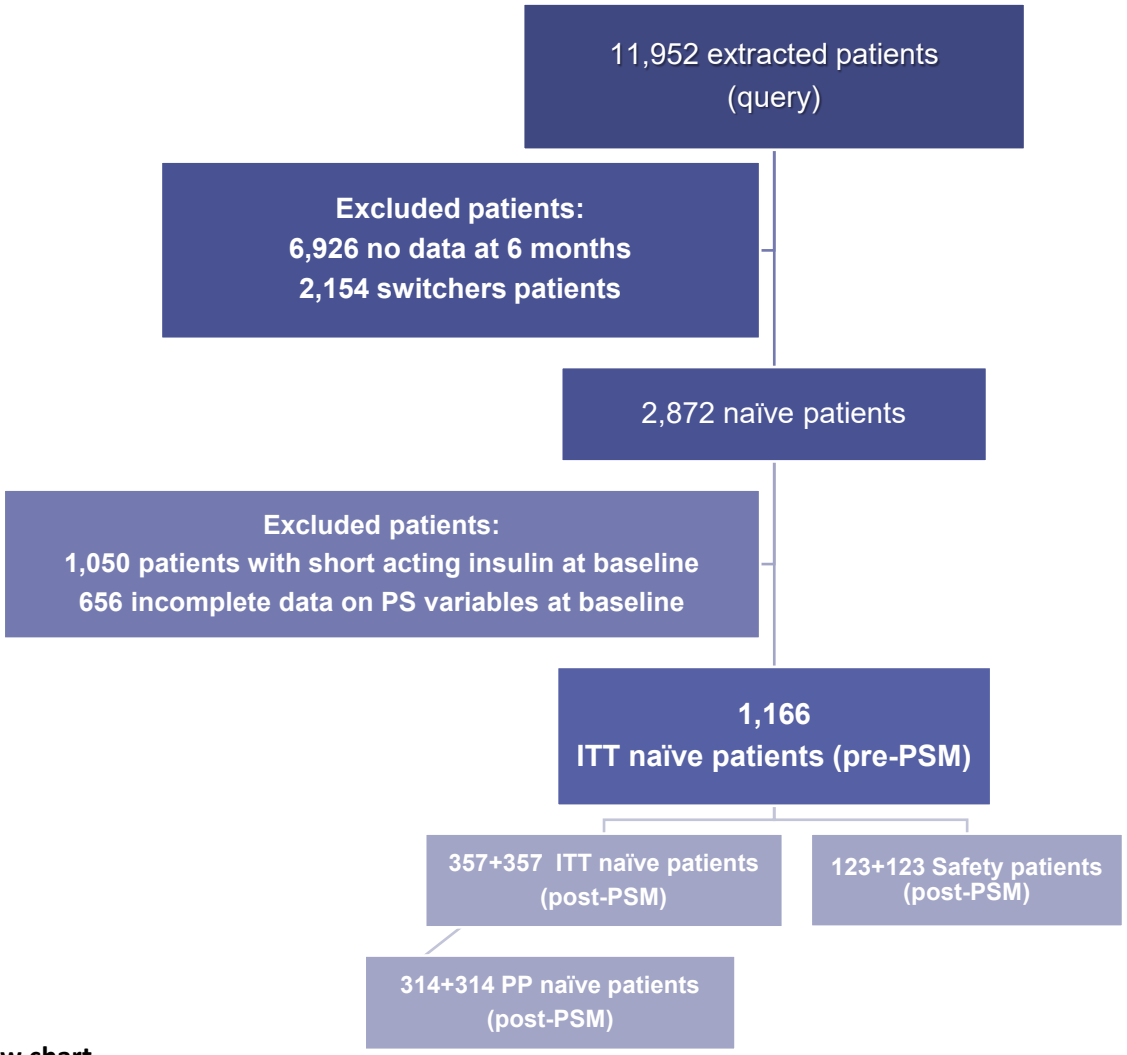


Figure 1: **Study flow chart**

- The main analysis was conducted on the **ITT population**.
- The **per-protocol (PP) population** was defined as the patients with HbA1c value available at baseline and at 6 months.
- The **safety population** was represented by all ITT patients for the evaluation of severe hypoglycemia
- For the **evaluation of glycemic values ≤70 mg/dl and <54 mg/dl** the sub-sample of the safety population having at least 1 SMBG value available was considered

Propensity Score Matching

Pre-defined variables showing statistically significant between-group differences at baseline were considered for the PSM.

Before PS matching, patients initiating Gla-300 were different from those initiating iDeg-100 in terms of use of secretagogues (42.6% vs. 50.0%; p=0.02), glitazones (5.9% vs. 11.2%; p=0.002), and SGLT2i (27.5% vs. 19.6%;p=0.004). Between-group p-value for BMI (29.3±5.8 vs. 29.9±5.6; p=0.07) and GLP1-RAs (18.6 vs. 23.5%; p=0.054) were borderline; however, their standardized differences were ≥10.

After PSM, a good balance was obtained between the two groups, and the standardized difference was below 10 for all the considered variables.

Table 1: **Variables used in PS matching pre-matching baseline patients' characteristics** (ITT population)

Variable	Category	Gla-300	iDeg-100	p-value	Standardized Difference
N Group		808	358		.
BMI (Kg/m²)		29.31 (5.79)	29.89 (5.64)	0.0679	10.0026
GLP1-RAs (%)	No	658 (81.44)	274 (76.54)	0.054	-12.0474
	Yes	150 (18.56)	84 (23.46)		.
SGLT2 inhibitors (%)	No	586 (72.52)	288 (80.45)	0.004	18.7626
	Yes	222 (27.48)	70 (19.55)		.
Glitazones (%)	No	760 (94.06)	318 (88.83)	0.0018	-18.7885
	Yes	48 (5.94)	40 (11.17)		.
Secretagogues (%)	No	464 (57.43)	179 (50.00)	0.0187	-14.9341
	Yes	344 (42.57)	179 (50.00)		.

Data are means and standard deviations or frequencies and proportions. p-values derived from unpaired t-test or the Mann-Whitney U-test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.
A standardized mean difference less than 10 (absolute values) indicates a good balance between groups.

Data analysis

- Linear mixed models for repeated measures were applied to assess changes during 6 months in HbA1c, fasting blood glucose (FBG), body weight, and insulin doses.
- Incidence rates (IR) of hypoglycemic events were compared using Poisson regression models.

Baseline characteristics

Table 2: **Baseline characteristics**

Variable	Gla-300	iDeg-100	P Value
N. Group	357	357	
Age (years)	68.7±11.7	69.8±10.9	0.32
Males (N, %)	217 (60.8)	213 (59.7)	0.76
Diabetes duration (years)	13.6±10.6	13.5±7.4	0.32
Weight (kg)	82.5±18.3	82.1±17.9	0.85
BMI (kg/m^2)	29.9±6.1	29.9±5.6	0.75
HbA1c (%)	9.3±1.9	9.2±1.6	0.87
HbA1c (mmol/l)	77.7±21.0	76.9±17.8	0.99
Fasting blood glucose (mg/dl)	212.3±74.9	201.9±63.1	0.16
eGFR <60 ml/min/1.73 m^2 (N, %)	59 (34.1)	38 (32.8)	0.81
Microalbuminuria (N, %)	56 (31.5)	54 (31.0)	0.93
Diabetes complications (N,%)	23 (6.4)	23 (6.4)	1.00
Glucose-lowering therapy:			
Daily basal insulin dose (U)	11.8±5.5	12.5±6.3	0.24
No. of glucose-lowering drugs other than insulin (N, %):			
<2	72 (20.2)	68 (19.0)	0.71
≥2	285 (79.8)	289 (81.0)	
Metformin (N, %)	275 (77.0)	285 (79.8)	0.36
Secretagogues (N, %)	161 (45.1)	178 (49.9)	0.20
Glitazones (N, %)	32 (9.0)	39 (10.9)	0.38
Acarbose (N, %)	11 (3.1)	17 (4.8)	0.25
DPPIV inhibitors (N, %)	180 (50.4)	175 (49.0)	0.71
GLP1-RAs (N, %)	79 (22.1)	84 (23.5)	0.66
SGLT2 inhibitors (N, %)	67 (18.8)	70 (19.6)	0.78

Data are means and standard deviations or frequencies and proportions. p-values derived from unpaired t-test or the Mann-Whitney U-test in case of continuous variables and the chi-square test or; Fisher exact test for categorical variables, as appropriate..

RESTORE

Effectiveness

Figure 2: **Changes in HbA_{1c} estimated mean levels during the follow-up by treatment** (ITT population)

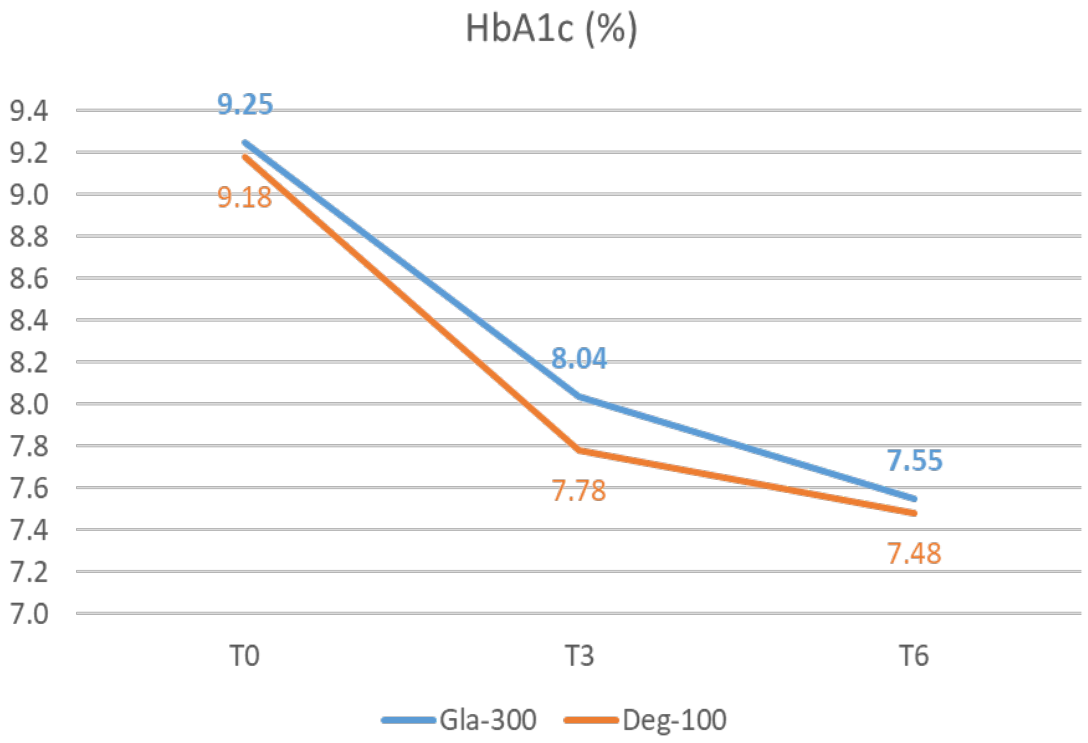


Table 3: **Comparison of between-group estimated mean changes in continuous endpoints levels (between-group differences T6 vs. T0)** (ITT population)

Change in	Visit	Gla-300			iDeg-100			T6 vs T0
		Estimated mean; 95% CI	Mean difference; 95% CI	Within group* p-value	Estimated mean; 95% CI	Mean difference; 95% CI	Within group* p-value	Between group difference** p-value
FBG (mg/dl)	T0	212.60 (204.86;220.34)			201.61 (193.73;209.49)			-2.09 (14.56;10.38)
	T6	149.36 (144.07;154.65)	-63.23 (-71.95;-54.51)	<0.0001	140.47 (135.00;145.94)	-61.14 (-70.06;-52.22)	<0.0001	0.74
Body weight (Kg)	T0	82.55 (80.68;84.42)			82.12 (80.25;83.99)			-0.23 (0.88;0.42)
	T6	82.28 (80.44;84.12)	-0.26 (-0.72;0.20)	0.27	82.09 (80.25;83.93)	-0.03 (-0.49;0.43)	0.91	0.48
Daily basal insulin dose (U)	T0	11.79 (11.18;12.40)			12.45 (11.84;13.06)			0.92 (0.23;2.07)
	T6	16.25 (15.28;17.22)	4.45 (3.63;5.27)	<0.0001	15.99 (15.03;16.95)	3.54 (2.73;4.35)	<0.0001	0.12
Daily basal insulin dose (U/Kg)	T0	0.15 (0.14;0.16)			0.16 (0.15;0.17)			0.01 (0.01;0.03)
	T6	0.20 (0.19;0.21)	0.05 (0.04;0.06)	<0.0001	0.20 (0.19;0.21)	0.04 (0.03;0.05)	<0.0001	0.06

**Paired t-test derived from linear mixed models for repeated measurements. **Unpaired t-test derived from linear mixed models for repeated measurements.*

- Estimated mean baseline levels of HbA_{1c} were 9.2%. Marked reductions in HbA_{1c} after 6 months were documented: -1.70%; (95%CI -1.90; -1.50) in Gla-300 group and -1.69%; (95%CI -1.89; -1.49) in IDeg-100 group (between group mean difference: 0.01; 95%CI -0.29; 0.27, p-value 0,49), **confirming non-inferiority of Gla-300 vs. iDeg-100.**
- FBG was reduced by about 60 mg/dl in both groups;
- Minor changes in body weight were documented.
- In both groups, the mean prescribed dose was about 12 U (0.15 U/Kg) and was slightly titrated during 6 months up to +4U (0.20 U/Kg).

Safety: hypoglycemia

Table 4: Incidence rate of hypoglycemic events (BG ≤70 mg/dl and <54 mg/dl) during the 6-month follow-up by treatment and between-group difference (Safety population)

Outcome	Group	Subjects	N SMBG	Events	Person-Months	IR (95%CI)	IRR (95%CI)	Between-group p-value
BG ≤ 70 mg/dl	Gla-300	123	18,353	81	615	0.13 (0.07;0.26)	0.92 (0.36;2.38)	0.87
BG ≤ 70 mg/dl	iDeg-100	123	19,621	90	631.7	0.14 (0.07;0.27)		.
BG < 54 mg/dl	Gla-300	123	18,353	15	615	0.02 (0.01;0.05)	1.54 (0.45;5.30)	0.49
BG < 54 mg/dl	iDeg-100	123	19,621	10	631.7	0.02 (0.01;0.04)		.

Overall, 18,353 SMBG tests were available in Gla-300 group and 19,621 SMBG tests were available for Deg-100 group. **No between-group difference in the incidence of BG events ≤70 mg/dl and <54 mg/dl during 6-month was documented.**

IR (episodes per patient-months) of BG ≤70 mg/dl was 0.13 (95%CI 0.07;0.26) in Gla-300 group and 0.14 (95%CI 0.07;0.27) in iDeg-100 group (p=0.87). IR of BG <54 mg/dL was 0.02 (95%CI 0.01;0.05) in Gla-300 group and 0.02 (95%CI 0.01;0.04) in IDeg-100 group (p=0.49).
No severe hypoglycemic episodes were reported.

RESTORE

Discussion and conclusion

- In this Italian retrospective real-life study conducted in T2D adults through electronic medical records, **non-inferiority of Gla-300 vs. iDeg-100 has been demonstrated, consistently with BRIGHT (RCT) and DELIVER Naïve D (real world study)** (3,4).
  - Concerning HbA_{1c}, no statistically significant differences between Gla-300 and iDeg-100 at month 6 were detected.
  - The other effectiveness endpoints (especially FPG) significantly improved with no effect on the body weight, despite the still sub-optimal titration. Nonetheless, the increase in insulin dose was greater than what was observed in RESTORE-1 (5), suggesting a greater tendency in titrating by clinicians.

- Concerning safety**, hypoglycemia rates were low and comparable between the two groups, with no severe episodes.**

- In conclusion, **initiating Gla-300 or iDeg-100 was associated with similar improvements in glycemic control, no weight gain and low hypoglycemia rates**. These findings can contribute to overcoming clinical inertia in BI initiation and dose titration in insulin naïve people affected by T2D.

3. R.Roussel , et al Diabetes & Metabolism Volume 44, Issue 5, November 2018, Pages 402-409 . 4. Reinhard H.A. Becker, et al. Diabetes Care Apr 2015, 38 (4) 637-643; DOI: 10.2337/dc14-0006; 3 . J. Rosenstock et al. Diabetes Care 2018; https://doi.org/10.2337/dc18-0559. 4. S.D. Sullivan et al. Diabetes Obes Metab 2019 Sep;21(9):2123-2132.L. Laviola et al. Diabetes Ther https://doi.org/10.1007/s13300-020-00982-z

RESTORE