VIII Convegno Nazionale Fondazione AMD

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
1974 ANNO DI FONDAZIONE

AMD FONDAZIONE onlus ASSOCIAZIONE MEDICI DIABETOLOGI

10.00 SIMPOSIO AZIENDALE NOVO NORDISK

11.00 NUOVE OPPORTUNITÀ NELLA GESTIONE DELLA COMPLESSITÀ DEL TRATTAMENTO DEL DIABETE

PALERMO, 17-19 NOVEMBRE 2016

QUANDO L'INSULINA BASALE NON BASTA PIU'

Prof. CARLA GIORDANO

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POTENZIALI CONFLITTI DI INTERESSE

La Prof. Carla Giordano dichiara di aver ricevuto negli ultimi 2 anni compensi o finanziamenti dalle seguenti aziende Farmaceutiche e/o Diagnostiche:

Novo Nordisk, Eli Lilly, Boeringher-Ingelheim, Novartis, Medtronic, Abbott, Bruno, M SD, Astra Zeneca, Takeda, Sanofi, ItaPharma, Roche per finanziamenti a convegni

Novo Nordisk, Lilly, Boehringer-Ingelheim, Janssen, Shire, Novartis per Attività di Consulenza

Agenda

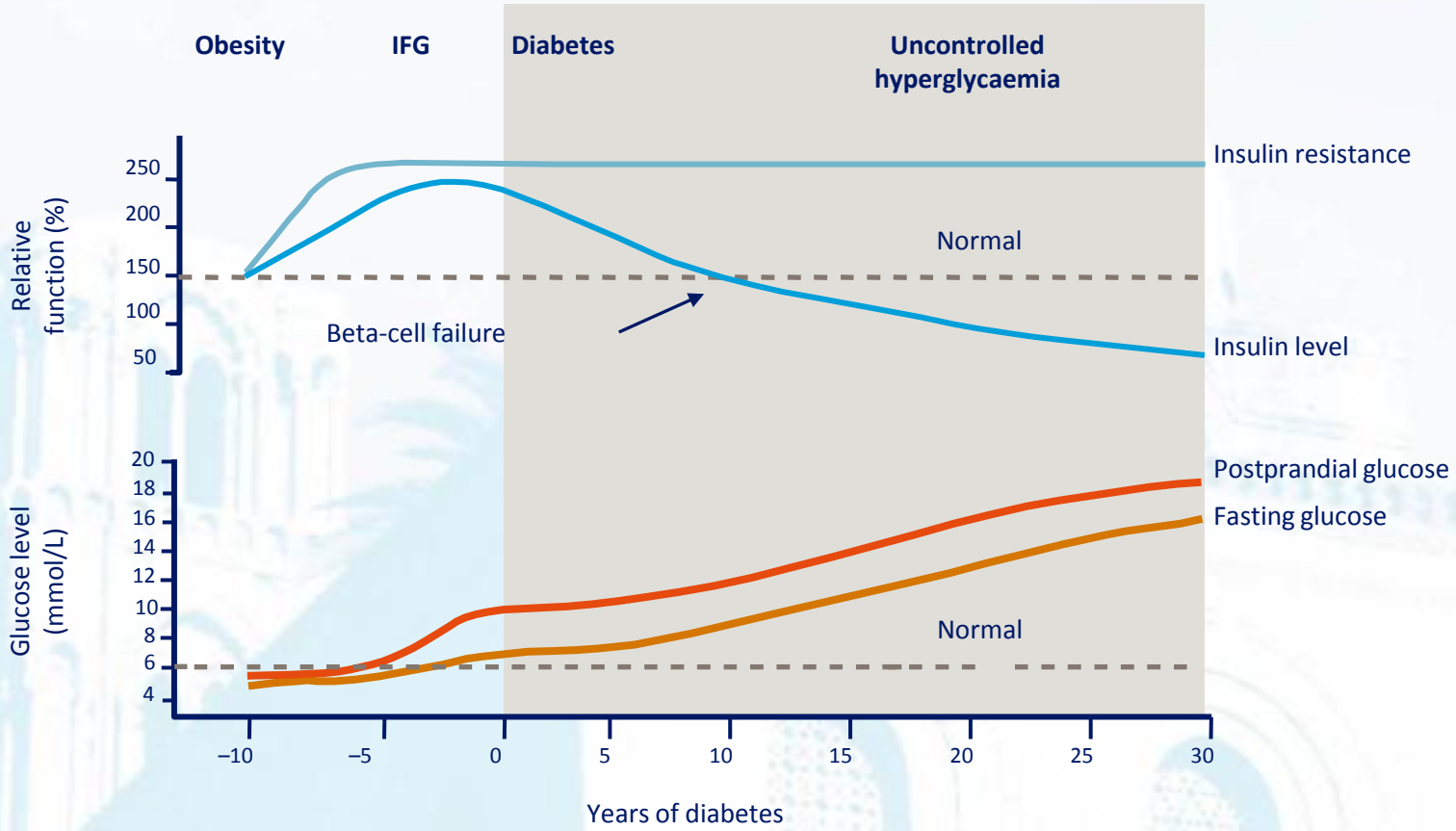
- *Unmet Needs* e recenti proposte terapeutiche in tema di basalizzazione insulinica:
- *Degludec*

- *Unmet Needs* e recenti proposte terapeutiche in tema di intensificazione insulinica:
- *Insulina Basale + GLP-1RA*

- IdegLira : DUAL V trial

- Conclusioni

Disease progression: insulin replacement therapy becomes necessary in type 2 diabetes



IFG, impaired fasting glucose

Adapted from Bergenstal *et al. Endocrinology.* Philadelphia, PA: WB Saunders Co; 2001:821–35

Good glycaemic control matters

Impact on diabetes-related complications and treatment cost

Good glycaemic control

UKPDS

Reduces diabetes-related complications[1]

1% reduction in mean HbA_{1c}

- **37%** reduction in microvascular complications
- **14%** reduction in myocardial infarction
- **21%** reduction in diabetes-related mortality

Retrospective database analysis

Reduces total diabetes-related costs[2]

Patients with HbA_{1c} ≤7% continuously for 1 year

25% lower overall diabetes-related treatment costs i.e.:

- **22%** lower diabetes medical costs
- **28%** lower diabetes pharmacy costs

UKPDS, United Kingdom Prospective Diabetes Study

1. Stratton *et al. BMJ* 2000;321:405–12. 2. Shetty *et al. J Manag Care Pharm* 2005;11:559–64

Standard italiani per la cura del diabete mellito 2014

'ASSISTENZA

SID Società Italiana di Diabetologia

5. Quando si avvia la terapia insulinica:

5.1. Iniziare preferibilmente con un'insulina basale come glargine, detemir, ILPS o umana NPH (con umana NPH il rischio di ipoglicemia è tuttavia maggiore), tenendo comunque in considerazione le diverse farmacocinetiche

oppure, in seconda analisi

5.2. Utilizzare direttamente uno schema basal-bolus

oppure, in terza analisi

5.3. Utilizzare un analogo rapido ai pasti

oppure, in casi partico

5.4. In presenza di somministrazione paziente verso uno

Standard Italiani per la Cura del Diabete - 2016

5.1. Iniziare preferibilmente con un'insulina basale, tenendo in considerazione le diverse farmacocinetiche delle varie basali disponibili, ma senza dimenticare che ci sono alternative efficaci (terapia orale con 1-2 iniezioni di insulina rapida ai pasti)

oppure, in seconda analisi

5.2. Utilizzare direttamente uno schema basal-bolus

oppure, in terza analisi

5.3. Utilizzare schemi alternativi come il basal-plus oppure il basal-plus-plus

oppure, in casi particolari,

5.4. In presenza di gravi ed evidenti problemi di compliance, utilizzare una singola o doppia somministrazione di insulina premiscelata (bifasica), tentando comunque di educare il paziente verso uno schema basal-bolus.

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974

Unmet Needs in Insulin Therapy

Durata d'azione

Patients are in poor blood glucose control

Variabilità

Insulin doses are being missed or not taken as prescribed

Aderenza alla terapia

Patients struggle to remain fully adherent to their insulin regimens

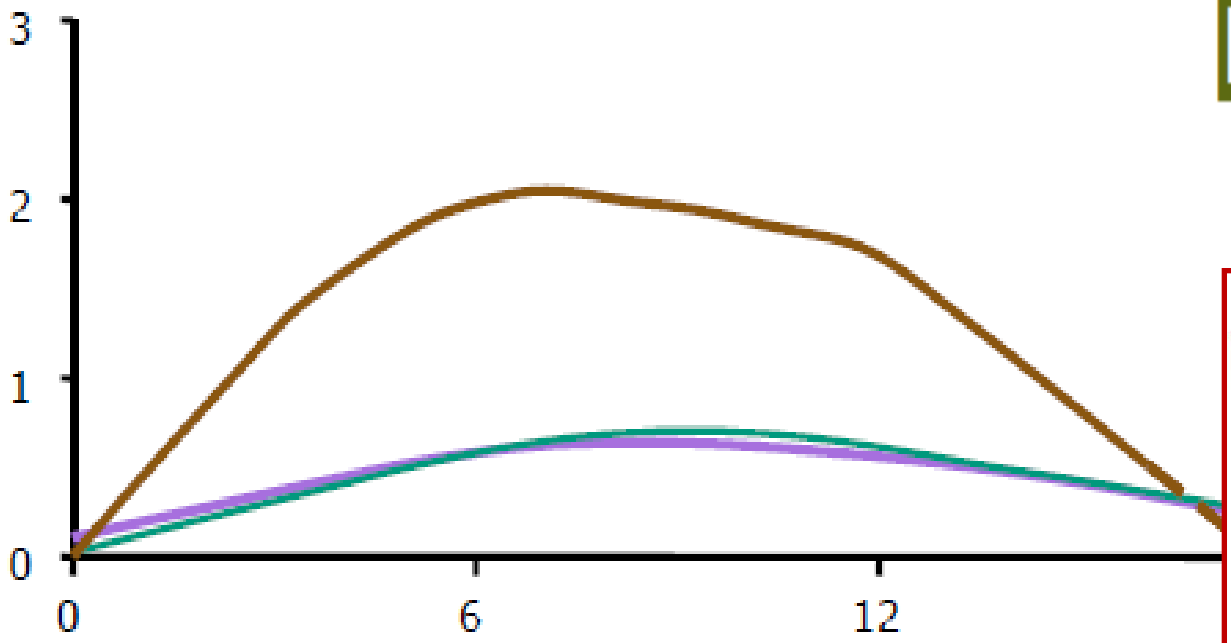
Ipoglicemie

Patients and physicians are concerned about hypoglycaemia

Peyrot et al. Diabetes Care 2010;33:240–5; Peyrot et al. Diabetes 2011;60(Suppl. 1):A225

PROFILO DELLE INSULINE BASALI

NPH-insulin (0.3 IU/kg; type 2 diabetes)[1]
Insulin detemir (0.4 U/kg; type 2 diabetes)[2]
Insulin glargine (0.4 U/kg; type 2 diabetes)[2]



Durata d'azione

Not enough insulin to cover 24 hrs basal needs:
The «Dusk» Phenomenon

1Hompesch M. Diabetes Obes Metab 2006; 8:568
2. Klein O. Diabetes Obes Metab 2007; 9:290

Variabilità

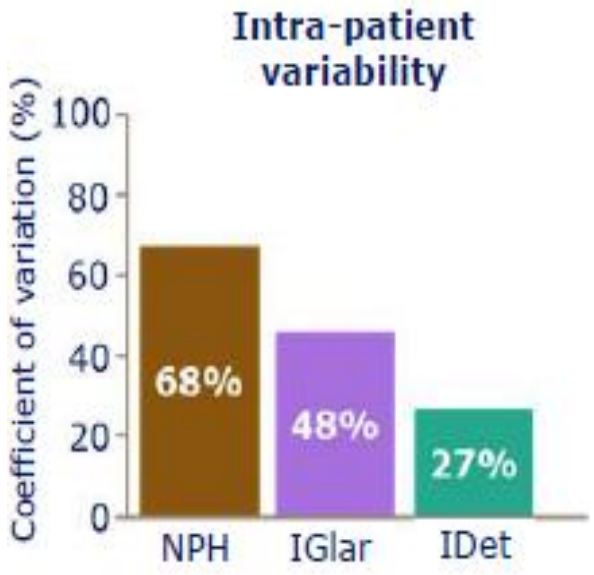
Pathophysiology/Complications
ORIGINAL ARTICLE

Increased Glycemic Variability Is Independently Associated With Length of Stay and Mortality in Noncritically Ill Hospitalized Patients

CARLOS E. MENDEZ, MD[1]
KI-TAE MOK, MD[1]
ASHAR ATA, MBBS, MPH[2]
ROBERT J. TANENBERG, MD[1]
JORGE CALLES-ESCANDON, MD[4]
GUILLERMO E. UMPIERREZ, MD[3]

CONCLUSIONS—Our results indicate that increased GV during hospitalization is independently associated with longer LOS and increased mortality in noncritically ill patients. Prospective studies with continuous glucose monitoring are necessary to investigate this association thoroughly and to generate therapeutic strategies targeted at decreasing GV.

Diabetes Care 36:4091–4097, 2013



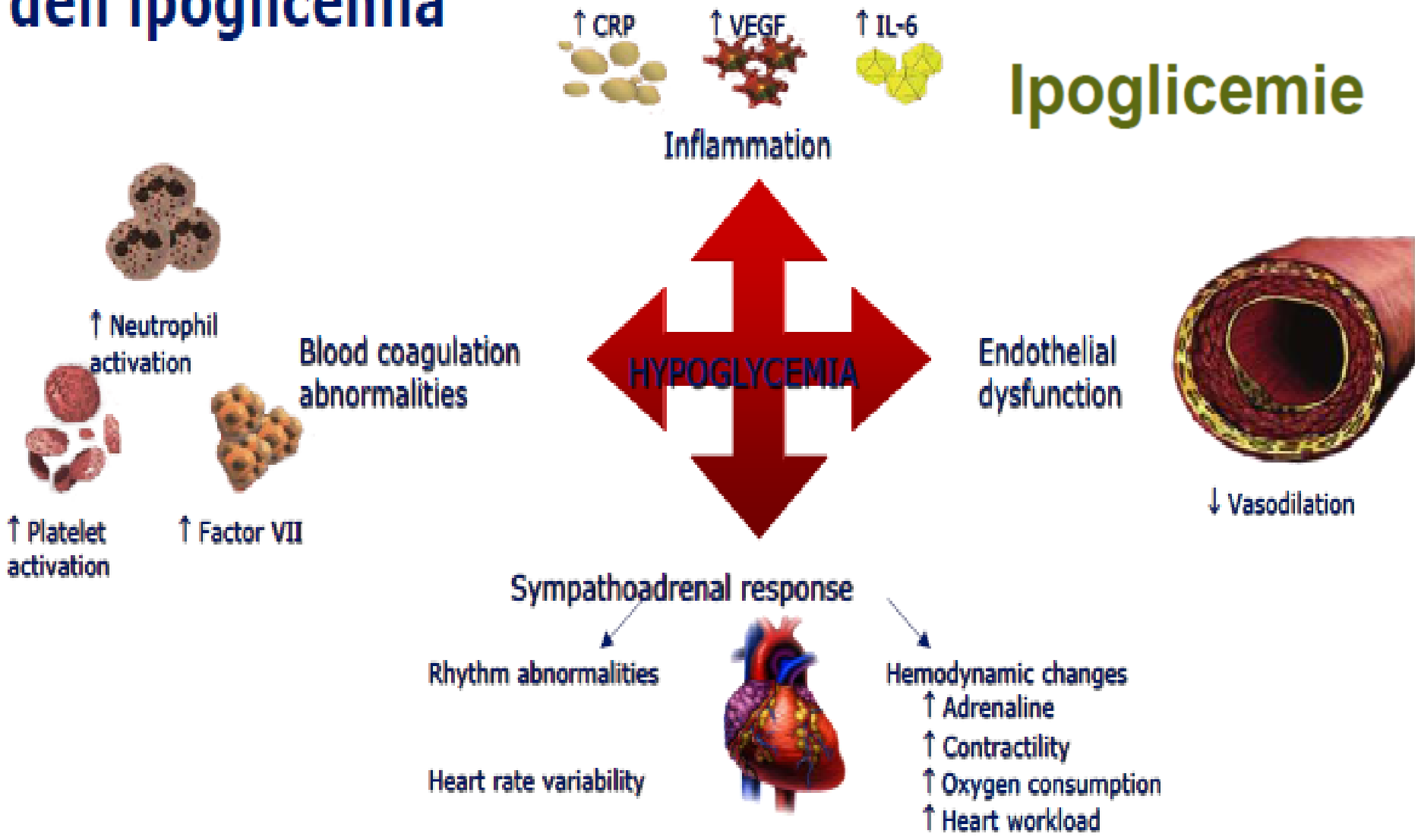
Original Article

GLUCOSE VARIABILITY IS AN INDEPENDENT PREDICTOR OF MORTALITY IN HOSPITALIZED PATIENTS TREATED WITH TOTAL PARENTERAL NUTRITION

Farnoosh Farrokhi, MD[1]; Prakash Chandra, MD[1]; Dawn Smiley, MD[1]; Francisco J. Pasquel, MD[1]; Limin Peng, PhD[2]; Christopher A. Newton, MD[1]; Guillermo E. Umpierrez, MD[1]

Conclusion: High GV is associated with increased hospital mortality independent of the presence and severity of hyperglycemia or hypoglycemia during TPN therapy. Prospective randomized trials are needed to determine if reduction in GV with intensive glycemic control improves clinical outcomes in patients treated with TPN. **(Endocr Pract. 2014;20:41-45)**

Conseguenze fisiopatologiche cardiovascolari dell'ipoglicemia



CRP=C-reactive protein; IL-6=interleukin 6; VEGF=vascular endothelial growth factor.

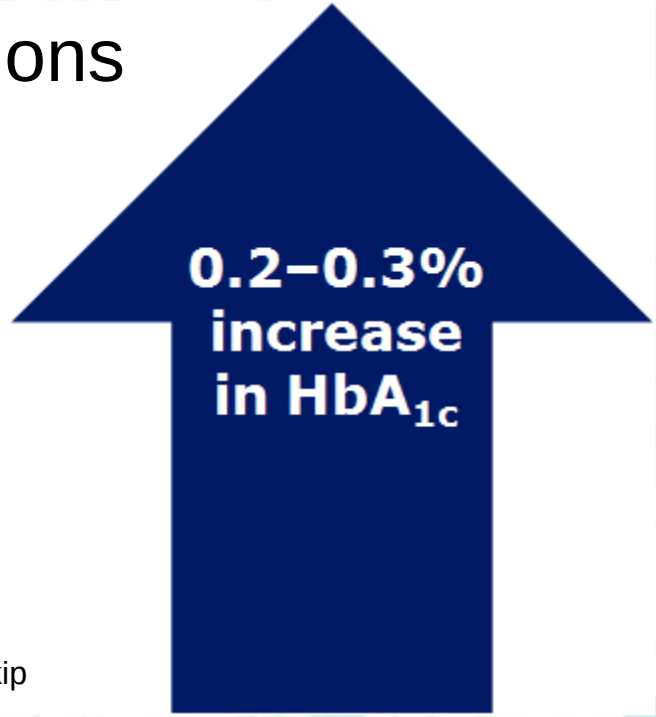
Desouza CV et al. *Diabetes Care*. 2010;33(6):1389-1394.

Adherence and intentional insulin omission in type 1 and 2 diabetes

Aderenza alla terapia

- Of patients questioned:
  - 57% omitted insulin injections
  - 20% omitted regularly*

Missing two basal insulin injections per week =

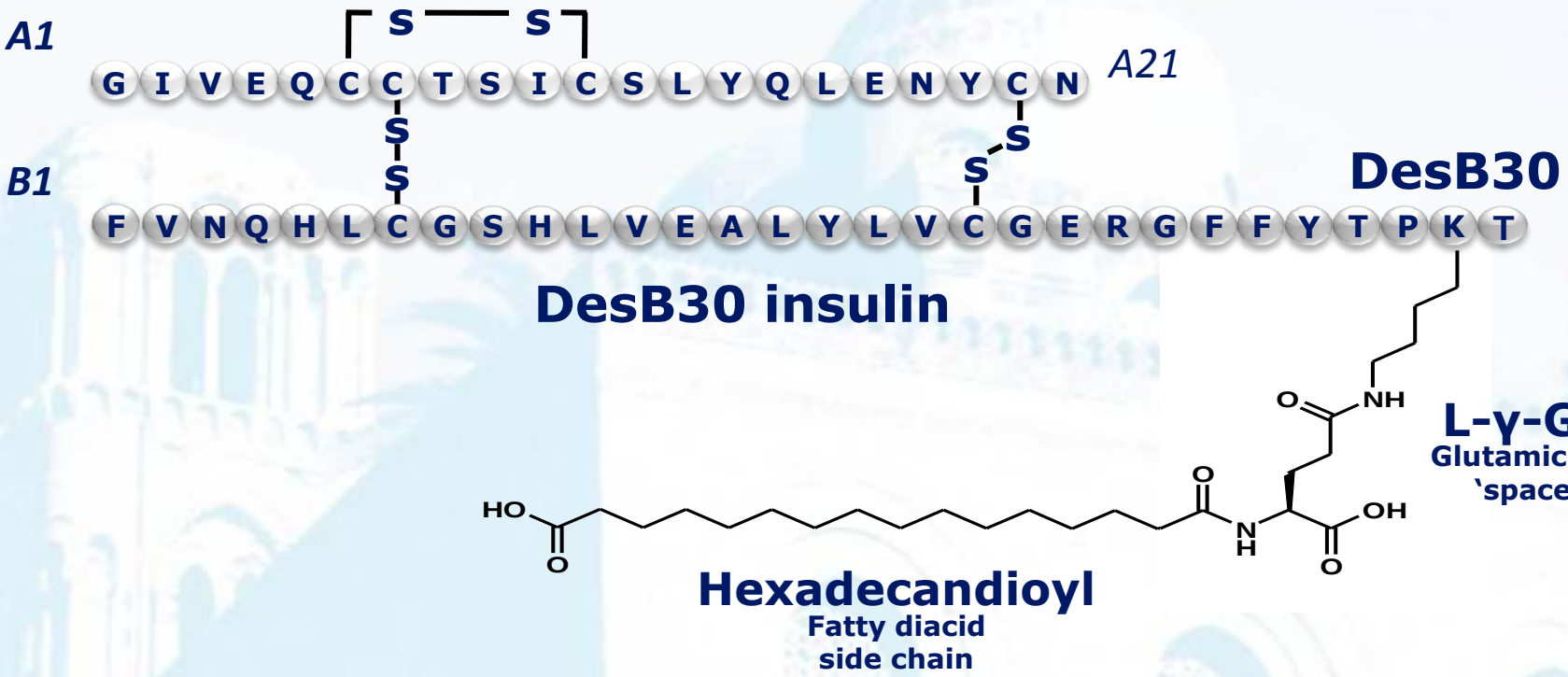


*Response of "sometimes" or "often" to the question: "How often do you skip insulin injections that you know you should take?"

Peyrot et al. Diabetes Care 2010;33:240–5; Randløv et al. J Diabetes Sci Technol 2008;2:229–35

Insulin degludec: rationally designed, beyond sequence modification

Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin



Degludec: Proprietà Farmacologiche (RCP)

L'emivita dopo somministrazione sottocutanea di degludec è determinata dal grado di assorbimento dai tessuti sottocutanei. L'emivita di degludec è di circa 25 ore indipendentemente dalla dose.

Durante un periodo di 24 ore con trattamento una volta al giorno, l'effetto ipoglicemizzante di degludec, contrariamente all'insulina glargine, era distribuito in modo uniforme tra le prime e le seconde 12 ore (AUCGIR,0-12h,SS/AUCGIR,totale,SS = 0,5)

Lo steady state si raggiunge dopo 2-3 giorni dalla somministrazione della dose.

L'azione ipoglicemizzante dell'insulina degludec allo steady state mostra una variabilità da giorno a giorno quattro volte inferiore in termini di coefficienti di variazione (CV) per l'effetto ipoglicemizzante in 0-24 ore (AUCGIR,τ,SS) e 2-24 ore (AUCGIR2-24h,SS) rispetto all'insulina glargine

Degludec RCP
Heise et al. Diabetologia 2011;54(Suppl. 1):S425; Heise et al. Diabetes 2012;61(Suppl. 1):A259; Heise et al. Diabetes Obes Metab 2012;14:859-64

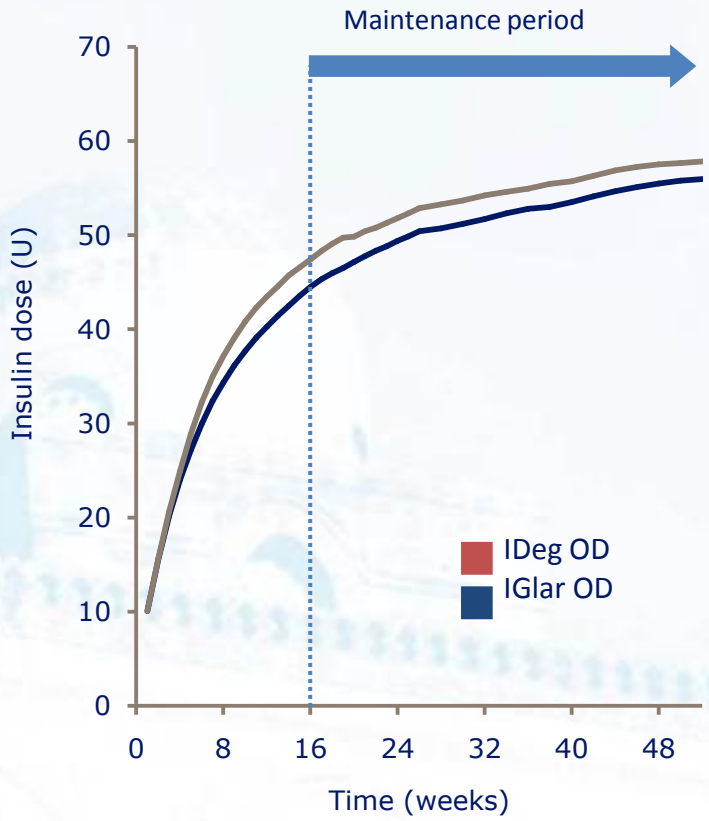
Insulin degludec phase 3a study programme: meta-analysis

	Full trial	Maintenance
Overall		
Pooled T2D/T1D	–9%*	–16%*
Nocturnal		
Pooled T2D/T1D	–26%*	–32%*

Hypoglycaemia risk reduction IDeg versus IGlar

*Statistically significant, $p<0.05$

Ratner *et al. Diabetes Obes Metab* 2013;15:175–84



SPC (par. 5.1)
In a prospectively planned meta-analysis across seven treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, **Tresiba was superior in terms of a lower number of treatment emergent confirmed hypoglycaemic episodes** (driven by a benefit in type 2 diabetes mellitus) **and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine** (administered according to label).
The reduction in hypoglycaemia was achieved at a **lower average FPG level with Tresiba than with insulin glargine**.

ADA Congress , June 2016

SWITCH 2: reduced hypoglycemia with insulin degludec (IDeg) versus insulin glargine (IGlar), both U100, in patients with T2D at high risk of hypoglycemia: a randomized, double-blind, crossover trial

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Valley Research, Fresno, CA, USA

Introduction

- Insulin degludec (IDeg) is a basal insulin with a unique mode of protraction and duration of action of greater than 42 hours.[1-3]
- The phase 3a development program included five trials in patients with type 2 diabetes (T2D), which demonstrated non-inferiority of IDeg to insulin glargine U100 (IGlar) with respect to HbA_{1c}.[4-8]
- A pre-specified meta-analysis of these trials showed that the rates of confirmed and nocturnal confirmed hypoglycemia were significantly lower with IDeg versus IGlar.[9]
- Potential limitations of the phase 3a trials included: the lack of blinding, inclusion of non-symptomatic hypoglycemia in the hypoglycemia endpoints, exclusion of patients with one or more hypoglycemia risk factors, and no recording of the timing of IGlar administration.
- SWITCH 2 was designed to confirm the data from the meta-analysis and address these limitations.

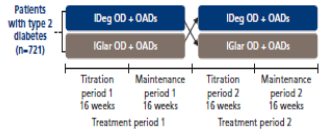
Aims

- Primary: To confirm superiority of IDeg compared with IGlar in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycemia during the maintenance period (after 16 weeks of treatment).
- Secondary: To confirm superiority of IDeg compared with IGlar in the rates of severe or BG-confirmed symptomatic nocturnal hypoglycemia and the proportion of patients with severe hypoglycemia during the maintenance period.

Methods

- This was a 2× 32-week randomized, double-blind, crossover, multicenter, treat-to-target phase 3b clinical trial conducted in patients with T2D (Figure 1).
- Patients were randomized 1:1 to 100 U/mL (U100) of IDeg or IGlar once daily and 1:1 to administer basal insulin in the morning or evening throughout the trial.
- Patients included were previously treated with basal insulin with or without oral antidiabetic drugs, excluding sulfonylurea/meglitinides.
- Eligible patients had at least one of the following hypoglycemia risk factors:
  - ≥1 severe hypoglycemic episode within the last year
  - Moderate chronic renal failure (glomerular filtration rate 30-59 mL/min/1.73m²)
  - Hypoglycemic symptom unawareness
  - Exposure to insulin >5 years
  - Episode of hypoglycemia within the last 12 weeks (according to ADA definition ≤70 mg/dL [≤3.9 mmol/L]).
- Insulin was administered using a vial and syringe: if switching from once-daily dosing, the starting dose was the pre-trial dose, and if switching from twice-daily dosing, the pre-trial dose was reduced by 20%. The starting dose for treatment period 2 was the dose from the end of treatment period 1.
- Basal insulin was titrated weekly based on the mean of three pre-breakfast self-measured BG readings to a fasting target of 71–90 mg/dL (3.9–5.0 mmol/L).
- Confirmation of non-inferiority in HbA_{1c} reduction at the end of each 32-week period was a prerequisite for conducting the hypoglycemia analyses.
- Confirmed symptomatic hypoglycemia was defined by a BG <56 mg/dL (<3.1 mmol/L) and nocturnal hypoglycemia was predefined as any episode occurring between 00:01 and 05:59, both inclusive. The ADA definition of severe hypoglycemia was utilized,[10] and all reported episodes of severe hypoglycemia were adjudicated by an independent external committee.

Figure 1 Trial design.



Randomized 1:1 to morning or evening dosing
IDeg, insulin degludec; IGlar, insulin glargine U100; OAD, oral antidiabetic drug; OD, once daily.

- *P*-values were derived using a Poisson model with logarithm of the exposure time as offset; estimates were adjusted for treatment, period, sequence and dosing time as fixed effects, and patient as a random effect. Proportion analysis was conducted using McNemar's test.

Results

- Baseline characteristics are shown in Table 1.
- In total, 721 patients were randomized and 713 were exposed to trial product, with 580 (80.4%) completing the trial.
- The full analysis set included 720 patients; one patient was excluded due to an unsigned casebook.

Efficacy

- The prerequisite of achieving non-inferiority for change in HbA_{1c} in both treatment periods was met (Figure 2).
- Mean HbA_{1c} at the end of treatment period 1 was 7.06% (IDeg) versus 6.98% (IGlar), and at the end of treatment period 2 was 7.08% (IDeg) versus 7.11% (IGlar) (Figure 2).
- Mean fasting plasma glucose (FPG) for both groups also decreased to mean values, at the end of the maintenance period, of 107.4 mg/dL (IDeg) versus 110.4 mg/dL (IGlar).

Hypoglycemia (Figure 3, Table 2)

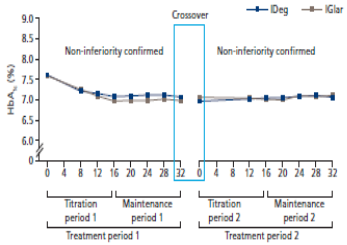
- Superiority for the primary endpoint was achieved (30% lower rate of severe or BG-confirmed symptomatic hypoglycemia; $p<0.0001$) with IDeg versus IGlar. Using numbers needed to treat, to avoid an episode of severe or BG-confirmed symptomatic hypoglycemia one patient would need to be treated for 1 year with IDeg instead of IGlar.
- Superiority for the secondary endpoint of the number of severe or BG-confirmed symptomatic nocturnal hypoglycemic episodes was also achieved (42% reduction; $p<0.0001$) for IDeg versus IGlar. To avoid one severe or BG-confirmed symptomatic nocturnal hypoglycemic episode, three patients would need to be treated for 1 year with IDeg instead of IGlar.
- Similar hypoglycemia results were seen for the full treatment period.
- The rate of severe hypoglycemia was significantly lower with IDeg versus IGlar for the full treatment period (51% lower; $p=0.0306$). To avoid an episode of severe hypoglycemia, 21 patients would need to be treated for 1 year with IDeg instead of IGlar.
- The proportion of patients experiencing severe hypoglycemia during the maintenance period was numerically but not significantly lower with IDeg versus IGlar.

Table 1 Baseline characteristics.

Characteristic	All patients
Full analysis set, n (%)	720 (100%)
Male, n (%)	382 (53.1%)
Race, n (%)	
White	578 (80.3%)
Black	106 (14.7%)
Asian	22 (3.1%)
Other	14 (1.9%)
Ethnicity, Hispanic or Latino, n (%)	262 (36.4%)
Age, years	61.4 (10.5)
Body weight, kg	91.7 (19.5)
BMI, kg/m²	32.2 (5.6)
Duration of diabetes, years	14.1 (8.1)
HbA_{1c}, %	7.6 (1.1)
FPG, mg/dL	137.0 (52.6)
eGFR, mL/min/1.73m²	78.3 (21.3)
Pre-trial insulin treatment, n (%)	
NPH	59 (8.2%)
IDet	159 (22.1%)
IGlar	502 (69.7%)
Pre-trial treatment regimen, n (%)	
Basal once daily	606 (84.2%)
Basal twice daily	114 (15.8%)
OADs at screening, n (%)	
0 agents	150 (20.8%)
1 agent	448 (62.2%)
≥2 agents	122 (16.9%)

Data are mean ± standard deviation unless otherwise stated. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IDet, insulin detemir; IGlar, insulin glargine U100; n, number of patients; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug.

Figure 2 Mean HbA_{1c} over time in treatment periods 1 and 2.



Data are mean ± standard error. IDeg, insulin degludec; IGlar, insulin glargine U100.

Table 2 Hypoglycemia summary.

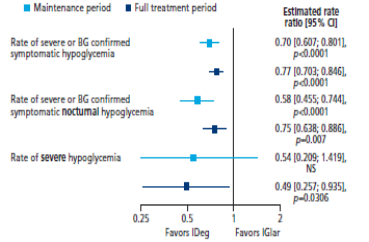
Definition	IDeg		IGlar	
	Incidence n (%)	Rate/100 PYE	Incidence n (%)	Rate/100 PYE
Maintenance period	n=632		n=618	
Severe or BG-confirmed symptomatic	142 (22.5)	185.6	195 (31.6)	265.4
Nocturnal severe or BG-confirmed symptomatic	61 (9.7)	55.2	91 (14.7)	93.6
Severe hypoglycemia	10 (1.6)	5.3	15 (2.4)	9.1
Full treatment period	n=671		n=665	
Severe or BG-confirmed symptomatic hypoglycemia	243 (36.2)	219.9	277 (41.7)	275.1
Nocturnal severe or BG-confirmed symptomatic hypoglycemia	116 (17.3)	72.0	145 (21.8)	88.4
Severe hypoglycemia	15 (2.2)	4.4	26 (3.9)	9.4

All episodes of severe hypoglycemia were confirmed by external adjudication committee. Data are for safety analysis set. %, proportion of patients with events; BG, blood glucose; IDeg, insulin degludec; IGlar, insulin glargine U100; n, number of patients with events; PYE, patient-year of exposure.

Safety

- At baseline, the mean insulin dose was 40 U in the IDeg group and 43 U in the IGlar group. At the end of treatment period 1, mean IDeg dose increased to 70 U and IGlar to 74 U. At the end of treatment period 2, the dose in both groups was 83 U. A *post hoc* analysis showed a 4% significantly lower insulin dose with IDeg versus IGlar after 32 weeks of treatment.
- Weight changes were similar between IDeg and IGlar in treatment periods 1 and 2 (1.5 vs. 1.8 kg and 0.9 vs. 0.5 kg, respectively).
- Adverse event and serious adverse event rates were similar between treatments (332.6 vs. 360.1 events/100 patient-years and 20.6 vs. 25.0 events/100 patient-years for IDeg versus IGlar, respectively).
- The most frequently reported adverse events in ≥5% patients were nasopharyngitis and upper respiratory tract infection.

Figure 3 Hypoglycemia estimated rate ratios.



P-values derived using a Poisson model with logarithm of the exposure time (100 years) as offset; estimates adjusted for treatment, period, sequence and dosing time as fixed effects and patient as a random effect. BG, blood glucose (<56 mg/dL); CI, confidence interval; IDeg, insulin degludec; IGlar, insulin glargine U100; NS, not significant.

- There were seven fatal events during the trial, two with IDeg (cardiovascular deaths) and five with IGlar (one cardiovascular death, one undetermined death, one due to hepatobiliary causes and two due to malignancy).

References

1. Jonassen *et al. Pharm Res* 2012;29:2104–14.
2. Heise *et al. Diabetes Obes Metab* 2012;14:859–64.
3. Heise *et al. Diabetes Obes Metab* 2012;14:944–50.
4. Garber *et al. Lancet* 2012;379:1498–507.
5. Gough *et al. Diabetes Care* 2013;36:2536–42.
6. Meneghini *et al. Diabetes Care* 2013;36:858–64.
7. Onishi *et al. J Diabetes Investig* 2013;4:605–12.
8. Zinman *et al. Diabetes Care* 2012;35:2464–71.
9. Ratner *et al. Diabetes Obes Metab* 2013;15:175–84.
10. Seaquist *et al. Diabetes Care* 2013;36:1384–95.

Conclusions

- In this double-blind crossover trial in patients with T2D, IDeg showed a consistent hypoglycemia benefit compared with IGlar:
  - Significantly lower rate of severe or BG-confirmed symptomatic hypoglycemia in the **maintenance (30%)** and **full (23%)** treatment periods;
  - Significantly lower rate of severe or BG-confirmed symptomatic nocturnal hypoglycemia in the **maintenance (42%)** and **full (25%)** treatment periods;
  - Significantly lower rate **(51%)** of **severe** hypoglycemia in the full treatment period;
  - Numerically lower proportion of patients with severe hypoglycemic episodes in both the **maintenance** and **full** treatment periods.
- IDeg was non-inferior in terms of reduction in HbA_{1c}.
- There was no apparent difference between IDeg and IGlar for the standard efficacy parameters or in terms of adverse events.
- This SWITCH 2 trial confirmed, in a randomized blinded setting, the previous finding of less hypoglycemia with IDeg compared with IGlar.

Objective

Primary objective:

- To confirm superiority of IDeg OD compared with IGlar U100 OD in the rates of severe or BG-confirmed symptomatic hypoglycaemia during the maintenance period (after 16 weeks of treatment)

Secondary objectives:

- To confirm superiority of IDeg OD compared with IGlar U100 OD in the rates of severe or BG-confirmed symptomatic **nocturnal** hypoglycaemia and the proportion of patients with severe hypoglycaemia during the maintenance period

BG, blood glucose; IDeg, insulin degludec; IGlar U100, insulin glargine U100; OD, once daily

Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

SWITCH hypoglycaemia classification

Suspected hypoglycaemia (or routine BG measurement)

Patient able to self-treat?

No

Yes

SMBG measurement

Not hypoglycaemia
>56 mg/dL
(3.1 mmol/L)

Asymptomatic
<56 mg/dL
(3.1 mmol/L)
no symptoms

Symptomatic
<56 mg/dL
(3.1 mmol/L)
Symptoms

Severe hypoglycaemia
(ADA 2013)*

Nocturnal hypoglycaemia: events between 00:01 and 05:59 (both inclusive)

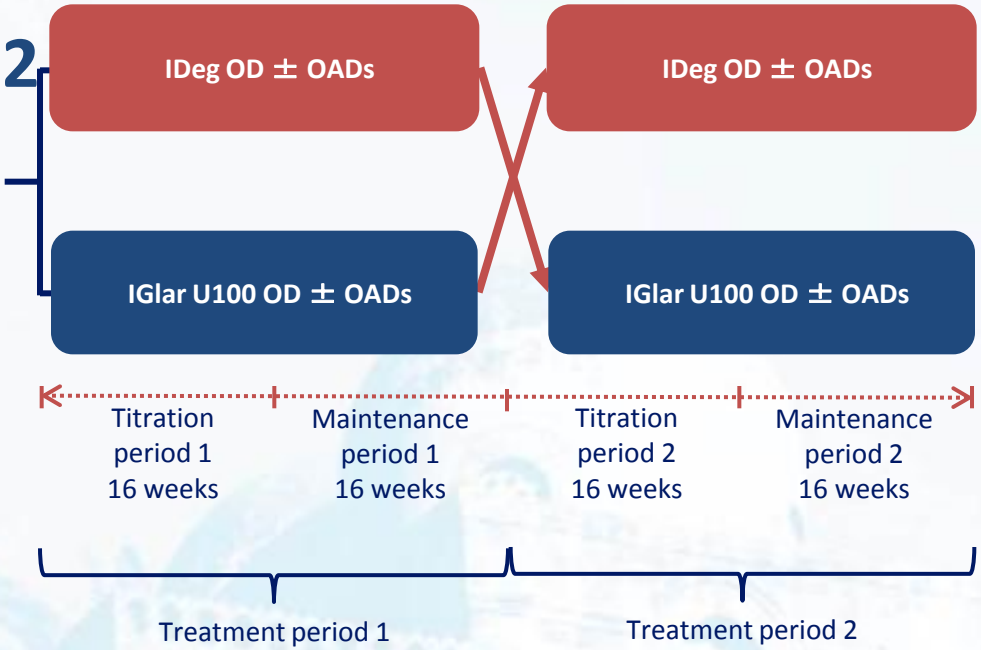
*An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions and/or neurological recovery following the return of plasma glucose to normal

SMBG, self-measured blood glucose

Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Trial design: SWITCH 2

Patients with type 2 diabetes (n=721)



Inclusion criteria
- Age ≥18 years
- T2D ≥26 weeks
- Basal insulin ± OADs ≥26 weeks
- HbA_{1c} ≤9.5%
- BMI ≤45 kg/m^2

Trial information
- Double-blind
- Crossover
- Treat-to-target
- Randomised 1:1 to morning or evening dosing admin.
- 20% dose reduction for pre-trial BID regimen

twBID, ice daily; BMI, body mass index; OAD, oral antidiabetic drug; T2D, type 2 diabetes

Wysham *et al.*
Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Trial treatment regimens

IDeg and IGlar U100

- Once-daily administration morning **or** evening (randomized 1:1)
- Starting dose:
  - Treatment period 1:
    - OD pre-trial: pre-trial dose
    - BID pre-trial: 20% reduction of total pre-trial dose
  - Treatment period 2:
    - Continue with end-dose of treatment period 1
- Vial and syringe
- Continue pre-trial OADs

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Baseline characteristics

Characteristic	All patients
Full analysis set (FAS), n (%)	**720** (100%)
Male, n (%)	**382** (53.1%)
Race, n (%) White Black Asian Other	 **578** (80.3%) **106** (14.7%) **22** (3.1%) **14** (1.9%)
Ethnicity, Hispanic or Latino, n (%)	**262** (36.4%)
Age, years	**61.4** (10.5)
Weight, kg	**91.7** (19.5)
BMI, kg/m^2	**32.2** (5.6)
Duration of diabetes, years	**14.1** (8.1)
HbA_{1c}, %	**7.6** (1.1)
FPG, mg/dL	**137.0** (52.6)
eGFR (mL/min/1.73 m^2)	**78.3** (21.3)

Values are mean (SD) unless otherwise stated
FPG, fasting plasma glucose; SD, standard deviation
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Treatment at screening

	All patients n (%)
Pre-trial insulin treatment, n (%)	720 (100%)
NPH	59 (8.2%)
IDet	159 (22.1%)
IGlar U100	502 (69.7%)
Pre-trial treatment regimen, n (%)	
Basal OD	606 (84.2%)
Basal BID	114 (15.8%)
OADs at screening, n (%)	
0 agents	150 (20.8%)
1 agent	448 (62.2%)
≥2 agents	122 (16.9%)

IDet, insulin detemir; NPH, neutral protamine Hagedorn

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Hypoglycaemia risk: inclusion criteria

Eligible patients had at least one of the following hypoglycaemia risk factors:
• ≥1 severe hypoglycaemic episodes within the last year
• Moderate chronic renal failure (eGFR 30–59 mL/min/1.73 m^2)
• Hypoglycaemic symptoms unawareness
• Exposure to insulin >5 years
• Episode of hypoglycaemia episode within the last 12 weeks (according to ADA definition: ≤70 mg/dL [≤3.9 mmol/L])

ADA, American Diabetes Association; eGFR, estimated glomerular filtration rate
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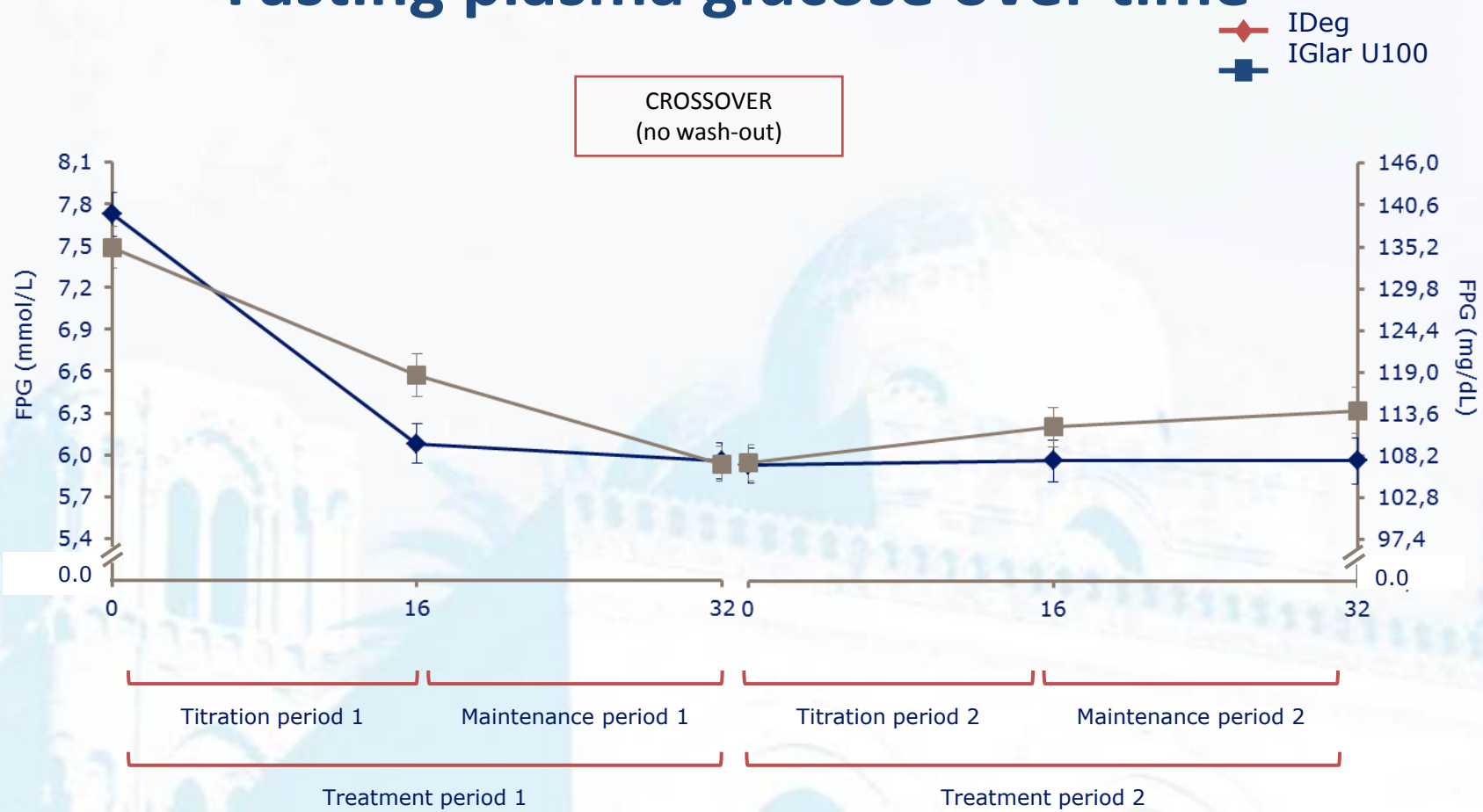
Fasting plasma glucose over time



Mean±SEM

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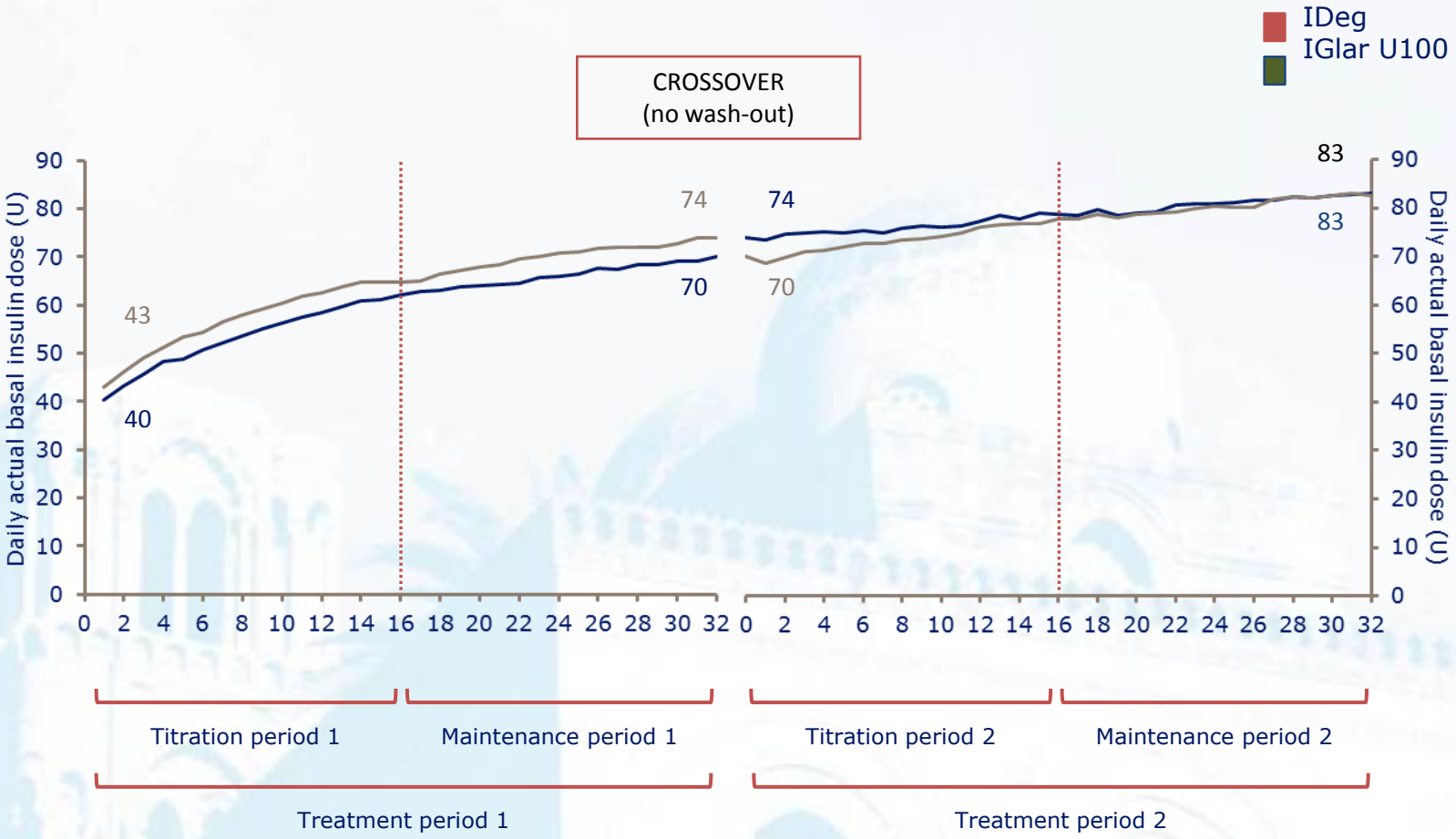
Insulin dose



A *post hoc* analysis confirmed a 4% significantly lower insulin dose in the IDeg arm compared with the IGlar U100 arm after 32 weeks of treatment

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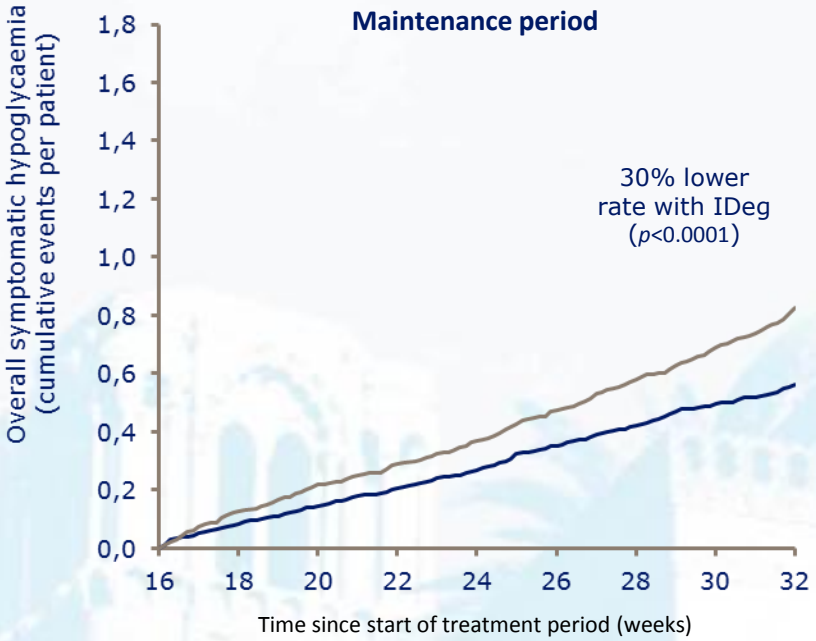
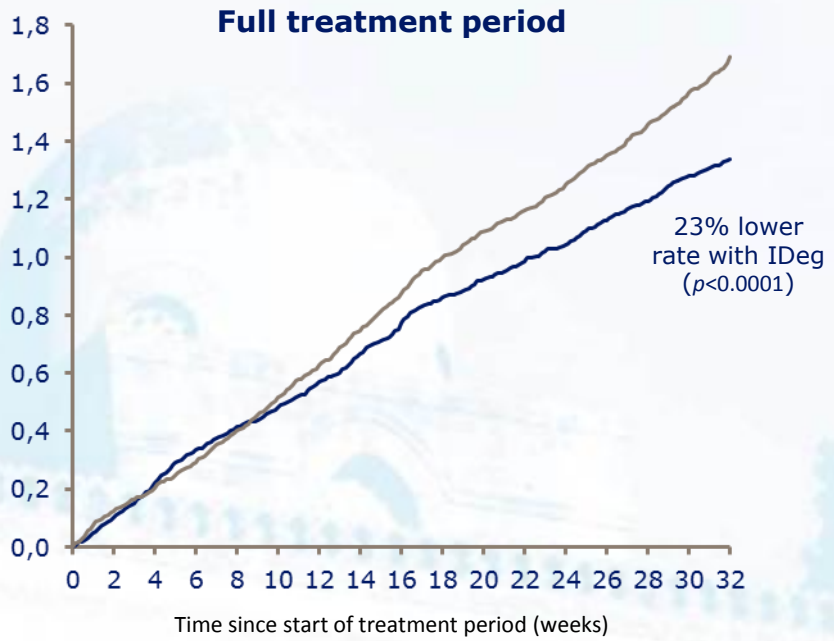
Severe or BG-confirmed symptomatic hypoglycaemia



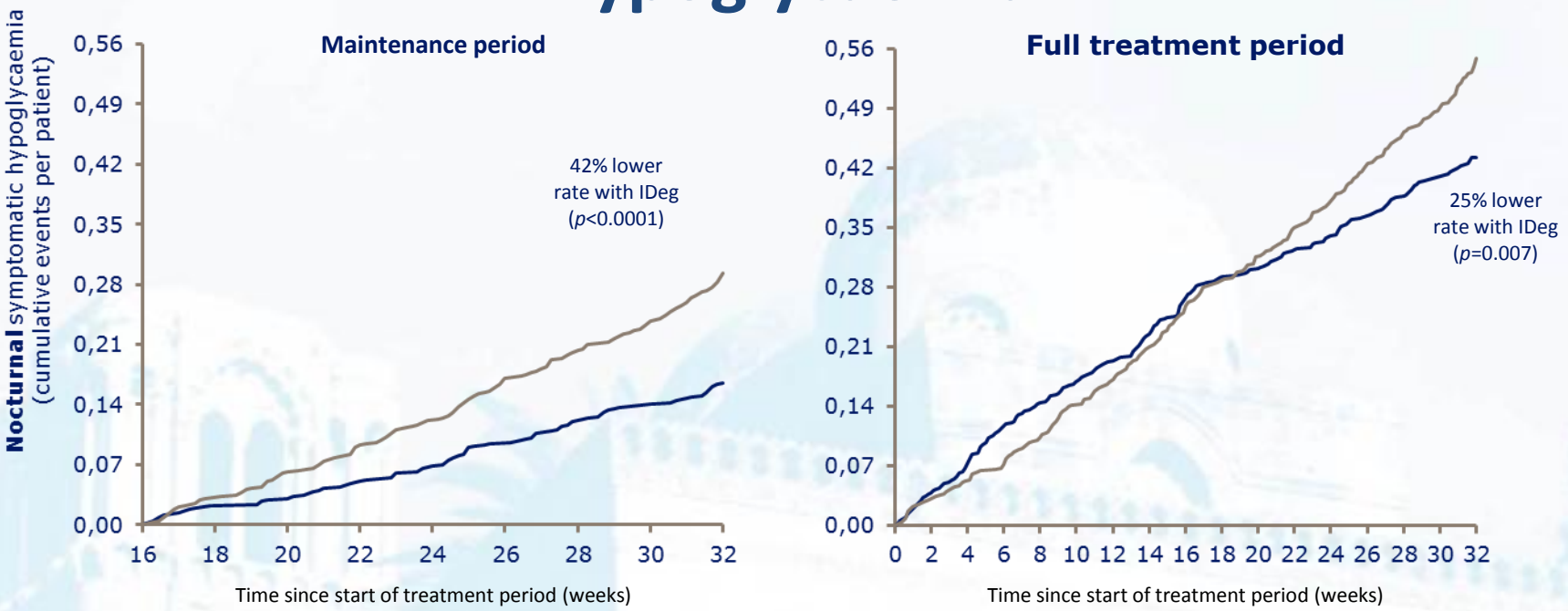


IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
22.5%	185.6	31.6%	265.4

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
36.2%	219.9	41.7%	275.1

SAS
Comparisons: Estimates adjusted for multiple covariates
Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Severe or BG-confirmed symptomatic nocturnal hypoglycaemia

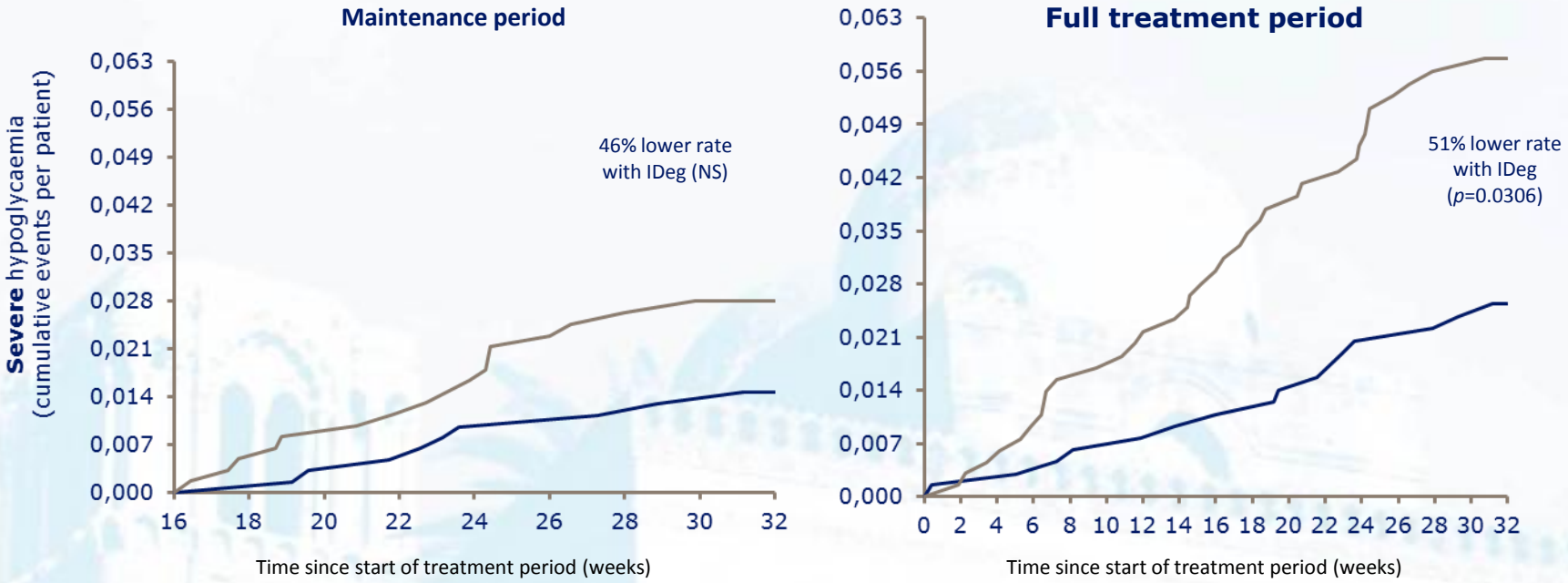


IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
9.7%	55.2	14.7%	93.6

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
17.3%	72.0	21.8%	88.4

SAS
Comparisons: Estimates adjusted for multiple covariates
Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Severe hypoglycaemia



IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
1.6%	5.3	2.4%	9.1

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
2.2%	4.4	3.9%	9.4

SAS
Comparisons: Estimates adjusted for multiple covariates
Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Clinical interpretation of the hypoglycaemia evidence (Numbers Needed to Treat)

Type of event	Risk reduction (significance)	To avoid one severe or BG-confirmed symptomatic hypoglycaemic episode, you would need to treat:
Maintenance period		
Severe or BG-confirmed symptomatic hypoglycaemia	30%, $p<0.0001$ (in favour of IDeg)	1 patient for 1 year
Severe or BG-confirmed symptomatic **nocturnal** hypoglycaemia	42%, $p<0.0001$ (in favour of IDeg)	3 patients for 1 year
Full treatment period		
Severe hypoglycaemia	51%, $p=0.0306$ (in favour of IDeg)	21 patients for 1 year

SAS
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Conclusion

Hypoglycaemia

In the maintenance period for IDeg vs. IGlar U100:

- Significantly lower rate (30%) of severe or BG-confirmed hypoglycaemia
- Significantly lower rate (42%) of severe or BG-confirmed **nocturnal** hypoglycaemia

In the full treatment period for IDeg vs. IGlar U100:

- Significantly lower rate (23%) of severe or BG-confirmed hypoglycaemia
- Significantly lower rate (25%) of severe or BG-confirmed **nocturnal** hypoglycaemia
- Significantly lower rate (51%) of **severe** hypoglycaemia

Numerically lower proportion of patients with severe hypoglycaemic episodes in both the maintenance and full treatment periods

Other endpoints

- IDeg was non-inferior in terms of reduction in HbA_{1c} compared with IGlar U100
- There was no apparent difference between IDeg and IGlar U100 for the standard efficacy parameters or in terms of adverse events
- This SWITCH 2 trial confirmed, in a randomised blinded setting, the previous finding of less hypoglycaemia with IDeg compared with IGlar U100

Wysham *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Agenda

- *Unmet Needs* e recenti proposte terapeutiche in tema di basalizzazione insulinica:
- *Degludec*

- *Unmet Needs* e recenti proposte terapeutiche in tema di intensificazione insulinica:
- *Insulina Basale + GLP-1RA*

- IdegLira : DUAL V trial

- Conclusioni

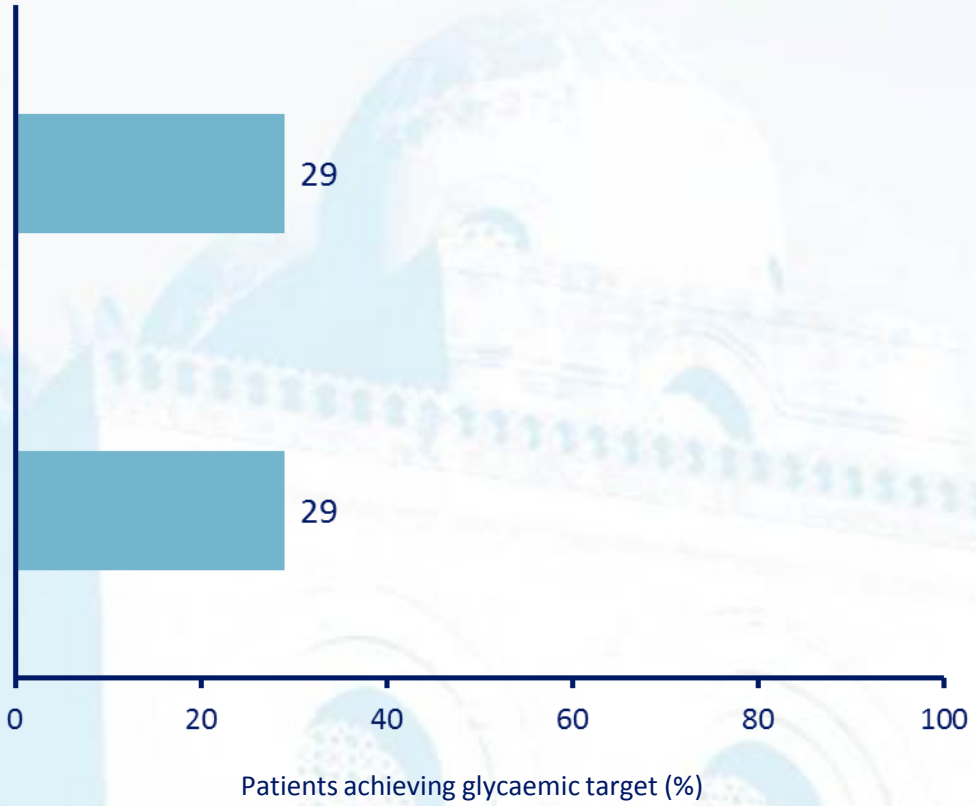
In clinical practice many patients do not achieve glycaemic target after basal insulin initiation

2-year retrospective cohort study of basal insulin initiation in the US (n=14,458)[1]

Baseline HbA_{1c}: 8.6%

3-year retrospective audit of basal insulin initiation in the UK (n=516)[2]

Baseline HbA_{1c}: 9.3%



1. Curtis & Lage. J Med Econ 2014;17:21–31
2. Dale et al. Prim Care Diabetes 2010;4:85–9

Barriers to traditional basal insulin intensification with prandial insulin

Hypoglycaemia

Most diabetes specialists would treat their patients more aggressively if there was no concern about hypoglycaemia[1]

Weight gain

Many patients on insulin therapy are anxious about their weight[2]
Insulin intensification is commonly associated with weight gain[3,4]

Regimen complexity

Patients prefer fewer daily injections[5] Increasing the number of injections can decrease adherence and increase perceived therapy burden[5–7]

1. Peyrot et al. Diabet Med 2012;29:682–9
2. Peyrot et al. Curr Med Res Opin 2009;25:1985–93
3. Davidson et al. Endocr Pract 2011;17:395–403
4. Meneghini et al. Endocr Pract 2011;17:727–36
5. Rubin et al. Diabetes Educ 2009;35:1014–22
6. Vijan et al. J Gen Intern Med 2005;20:479–82
7. Donnelly et al. QJM 2007;100:345–50

ADA/EASD position statement 2015

Combination of basal insulin and GLP-1 RA therapy is supported as triple therapy or combination injectable therapy

Healthy eating, weight control, increased physical activity, and diabetes education

Mono-therapy

Metformin

Dual therapy

+ Sulphonylurea	+ Thiazolidinedione	+ DPP-4 inhibitor	+ SGLT2 inhibitor	+ GLP-1 receptor agonist	+ Insulin (basal)

Triple therapy

Metformin + Sulphonylurea +	Metformin + Thiazolidinedione +	Metformin + DPP-4 inhibitor +	Metformin + SGLT2 inhibitor +	Metformin + GLP-1 RA +	Metformin + Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4i	or DPP-4i	or TZD	or TZD	or TZD	or DPP-4i
or GLP-1 RA	or GLP-1 RA	or Insulin	or Insulin	or Insulin	or GLP-1 RA
or Insulin	or Insulin	or SGLT2i	or DPP-4i		or SGLT2i
or SGLT2i	or SGLT2i				

Combination injectable therapy

Metformin +

Basal insulin + Mealtime insulin or GLP-1 RA

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose cotransporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione. Adapted from: Inzucchi *et al. Diabetes Care* 2015;38:140–9

Complementary actions of GLP-1 and insulin target underlying pathophysiology of type 2 diabetes

GLP-1 analogue

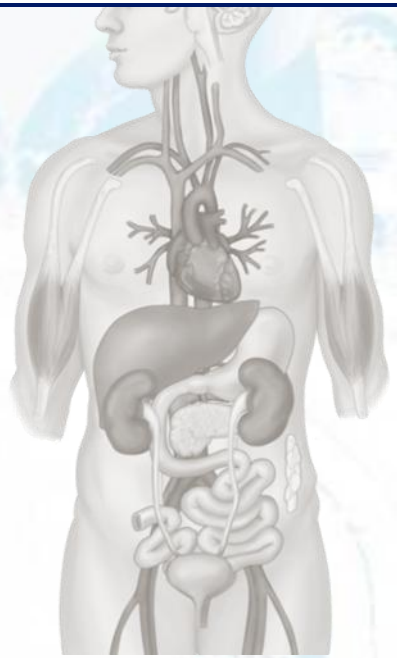
Heart
Cardiac function

Pancreas
Glucose-dependent insulin and glucagon secretion
Insulin synthesis

Liver
Hepatic glucose output

GI tract
Gastric emptying

Brain
Energy intake
Satiety
Neuroprotection



Basal insulin

Skeletal muscle
Glucose disposal

Liver
Hepatic glucose production

Adipose tissue
Insulin receptor activation

Baggio, Drucker. Gastroenterol 2007;132:2131–57

Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature

R. Balena[1], I. E. Hensley[2], S. Miller[3] & A. H. Barnett[4]

	Basal insulin	GLP-1 receptor agonist
Primary effects	↓Fasting glucose ↓Interprandial glucose	↓Postprandial glucose excursions ↓Fasting glucose*
Mechanism	↓Hepatic glucose production ↑Non-glucose dependent endogenous insulin ↓Glucagon secretion ↑Insulin concentration	↑Glucose-dependent insulin secretion ↓Glucagon secretion ↓Hepatic glucose production ↓Gastric emptying rate ↑Satiety ↓Food intake
Effect on weight	↑Body weight	↓Body weight

*The most salient effect of GLP-1 RAs is on postprandial glucose, however, fasting glucose is also reduced, especially with longer acting GLP-1 RAs such as liraglutide and exenatide once weekly.

Diabetes, Obesity and Metabolism 15: 485–502, 2013.

Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran*

Interpretation GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes.

www.thelancet.com **Published online September 12, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61335-0**

Clinical Features To Consider When Selecting either a GLP-1 RA or Prandial Insulin To Escalate Basal Insulin Therapy

	Basal insulin plus GLP-1 RA	**Basal insulin plus multiple daily insulin doses**
Body weight	Overweight/Obese (BMI ≥ 28 kg/m^2)	Normal weight/Overweight (BMI < 28 kg/m^2)
Duration of disease	Relatively short (< 10 years)	Relatively long (> 10 years)
Metabolic control	Closer to target (HbA_{1c} < 8%/8.5%)	Further from target (HbA_{1c} ≥ 8%/8.5%)
Residual β-cell function	Maintained (C-peptide ≥ 0.6–0.8 ng/mL)	Reduced (C-peptide < 0.6–0.8ng/mL)

Giorgino F. et al., *DMRR* 2016

Insulin and GLP-1 RA Combination Studies

Basal insulin + short-acting GLP-1 RA

Glargine + Exenatide BID	Buse JB et al, *Ann Intern Med* 54:103-12, 2011 Diamant M et al, *Diabetes Care* 37:2763-73, 2014
Glargine + Lixisenatide	Riddle MC et al, *Diabetes Care* 36:2489-96, 2013 Seino Y et al, *Diabetes Obes Metab* 14:910-7, 2012 Riddle MC et al, *Diabetes Care* 36:2497-503, 2013 Rosenstock J et al, *Diabetes Care* 2016

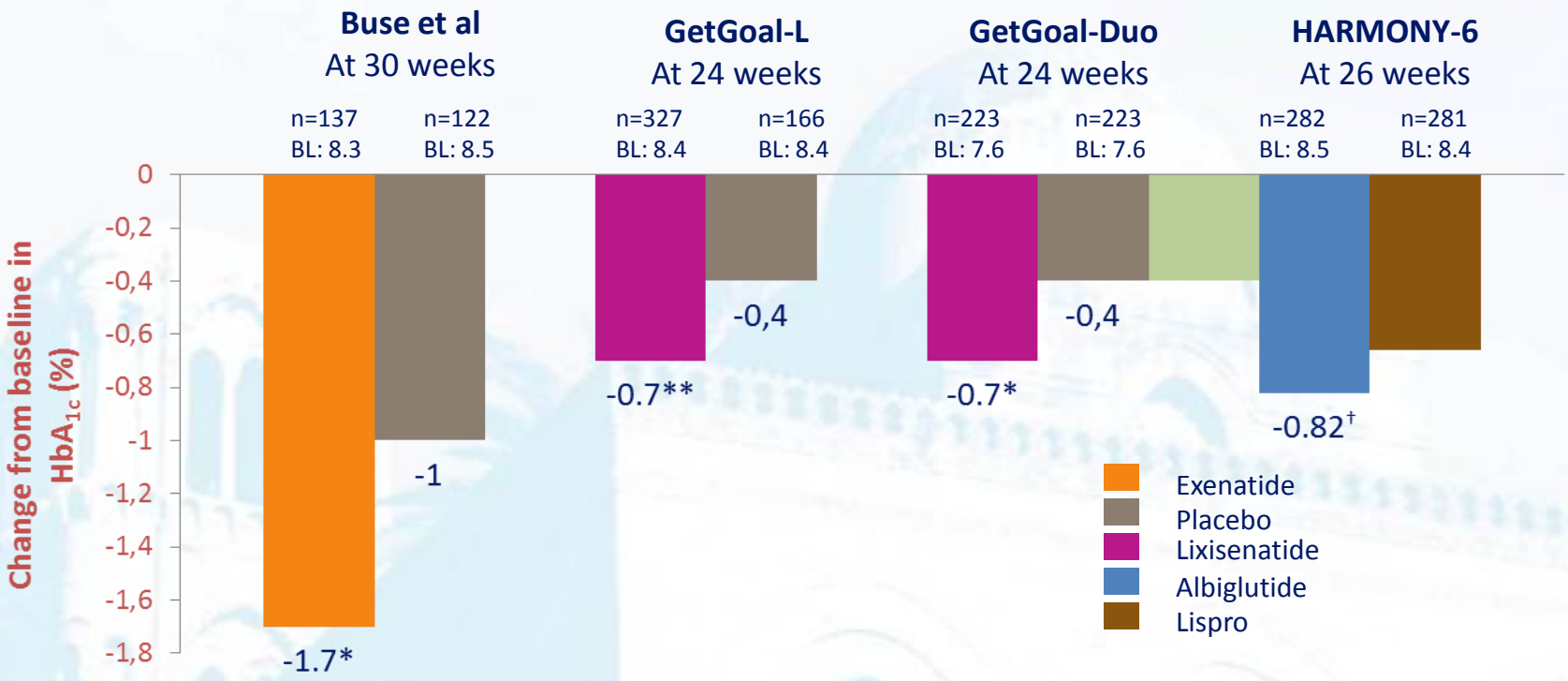
Basal insulin + long-acting GLP-1 RA

Detemir + Liraglutide	Rosenstock J et al, *J Diab Compl* 27:492–500, 2013
Degludec + Liraglutide	Mathieu C et al, *Diabetes Obes Metab* 16:636-44, 2014 Gough SC et al, *Lancet Diabetes Endocrinol* 2:885-93, 2014 Gough SC et al, *Diabetes Obes Metab* , 2015
Glargine + Albiglutide	Rosenstock J et al, *Diabetes Care* 37:2317-25, 2014

Long-acting GLP-1 RA + prandial insulin

Dulaglutide + Lispro	Blonde L et al, Lancet 2015

Addition of GLP-1 analogues to basal insulin: Change from baseline in HbA1c

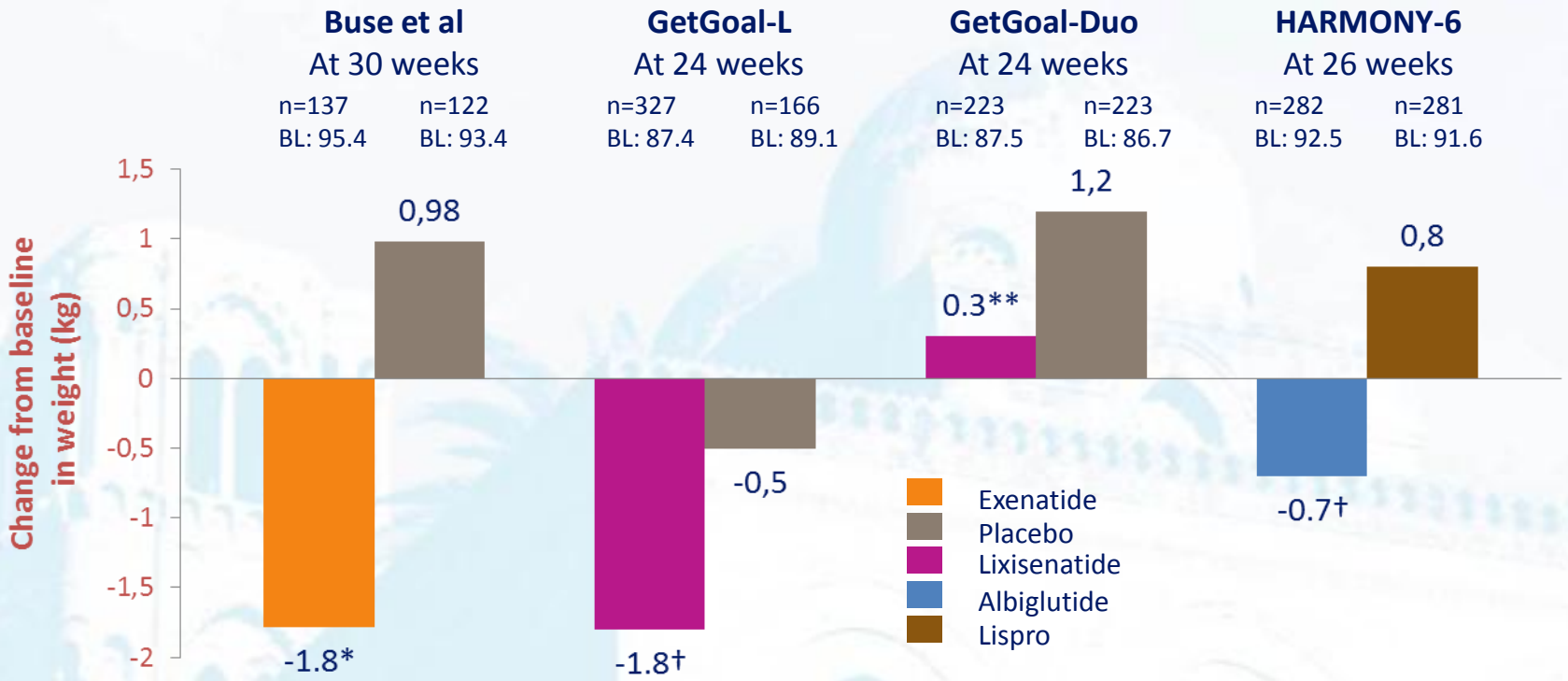


Treatment difference for GLP-1 vs. comparator: *$p<0.001$; **$p=0.0002$; †$p=NS$

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. *Diabetes Care* 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin: Change from baseline in body weight



Treatment difference for GLP-1 vs. comparator: *$p<0.001$; **$p=0.0012$; †$p<0.0001$

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. *Diabetes Care* 2014; Published online 04 June. DOI: 10.2337/dc14-0001

BEGIN®: LIRAGLUTIDE ADD-ON

Type 2 diabetes inadequately controlled on basal insulin and metformin

Study design

original article

Diabetes, Obesity and Metabolism 2014.

A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: LIRAGLUTIDE ADD-ON)

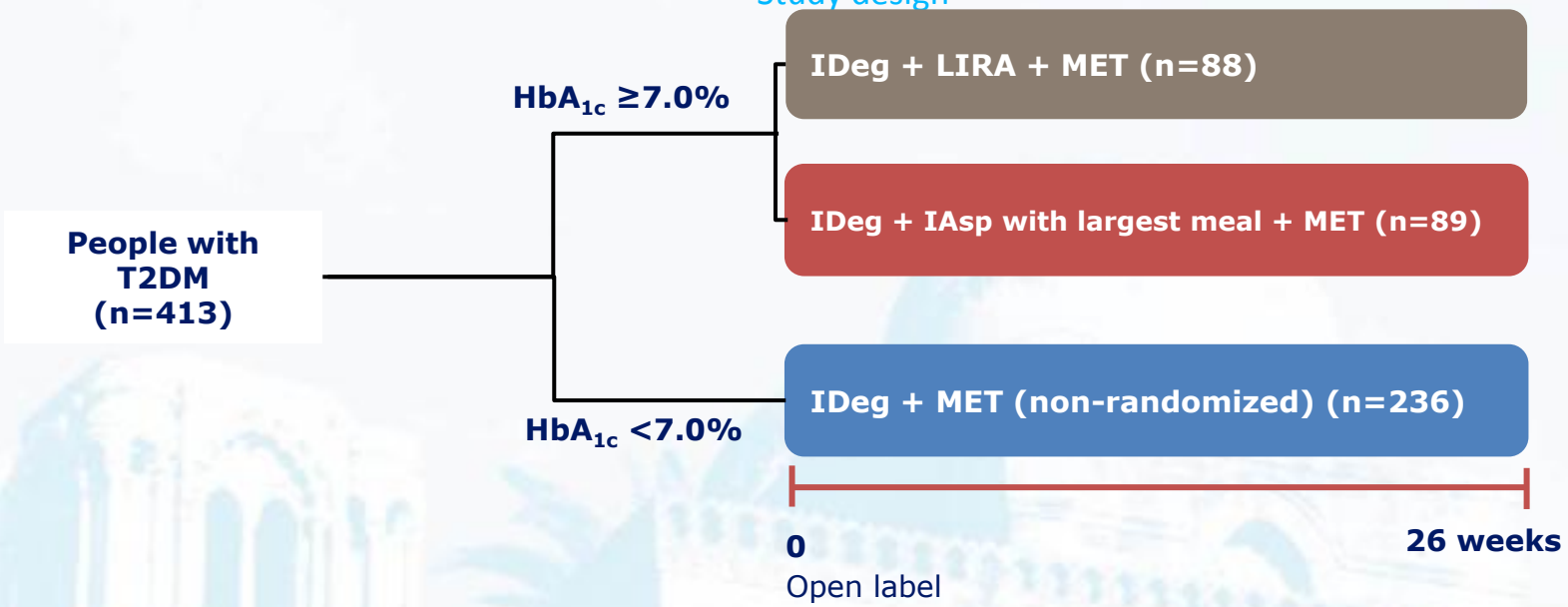
ORIGINAL ARTICLE

C. Mathieu[1], H. W. Rodbard[2], B. Cariou[3], Y. Handelsman[4], A. Philis-Tsimikas[5], A. M. Ocampo Francisco[6], A. Rana[7] & B. Zinman[8] on behalf of the BEGIN: VICTOZA ADD-ON (NN1250-3948) study group

[1] *UZ Leuven, University of Leuven, Leuven, Belgium*
[2] *Endocrine and Metabolic Consultants, Rockville, MD, USA*
[3] *Clinique d'Endocrinologie, l'Institut du Thorax, CHU Nantes, Nantes, France*
[4] *Metabolic Institute of America, Tarzana, CA, USA*
[5] *Scripps Whittier Diabetes Institute, La Jolla, CA, USA*
[6] *Novo Nordisk A/S, Søborg, Denmark*
[7] *Novo Nordisk Canada, Inc., Mississauga, Canada*
[8] *Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada*

BEGIN: VICTOZA® ADD-ON

Study design



Inclusion criteria

- All participants completed **NN1250-3579** and **NN1250-3643**: 104 weeks of IDeg QD plus MET

Randomization criteria

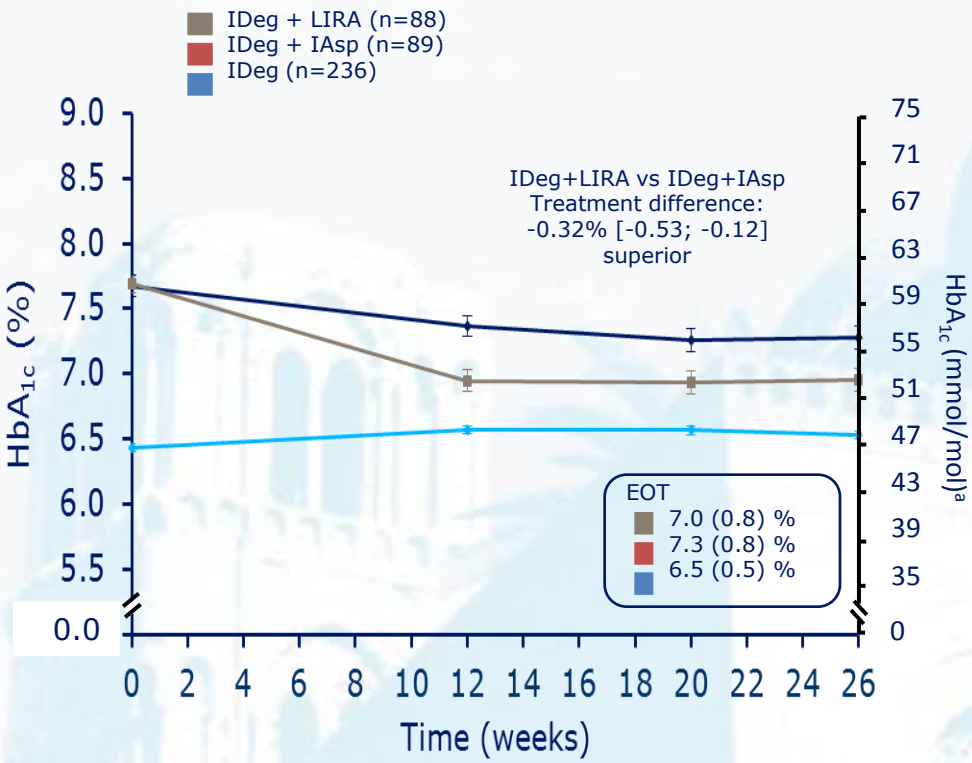
- HbA_{1c} ≥7.0% at end of treatment in NN1250-3643
- Calcitonin <50 ng/L at Visit 1
- No history of pancreatitis
- No family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- No clinically significant diseases of the major organ systems

FAS, full analysis set; NAS, Non-randomized analysis set
IAsp, insulin aspart; IDeg, insulin degludec; HbA_{1c}, glycated hemoglobin; MET, metformin; QD, once-daily; T2DM, type 2 diabetes mellitus
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

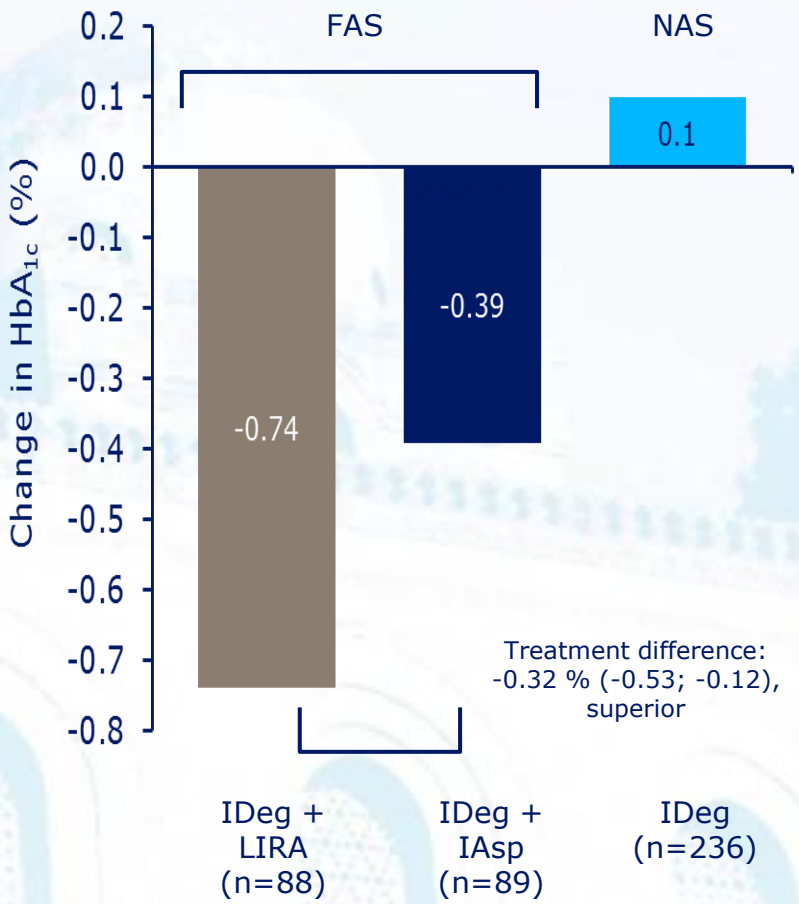
BEGIN: VICTOZA® ADD-ON

HbA_{1c} measurements

HbA_{1c} Over Time: FAS and NAS



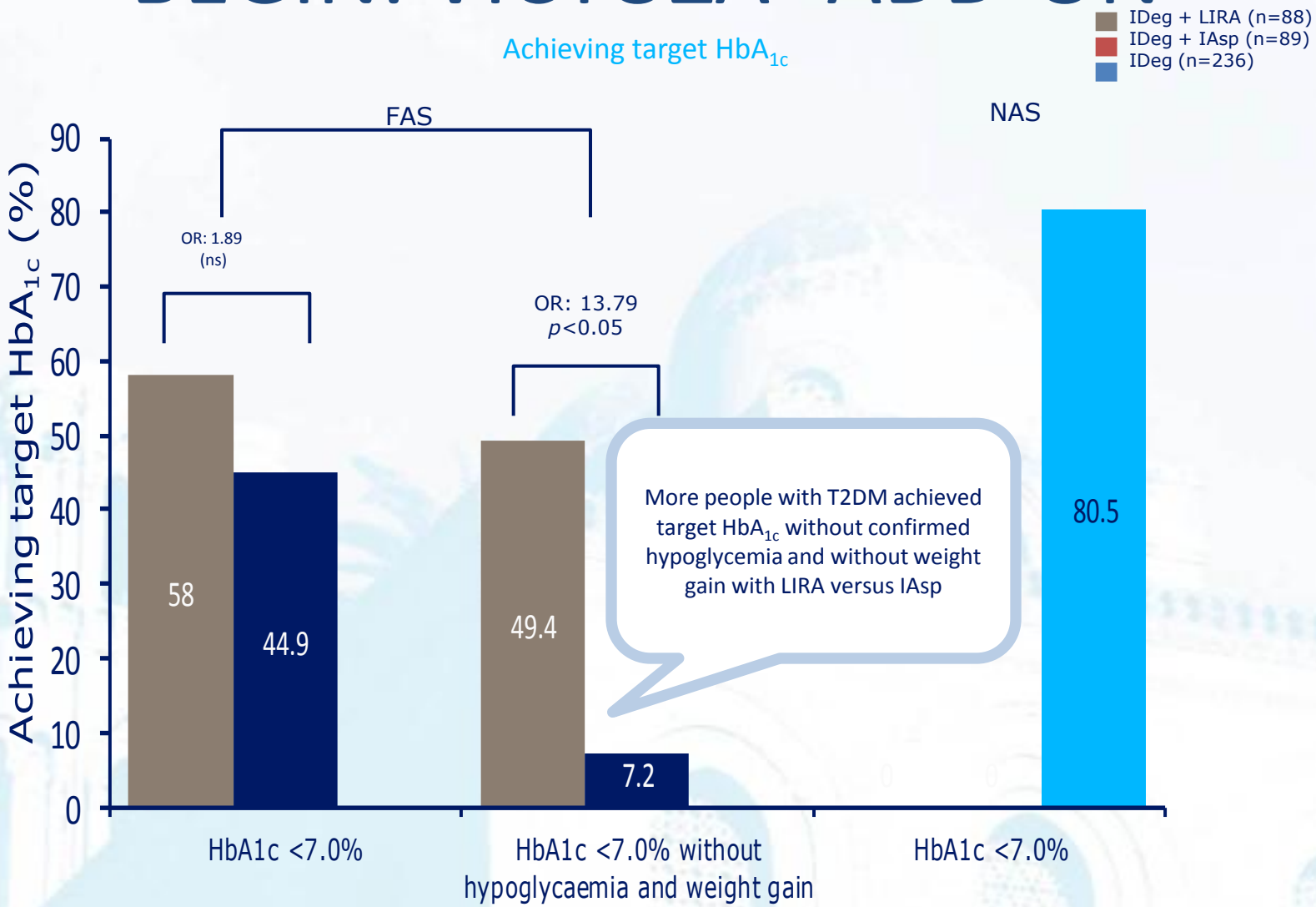
Change in HbA_{1c}: FAS and NAS



FAS, full analysis set; NAS, non-randomized analysis set; LOCF, last observation carried forward; Mean±SEM
HbA_{1c}, glycated hemoglobin, IAsp, insulin aspart; IDeg, insulin degludec; LIRA, liraglutide
[a]Calculated, not measured
Comparisons: Estimates adjusted for multiple covariates
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

BEGIN: VICTOZA® ADD-ON

Achieving target HbA_{1c}

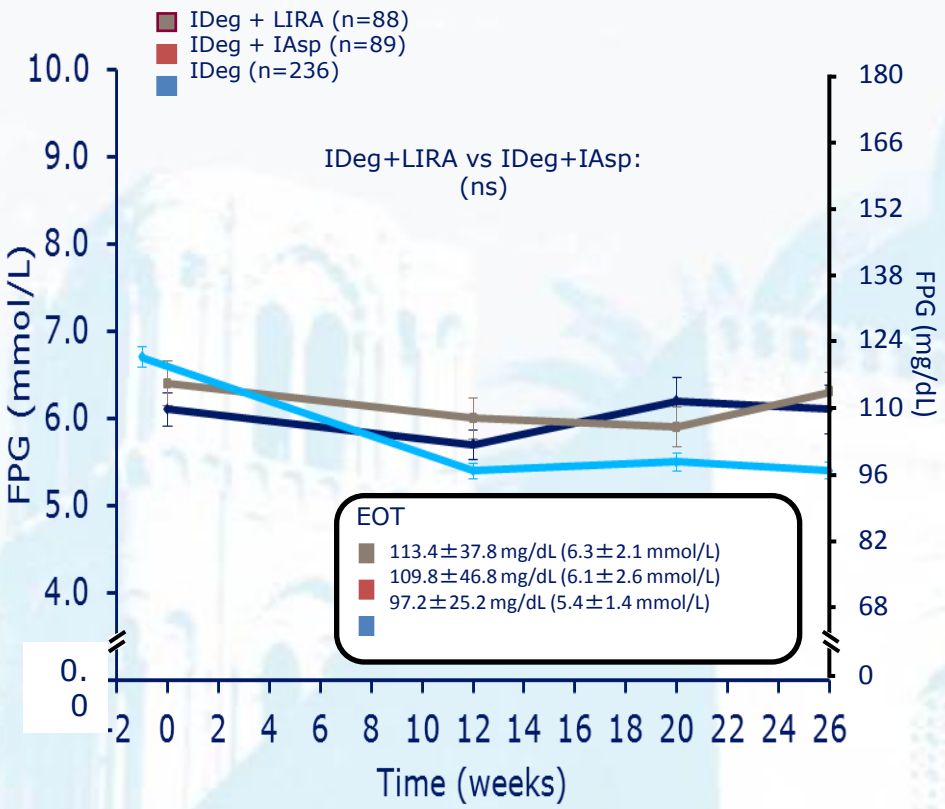


FAS, full analysis set; NAS, non-randomized analysis set; LOCF, last observation carried forward
HbA1c, glycated hemoglobin; OR, odds ratio; T2DM, type 2 diabetes mellitus
Comparisons: Estimates adjusted for multiple covariates
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

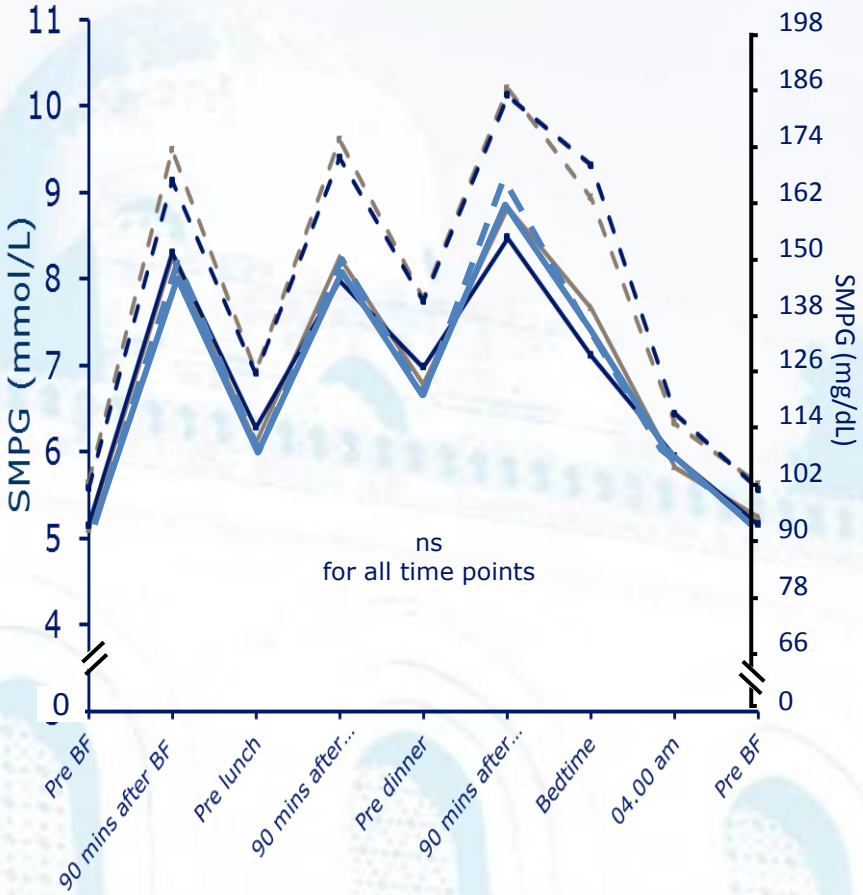
BEGIN: VICTOZA® ADD-ON

Changes in FPG and SMPG

Fasting plasma glucose over time: FAS and NAS



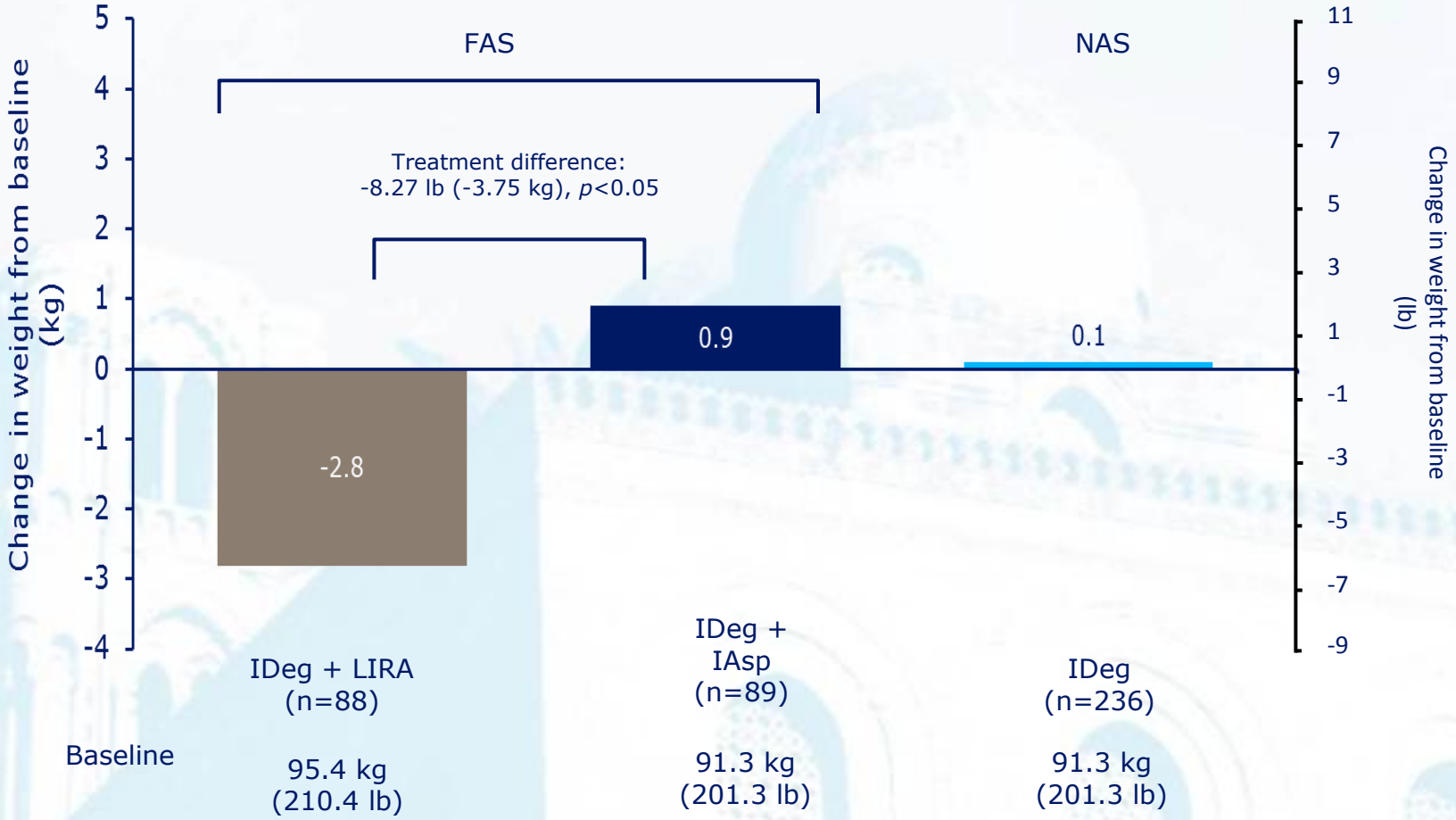
9-point self-measured plasma glucose: FAS and NAS



FAS, full analysis set; NAS, non-randomized analysis set; LOCF, last observation carried forward; Mean±SEM
BF, breakfast; FPG, fasting plasma glucose; IAsp, insulin aspart; IDeg, insulin degludec; LIRA, liraglutide; SMPG, self-measured plasma glucose
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

BEGIN: VICTOZA® ADD-ON

Weight Change



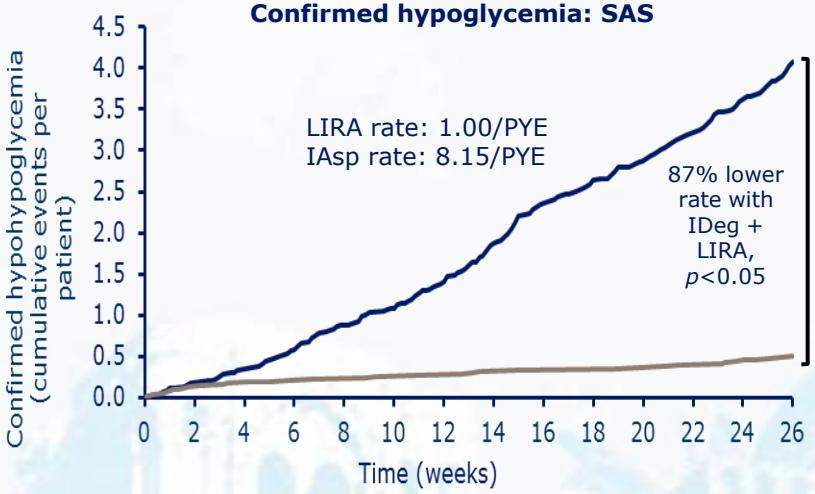
FAS, full analysis set; NAS, non-randomized analysis set; LOCF, last observation carried forward
IAsp, insulin aspart; IDeg, insulin degludec; LIRA, liraglutide
Comparisons: Estimates adjusted for multiple covariates
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

BEGIN: VICTOZA® ADD-ON

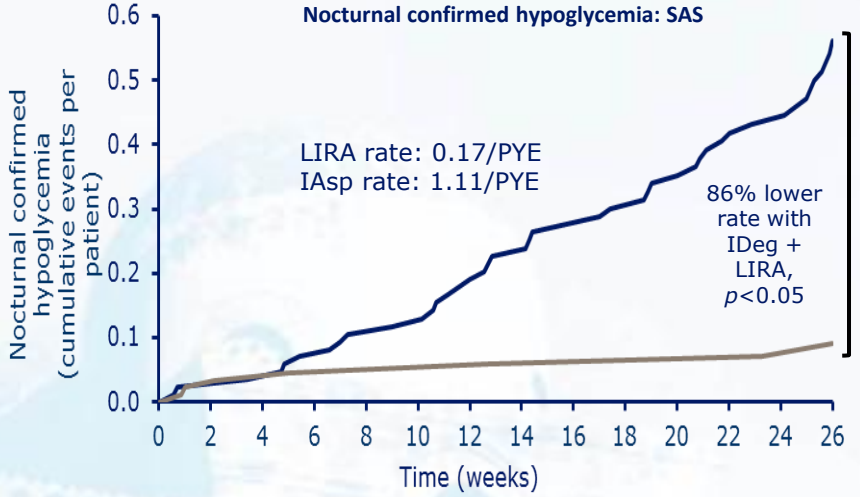
Risk of hypoglycemia

IDeg + LIRA (n=87)
IDeg + IAsp (n=86)
IDeg (n=236)

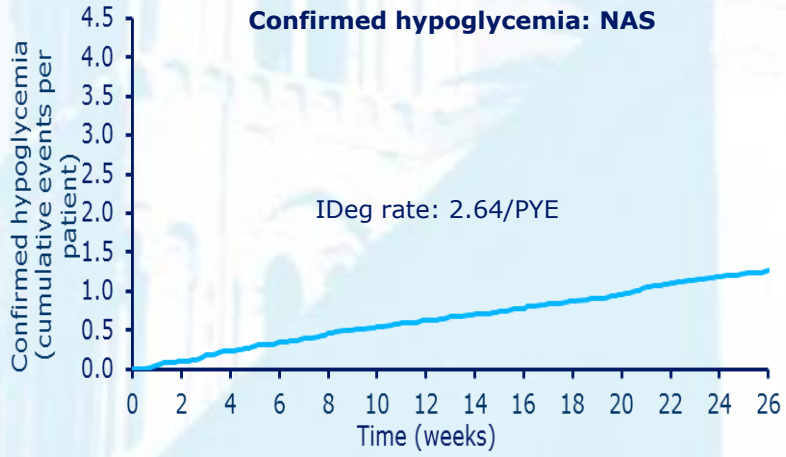
Confirmed hypoglycemia: SAS



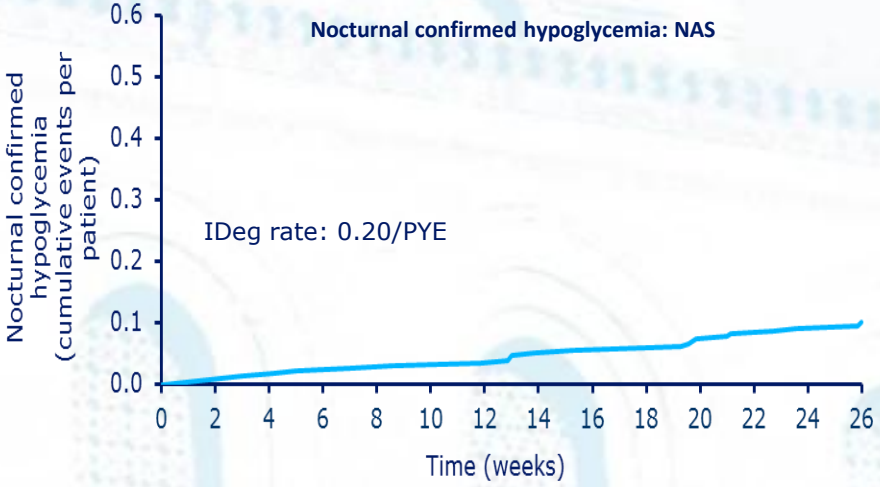
Nocturnal confirmed hypoglycemia: SAS



Confirmed hypoglycemia: NAS



Nocturnal confirmed hypoglycemia: NAS



*p<0.05
SAS, safety analysis set; NAS, non-randomized analysis set; % patients, proportion of patients with events; # patients, number of patients with events; PYE, patient-year of exposure
IAsp, insulin aspart; IDeg, insulin degludec; LIRA, liraglutide
Comparisons for top plots: Estimates adjusted for multiple covariates
Mathieu C et al. *Diabetes, obesity & metabolism.* 2014;16:636-644.

Agenda

- Introduzione: fisiopatologia della secrezione insulinica

- *Unmet Needs* e recenti proposte terapeutiche in tema di basalizzazione insulinica:

- *Degludec*

- *Unmet Needs* e recenti proposte terapeutiche in tema di intensificazione insulinica:

- *Insulina Basale + GLP-1RA*

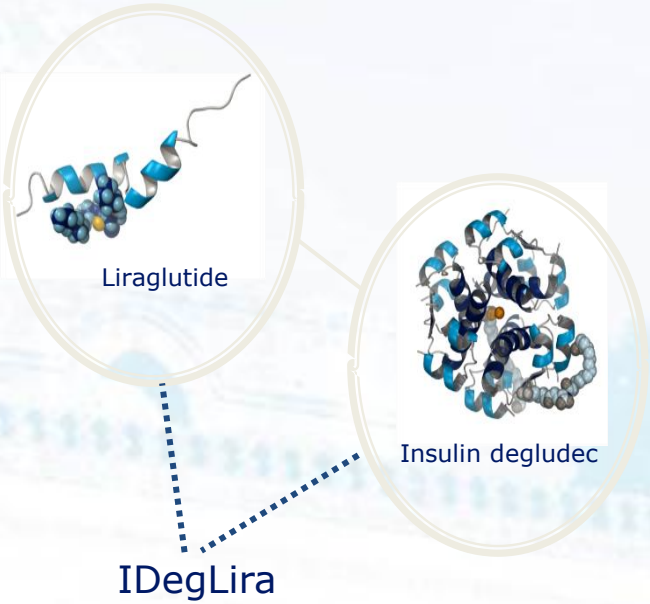
- IdegLira : DUAL V trial

- Conclusioni

Rational drug design
Formulation feasible due to distinct, stable association forms

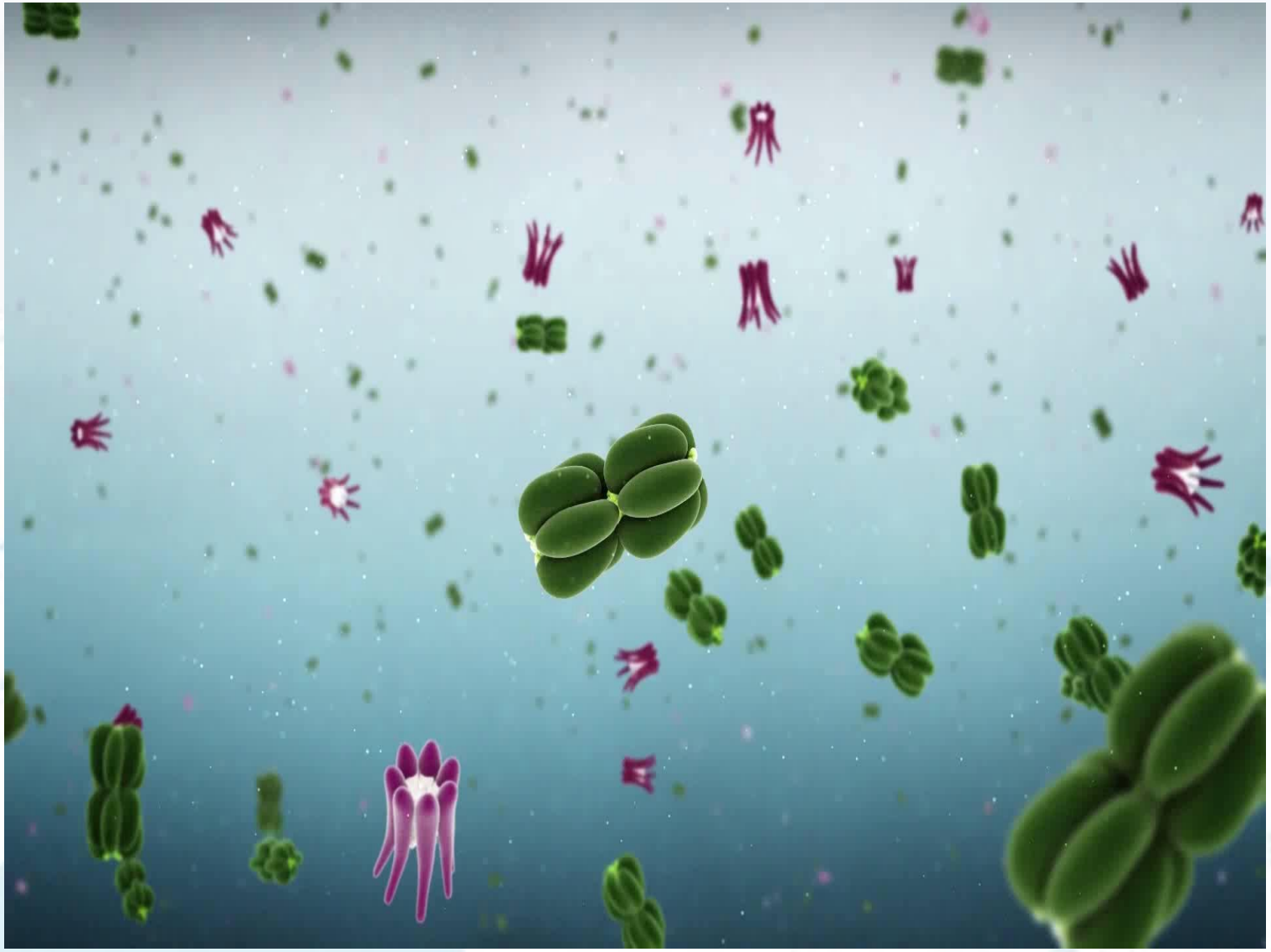
Unique anticipated properties of the liraglutide and insulin degludec combination:

- Glycaemic control throughout the day with FPG reduction and PPG coverage at all meals
- Steady titration and a more favourable safety profile
- Once-daily administration in a single pen device



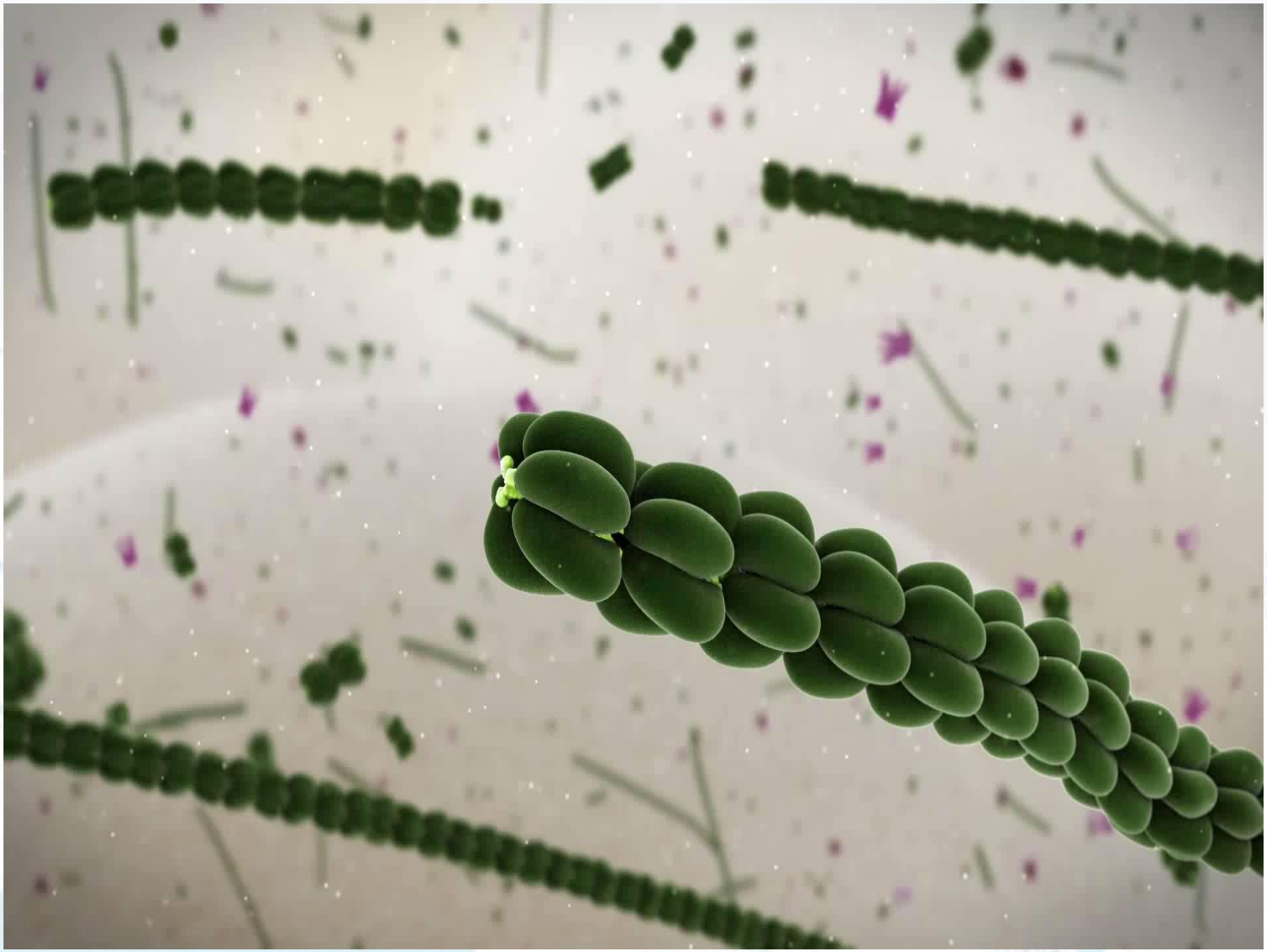
IDegLira, insulin degludec/liraglutide

Liraglutide & Insulina Degludec (prima dell'iniezione sc)



Liraglutide release from s.c. and albumin binding

Degludec release from s.c.



2. Composizione qualitativa e quantitativa

1 mL di soluzione contiene 100 unità di insulina degludec* e 3,6 mg di liraglutide*.

*Prodotta con tecnologia del DNA ricombinante da *Saccharomyces cerevisiae*.

Una penna preriempita contiene 3 mL equivalenti a 300 unità di insulina degludec e 10,8 mg di liraglutide.

Una dose unitaria contiene 1 unità di insulina degludec e 0,036 mg di liraglutide.

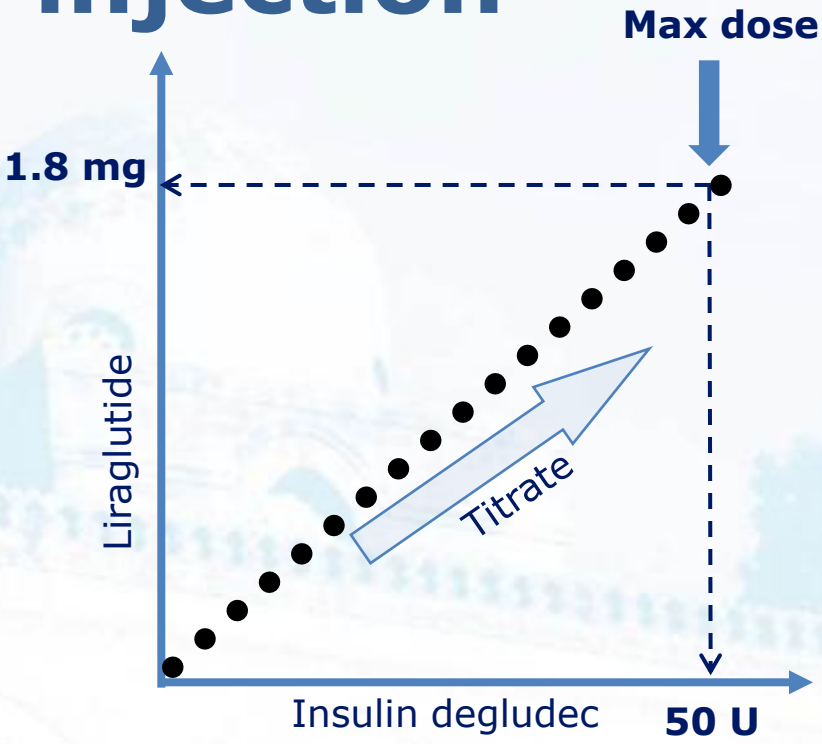
IDegLira: combination in a single daily injection

- Subcutaneous injection
  - 3 mL pre-filled pen
  - Fixed ratio of insulin degludec (100 U/mL) and liraglutide (3.6 mg/mL)

Insulin titration to achieve glycaemic control

50 dose steps

50 U insulin degludec + 1.8 mg liraglutide



Categoria farmacoterapeutica: farmaci usati per il diabete.
Insuline e analoghi per iniezione, ad azione prolungata.
Codice ATC: A10AE56.

4.1 Indicazioni terapeutiche

Xultophy è indicato per il trattamento di adulti affetti da diabete mellito di tipo 2 per migliorare il controllo glicemico in associazione con medicinali ipoglicemizzanti orali quando questi in monoterapia o in associazione con agonisti del recettore del GLP-1 o con insulina basale non permettano un controllo glicemico adeguato (vedere paragrafi 4.4 e 5.1 per i dati disponibili sulle diverse associazioni).

IDegLira: Phase 3 Clinical Development Plan

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

DUAL IV
IDegLira add-on to SU vs. placebo

DUAL V
IDegLira vs. basal insulin optimisation

DUAL VI
Easy Titration

DUAL VII
IDegLira vs. BB (glargine + aspart)

DUAL VIII
IDegLira vs. glargine (durability - 104 months)

....DUAL IX, DUAL X

www.clinicaltrials.gov

IDegLira: Phase 3 Clinical Development Plan

Phase 3A

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

DUAL IV
IDegLira add-on to SU vs. placebo

DUAL V
IDegLira vs. basal insulin optimisation

DUAL VI
Easy Titration

DUAL VII
IDegLira vs. BB (glargine + aspart)

DUAL VIII
IDegLira vs. glargine (durability - 104 months)

www.clinicaltrials.gov

IDegLira: Phase 3 Clinical Development Plan

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

Phase 3B

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

DUAL VI
Easy Titration

DUAL IV
IDegLira add-on to SU vs. placebo

DUAL VII
IDegLira vs. BB (glargine + aspart)

DUAL V
IDegLira vs. basal insulin optimisation

DUAL VIII
IDegLira vs. glargine (durability - 104 months)

www.clinicaltrials.gov

IDegLira: Phase 3 Clinical Development Plan

Completed trials

DUAL I *
IDegLira compared with the mono-components added on to OAD

DUAL II *
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL III #
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

DUAL IV #
IDegLira add-on to SU vs. placebo

DUAL V #
IDegLira vs. basal insulin optimisation

*published

#presented at EASD and IDF 2015, publication expected in 2016

www.clinicaltrials.gov

IDegLira: Phase 3 Clinical Development Plan

Uncontrolled on OADs

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

Uncontrolled on GLP-1RA

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

DUAL IV
IDegLira add-on to SU vs. placebo

DUAL V
IDegLira vs. basal insulin optimisation

Uncontrolled on basal insulin

www.clinicaltrials.gov

IDegLira: Phase 3 Clinical Development Plan

Uncontrolled on OADs

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL IV
IDegLira add-on to SU vs. placebo

Uncontrolled on GLP-1RA

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

Uncontrolled on basal insulin

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL V
IDegLira vs. basal insulin optimisation

www.clinicaltrials.gov

DUAL V

Subjects with T2DM (N=557)

- **IDegLira + metformin (n=278)**
- **IGlar + metformin (n=279)**

IDegLira
Starting dose: 16 dose steps
Maximum dose: 50 dose steps

IGlar
Starting dose: Pre-trial dose
Maximum dose: None

Inclusion criteria
- T2DM
- Metformin + IGlar (20–50 units)
- HbA_{1c} 7–10%
- Age ≥18 years
- BMI ≤40 kg/m^2

Mean FPG[a]		Dose change
mmol/L	mg/dL	dose steps/units
<4.0	<71	−2
4.0–5.0	71–90	0
>5.0	>90	+2

[a]Adjustments performed twice weekly based on mean of three preceding fasting self-measured blood glucose values obtained prior to dosing adjustment days

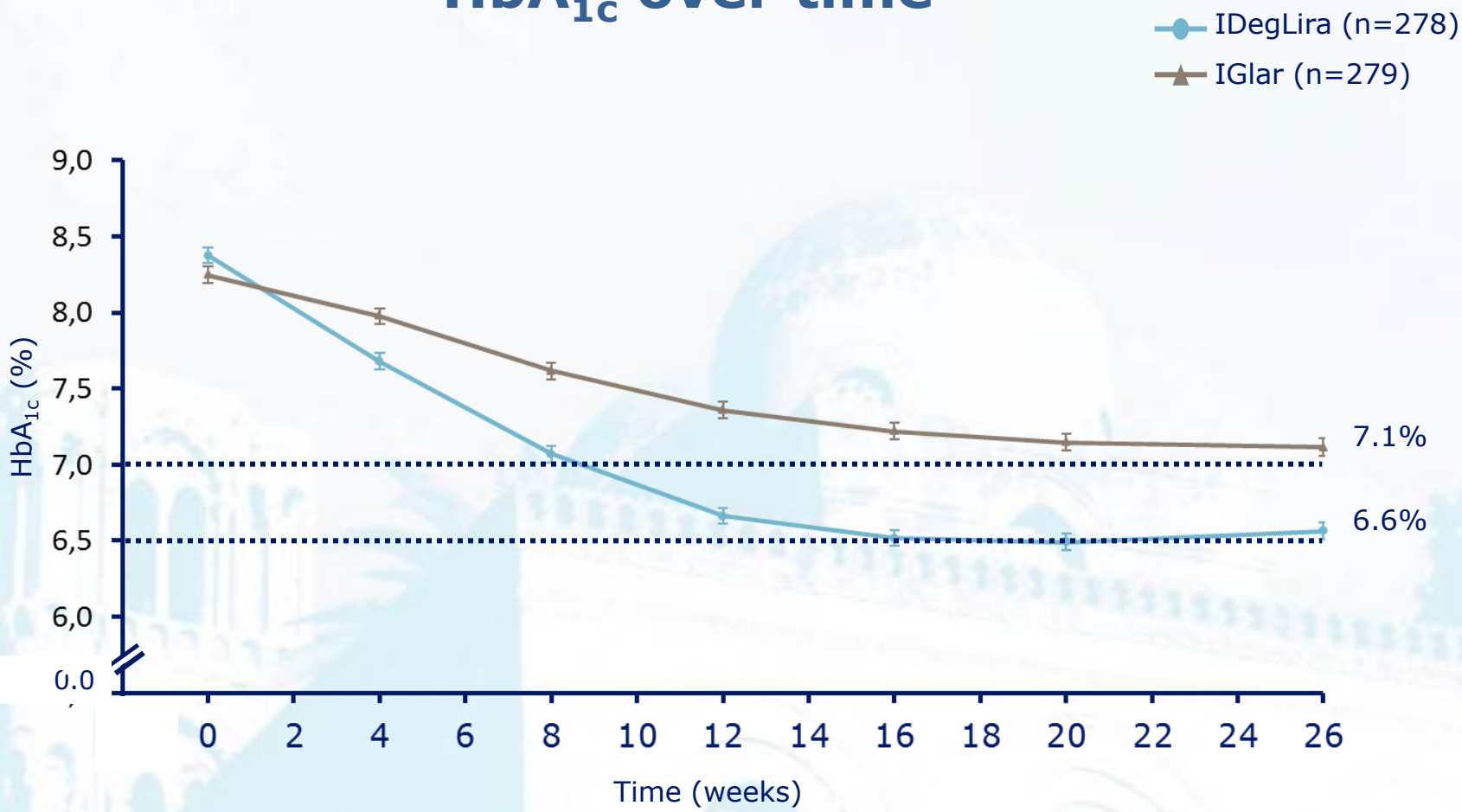
NN9068-3952; IDegLira vs. IGlar. BMI, body mass index; FPG, fasting plasma glucose

DUAL V
Baseline characteristics

Characteristic	IDegLira	IGlar
Full analysis set, n	278	279
Female/Male, %	48.6/51.4	50.9/49.1
Age, years	58.4 (±9.8)	59.1 (±9.3)
Weight, kg	IDegLira	IGlar
BMI, kg/m^2	31.7 (±4.4)	31.7 (±4.5)
Duration of diabetes, years	11.6 (±7.4)	11.3 (±6.6)
HbA_{1c}, % [HbA_{1c}, mmol/mol[a]]	8.4 (±0.9) [68.0 (±9.8)]	8.2 (±0.9) [66.6 (±9.6)]
FPG, mmol/L [mg/dL[a]]	8.9 (±2.6) [160.5 (±47.5)]	8.9 (±2.9) [159.8 (±52.0)]
Pre-trial insulin dose	31 (±10)	32 (±10)

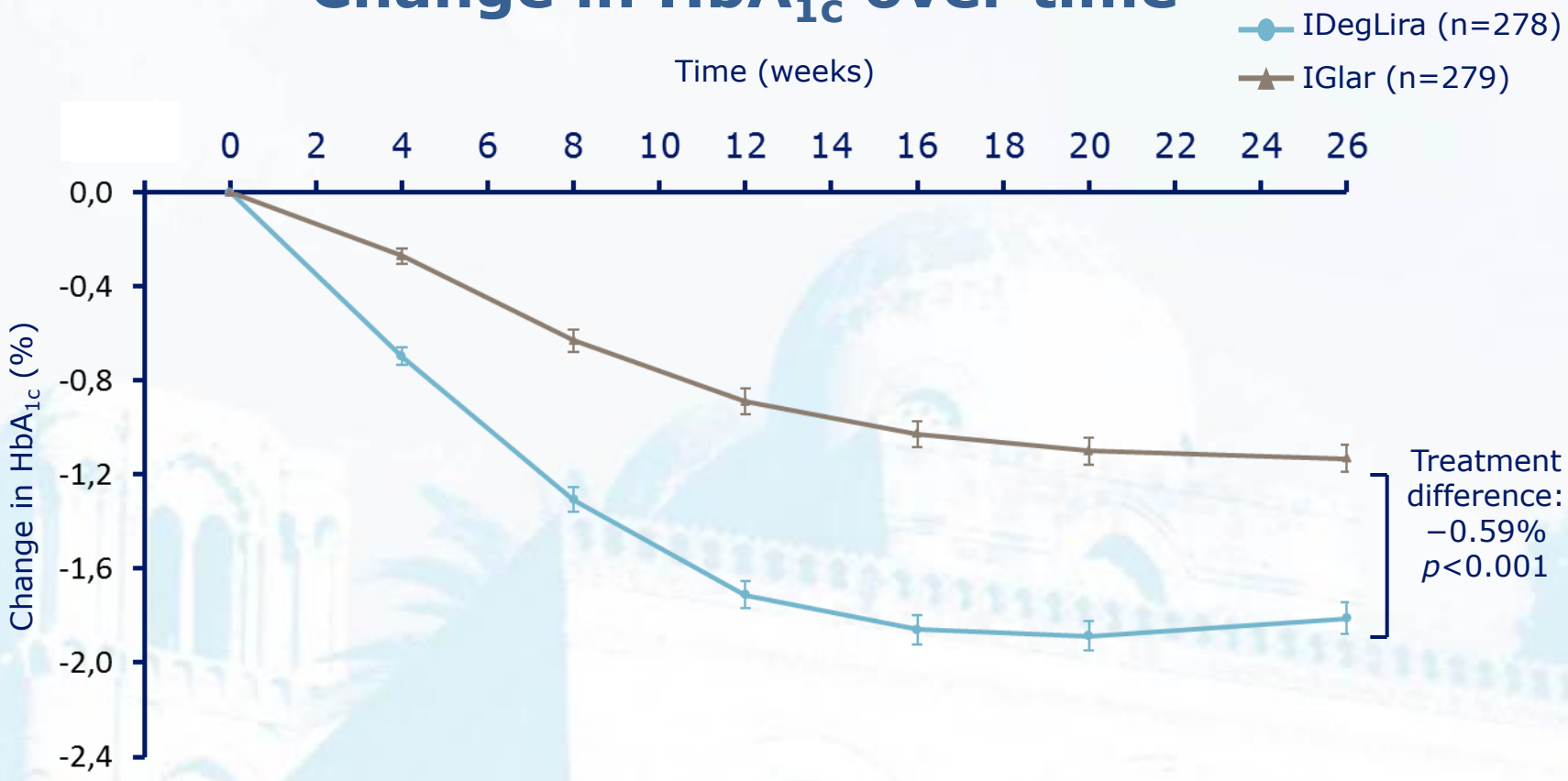
Values are mean unless otherwise stated; [a]Calculated, not measured
BMI, body mass index; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine
Lingvay *et al. JAMA* 2016;315:898-907

HbA_{1c} over time



Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data
---ADA/EASD HbA_{1c} target <7.0%; AACE HbA_{1c} target ≤6.5%
AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association, EASD, European Association for the Study of Diabetes; LOCF, last observation carried forward
NN9068-3952; IDegLira vs. IGlar

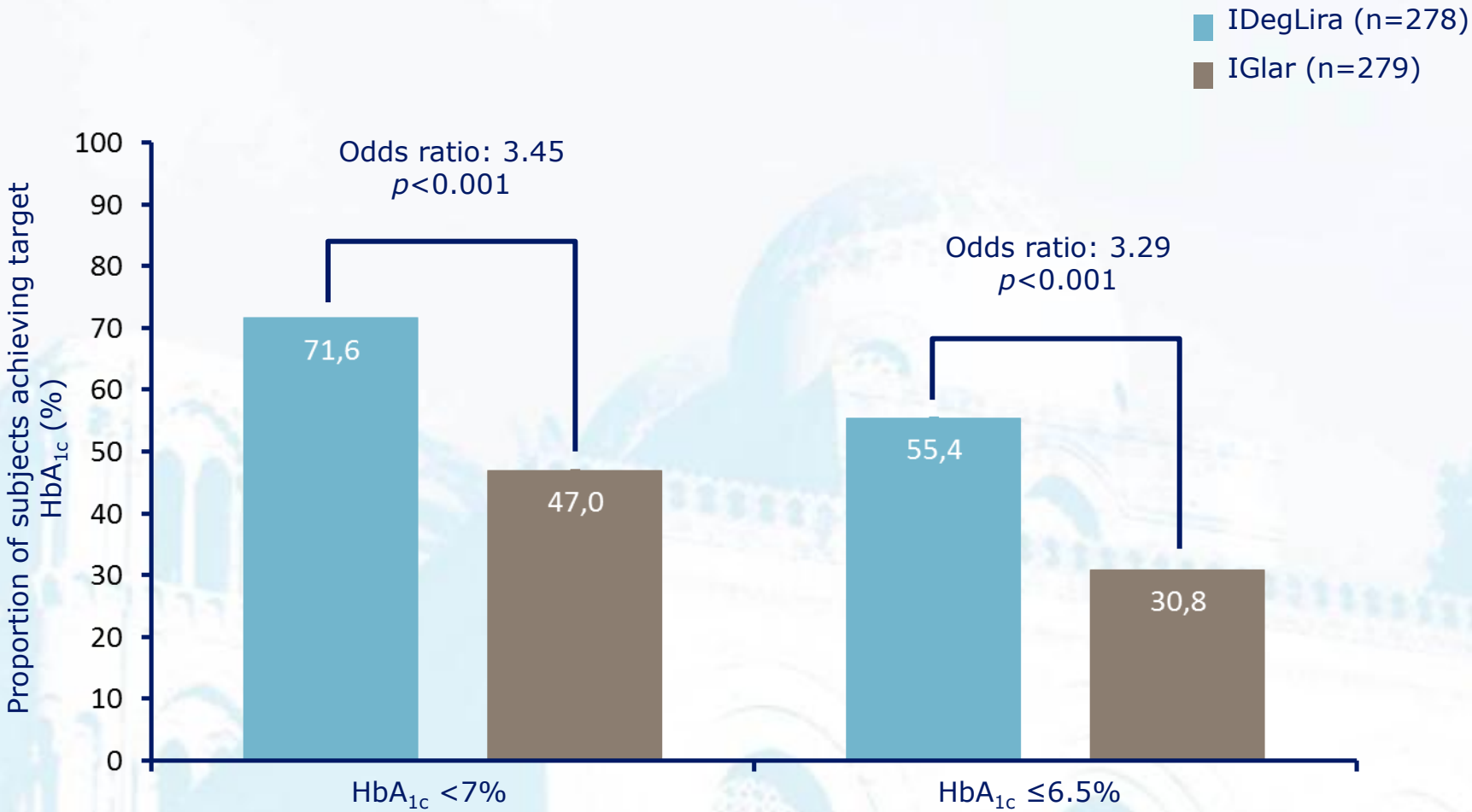
Change in HbA_{1c} over time



	IDegLira	IGlar
ΔHbA_{1c} (%)	−1.81	−1.13

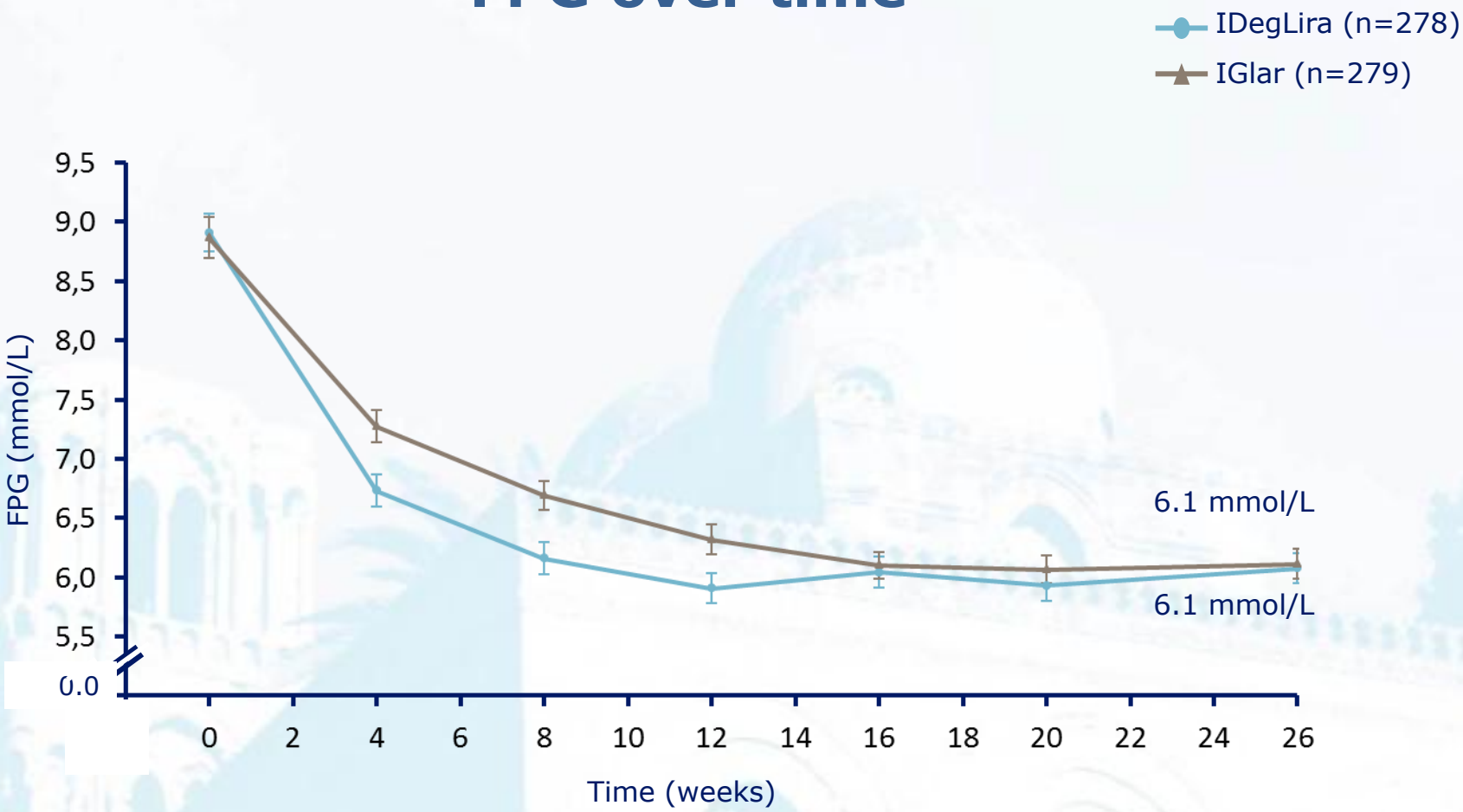
Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis while Δ values are observed LOCF
NN9068-3952; IDegLira vs. IGlar

Subjects achieving treatment targets



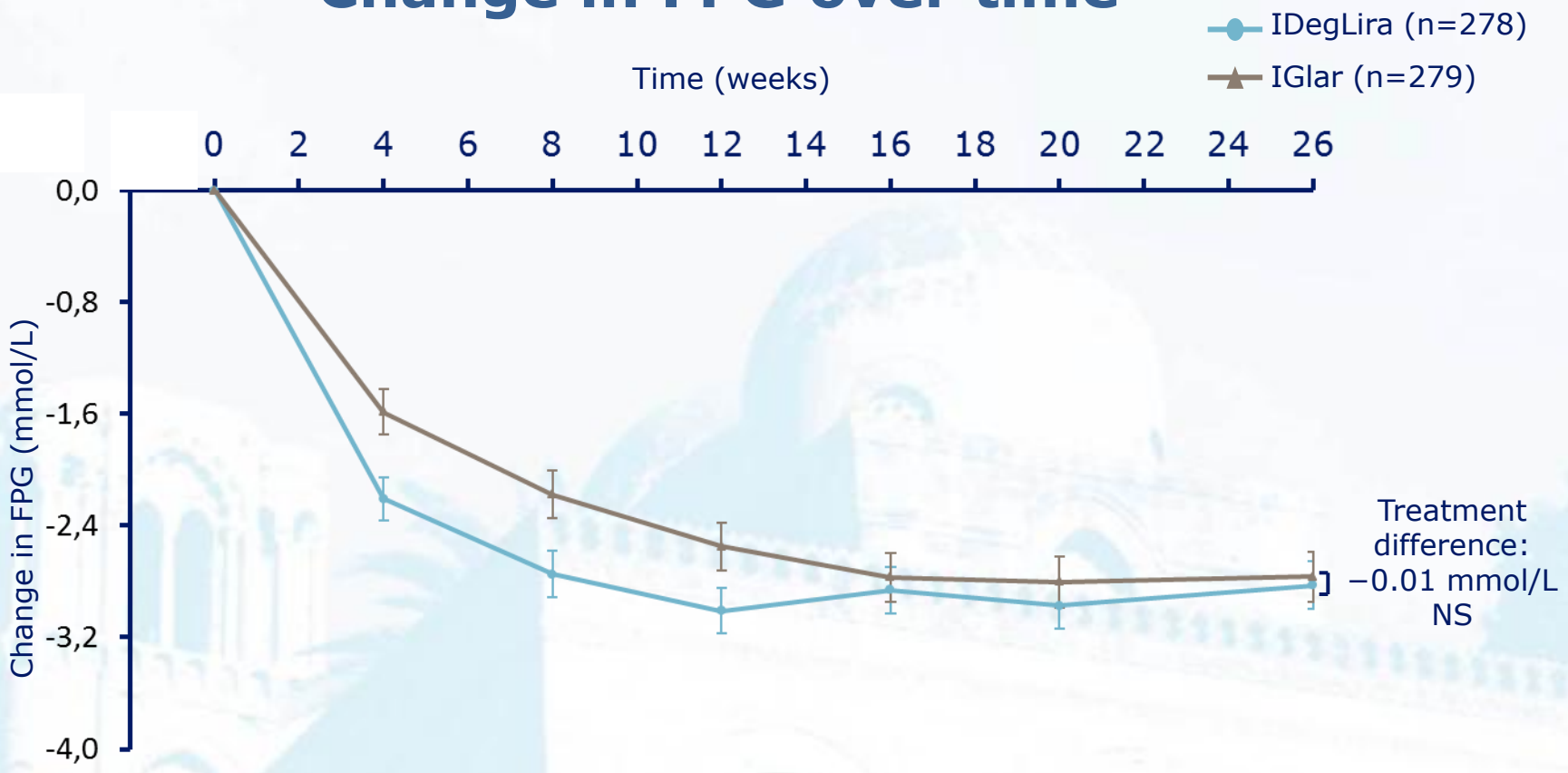
Responders are based on full analysis set and LOCF imputed data
Odds ratios (IDegLira/IGlar) are from a logistic regression model
NN9068-3952; IDegLira vs. IGlar

FPG over time



Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data
NN9068-3952; IDegLira vs. IGlar

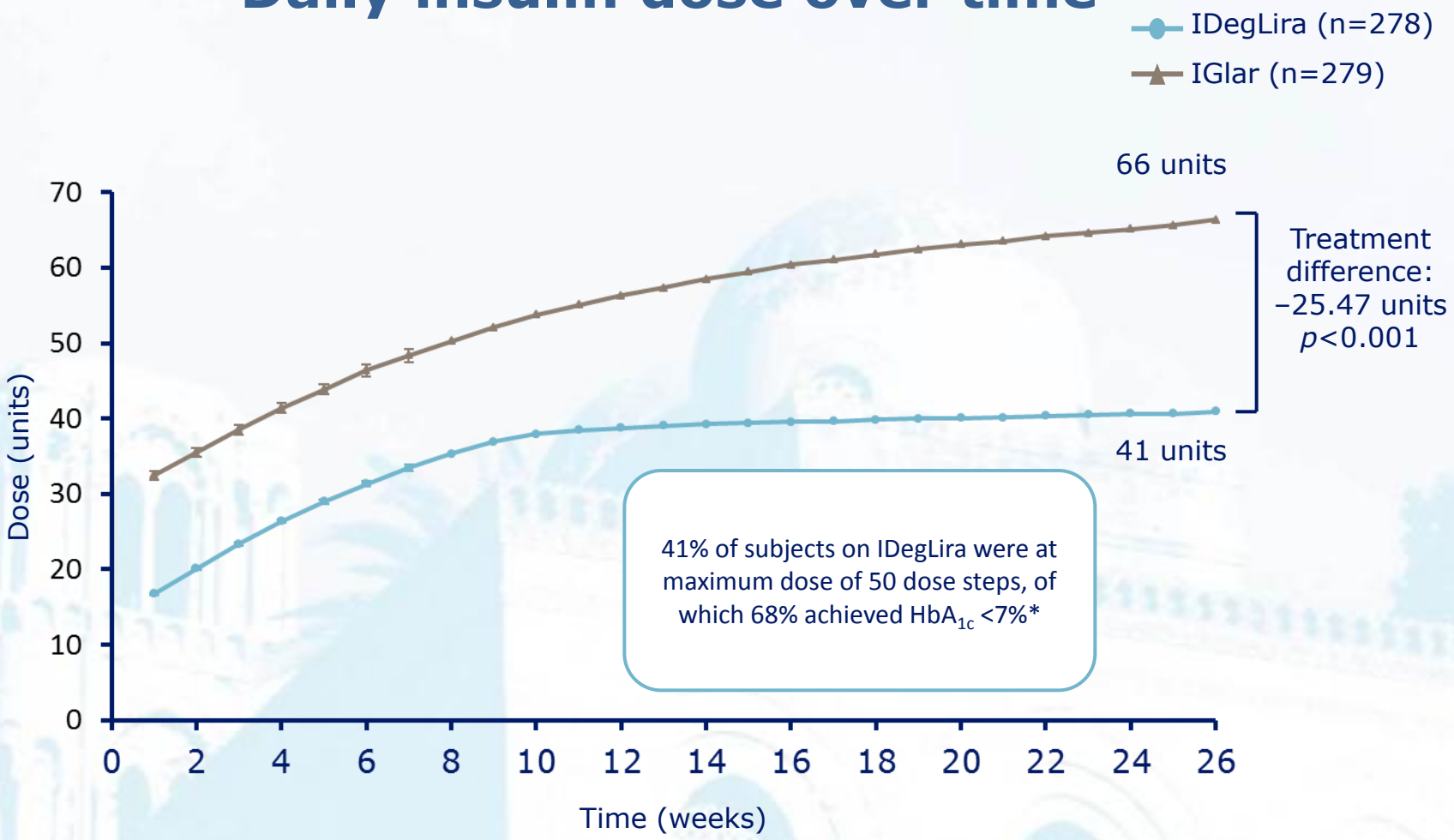
Change in FPG over time



	IDegLira	IGlar
ΔFPG (mmol/L)	−2.83	−2.77

Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed (LOCF) data
Treatment difference is estimated from an ANCOVA analysis while Δ values are observed LOCF
FPG, fasting plasma glucose
NN9068-3952; IDegLira vs. IGlar

Daily insulin dose over time



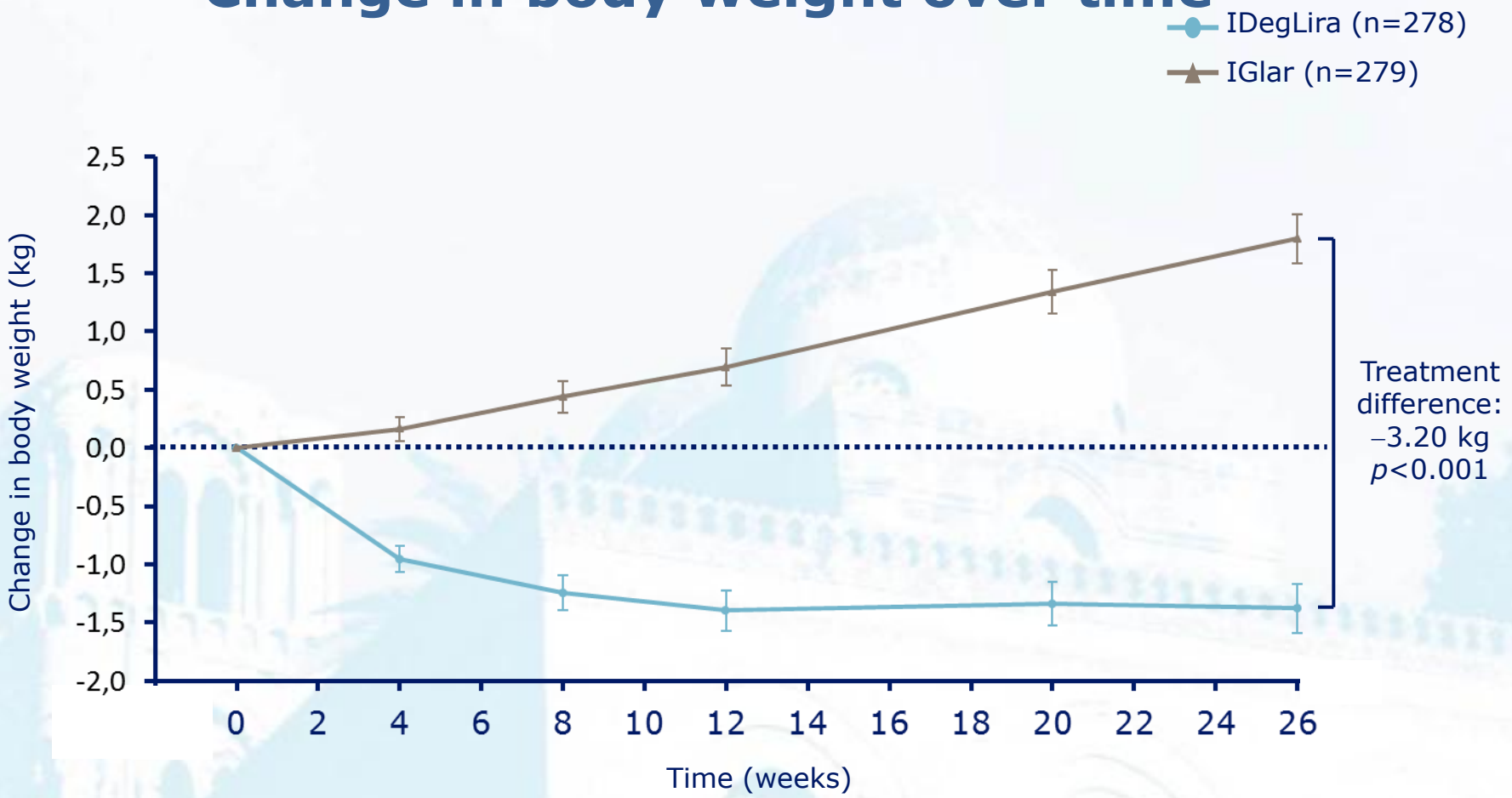
*There was no maximum dose for IGlar

Mean observed values with error bars (standard error mean) based safety analysis set and LOCF imputed data

Treatment difference is estimated from an ANCOVA analysis

NN9068-3952; IDegLira vs. IGlar

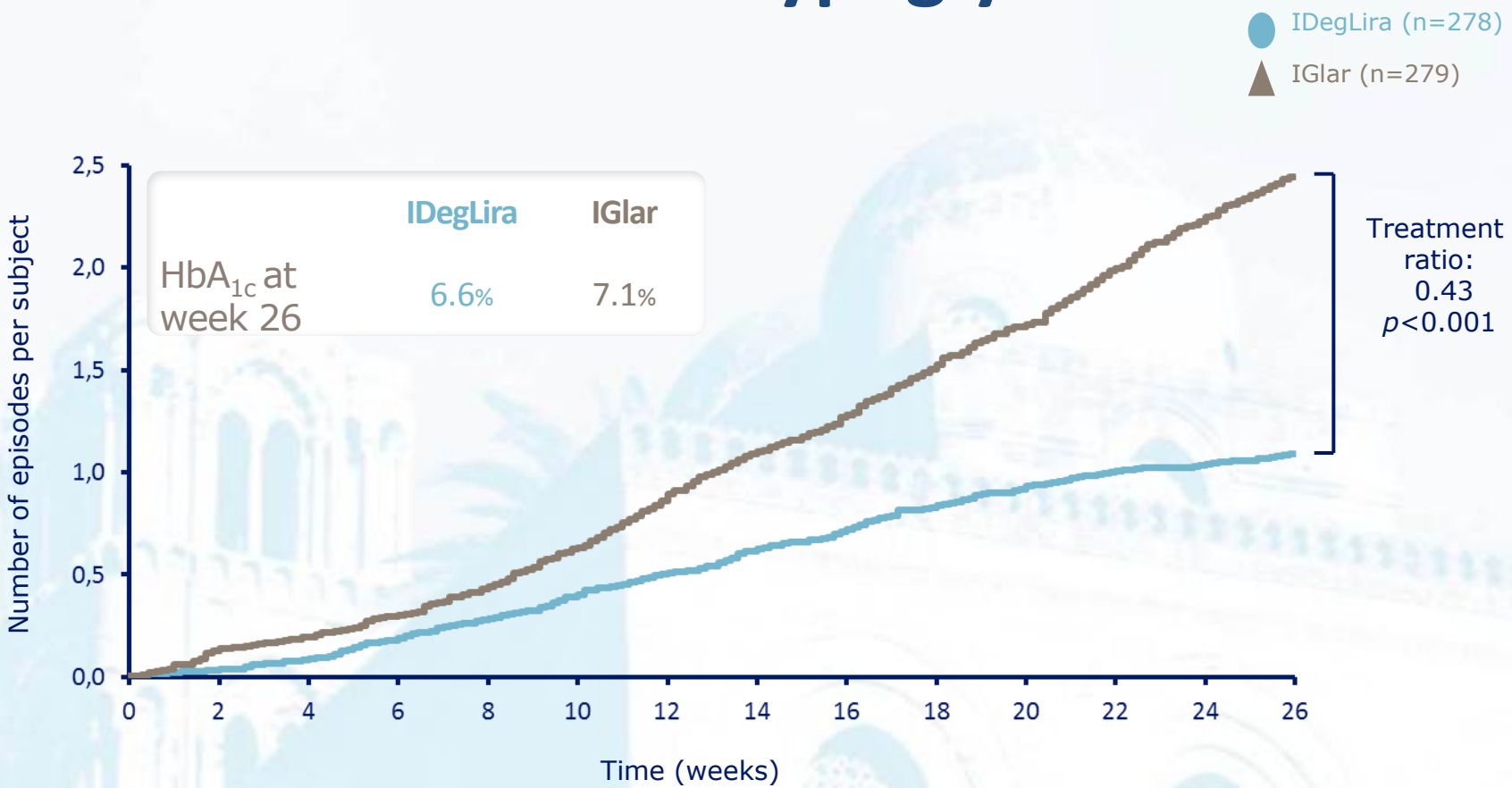
Change in body weight over time



	IDegLira	IGlar
ΔBody weight (kg)	−1.4	1.8

Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis while Δ values are observed LOCF
NN9068-3952; IDegLira vs. IGlar

DUAL V
Confirmed hypoglycaemia



Mean cumulative function based on SAS
Treatment ratio is estimated from a negative binomial model based on FAS
FAS, full analysis set; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine; SAS, safety analysis set
Lingvay *et al. JAMA* 2016;315:898-907

Agenda

- Introduzione: fisiopatologia della secrezione insulinica

- *Unmet Needs* e recenti proposte terapeutiche in tema di basalizzazione insulinica:

- *Degludec*

- *Unmet Needs* e recenti proposte terapeutiche in tema di intensificazione insulinica:

- *Insulina Basale + GLP-1RA*

- IdegLira : DUAL V trial

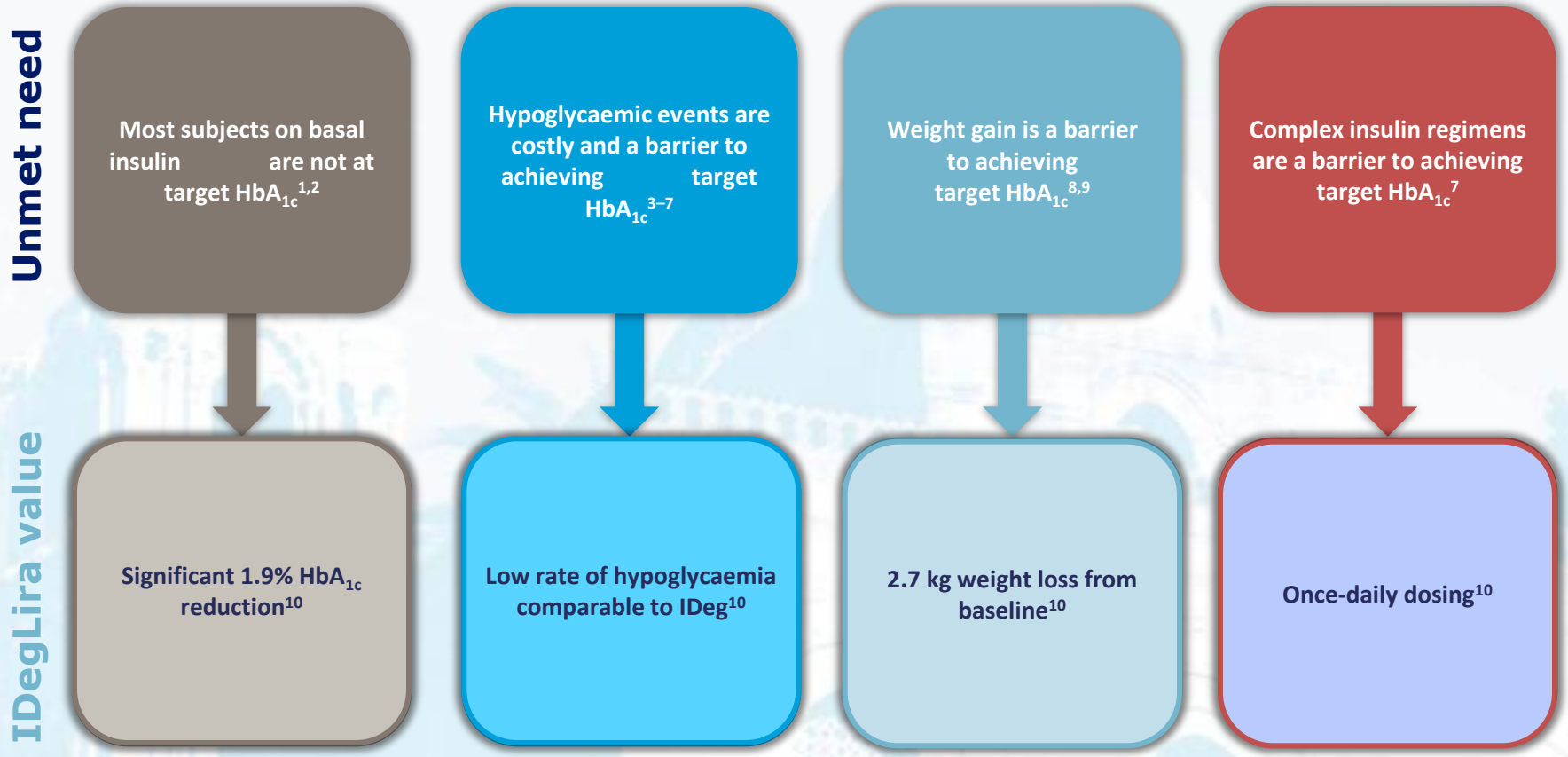
- Conclusioni

IDeg value vs. IGlar : patients with T2D starting on insulin

Unmet need	IDeg value
Economic burden of diabetes[1,2]	Equivalent reductions in HbA_{1c} achieved with significantly **lower** total daily **insulin dose**[11]
Hypoglycemic events are costly and a barrier to good glycemic control[3-6]	Reductions in risk of **hypoglycaemia** 11,13
SMBG test strips is a substantial cost driver in diabetes treatment[17]	Potential for less use of **SMBG** test strips
Complexity of insulin treatment regimens[10,16]	Dose time **flexibility**[15]
Diabetes negatively impacts patients' HRQoL[7-9]	Improved **HRQoL**[14]

1. IDF. Diabetes Atlas, Sixth Edition, 2013; 2. ADA. *Diabetes Care* 2013;36:1033–46; 3. Leiter *et al. Can J Diabetes* 2005;29:186–92; 4. Hammer *et al. JME* 2009;12:281–90; 5. Brod *et al. Value Health* 2011;14:665–71; 6. Leese *et al. Diabetes Care* 2003;26:1176–80; 7. UKPDS. *Diabetes Care* 1999;22:1125–36; 8. Rubin *et al. Diabetes Metab Res Rev* 1999;15:205–18; 9. Davis *et al. Curr Med Res Opin* 2005;21:1477–83; 10. Peyrot *et al. Diabetic Medicine* 2012;29:682–9; 11. Vora *et al. Diabetes Ther* 2014;5:435–46; 12. Zinman *et al. Diabetes Care* 2012;35:2464–71; 13. Ratner *et al. Diabetes Obes Metab* 2013;15:175–84; 14. Freemantle *et al. Diabet Med* 2013;30:226–32; 15. Tresiba, Summary of Product Characteristics, Novo Nordisk A/S; 16. Peyrot *et al. Diabetes Care* 2010;33:240–5; 17. Yeaw *et al. J Manag Care Pharm* 2012;18:21–32

IDegLira offers value by addressing the unmet needs of subjects with T2D uncontrolled on basal insulin



*i.e. on insulin for >5 years

1. Dale *et al. Prim Care Diabetes* 2010;4:85–9; 2. Giugliano *et al. Diabetes Care* 2011;34:510–17; 3. Farmer *et al. Diabet Med* 2012;29:1447–50;
4. Department of Health. Payment by Results Tariff Information Spreadsheet for 2013 to 2014. A&E Attendance. Accessed December 2013;
5. Department of Health. Payment by Results Tariff Information Spreadsheet for 2013 to 2014. Admitted patient care & outpatient procedures. Accessed December 2013; 6. Donnelly *et al. Diabet Med* 2005;22:749–55; 7. Peyrot *et al. Diabet Med* 2012;29:682–9;
8. UKPDS 33. *Lancet* 1998;352:837–53; 9. Peyrot *et al. Curr Med Res Opin* 2009;25:1985–93; 10. Buse *et al. Diabetes Care* 2014;37:2926–33

Grazie per la Cortese Attenzione

Diabete: i numeri che non vorremmo conoscere ma che non possiamo ignorare

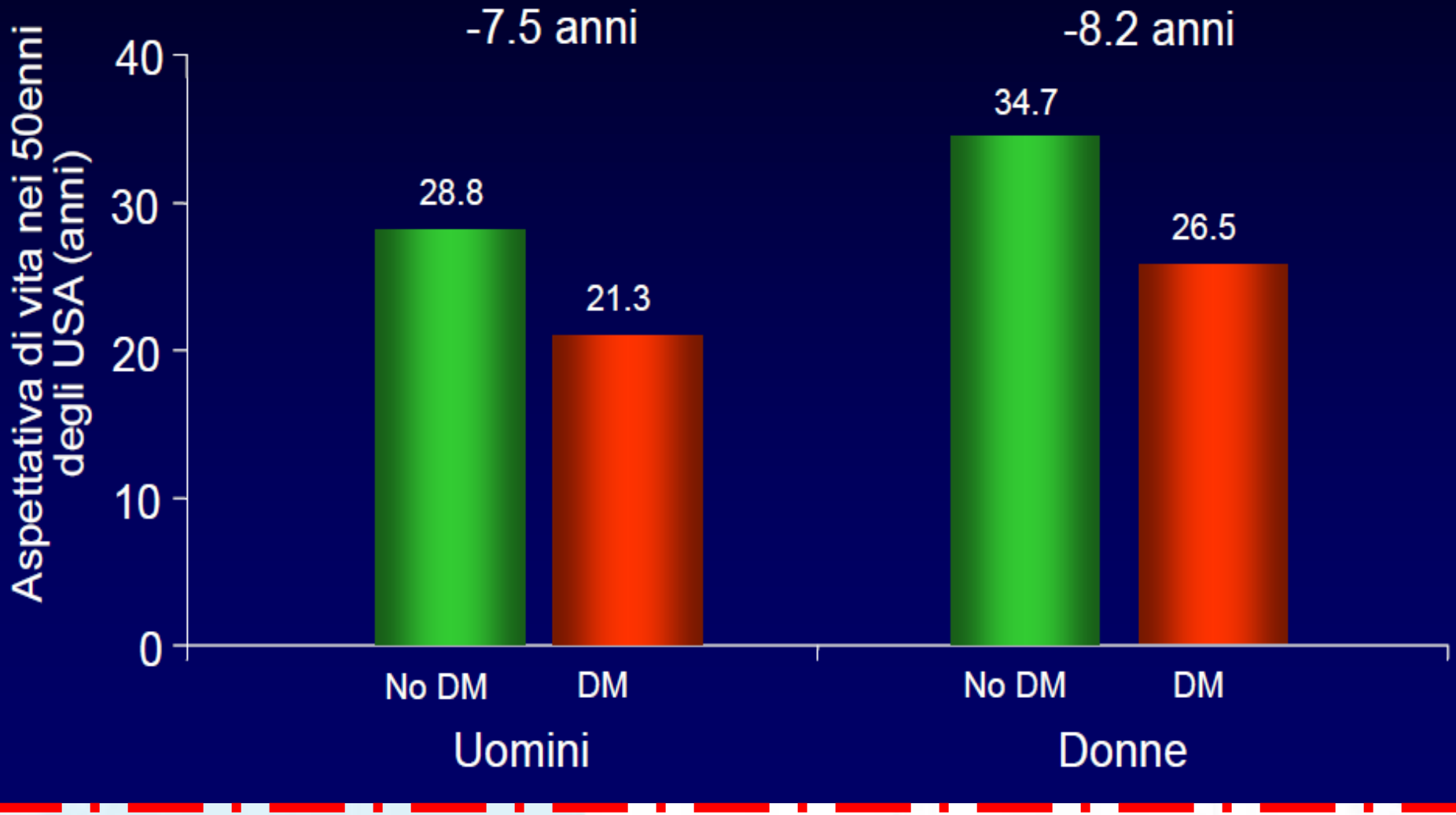
In Italia:

- Ogni 2 minuti una persona riceve la diagnosi di diabete
- Ogni 7 minuti una persona con diabete ha un attacco cardiaco
- Ogni 26 minuti una persona con diabete sviluppa un'insufficienza renale
- Ogni 30 minuti una persona con diabete ha un ictus
- Ogni 90 minuti una persona subisce un'amputazione a causa del diabete
- Ogni 180 minuti una persona con diabete entra in dialisi
- Ogni 20 minuti una persona muore a causa del diabete

UNIVERSITÀ DEGLI STUDI DI PALERMO

Diabete: ridotta quantità di vita

Franco et al; Arch Intern Med 167:1145, 2007



Il diabete uccide