Superior Efficacy of Insulin Degludec/Liraglutide (IDegLira) vs. Insulin Glargine (IGlar U100) as Add-on to Sodium-Glucose Co-Transporter-2 Inhibitor (SGLT-2i) ± Oral Antidiabetic Drug (OAD) Therapy in Patients with Type 2 Diabetes (T2D): DUAL IX Trial

Athena Philis-Tsimikas, MD	**Scripps Whittier Diabetes Institute, San Diego, CA, USA**
Liana K Billings, MD, MMSc	NorthShore University HealthSystem, Evanston, IL, USA; University of Chicago Pritzker School of Medicine, Chicago, IL, USA
Robert Busch, MD	Albany Medical Centre, New York, NY, USA
Cristóbal Morales-Portillo, MD	Hospital Virgen Macarena, Seville, Spain
Rajesh Sahay, MD	Osmania Medical College, Hyderabad, India
Natalie Halladin, MD, PhD	Novo Nordisk A/S, Søborg, Denmark
Ruta Gronskyte Juhl, PhD	Novo Nordisk A/S, Søborg, Denmark
Stewart Harris, MD, CM, MPH	Western University, London, ON, Canada

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Presenter disclosure

Dr. Philis-Tsimikas serves on behalf of Scripps Health and does not receive any direct or indirect reimbursement related to advisory and research roles.

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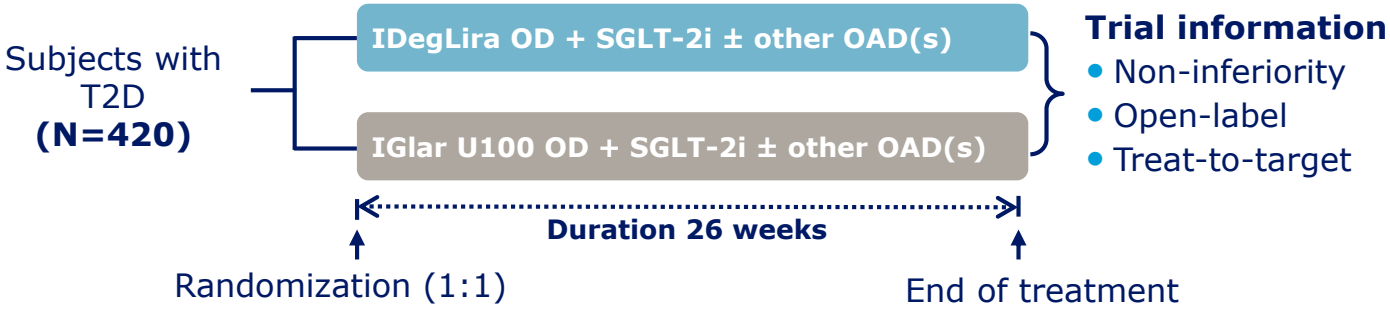
Background

- At the start of DUAL IX, there were no trials published with a **GLP-1RA** in combination with an **SGLT-2i**
- Since then, clinical trials have demonstrated the safety and efficacy of:
  - Concomitant initiation of GLP-1RA and SGLT-2i (DURATION-8)[1]
  - SGLT-2i as add-on therapy to GLP-1RA (CANVAS [CVOT])[2]
  - GLP-1RA as add-on to ongoing SGLT-2i therapy (AWARD-10)[3]
- DUAL IX examines the efficacy and safety of **IDegLira** as an add-on to **SGLT-2i** in patients with T2D failing to achieve glycemic control on SGLT-2i

CVOT, cardiovascular outcomes trial; IDegLira, insulin degludec/liraglutide; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes

1. Frias *et al. Lancet Diabetes Endocrinol* 2016;4:1004–16; 2. Neal *et al. NEJM* 2017;377:644–57; 3. Ludvik *et al. Lancet Diabetes Endocrinol* 2018;6:370–81

Trial design



Inclusion criteria

- Age ≥18 years
- Insulin-naïve
- HbA_{1c} 7.0–11.0%
- SGLT-2i ± other OADs*
- BMI ≥20 and <40 kg/m^2

Primary endpoint:

- Change from baseline in HbA_{1c} after 26 weeks

Confirmatory secondary endpoints:

- Change from baseline after 26 weeks in body weight
- Number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes
- Total daily insulin dose

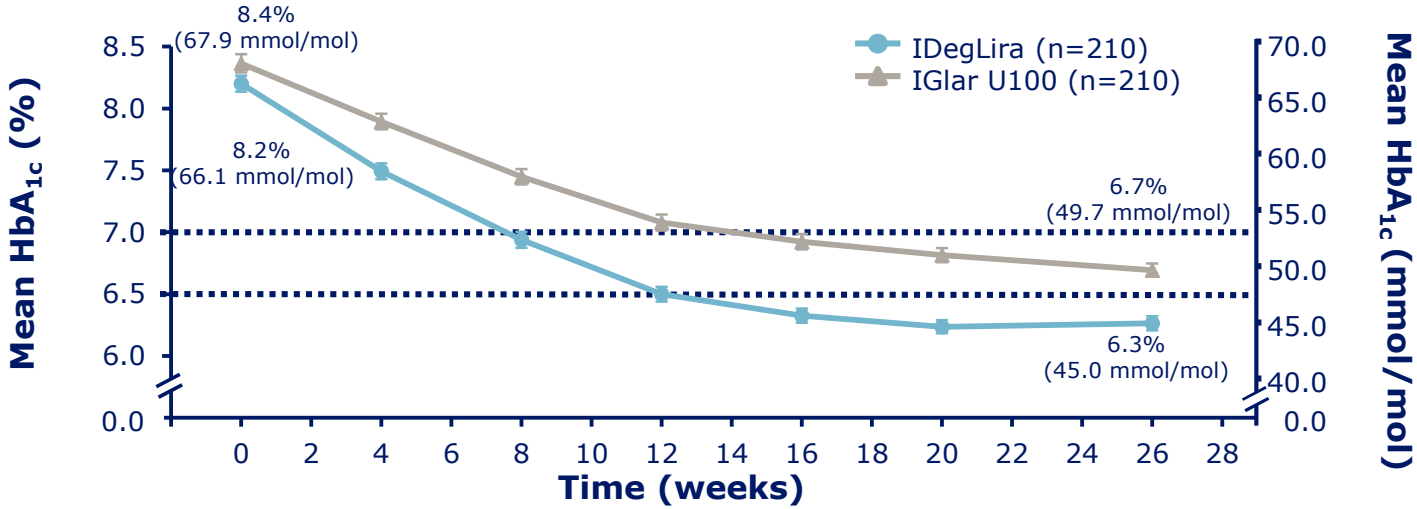
*Metformin, DPP-4i, pioglitazone; the combination of pioglitazone and dapagliflozin was not allowed. DPP-4i were discontinued at randomization
BG, blood glucose; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; OD, once daily; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes

Baseline characteristics

Characteristic	IDegLira	IGlar U100
Full analysis set, N	210	210
Male, %	57.6	60.0
Age, years	56.1	57.2
Weight, kg	89.3	87.2
BMI, kg/m^2	31.5	30.9
Duration of diabetes, years	9.80	9.31
HbA_{1c}, %	8.20	8.36
HbA_{1c}, mmol/mol	66.13	67.93
FPG, mmol/L (mg/dL)	9.51 (171.29)	9.57 (172.46)

Values are mean, unless otherwise stated
BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

HbA_{1c} over time (full analysis set)

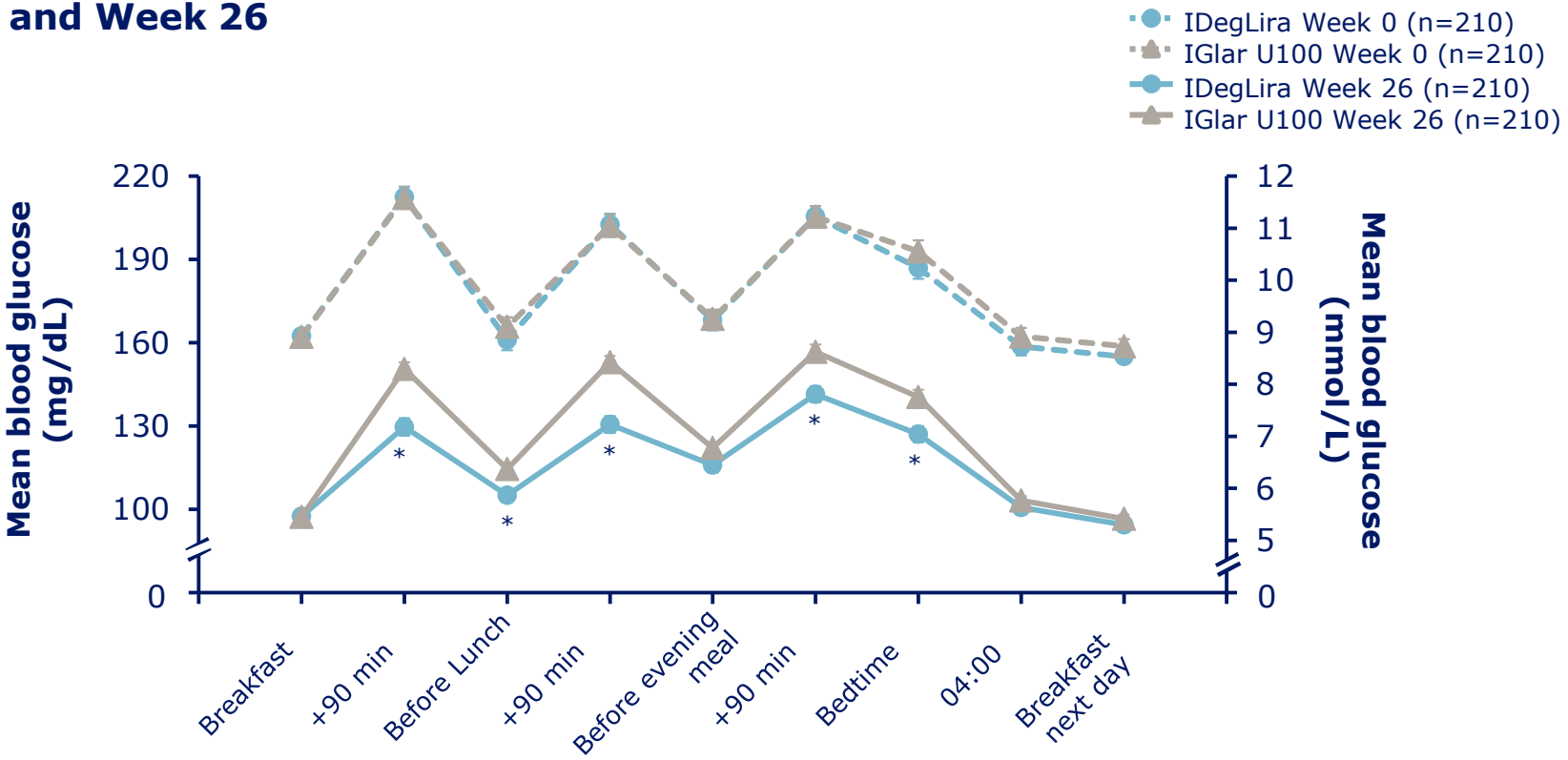


	IDegLira	IGlar U100	Estimated treatment difference [95% CI]
Δ HbA_{1c}, (%)	−1.94	−1.68	−0.36% [−0.50; −0.21], p<0.0001*
Δ HbA_{1c}, (mmol/mol)	−21.18	−18.41	−3.90 [−5.45; −2.35], p<0.0001*

Mean (SE) observed values, including data obtained after premature treatment discontinuation, based on full analysis set
*For superiority. Tested for superiority once non-inferiority (limit of 0.3%) was demonstrated. Estimated treatment difference is based on least squares mean change from baseline analyzed by ANCOVA with treatment, pre-trial OAD, and region as factors and baseline value as covariate. Missing data are imputed using unconditional multiple imputation including data obtained after premature treatment discontinuation. -----ADA/EASD HbA_{1c} target <7.0% and AACE HbA_{1c} target ≤6.5%
AACE; American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ANCOVA, analysis of covariance;
CI, confidence interval; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; SE, standard error of the mean

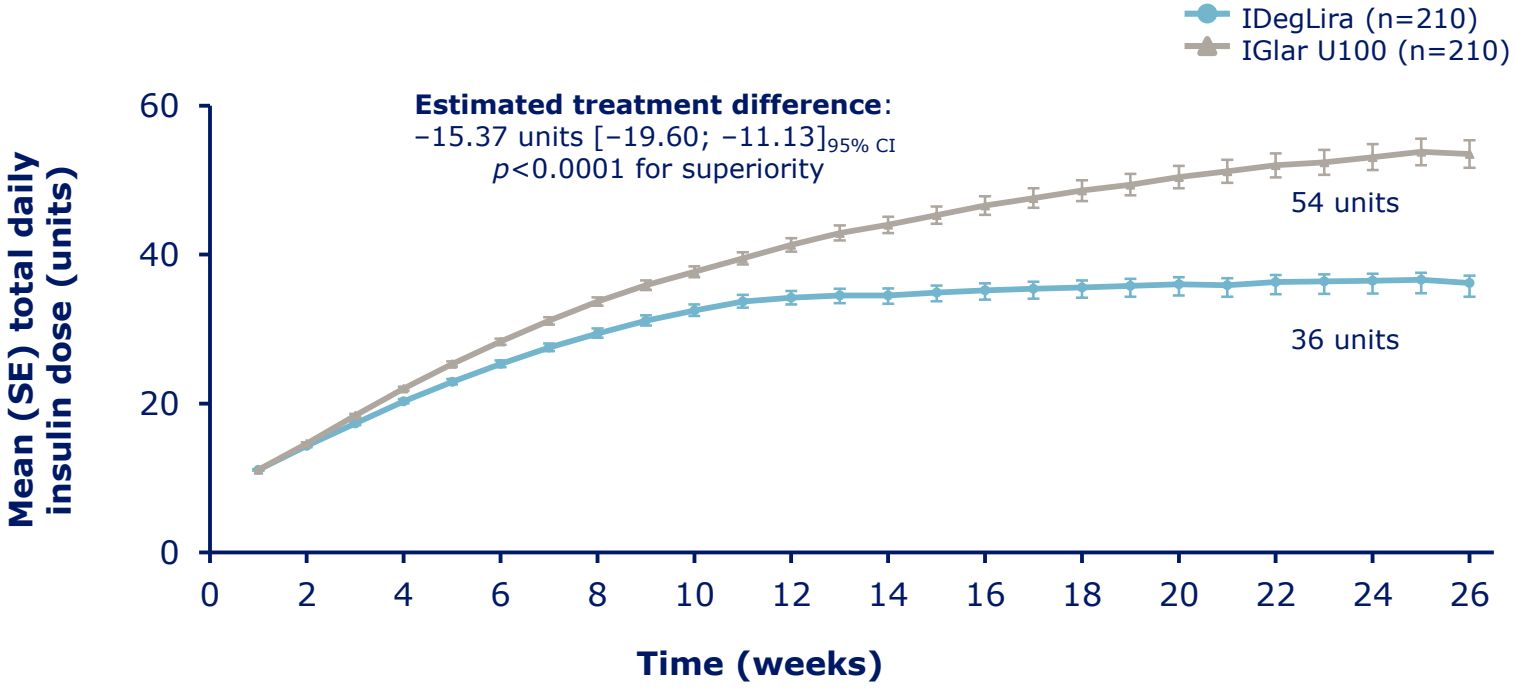
9-point self-measured blood glucose

Week 0 and Week 26



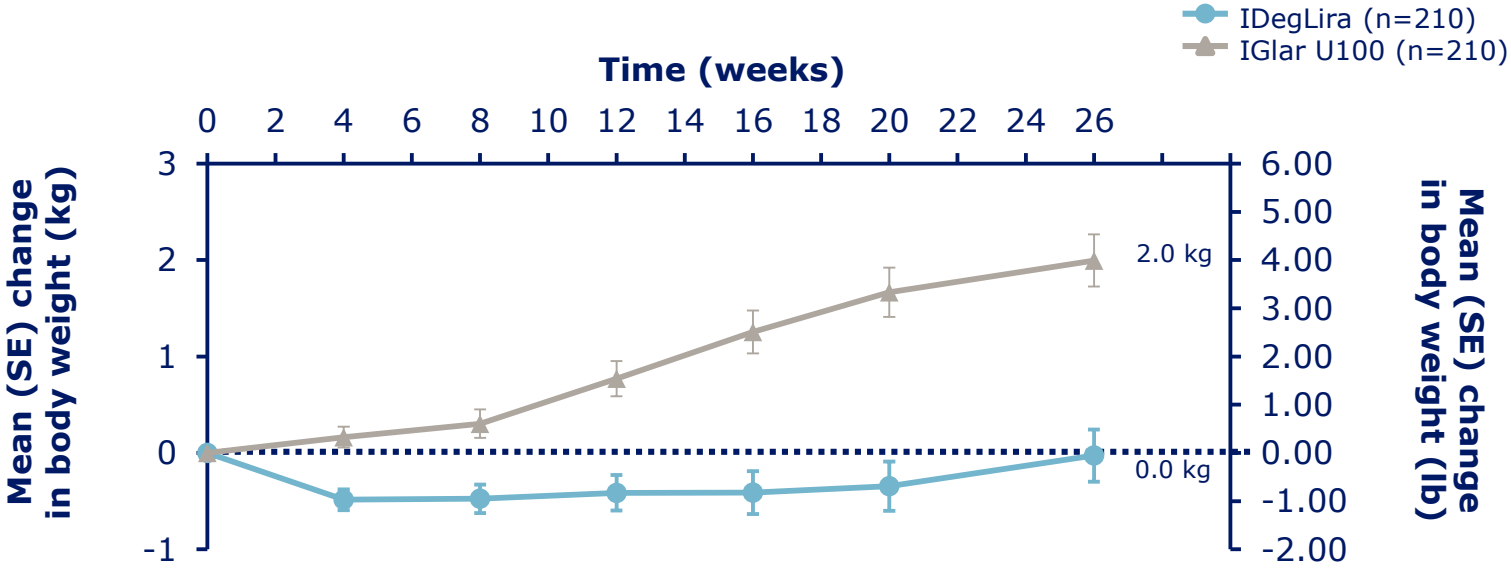
*Statistically significant difference in favor of IDegLira. Mean observed values with error bars based on full analysis set
IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL

Total daily insulin dose over time



End of trial doses analyzed using ANCOVA with treatment, pre-trial OAD, and region as factors and baseline HbA_{1c} as covariate
Mean (SE) values based on full analysis set. Missing data are imputed using unconditional multiple imputation including data obtained after premature treatment discontinuation
ANCOVA, analysis of covariance; CI, confidence interval; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; SE, standard error of the mean

Change in body weight over time

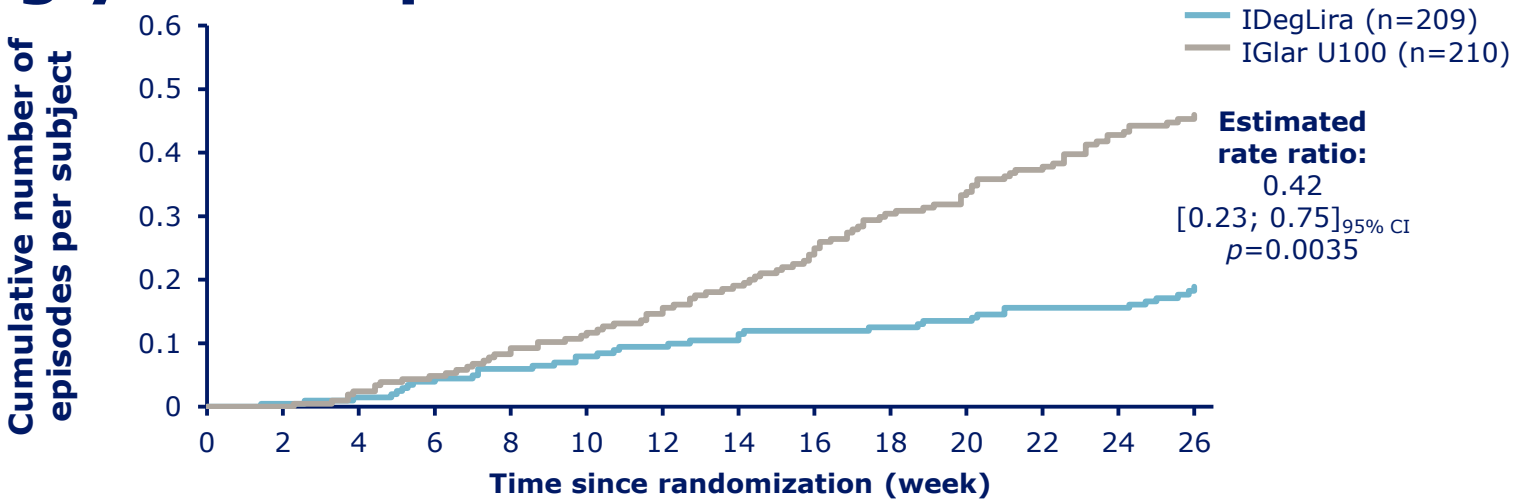


	IDegLira	IGlar U100	Estimated treatment difference [95% CI]
Δ Weight (kg)	−0.0	+2.0	−1.92 [−2.64; −1.19], $p<0.0001$*
Δ Weight (lb)	−0.1	+4.4	−4.22 [−5.81; −2.63], $p<0.0001$*

Mean (SE) values, including data obtained after premature treatment discontinuation, based on full analysis set. Missing data are imputed using unconditional multiple imputation including data obtained after premature treatment discontinuation. Change from baseline after 26 weeks was analyzed by ANCOVA with treatment, pre-trial OAD, and region as factors and baseline value as covariate. *For superiority

ANCOVA, analysis of covariance; CI, confidence interval; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; SE, standard error of the mean

Severe or BG-confirmed symptomatic hypoglycemic episodes over time



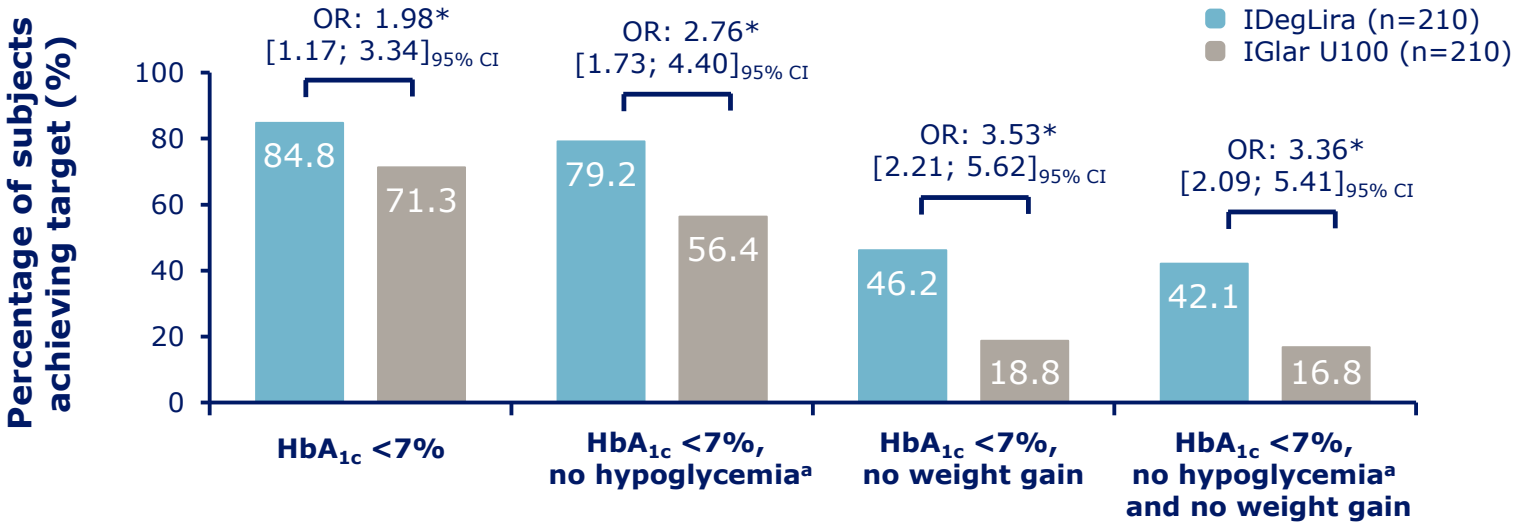
	% patients*	Number of Events	Rate (episodes/PYE)
IDegLira	12.9%	38	0.37
IGlar U100	19.5%	95	0.90

Mean cumulative function based on safety analysis set. Severe or BG-confirmed symptomatic hypoglycemic episode: severe according to the ADA classification or blood glucose value <56 mg/dL (<3.1 mmol/L) with symptoms consistent with hypoglycemia

*Percentage of patients experiencing one or more events. Number of episodes analyzed by negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model includes treatment, pre-trial OAD and region as fixed factors. Missing data are imputed using multiple imputation

ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; PYE, patient-year of exposure

Patients achieving HbA_{1c} <7% and composite outcomes at end of trial



*Statistically significant difference (in favor of IDegLira)

[a]Severe or BG-confirmed symptomatic hypoglycemia. Based on hypoglycemic episodes during last 12 weeks of treatment

Percentages based on observed values including data obtained after premature treatment discontinuation

Analyzed using a logistic regression model with treatment, pre-trial OAD and region as factors and HbA_{1c} baseline value (and body weight when body weight is included in the composite) as covariate. Missing data are imputed using unconditional reference based multiple imputation including data obtained after premature treatment discontinuation

BG, blood glucose; CI, confidence interval; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; OR, odds ratio

Treatment-emergent adverse events

	IDegLira (N=209)				IGlar U100 (N=210)			
	N	(%)	E	R	N	(%)	E	R
Adverse events	129	61.7	450	436.0	123	58.6	386	364.7
Serious	6	2.9	8	7.8	7	3.3	9	8.5
Fatal*	0	–	–	–	1	0.5	1	0.9
Occurring in ≥5% of patients								
Viral upper respiratory tract infection	16	7.7	22	21.31	22	10.5	24	22.68
Headache	18	8.6	35	33.91	19	9.0	27	25.51
Back pain	11	5.3	12	11.63	9	4.3	15	14.17
Lipase increased	12	5.7	15	14.53	3	1.4	3	2.83
Nausea	12	5.7	22	21.31	1	0.5	2	1.89

Data based on safety analysis set. *There was one fatal event in the IGlar U100 arm: a CV death which was adjudicated as a major cardiovascular event and occurred more than 7 days but less than 30 days after the last day of randomized treatment. %, percentage of subjects with one or more event; CV, cardiovascular; E, number of events; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; N, number of subjects with one or more event; R, events per 100 years of exposure; TE, treatment-emergent

Summary

Initiating IDegLira vs. initiating IGlar U100 in a population on combination OAD treatment including SGLT-2i resulted in:

• HbA_{1c} reduction	1.94% vs. 1.68%	**Superior**
• Hypoglycemia rate*	0.37 vs. 0.90	**Superior**
• Body weight change	0.0 kg vs. +2.0 kg	**Superior**
• Insulin dose	36 U vs. 54 U	**Superior**

*Events per patient year of exposure
HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Conclusions

- The DUAL IX study demonstrates the efficacy and safety of IDegLira treatment as an add-on to SGLT-2i in patients with T2D uncontrolled on SGLT-2i ±OADs
  - There were no unexpected safety or tolerability findings
- The results of DUAL IX indicate that IDegLira may be a better treatment option than IGlar U100 in patients on SGLT-2i in need of intensification

IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes