I CONGRESSO CONGIUNTO AMD – SID PIEMONTE E VALLE D'AOSTA
SINERGIE PER L'INNOVAZIONE
"Se ci mettiamo insieme ci sarà un perché"
Torino, 2 – 3 dicembre 2016

Il Diabetico tipo 1: "ouverture" per una molecola stra"nota"

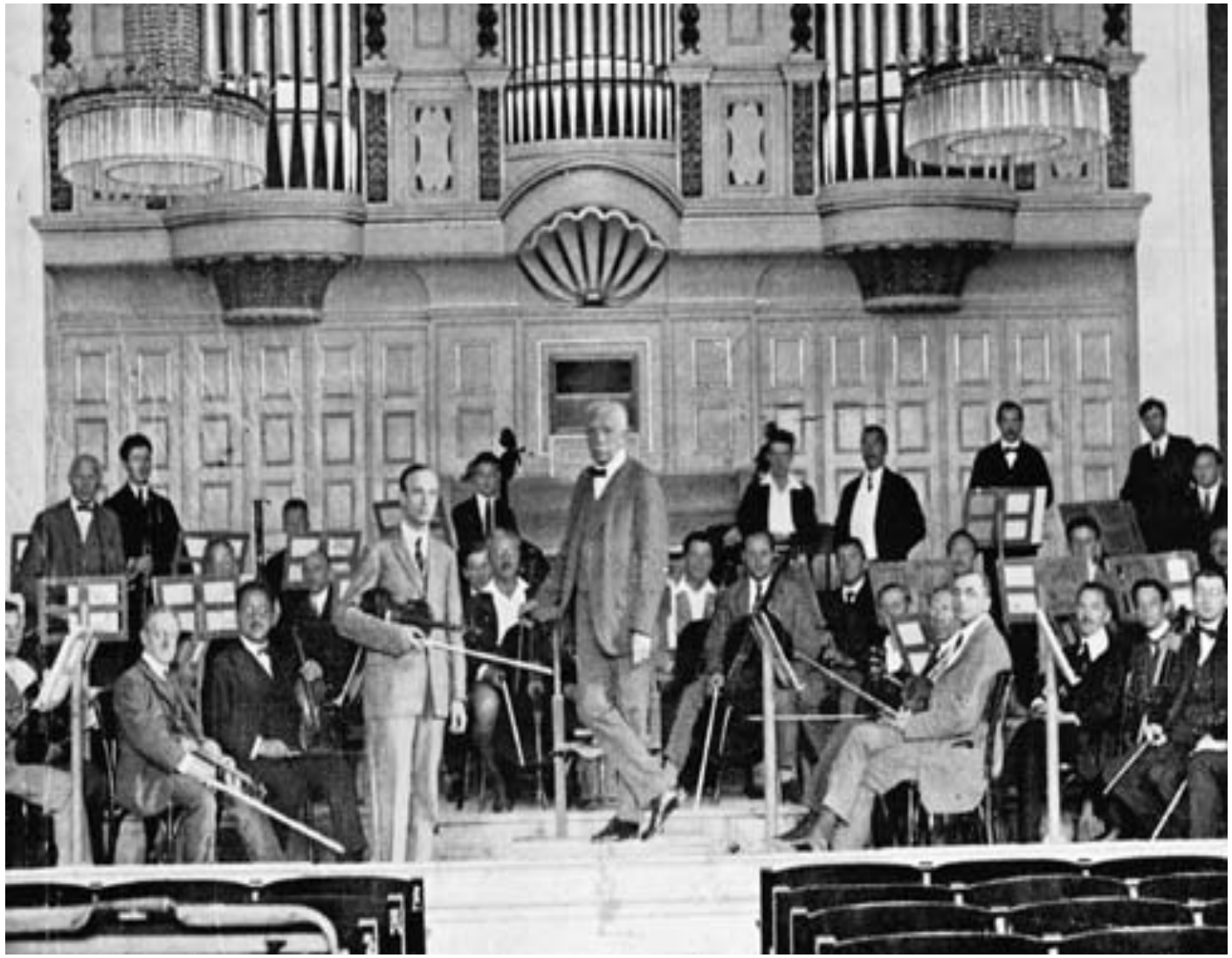
Giorgio Grassi

Endocrinologia Diabetologia e Metabolismo

Città della Salute e della Scienza

TORINO

1922: Richard Strauss conducting the orchestra of the Vienna Staatsoper at the Mozarteum



Intensive Insulin Replacement Compared with Natural, Non-diabetic Insulin Secretion

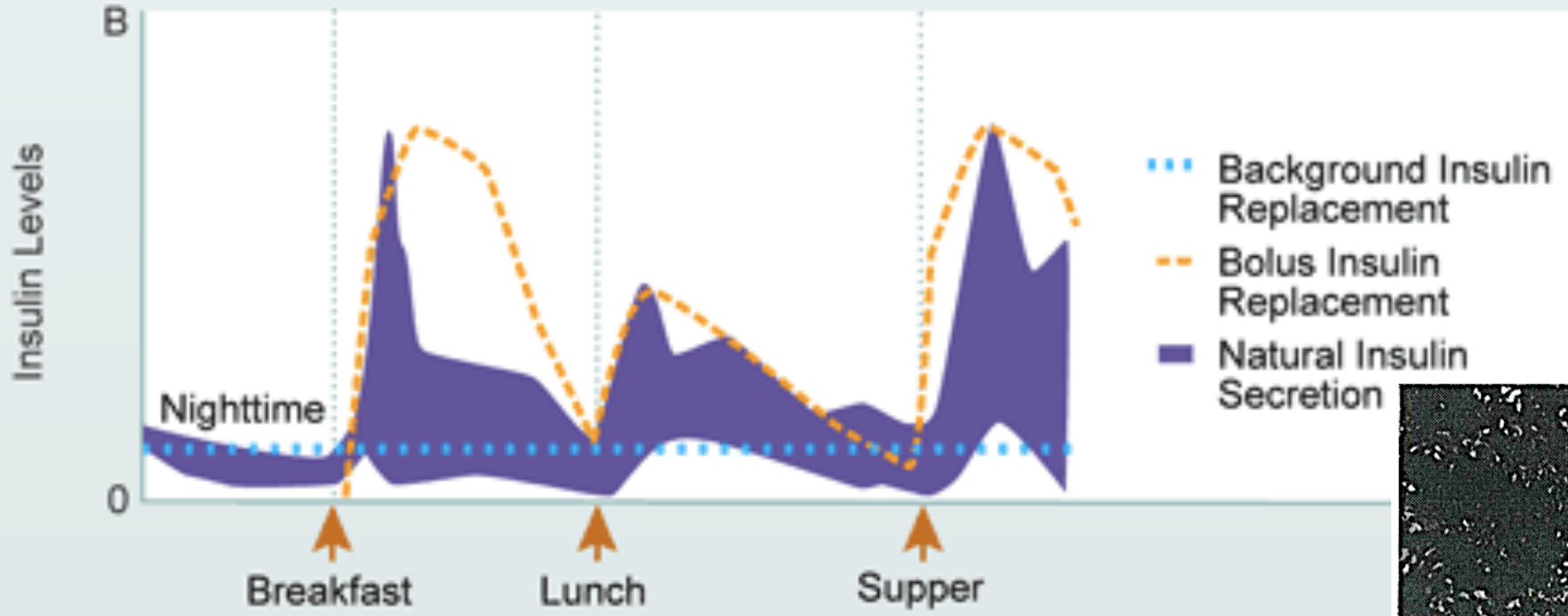
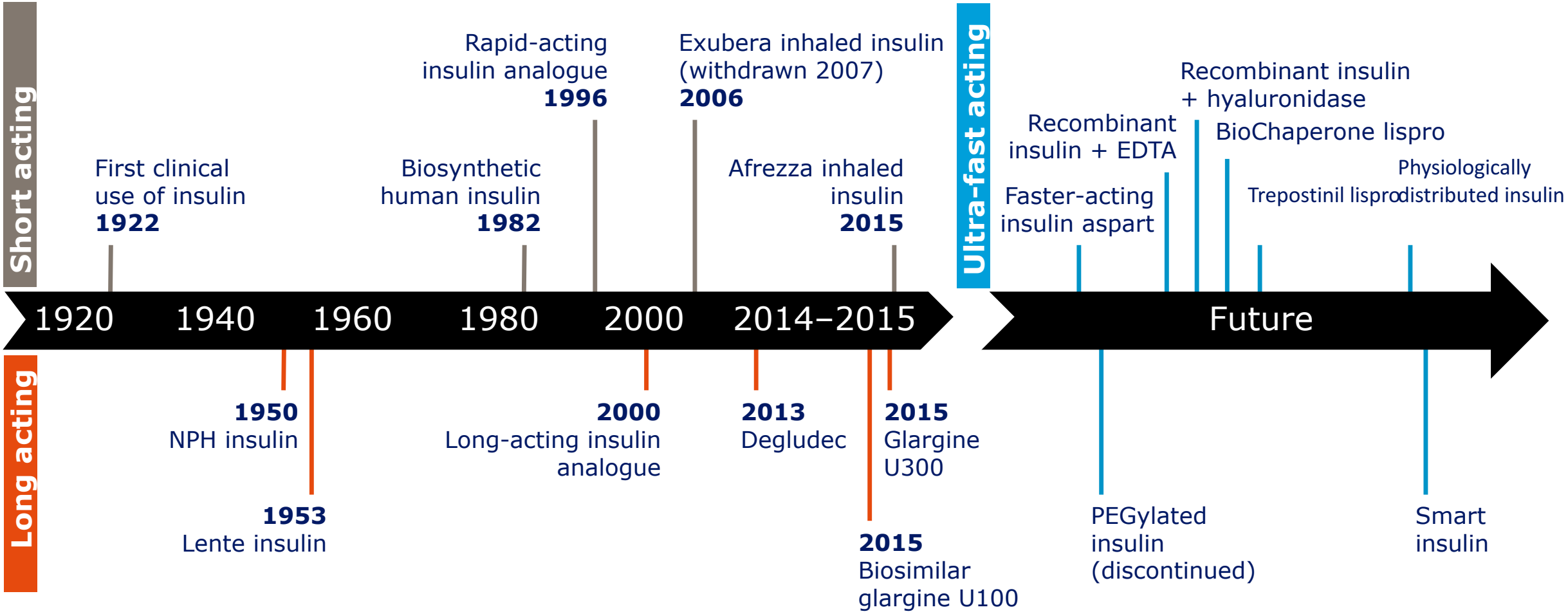


Fig. 2 - La cura della sdraio all'aria aperta, alla "Casa dei Diabetici tedeschi" di Garz (Rügen), nei primi anni Trenta. (Da Diabetes Journal, 1996).

Diabetes Education Online Diabetes Teaching Center at the University of California, San Francisco

Goal of insulin development: approach endogenous insulin secretion by healthy pancreatic beta cells

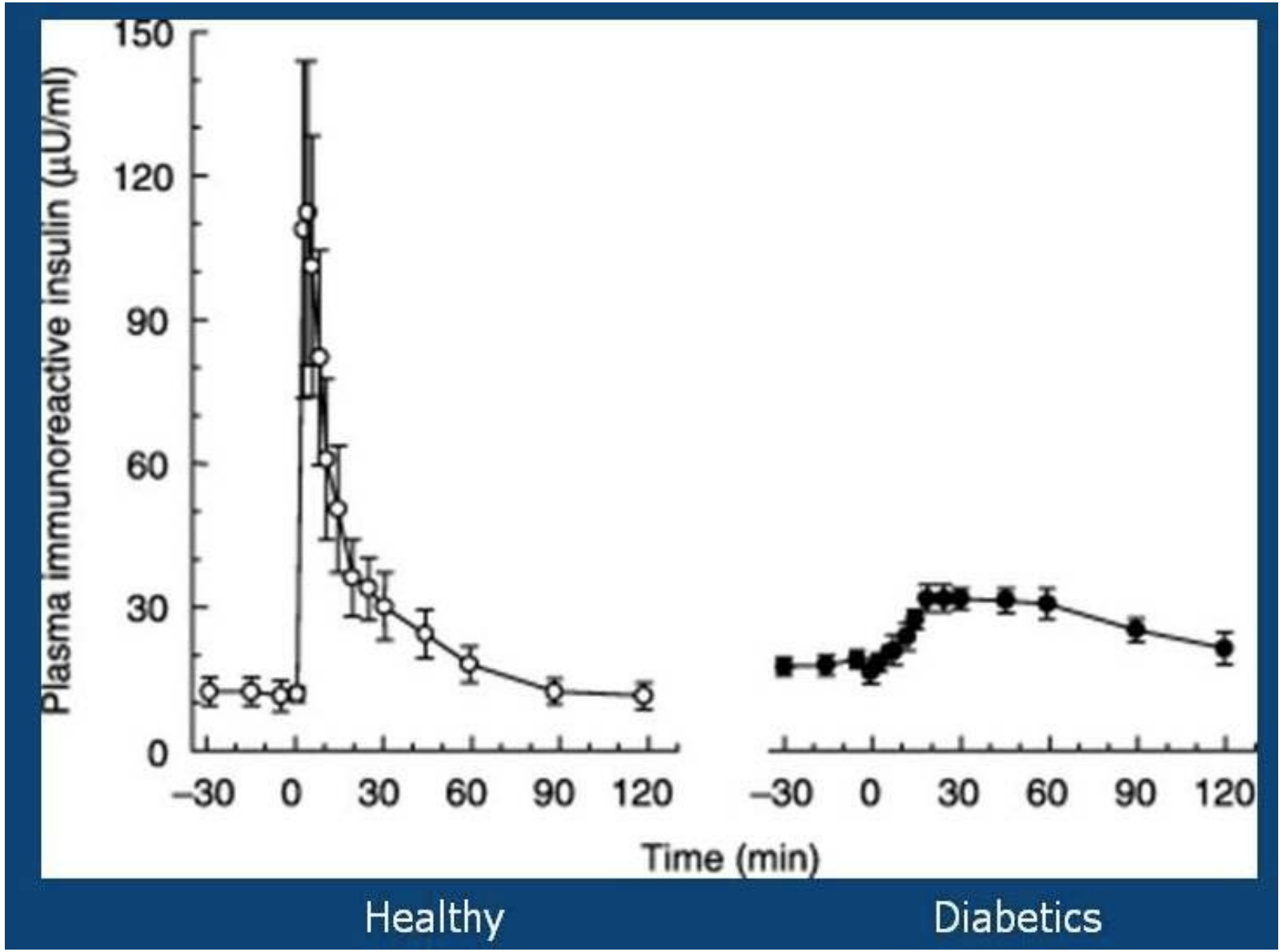


Adapted from Cahn A et al. *Lancet Diabetes Endocrinol* 2015;3:638–652.
Eli Lilly Patent Application 12 Nov 2015; Eli Lilly Press Release 4 Dec 2015; Novo Nordisk Capital Markets Day R&D update 19 Nov 2015

L'insulina si ottiene con la tecnologia del DNA ricombinante dal 1982, quando negli Stati Uniti fu messo a punto un sistema batterico in E. coli. L'insulina è collegata al primo brevetto e al primo farmaco biotecnologico, messo in commercio

- Esce l’album musicale più venduto di sempre: Centoquindicimilioni di copie vendute, di cui un milione soltanto nella prima settimana di vita. .

Insuline per la gestione dell'iperglicemia prandiale



Confronto Analoghi Rapidi e Insulina regolare

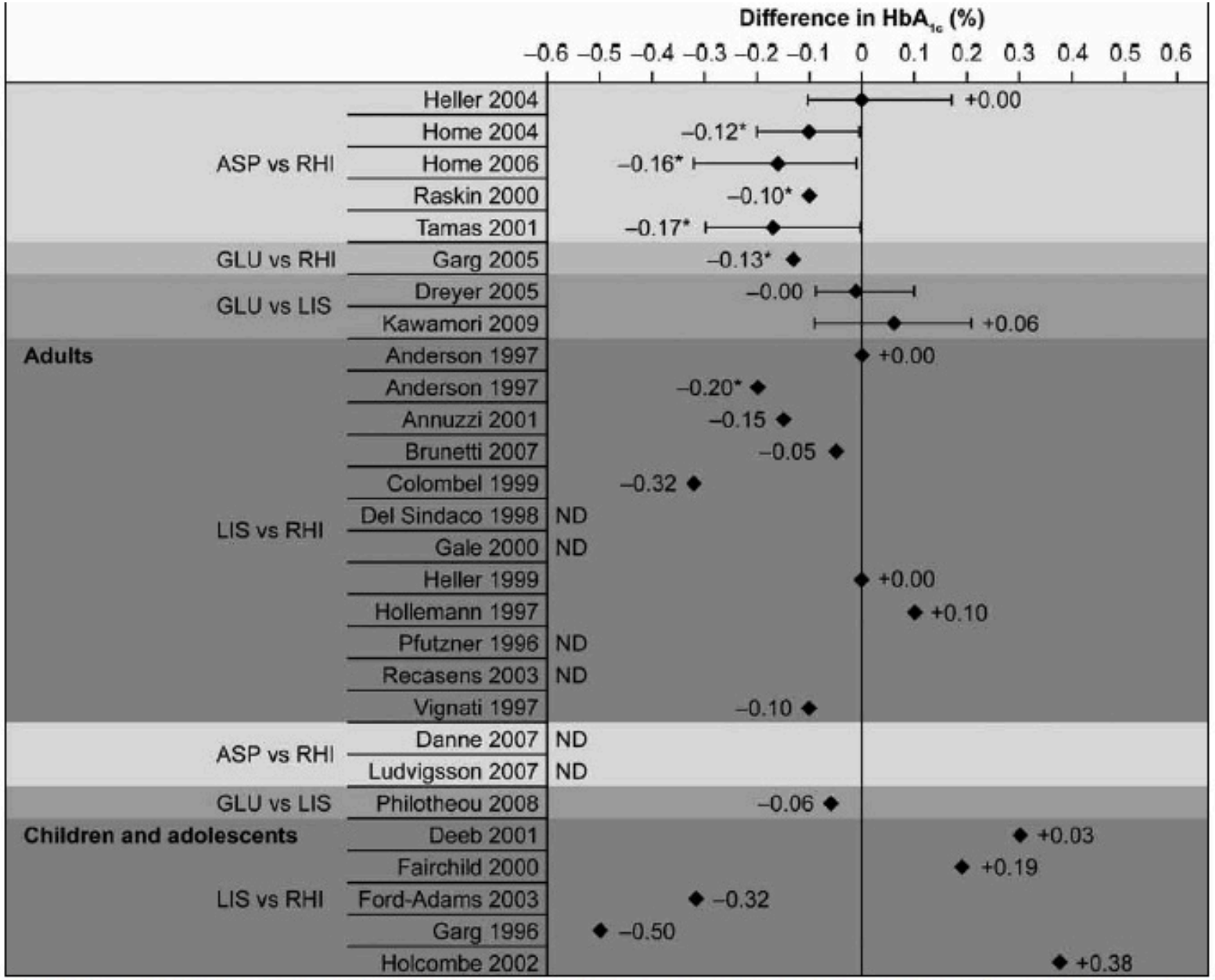


Fig. 2. Mean (with 95% confidence intervals, where available) between-group differences in magnitude of hemoglobin A_{1c} (HbA_{1c}) reduction in studies comparing rapid-acting insulin analogues with regular human insulins (RHIs) (or an alternative rapid-acting insulin analogue). Asterisk indicates $P<.05$ between-group differences. ASP, insulin aspart; GLU, glulisine; LIS, insulin lispro; ND, not done.

ENDOCRINE PRACTICE Vol 16 No. 3 May/June 2010

Designing an ultra-fast insulin

Administration

- Sprinkler needle
- Pulmonary

Formulation

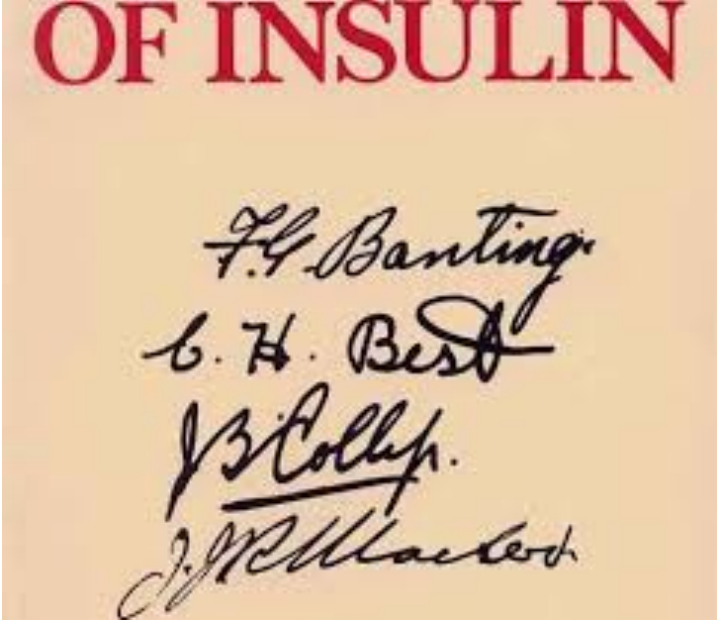
- **Additives, for example:**
  - **EDTA/citric acid**
  - **Magnesium**
  - **Bio-chaperone**
  - **Niacinamide**
  - **Other**

Injection site

- Application of heat
- Hyaluronidase

EDTA, ethylenediamine tetra-acetic acid

Clinical pharmacology results



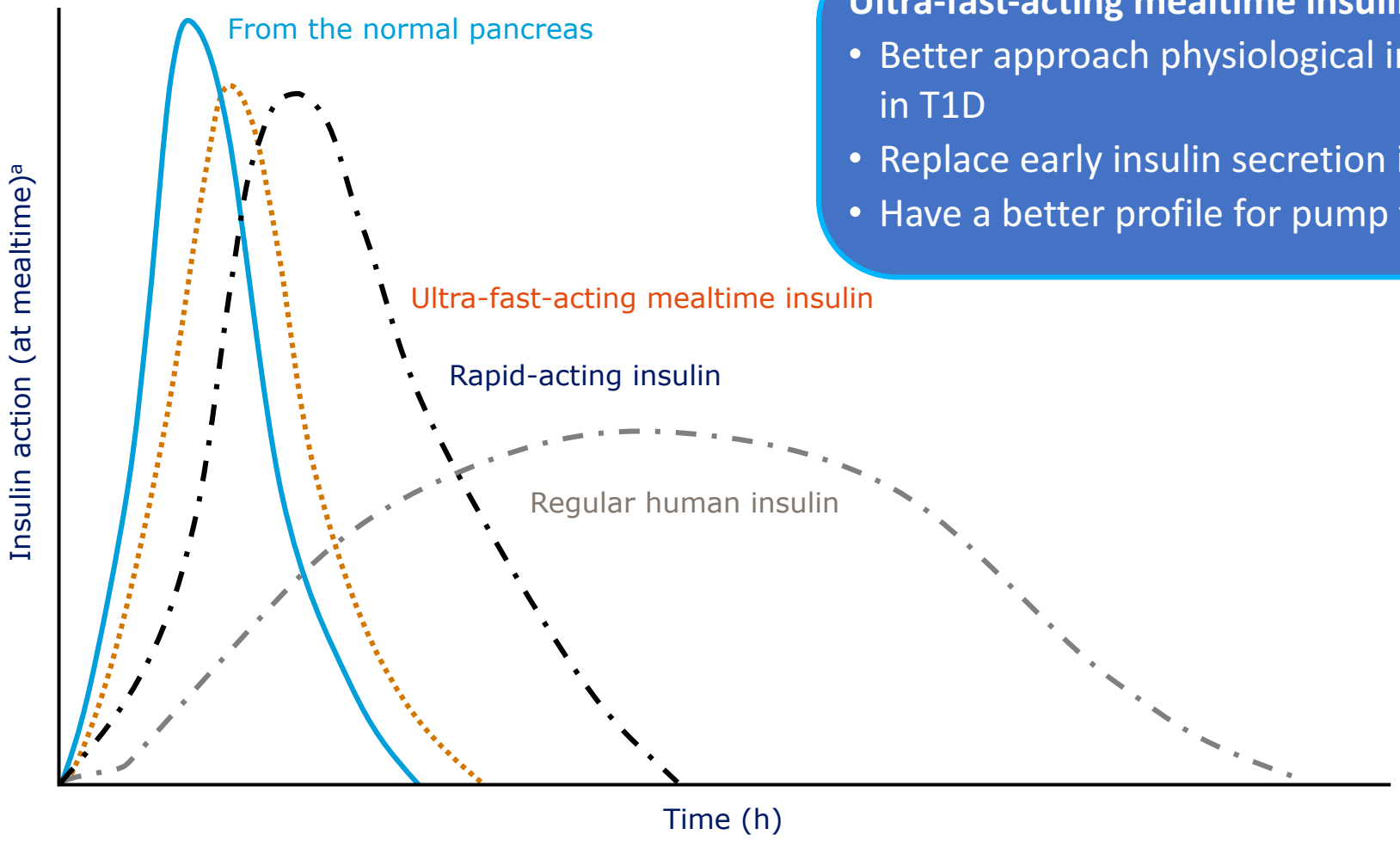
Formulation

- Additives, for example:
  - EDTA/citric acid
  - Magnesium
  - Bio-chaperone
  - Niacinamide
  - Other

Ultra-fast-acting mealtime insulins: approaching physiological insulin profile even further

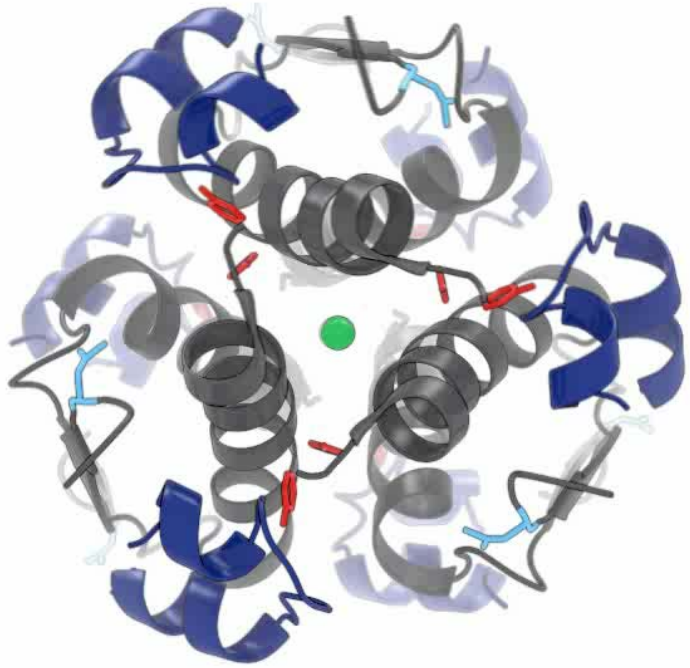
Ultra-fast-acting mealtime insulin should:

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Have a better profile for pump therapy



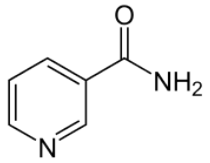
[a]Schematic representations. T1D, type 1 diabetes; T2D, type 2 diabetes.Adapted from Home PD. Diabetes Obes Metab 2015;17:1011–20.

Changing the formulation: Faster aspart is insulin aspart in a new formulation



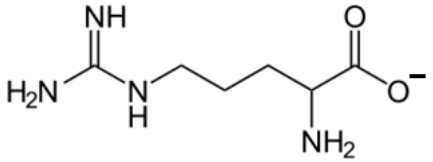
Insulin aspart

Niacinamide: absorption modifier



Vitamin B3

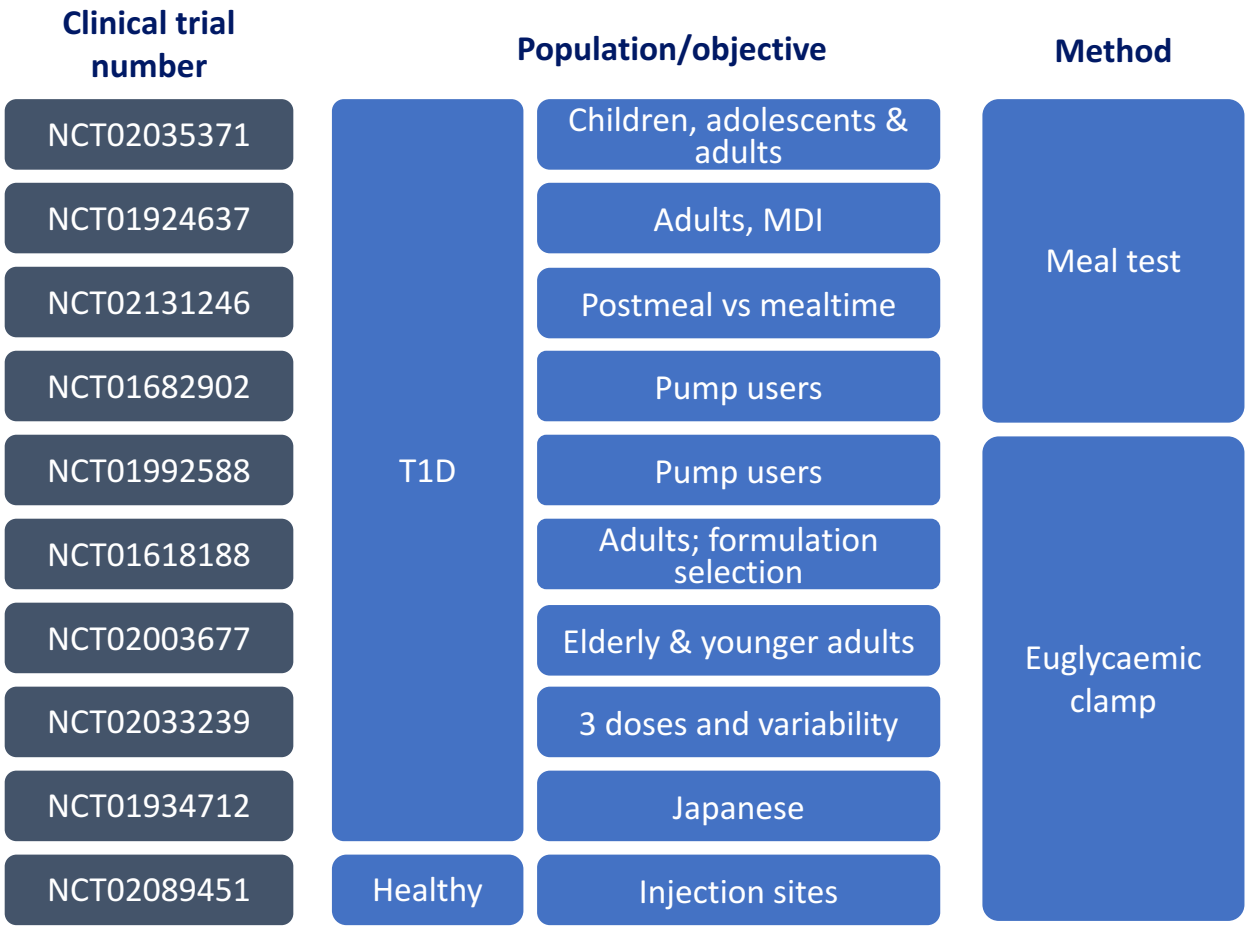
L-Arginine: added for stability



Naturally occurring amino acid

FDA's Inactive Ingredient Search for Approved Drug Products database. Available from: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Last accessed April 2015

Overview of the PK/PD studies with faster aspart



Pooled analyses: White adults T1D, dose 0.2 U/kg

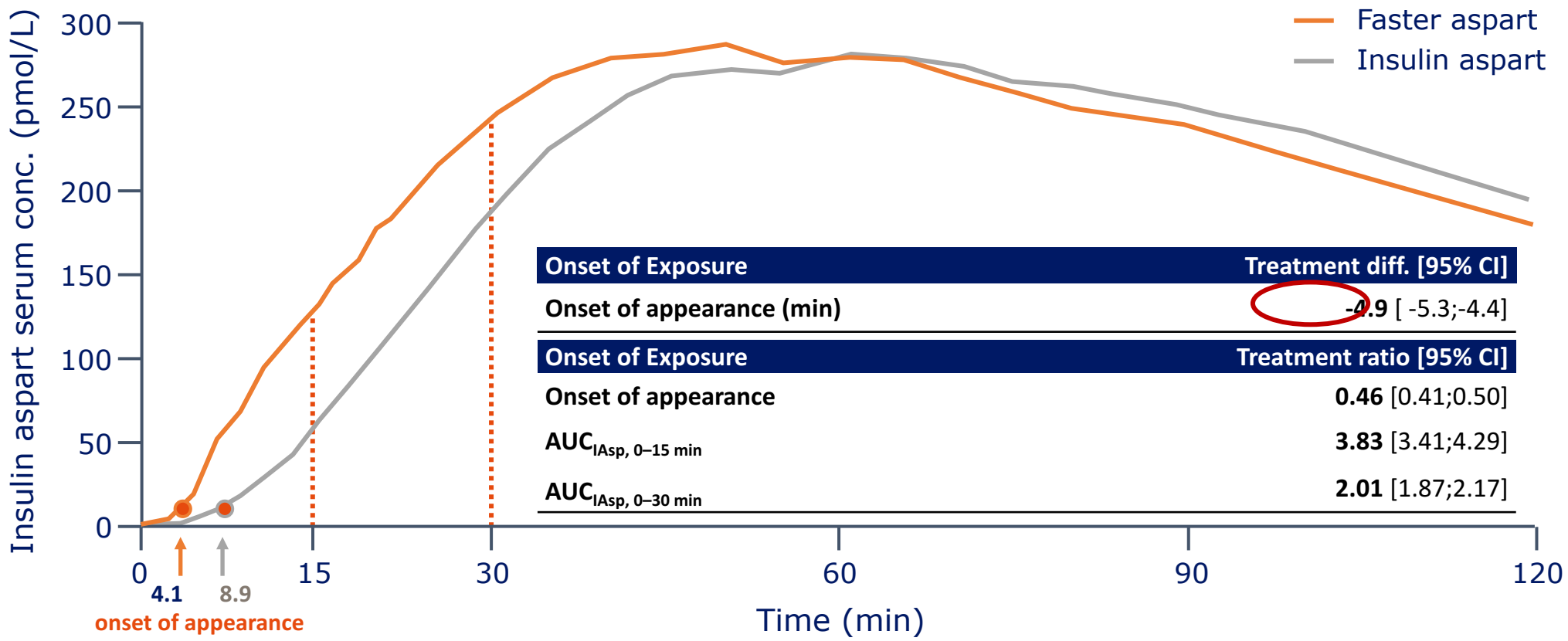
PK: 6 studies (218 subjects)

PD: 3 clamp studies (119 subjects)

PK, pharmacokinetics; PD, pharmacodynamics; T1D, type 1 diabetes; MDI, multiple daily injections
https://clinicaltrials.gov (Accessed April 2016)

PK – Onset of exposure

Pooled analysis 6 studies



Onset of Exposure	Treatment diff. [95% CI]
Onset of appearance (min)	**-4.9** [-5.3;-4.4]

Onset of Exposure	Treatment ratio [95% CI]
Onset of appearance	**0.46** [0.41;0.50]
$AUC_{IAsp,\ 0–15\ min}$	**3.83** [3.41;4.29]
$AUC_{IAsp,\ 0–30\ min}$	**2.01** [1.87;2.17]

Twice as fast onset of appearance in the bloodstream

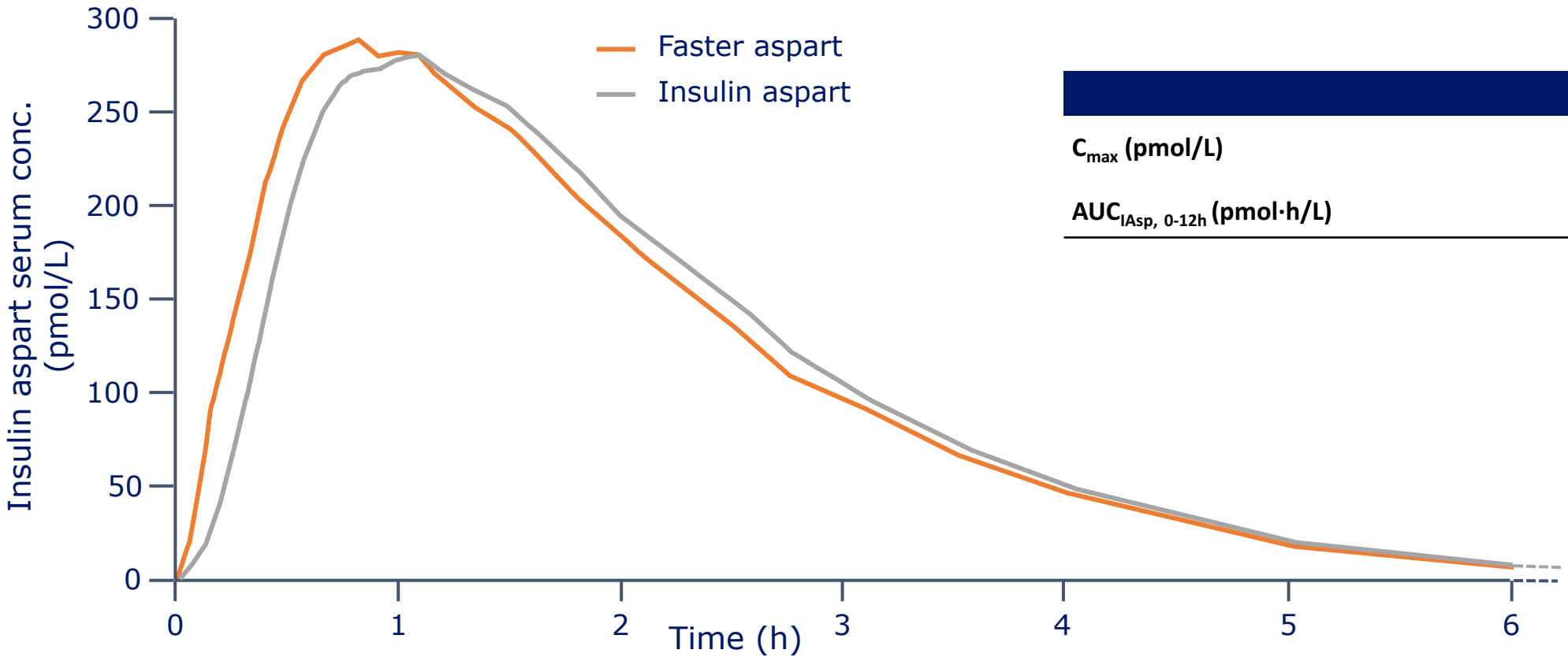
Two-fold higher insulin exposure within the first 30 minutes

AUC, area under the curve; CI, confidence interval

Heise T et al. *Diabetes* 2016;65(S1):A239.

PK – Total and Maximum exposure

Pooled analysis 6 studies



	Ratio [95%CI]
C_{max} (pmol/L)	**1.04** [1.00;1.08]
$AUC_{IAsp,\ 0\text{-}12h}$ (pmol·h/L)	**1.01** [0.98;1.04]

Similar total and maximum exposure

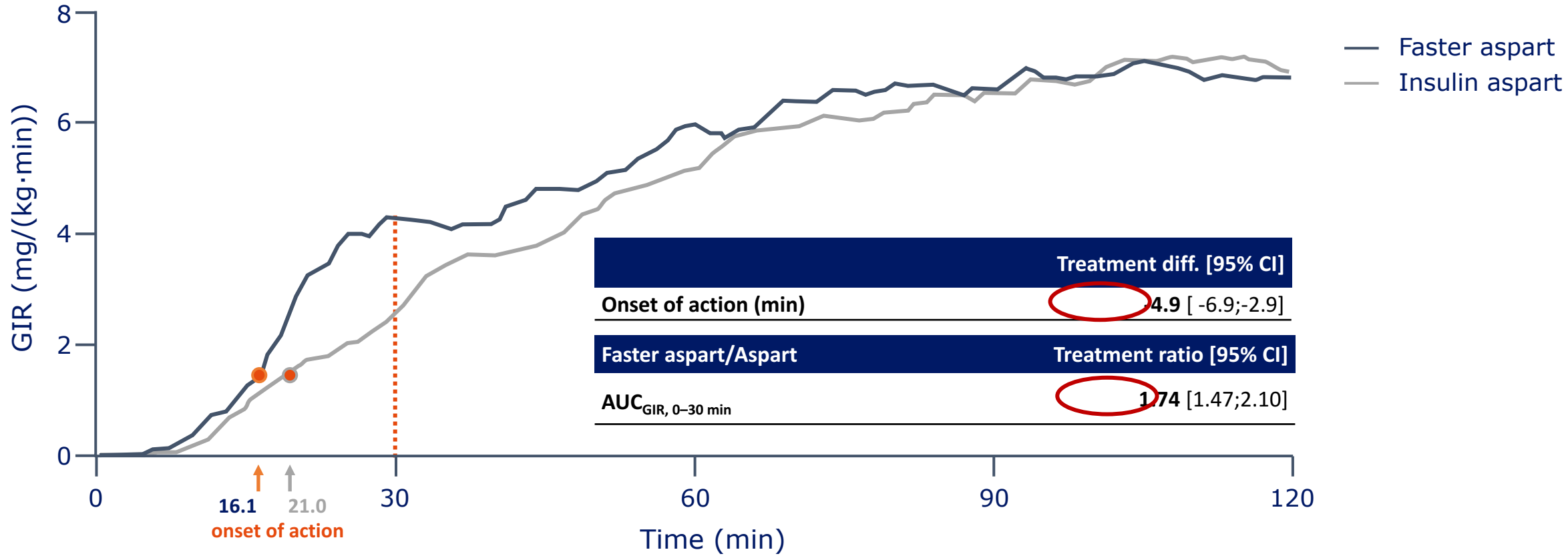
C_{max} ratio p=0.085

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; IAsp, insulin aspart

Heise T et al. *Diabetes* 2016;65(S1):A239.

PD – Early glucose-lowering effect

Pooled analysis 3 studies



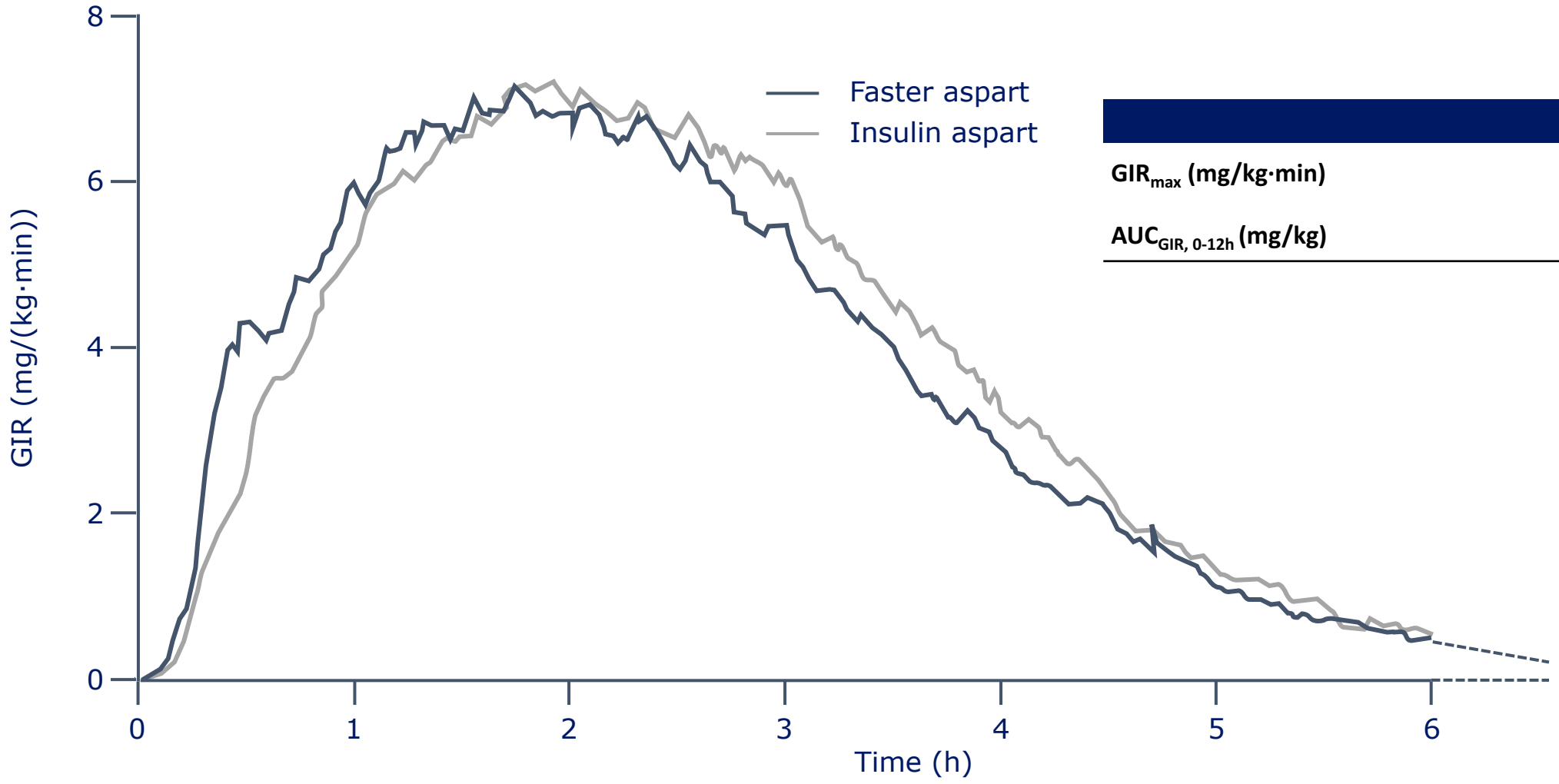
>50% greater insulin action within the first 30 minutes

AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate

Heise T et al. *Diabetes* 2016;65(S1):A239.

PD – Total and Maximum glucose-lowering effect

Pooled analysis 3 studies



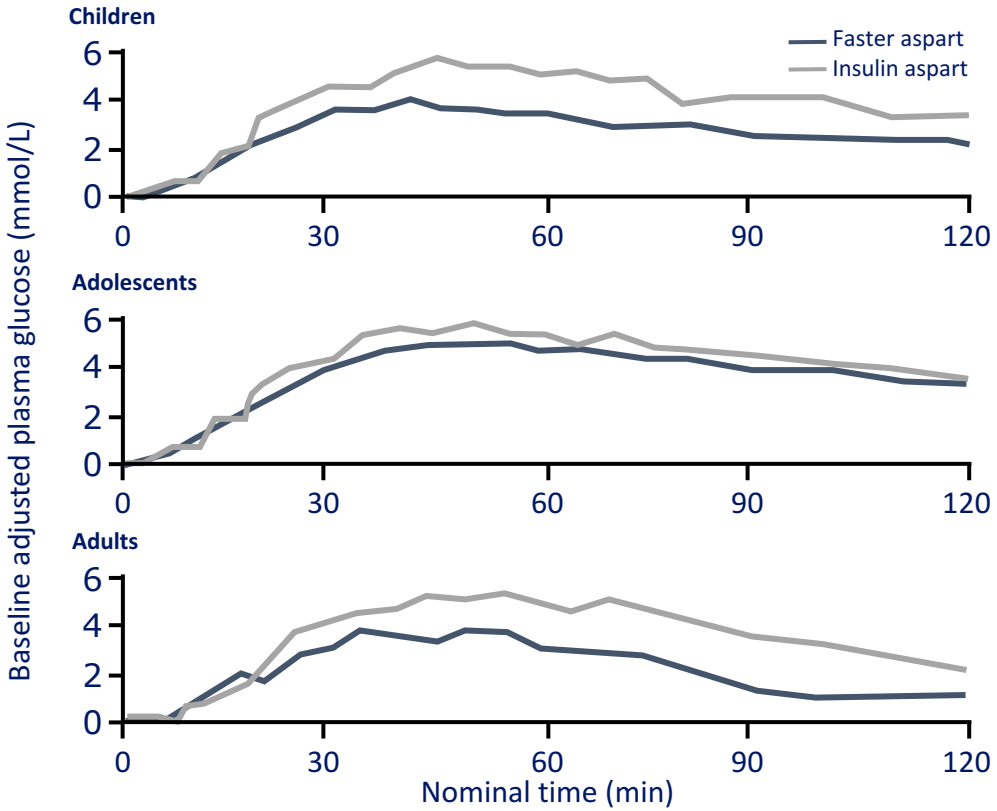
	Ratio [95%CI]
GIR_{max} (mg/kg·min)	**1.01** [0.96;1.05]
$AUC_{GIR,\ 0\text{-}12h}$ (mg/kg)	**0.98** [0.94;1.03]

AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate

Heise T et al. *Diabetes* 2016;65(S1):A239.

Significantly greater glucose-lowering effect in children with faster aspart vs. insulin aspart

Mean baseline-adjusted plasma glucose profiles for faster aspart and insulin aspart across the three age groups



Meal test

Change in PG (mmol/L)	Faster aspart	Insulin aspart	Treatment difference [95% CI]
$\Delta PG_{av,0–1h}$	2.54	3.72	**–1.18** [–1.93; –0.43]
$\Delta PG_{av,0–2h}$	2.53	4.02	**–1.50** [–2.79; –0.20

Change in PG (mmol/L)	Faster aspart	Insulin aspart	Treatment difference [95% CI]
$\Delta PG_{av,0–1h}$	3.51	3.79	**–0.27** [–0.95; 0.40]
$\Delta PG_{av,0–2h}$	3.90	4.10	**–0.20** [–1.55; 1.15]

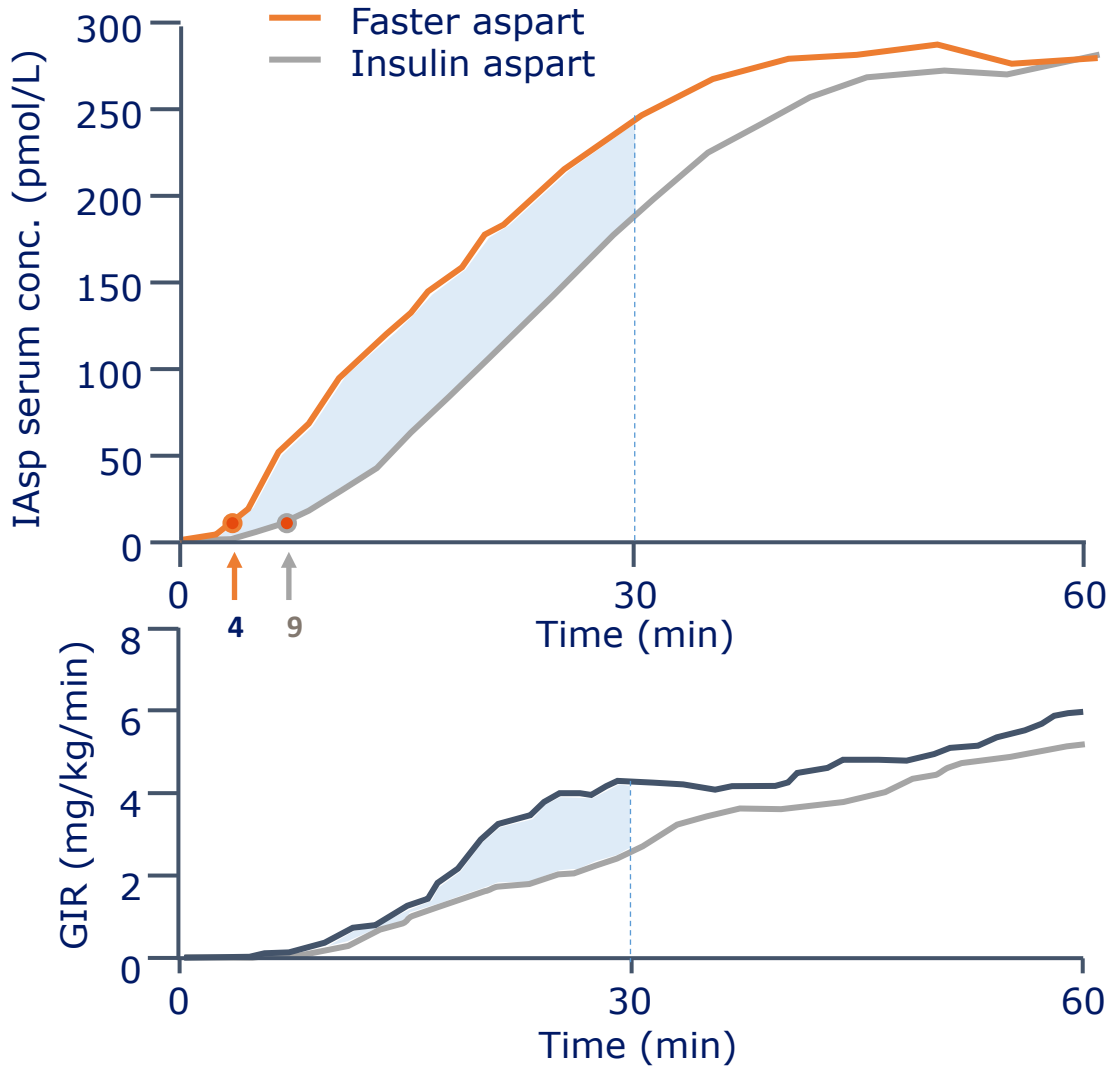
Change in PG (mmol/L)	Faster aspart	Insulin aspart	Treatment difference [95% CI]
$\Delta PG_{av,0–1h}$	2.68	2.99	**–0.31** [–1.48; 0.86]
$\Delta PG_{av,0–2h}$	2.36	2.93	**–0.57** [–1.83; 0.69]

Danne T *et al. Diabetes* 2015;64(Suppl 1):Abstract 976-P

What do we know about faster aspart via s.c. injection (PK/PD)?

Compared with insulin aspart, faster aspart has:

- Twice as fast onset of appearance in the bloodstream
- Two-fold higher insulin exposure within the first 30 min
- >50% greater insulin action within the first 30 min



GIR, glucose infusion rate; IAsp, insulin aspart; SC, subcutaneous

Heise T et al. *Diabetes* 2016;65(S1):A239.


B-D INSULIN SYRINGE
For use with
20 OR 40 UNIT INSULIN


120

Pump data


BOLUS HISTORY
CH: 0 BG:---
MiniMed
ESC
ACT


Had an insulin pump...
Before it was cool.

Comparing faster aspart and insulin aspart in CSII

14-day exploratory crossover trial

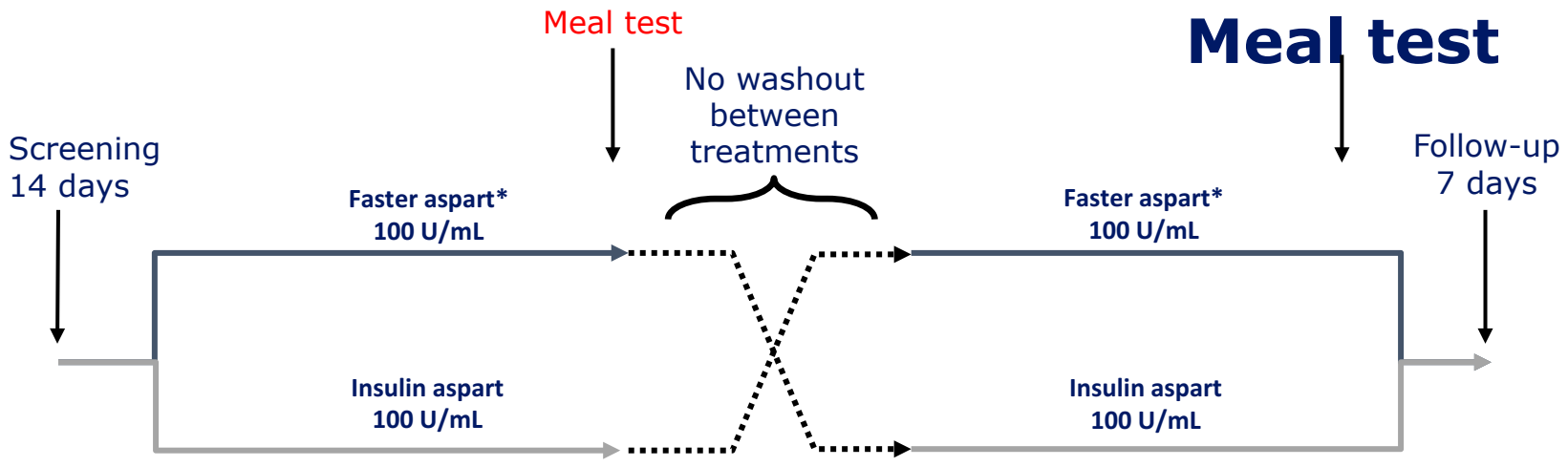
A double-blind, randomised, crossover, active-controlled trial comparing 14 days of continuous subcutaneous insulin infusion (CSII) of faster aspart with CSII of insulin aspart in 43 adults with T1D

Inclusion criteria

- T1D ≥12 months
- Treatment with the same insulin analogue by CSII for the previous 3 months
- Using a MiniMed Paradigm® pump for the previous 6 months
- BMI ≤35.0 kg/m^2
- HbA_{1c} ≤9.0%

Primary endpoint

- Change in PG after 2 h ($\Delta PG_{av,0–2\ h}$)



Standardized Breakfast: liquid meal;
68% carbohydrates, 17% protein, 15% fat

Meal test consisted of a standardised liquid meal

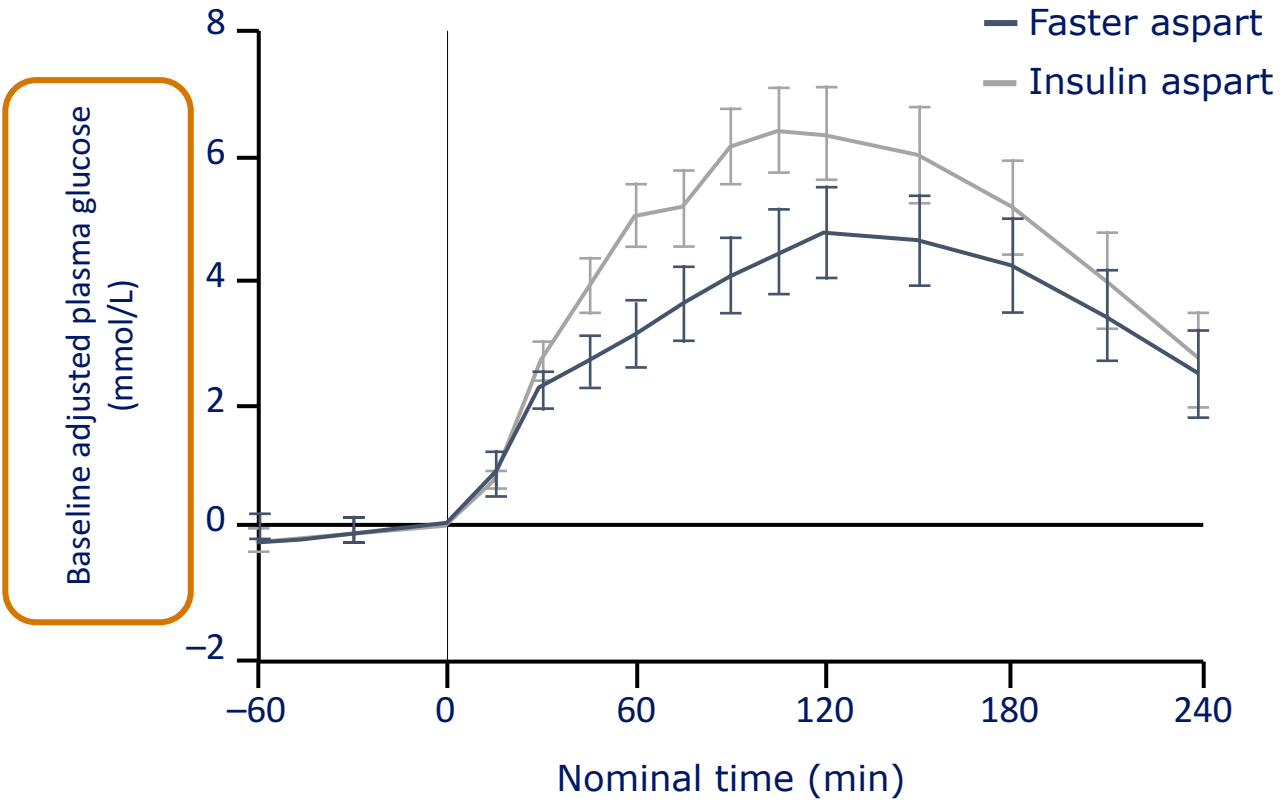
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; PG, plasma glucose; T1D, type 1 diabetes

Bode B *et al. Diabetes* 2015;64(S1):Abstract 994-P

PPG after standardised meal test

Improved PPG after a meal test in CSII with faster aspart vs. insulin aspart

Mean baseline adjusted PG profiles



Meal test PG profiles

	Difference [95% CI]	*P* value
$\Delta PG_{av,0–2h}$ (mmol/L) (mg/dL)	–0.99 (–1.95; –0.03) –17.8 (–35.2; –0.46)	0.044
$\Delta PG_{av,0–1h}$ (mmol/L) (mg/dL)	–0.50 (–1.07; 0.07) –9.0 (–19.3; 1.26)	0.084

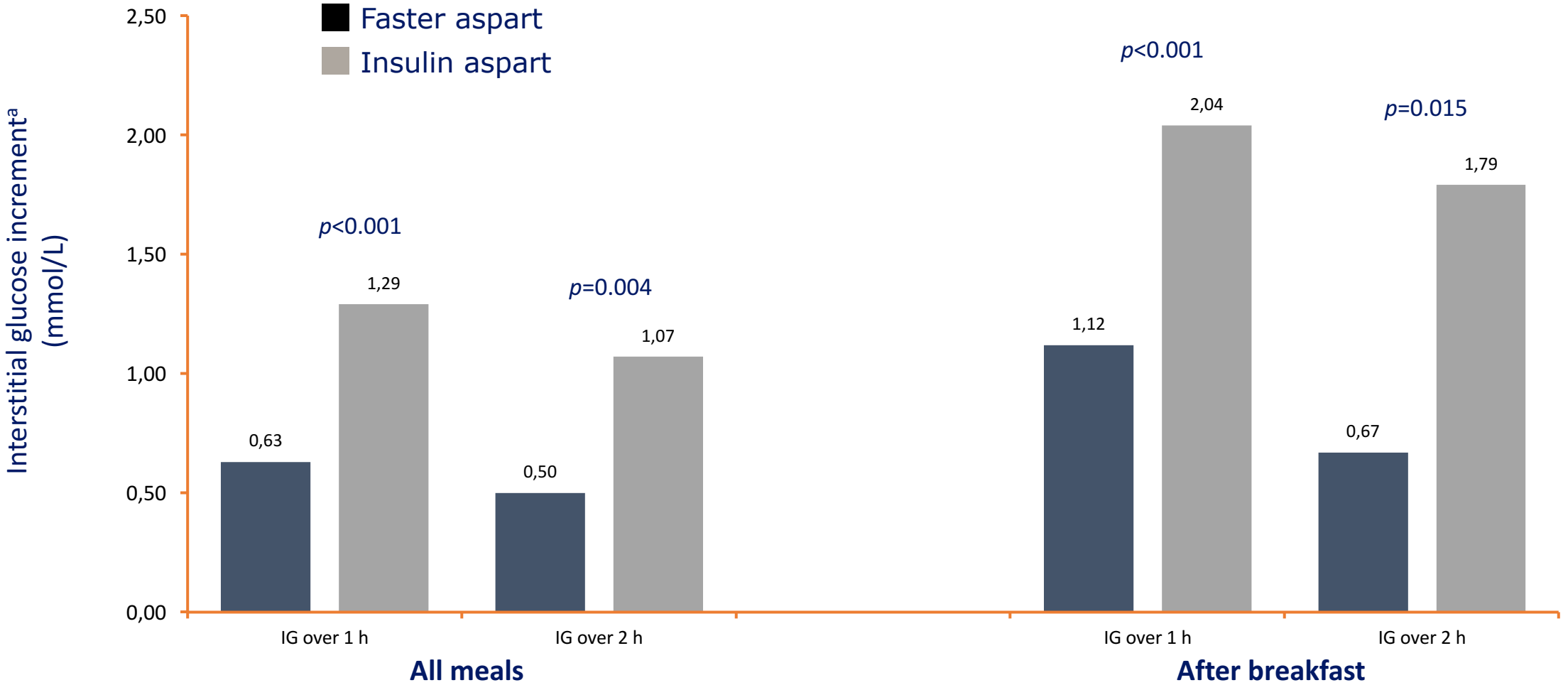
Faster aspart showed a significantly greater post-meal glucose-lowering effect after a standardised meal test with regard to 2-hour PPG response

[a]Error bars represent standard error of the mean. $\Delta PG_{av,0–2h}$ was calculated as $AUC_{PG,0-2h}/2h – PG_{Pre-dose}$ where $AUC_{PG,0-2h}$ was the area under the PG concentration time profile based on observed values and actual measurement times in relation to time of injection between 0 and 2 hours.

AUC, area under the curve; CI, confidence interval; PG, plasma glucose; PPG, post-prandial plasma glucose

Bode B *et al. Diabetes* 2015;64(S1):Abstract 994-P.

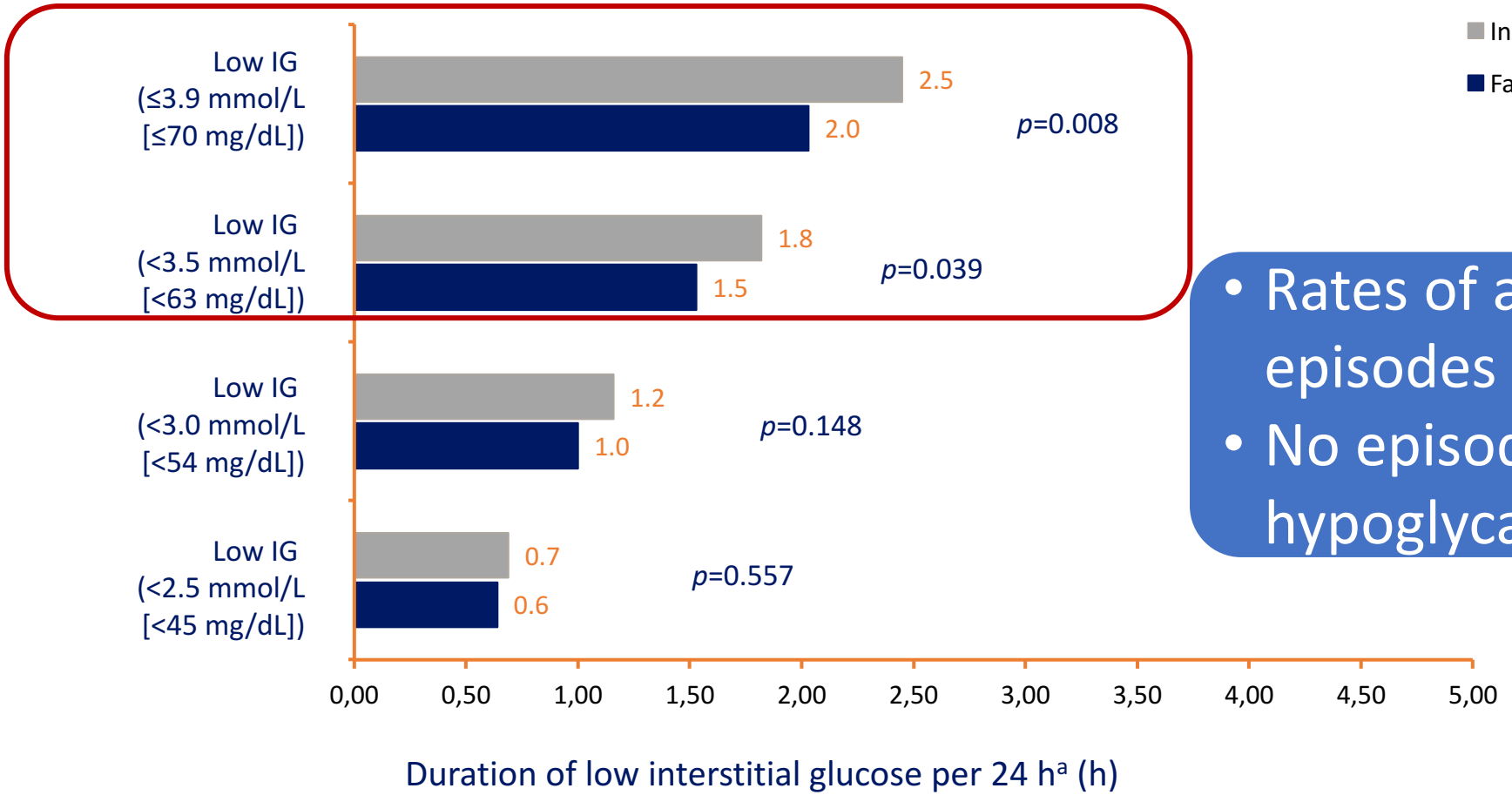
Post-prandial IG increments after 1 and 2 hours



[a]LSMean values were obtained using a mixed model with treatment and period as fixed effect and subject as a random effect. Meal characteristics were derived for 4 hours after meal. The mean IG profile was derived from measurements across all 14 days of treatment. IG, interstitial glucose; LSMean, least-squares mean

Bode B *et al. Diabetes* 2015;64(S1):Abstract 994-P.

Duration of low IG over 14 days



- Rates of all hypoglycaemic episodes per day were similar
- No episodes of severe hypoglycaemia

[a]LS mean values were obtained by a mixed model with treatment and period as fixed and subject as a random effect; corresponding 95% CIs were derived from this model. CI, confidence interval; IG, interstitial glucose

Bode B *et al. Diabetes* 2015;64(S1):Abstract 994-P.

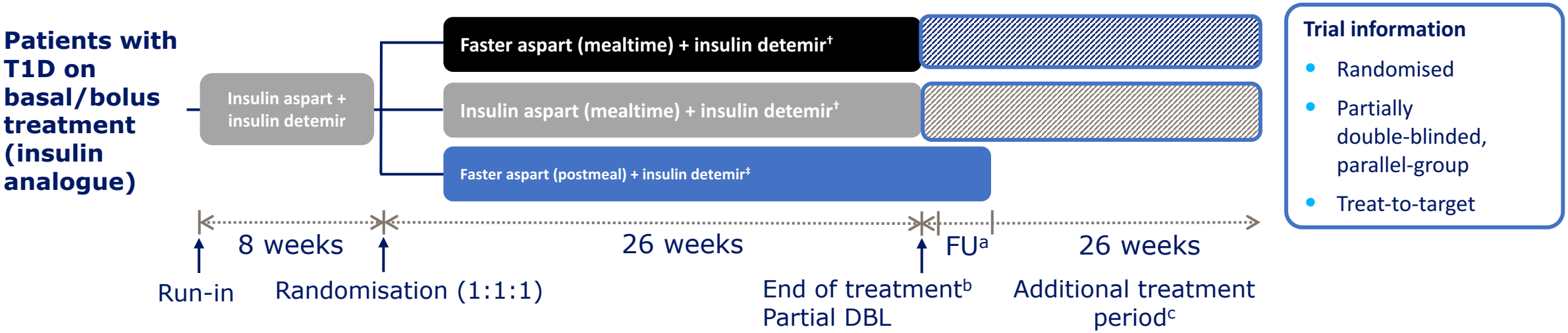
Phase 3a onset® programme

Efficacy and safety of faster-acting insulin aspart (faster aspart) compared with insulin aspart, both in combination with insulin detemir in adults with type 1 diabetes

NN1218-3852 (onset® 1)

This deck contains the results from the initial 26 weeks of treatment. This deck does not include results from the 3852 26-week additional treatment period

onset® 1: Trial design



Trial information

- Randomised
- Partially double-blinded, parallel-group
- Treat-to-target

Key inclusion criteria

- T1D ≥12 months
- Male or female ≥18 years
- Basal–bolus insulin ≥12 months
- Insulin detemir or insulin glargine U100 ≥4 months
- HbA_{1c} 7.0–9.5% (53–80 mmol/mol)
- BMI ≤35.0 kg/m^2

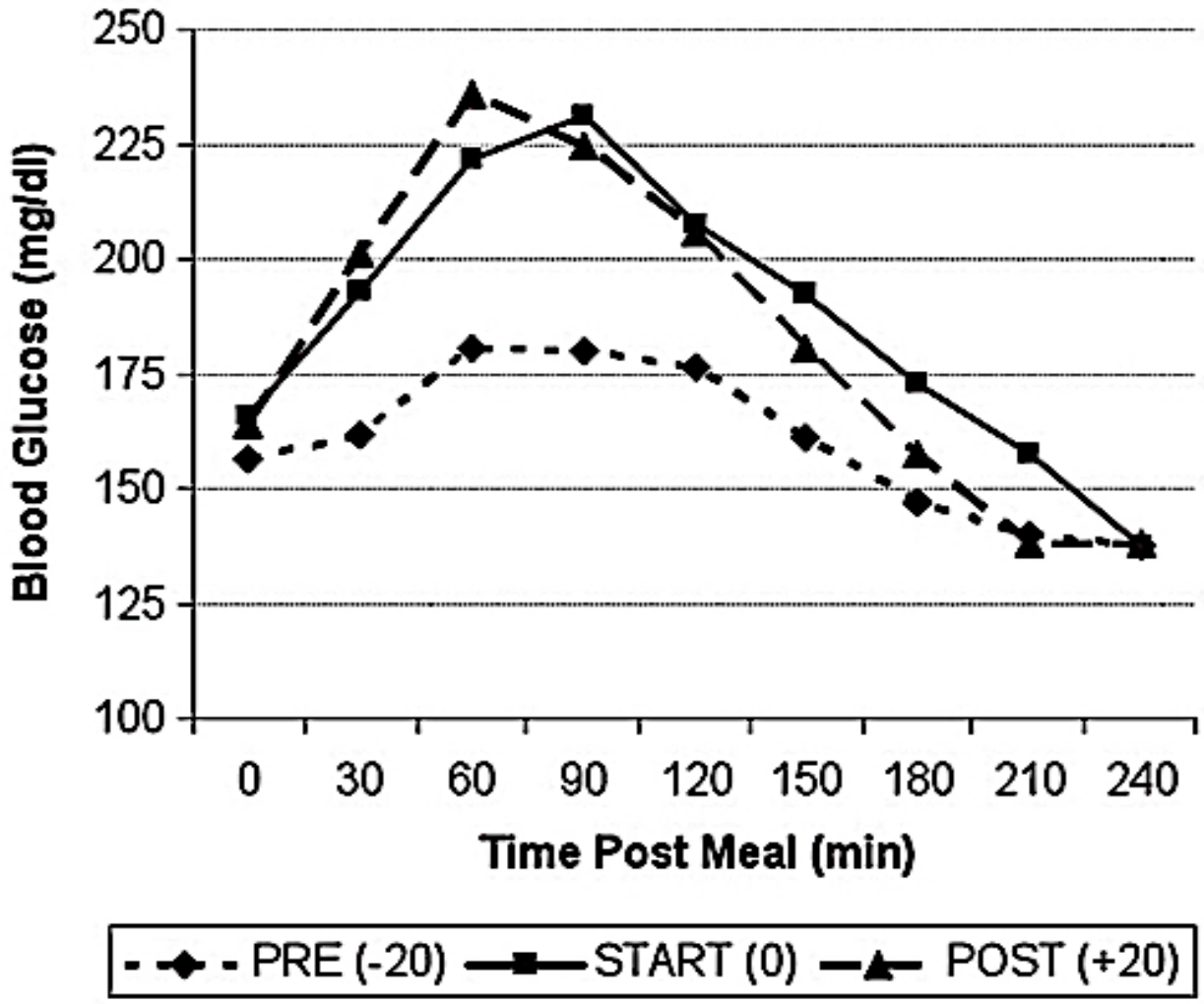
Key endpoints

- Change in HbA_{1c} from baseline at 26 weeks
- PPG regulation (based on meal test)
- Body weight regulation
- Number of hypoglycaemic episodes
- Number of treatment-emergent AEs

†Double-blind arm; ‡Open-label arm; aFollow-up (7–30 days). bPrimary endpoint. cResults from the additional treatment period will not be presented here
AE, adverse event; BMI, body mass index; CGM, continuous glucose monitoring; DBL, database lock; FU, follow-up; HbA_{1c}, glycosylated haemoglobin; PPG, postprandial plasma glucose; T1D, type 1 diabetes

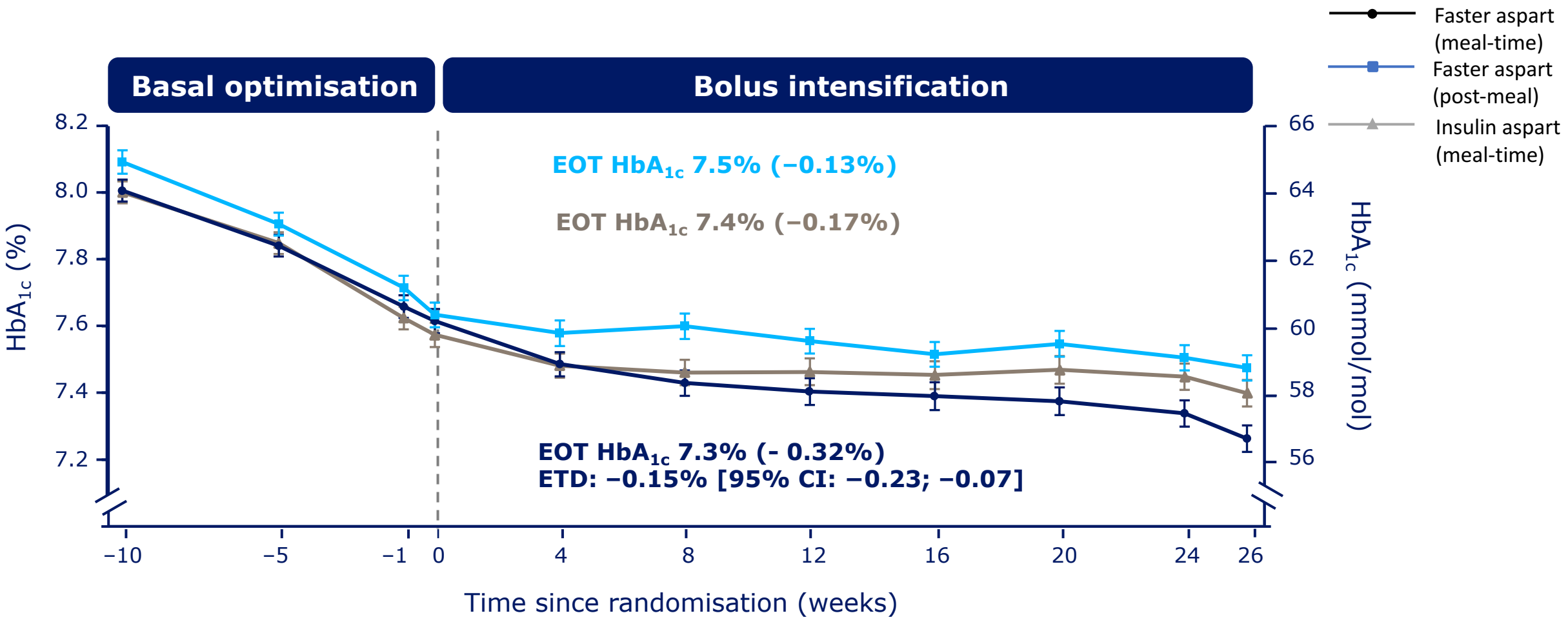
Russell-Jones D *et al*. *Diabetes* 2016;65(S1):A77

Timing of Meal Insulin Boluses to Achieve Optimal Postprandial Glycemic Control in Patients with Type 1 Diabetes



DIABETES TECHNOLOGY & THERAPEUTICS Volume 12, Number 3, 2010

Onset® 1: mean HbA_{1c} over time



Error bars: ± standard error (mean)
EOT, end of treatment

Russell-Jones *et al. Diabetes* 2016;65(Suppl. 1):A77

Summary

Faster aspart: onset® 1 efficacy

Faster aspart effectively improved glycaemic control in patients with T1D*

- Non-inferiority to insulin aspart was confirmed regarding HbA_{1c} change from baseline for both mealtime* and postmeal* administration
- Reduction in HbA_{1c} statistically significantly larger with faster aspart (mealtime)[a]

A statistically significant benefit in 2-hour PPG increment (meal test) was also confirmed for faster aspart (mealtime)*

- A statistically significant difference was demonstrated for 1-hour PPG increment (meal test) in favour of faster aspart (mealtime)

Russell-Jones *et al. Diabetes* 2016;65(Suppl. 1):A77

*Compared with insulin aspart (mealtime), [a] This statistical analysis was not part of the confirmatory strategy
T1D, type 1 diabetes; HbA_{1c}, glycosylated haemoglobin; PPG, postprandial plasma glucose

Summary

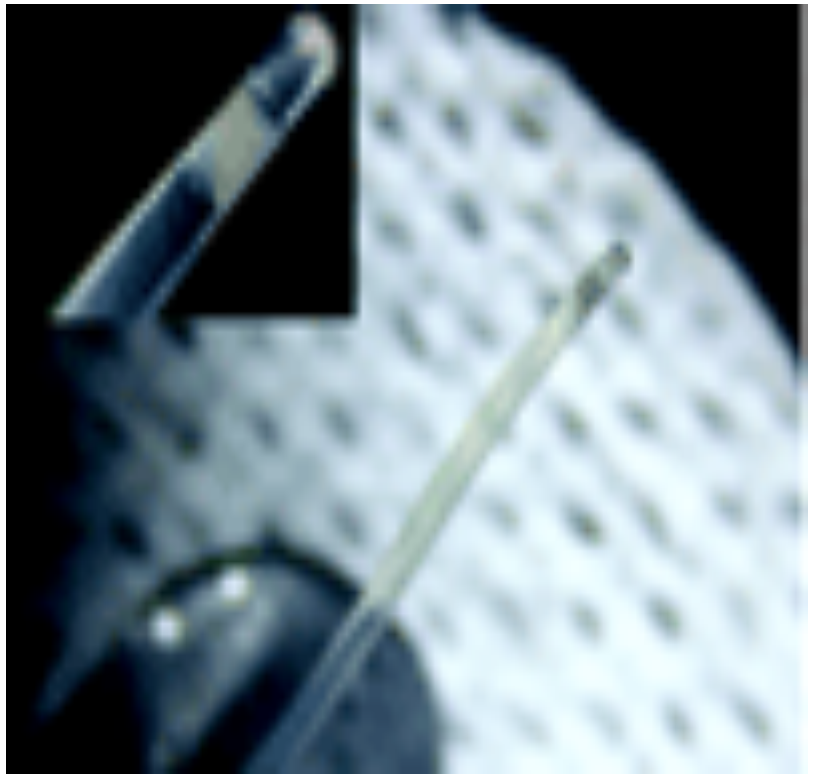
Faster aspart: onset® 1 safety

No statistical significant difference was seen in overall rate of severe or BG-confirmed hypoglycaemic episodes

- The rate during the first hour after the start of a meal (small fraction of the overall events) was statistically significantly higher for faster aspart (mealtime)

The overall safety profile for faster aspart and insulin aspart was similar and as expected for insulin aspart

Russell-Jones *et al. Diabetes* 2016;65(Suppl. 1):A77



Pump compatibility trial (faster aspart vs insulin aspart)

onset® 4

onset® 4 trial design

Conclusions

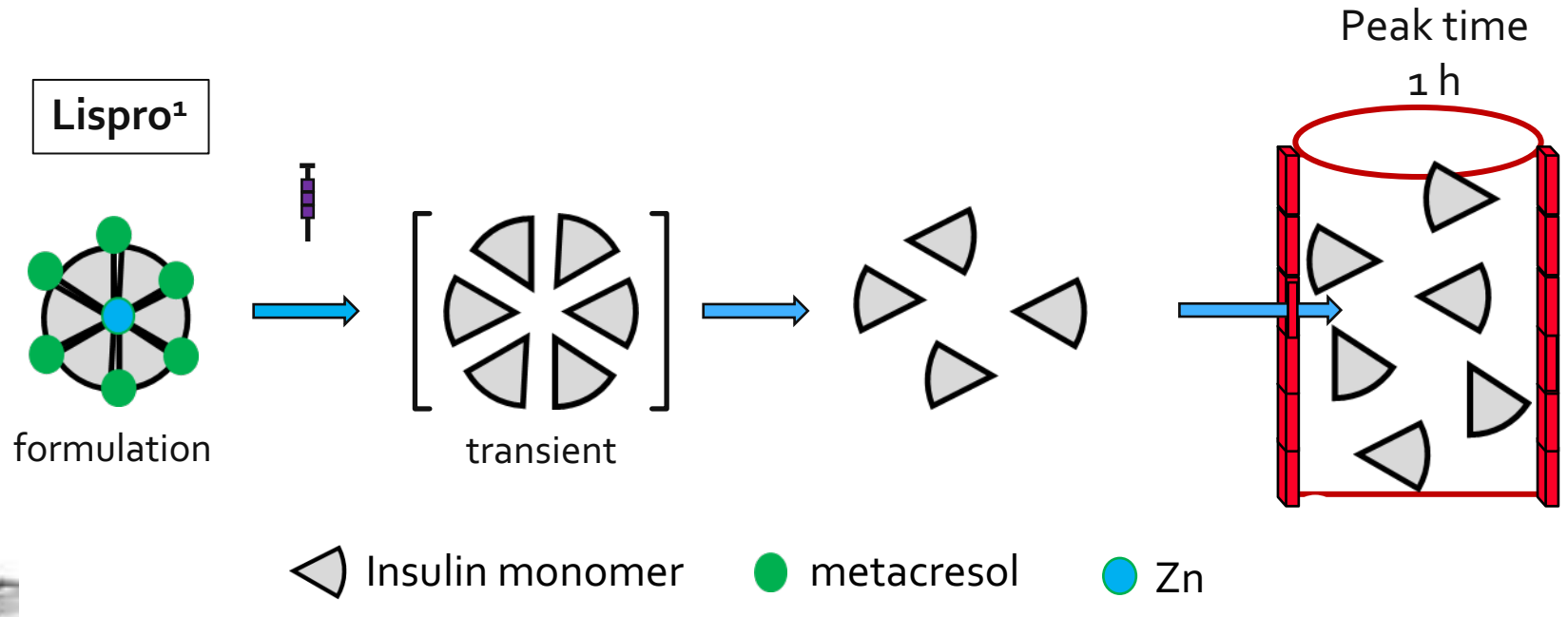
- **Primary endpoint achieved: no differences in pump compatibility as assessed by microscopically confirmed infusion set occlusions**.
- The estimated mean change in HbA_{1c} from baseline to Week 6 favored faster aspart, but was not statistically significantly different from IAsp in this small-scale, short-term trial (estimated treatment difference [ETD]: –0.14% [95% CI: –0.40; 0.11]).
- Treatments equally effective in controlling blood glucose levels
- No serious adverse events
- Both treatments appeared to have safe profiles with no unexpected adverse events

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycosylated haemoglobin; T1D, type 1 diabetes.
Zijlstra *et al.* Endocrine Society's 98th Annual Meeting and Expo, 2016: FRI-697.

Towards an ultra-rapid insulin

- [1]Ciczak E et al. Structure 1995; 3:615-622

BioChaperone® Lispro (Adocia) is a modified dextran molecule designed for fast absorption.



- BioChaperone: Small oligosaccharide-based molecule developed as a new excipient.
- BioChaperone Lispro remains hexameric in the vial.
- BioChaperone accelerates insulin lispro absorption as seen in previous clinical studies.

Trial objectives

- Primary objective
  - To compare the postprandial BG control after administration of BC Lispro and Humalog® in patients with type 1 diabetes
- Secondary objectives
  - To compare the postprandial pharmacokinetic (PK) profiles of BC Lispro and Humalog® after a standardised meal
- Safety objectives
  - To assess and compare the safety and tolerability of BC Lispro and Humalog®

Trial design

- Single centre, double-blind, randomised, single-dose, two-period cross-over study

- Standardised liquid meal (Ensure Plus®, 400 mL):
  600 kcal; 80 g carbohydrates; 25 g proteins; 20 g fat
- Pre-meal blood glucose stabilisation at 100 mg/dL with iv insulin glulisine or glucose
- No basal insulin during the meal
- Treatments:
  - BioChaperone (BC) Lispro U100 at 0.2 U/kg at meal time
  - Humalog U100 at 0.2 U/kg at meal time

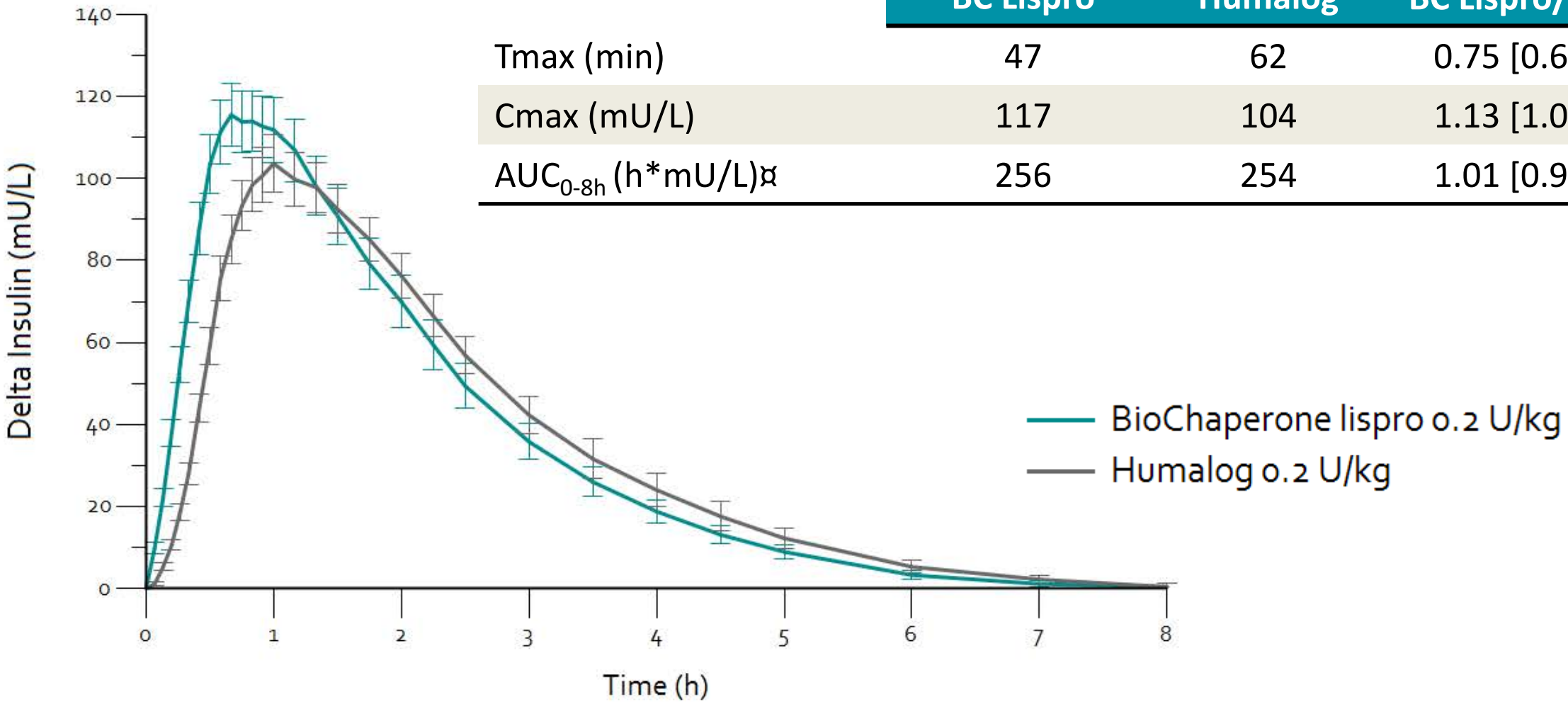
Trial population

- 38 patients with T1DM for at least 36 completers, no drop-out

Demographics	Mean (± SD)
Age (years)	44 ± 13
Diabetes Duration (years)	23 ± 9
BMI (kg/m^2)	25.0 ± 1.8
Body weight (kg)	81.0 ± 9.6
HbA1c (%)	7.4 ± 0.9
C-peptide (nmol/L)	0.04 ± 0.03

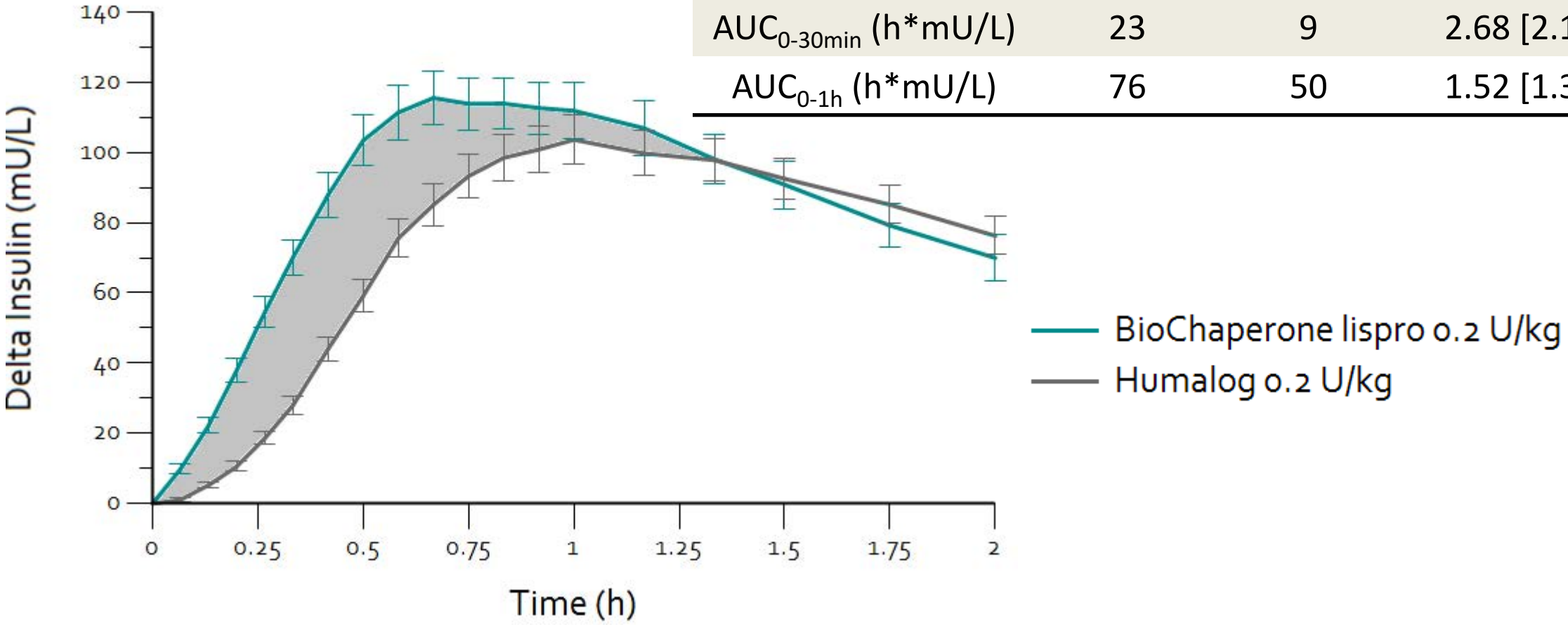
Shorter Tmax, higher Cmax and similar exposure

	GeoLSM BC Lispro	GeoLSM Humalog	Ratio [95% CI] BC Lispro/Humalog
Tmax (min)	47	62	0.75 [0.69; 0.83]
Cmax (mU/L)	117	104	1.13 [1.06; 1.20]
$AUC_{0\text{-}8h}$ (h*mU/L)¤	256	254	1.01 [0.97; 1.05]

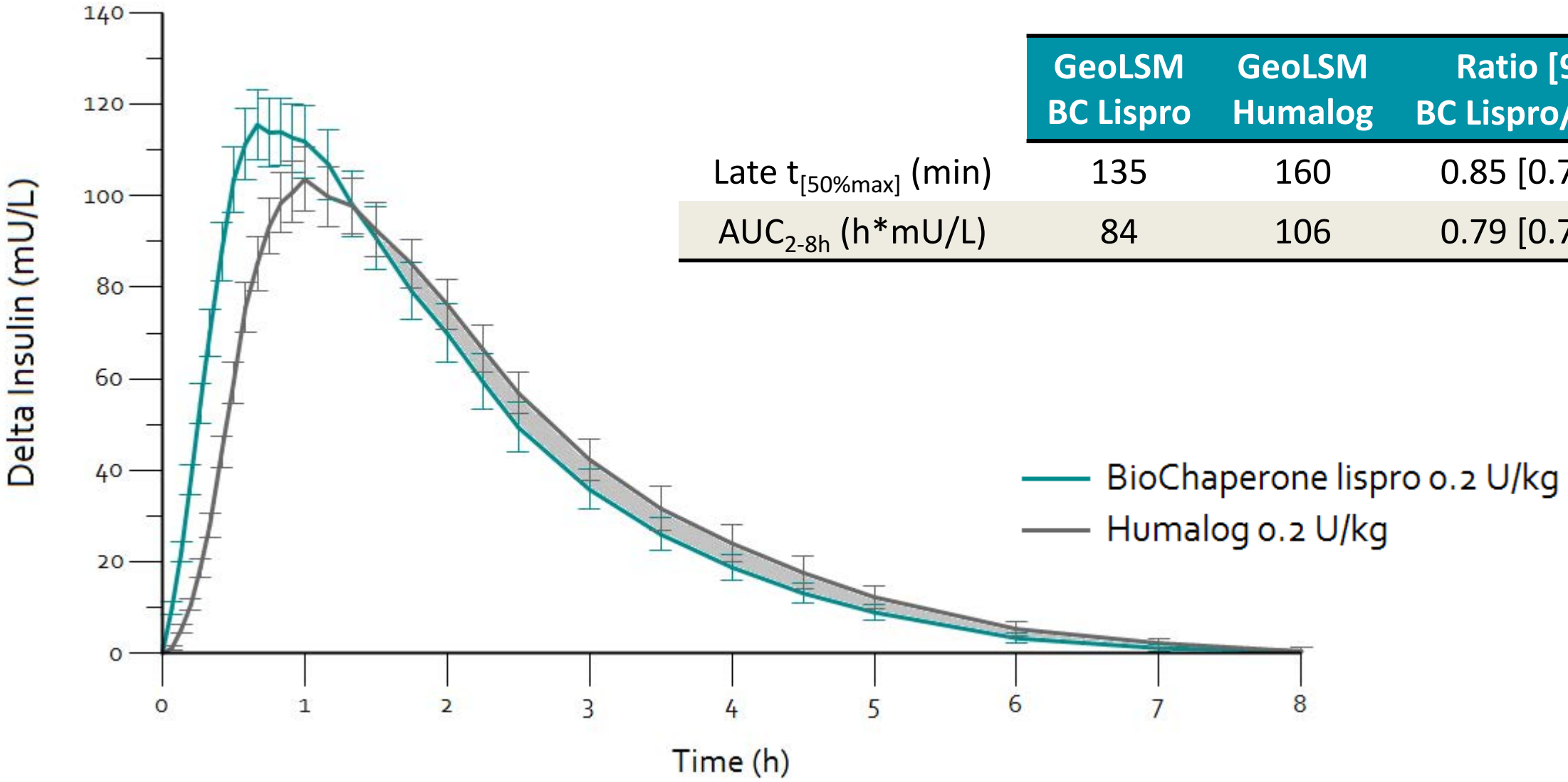


Greater earlier exposure: Faster-In

	GeoLSM BC Lispro	GeoLSM Humalog	Ratio [95% CI] BC Lispro/Humalog
Early $t_{[50\%max]}$ (min)	18	29	0.63 [0.57; 0.70]
$AUC_{0\text{-}30min}$ (h*mU/L)	23	9	2.68 [2.18; 3.30]
$AUC_{0\text{-}1h}$ (h*mU/L)	76	50	1.52 [1.37; 1.67]



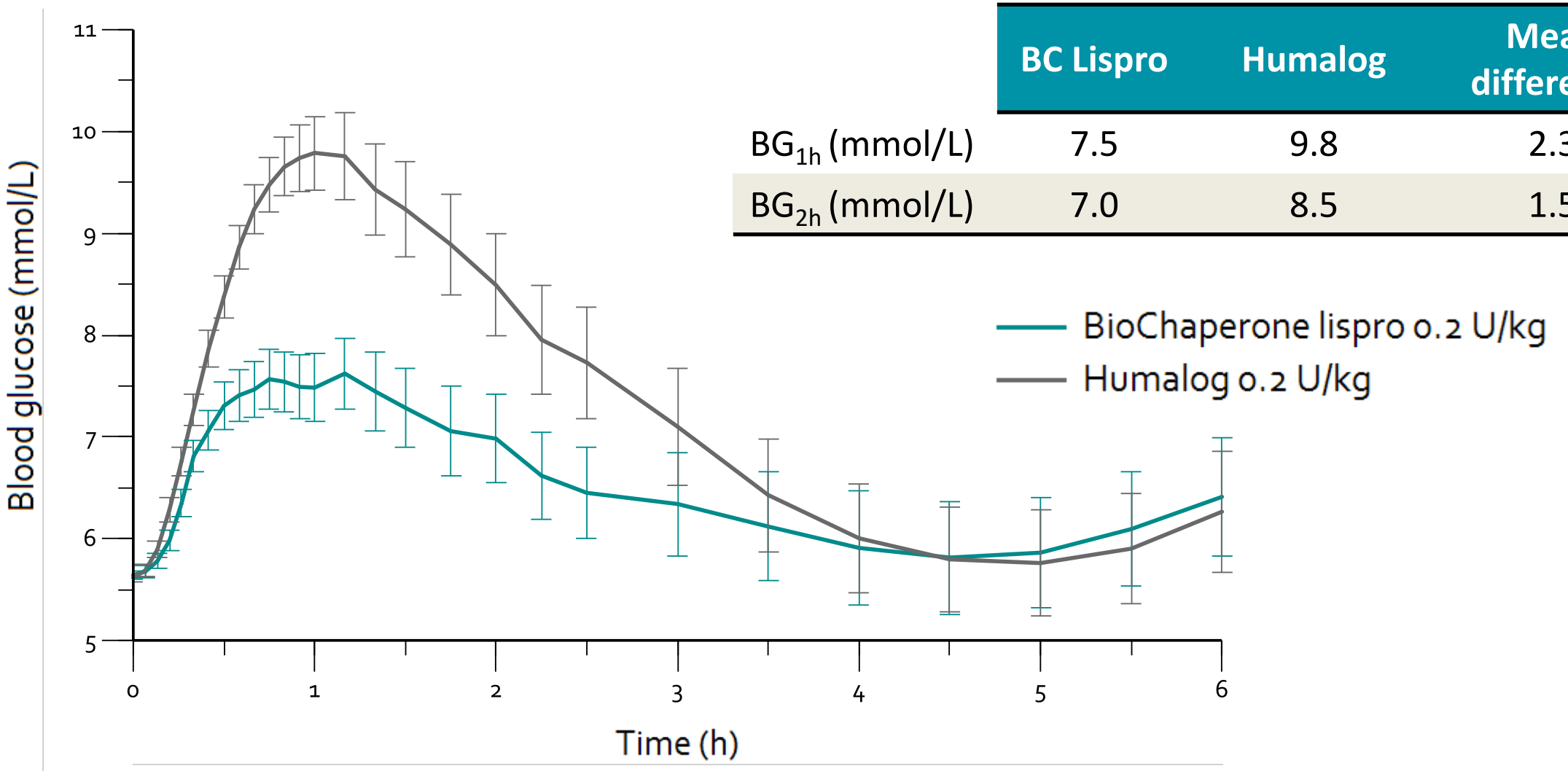
Lower late exposure: Faster-out



	GeoLSM BC Lispro	GeoLSM Humalog	Ratio [95% CI] BC Lispro/Humalog
Late $t_{[50\%max]}$ (min)	135	160	0.85 [0.78; 0.91]
$AUC_{2\text{-}8h}$ (h*mU/L)	84	106	0.79 [0.72; 0.87]

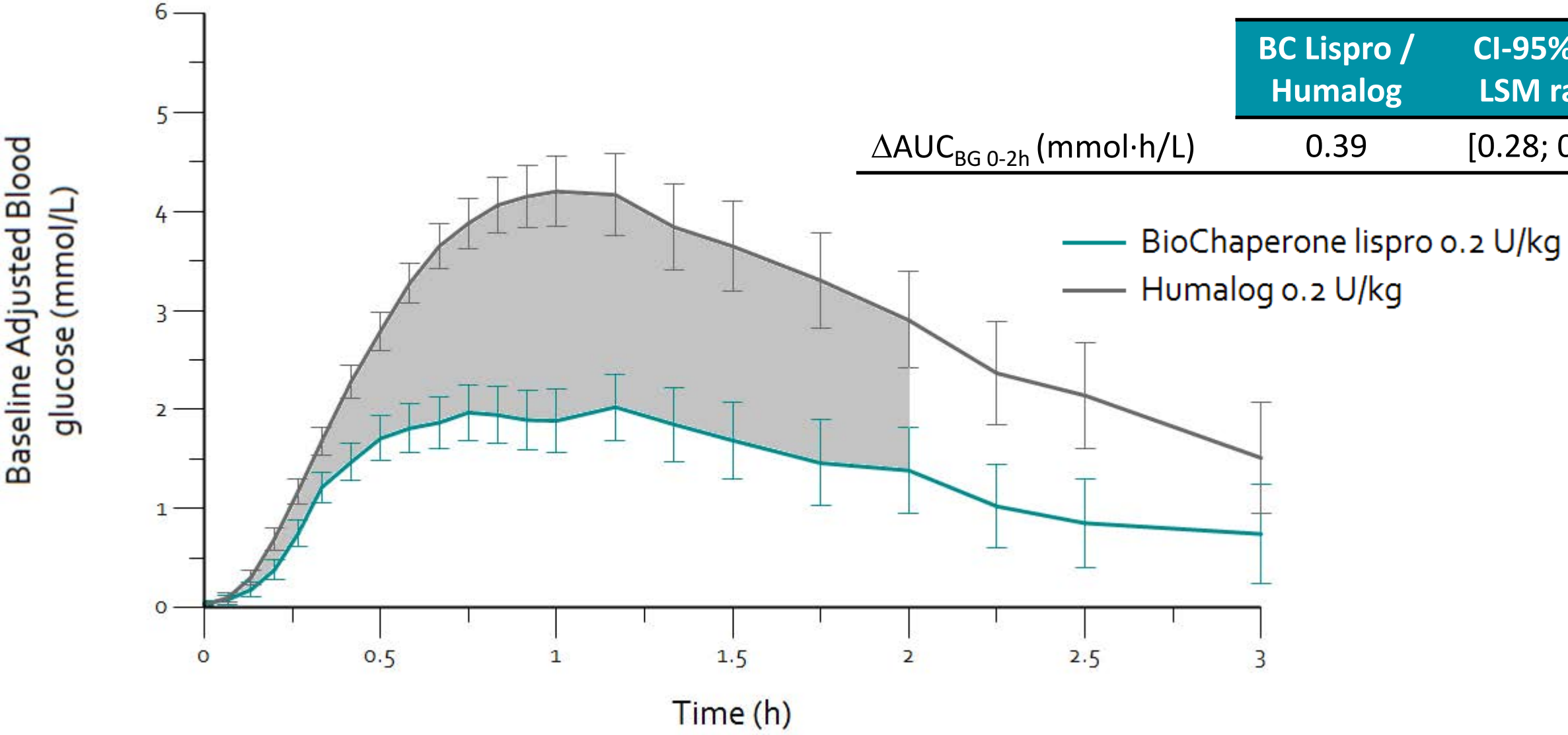
Better post-prandial glucose control

	BC Lispro	Humalog	Mean difference
BG_{1h} (mmol/L)	7.5	9.8	2.3
BG_{2h} (mmol/L)	7.0	8.5	1.5



Reduced blood glucose excursions

	BC Lispro / Humalog	CI-95% for LSM ratio
$\Delta AUC_{BG\ 0\text{-}2h}$ (mmol·h/L)	0.39	[0.28; 0.52]



Summary

BioChaperone Lispro in comparison with Humalog showed:

- Faster absorption
  - Faster-in (Early $t_{[50\%max]}$, t_{max}, $AUC_{0\text{-}30min}$)
  - Faster-out (Late $t_{[50\%max]}$, $AUC_{2\text{-}8h}$)
- Similar total exposure
- Reduced post prandial glucose excursions
  - 61% PPG reduction over the first two hours
  - Reduction of blood glucose by 42 mg/dL at 1 hour
- Similar safety profile at single dose conditions based on local tolerance and number of hypoglycemic events

- Comprehensive work to further evaluate BioChaperone Lispro ongoing, including a concentrated U200 formulation

PD Results

	LSM BC Lispro	LSM Humalog	Ratio [95% CI] BC Lispro/Humalog	p value
$\Delta AUC_{BG,0\text{-}30min}$ [mmol·h/L]	0.25	0.51	0.49 [0.34; 0.71]	0.0004
ΔAUCBG,0-1h [mmol·h/L]	0.96	2.26	0.42 [0.33; 0.55]	<.0001
ΔAUCBG,0-3h [mmol·h/L]	1.22	4.89	0.25 [0.13; 0.49]	0.0002
ΔAUCBG,0-8h [mmol·h/L]	4.53	7.88	0.58 [0.34; 0.97]	0.04

Future directions … overcome new ultra-fast insulin ?

- VIAject: VIAject® (LinjetaTM; Biodel Inc.) is an ultra-fast insulin formulation with significantly faster absorption than either RHI or insulin lispro. VIAject uses ethylenediaminetetra-acetic acid (EDTA) to chelate zinc and, therefore, destabilize insulin hexamers.
- Technosphere insulin: Technosphere® insulin (Afrezza® , MannKind Corporation) is an inhaled preparation consisting of insulin adsorbed on to microparticles
- Site-warming devices: InsuPatchTM; Insuline Medical Ltd , InsuPad®; Insuline Medical Ltd
- Administration via intradermal microneedles: Intradermal (ID) administration could enable faster insulin absorption because of the skin's greater vascularity, in comparison with the SC space, Currently, there are no ID micro- needles available on the market

Expert Rev. Med. Devices 13(1), 57–69 (2016)

INSULINE BASALI

- DEGLUDEC
- GLARGINE U300

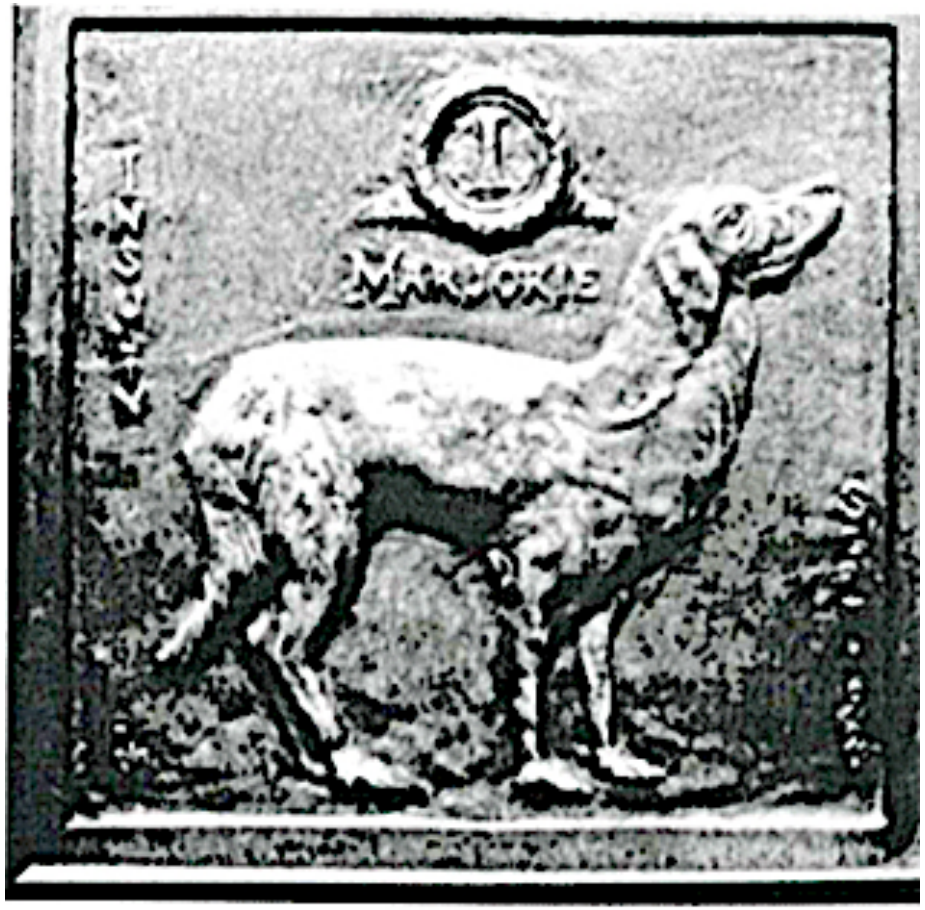
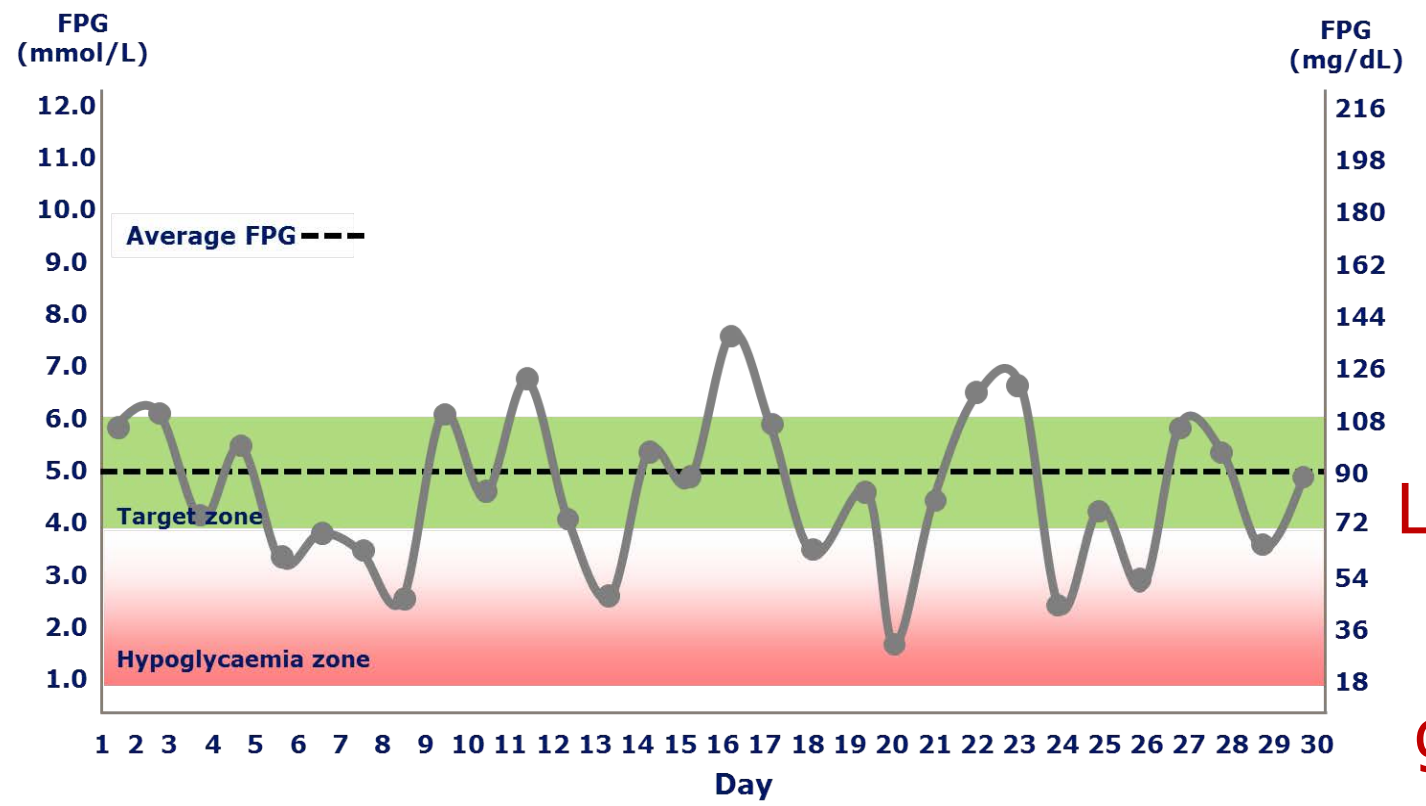
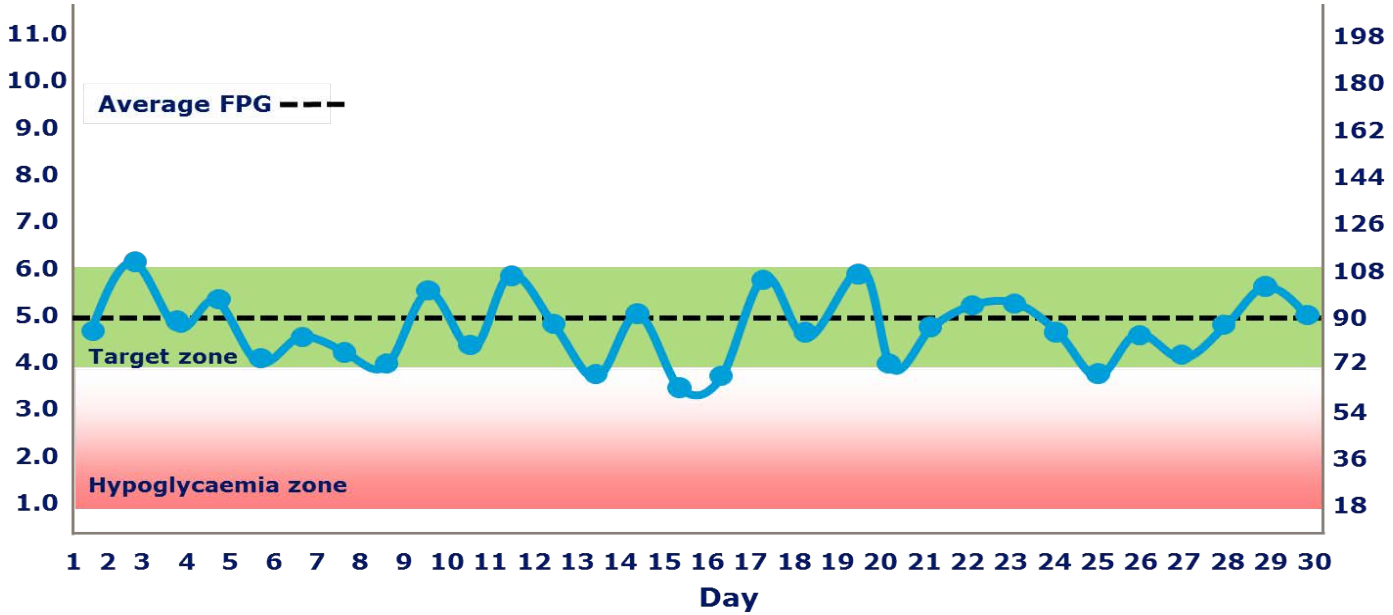


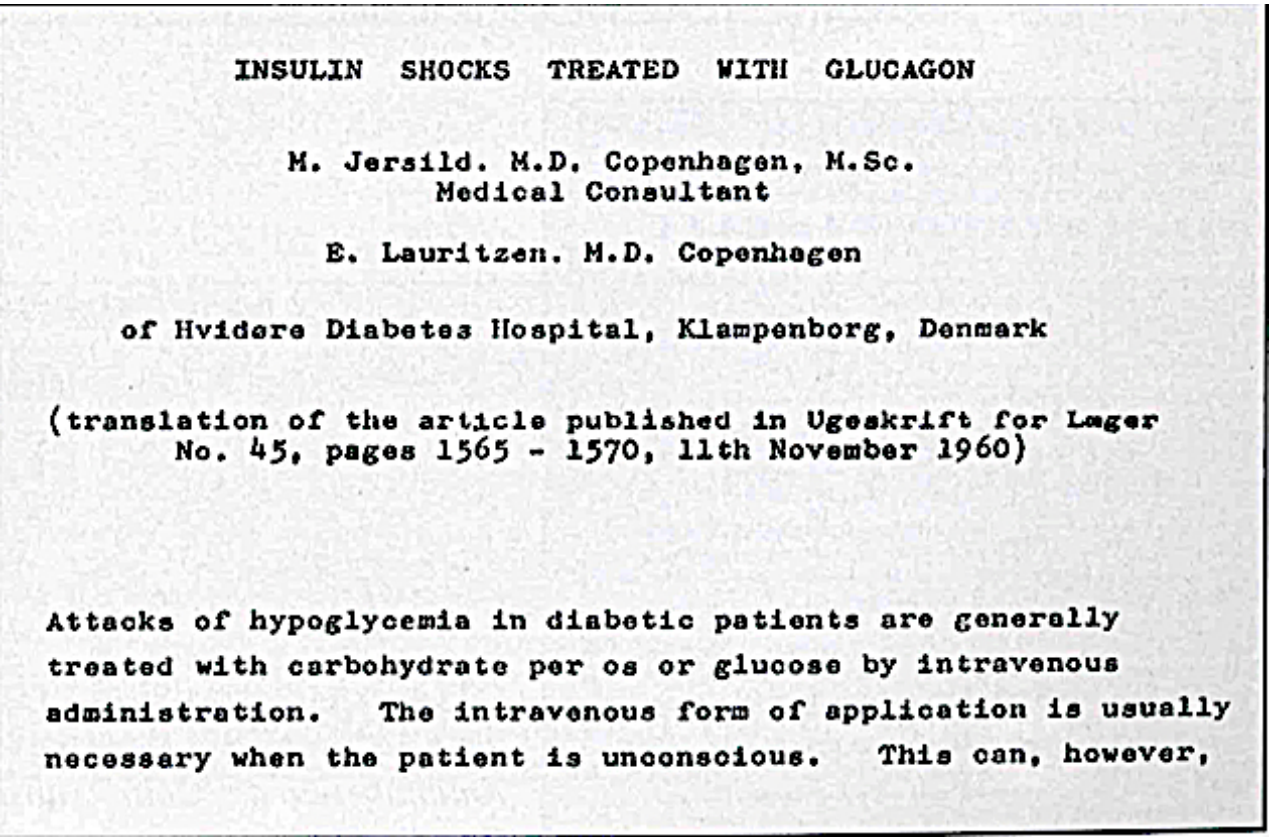
***Fig. 4** - Bassorilievo di Marjorie, opera di ignoto artista americano. Il modello fu conservato da Best nel suo studio a Toronto.*





L'insulina basale ideale deve abbassare la glicemia media riducendo la variabilità glicemica

Paura dell'Ipoglicemia



INSULIN SHOCKS TREATED WITH GLUCAGON

M. Jersild. M.D. Copenhagen, M.Sc.
Medical Consultant

E. Lauritzen. M.D. Copenhagen

of Hvidøre Diabetes Hospital, Klampenborg, Denmark

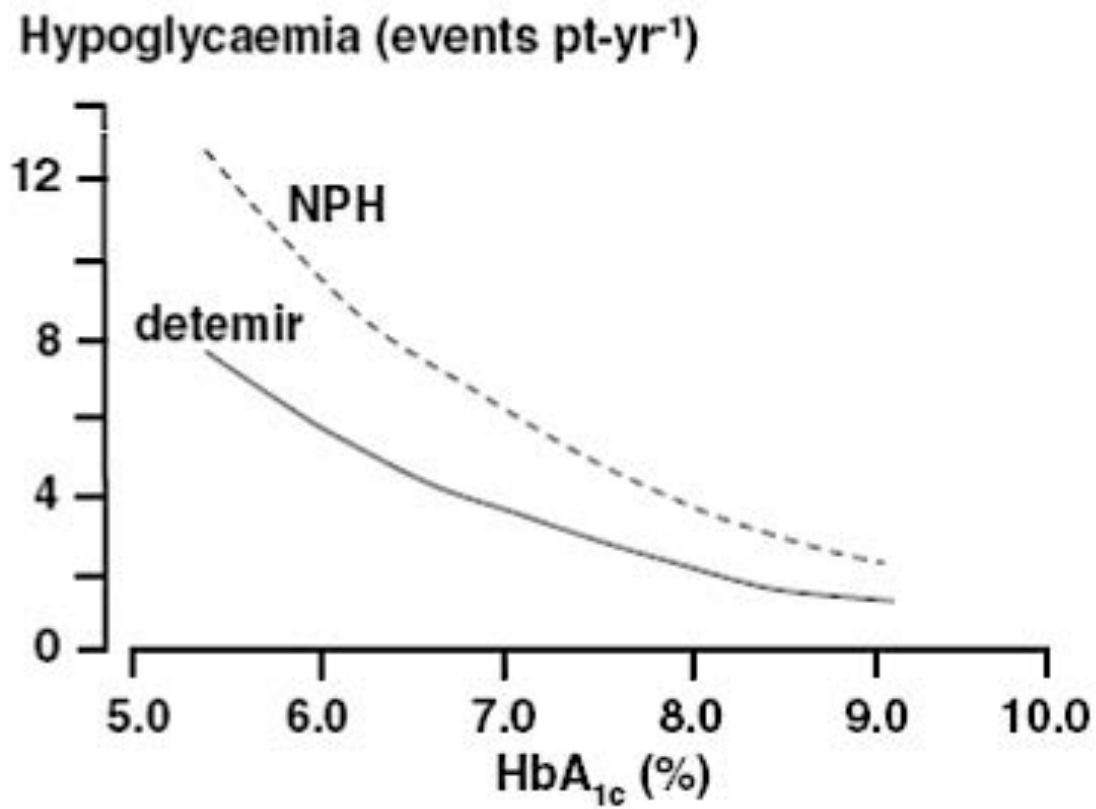
(translation of the article published in Ugeskrift for Læger No. 45, pages 1565 - 1570, 11th November 1960)

Attacks of hypoglycemia in diabetic patients are generally treated with carbohydrate per os or glucose by intravenous administration. The intravenous form of application is usually necessary when the patient is unconscious. This can, however,

- Indagine condotta su pazienti con DMT1 e DMT2:
  - 1/3 degli intervistati dichiara di aver maggior paura dell'ipo dopo un episodio lieve/moderato
  - 2/3 dei portatori di DMT1 e l'80% dei portatori di DMT2 dopo ipo severa sviluppavano paura
  - Atteggiamento più frequente: autoriduzione della dose di insulina

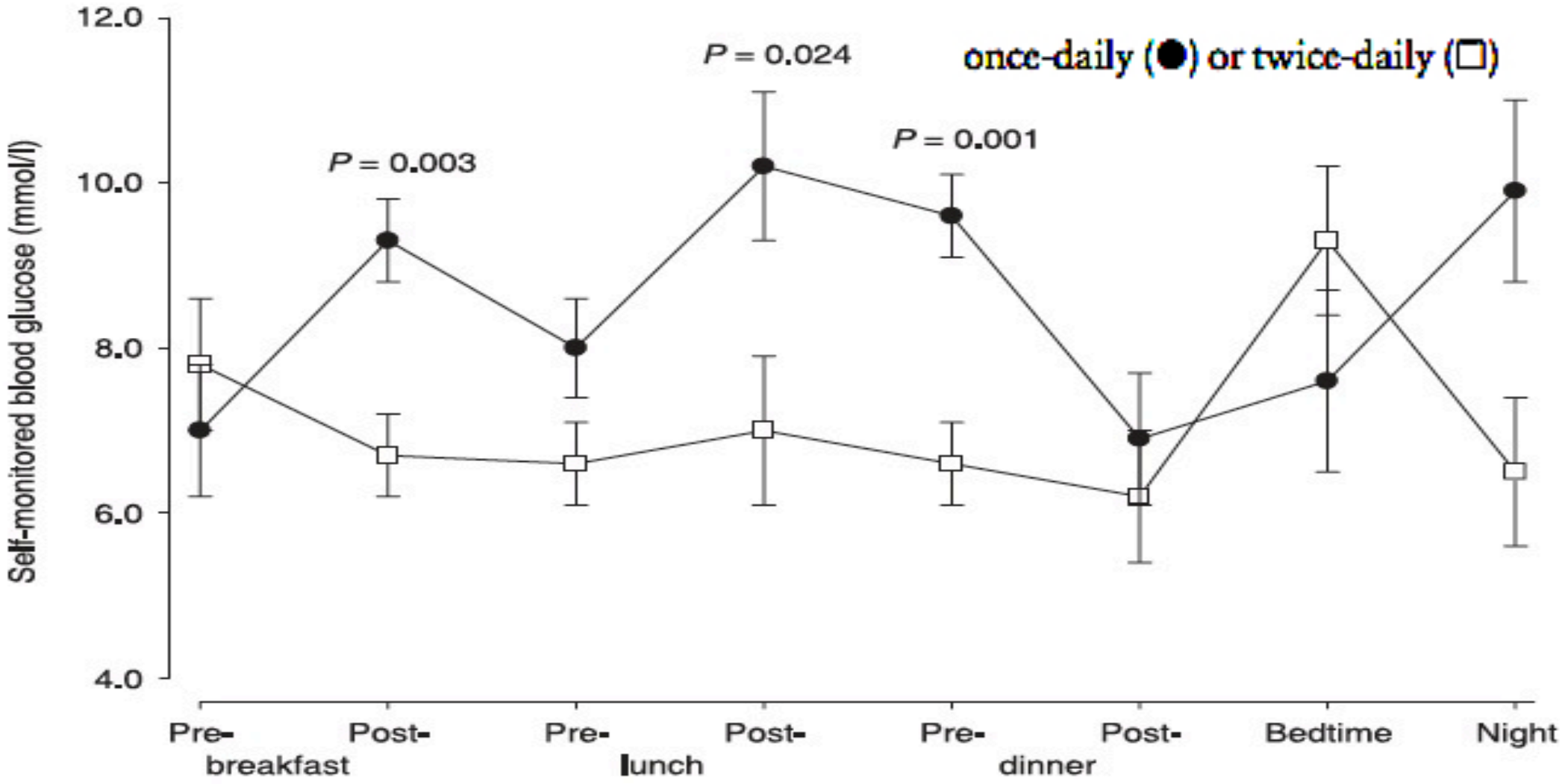
A. Nicolucci Il giornale di AMD, 2012;15;S3: 15-18

Hypoglycemia



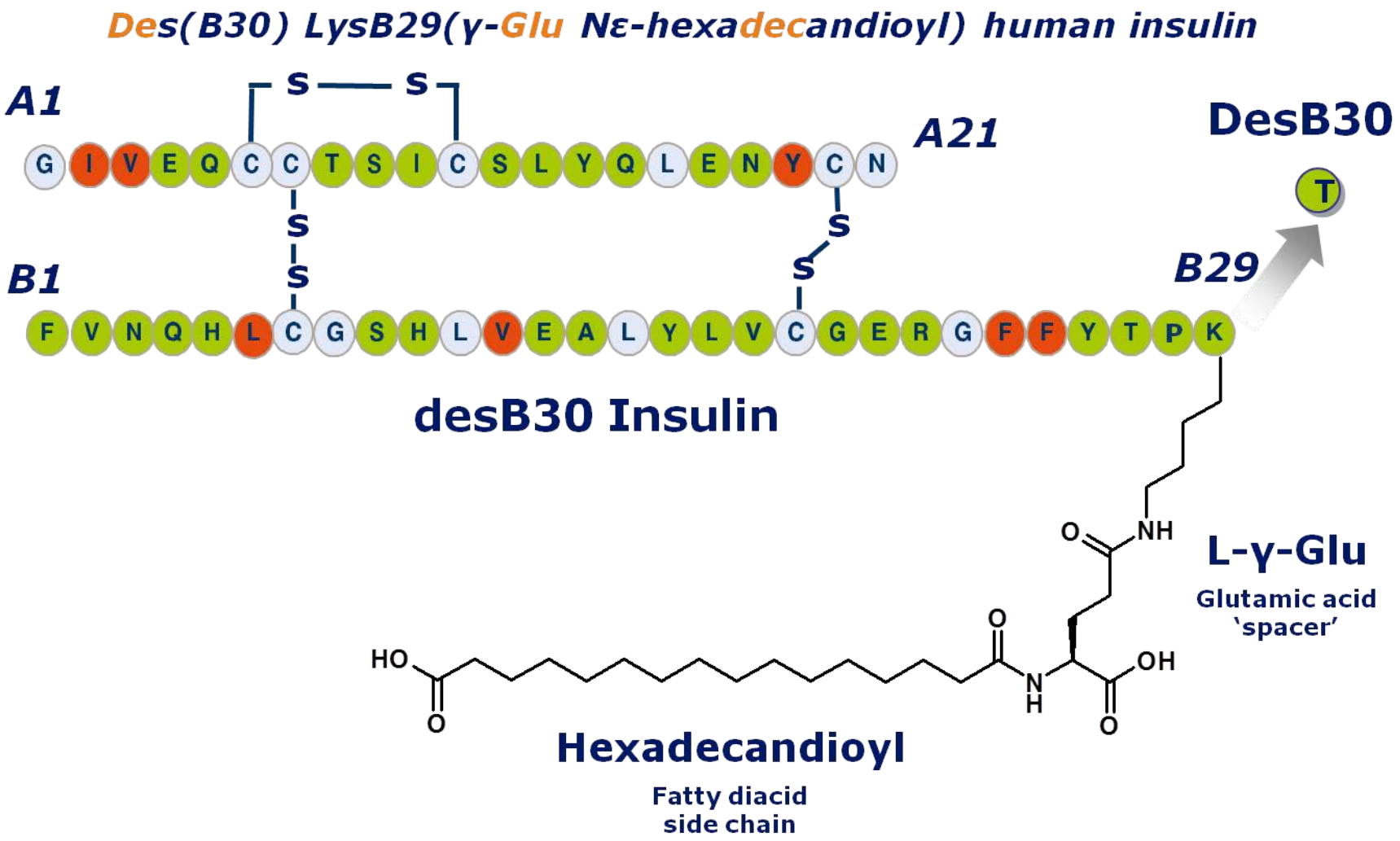
Little S et al, Diabetes Technol Ther 2011

Glargine twice-daily



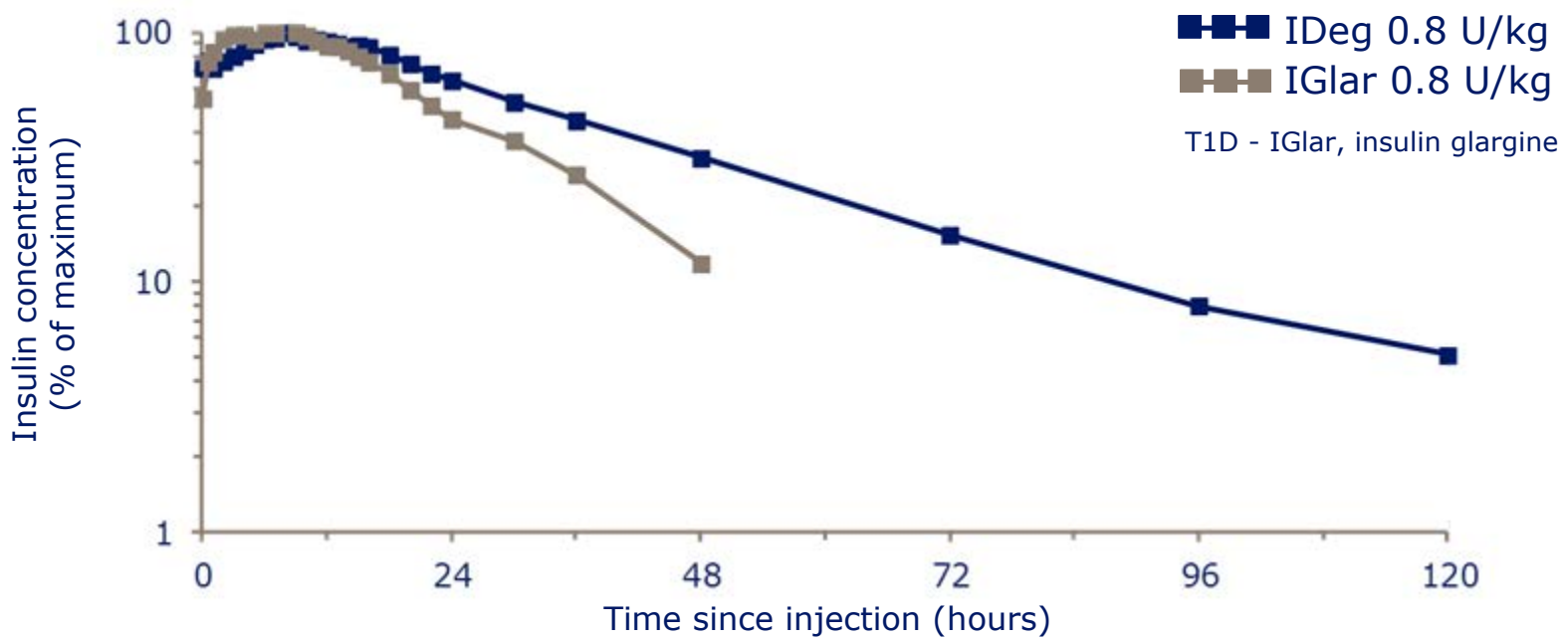
2006 Diabetes UK. *Diabetic Medicine* **23** , 879–886

Insulina **DEGLUDEC**: struttura



Jonassen et al., Pharm Res 2012 – Published online April 2012 DOI 10.1007/s11095-012-0739-z

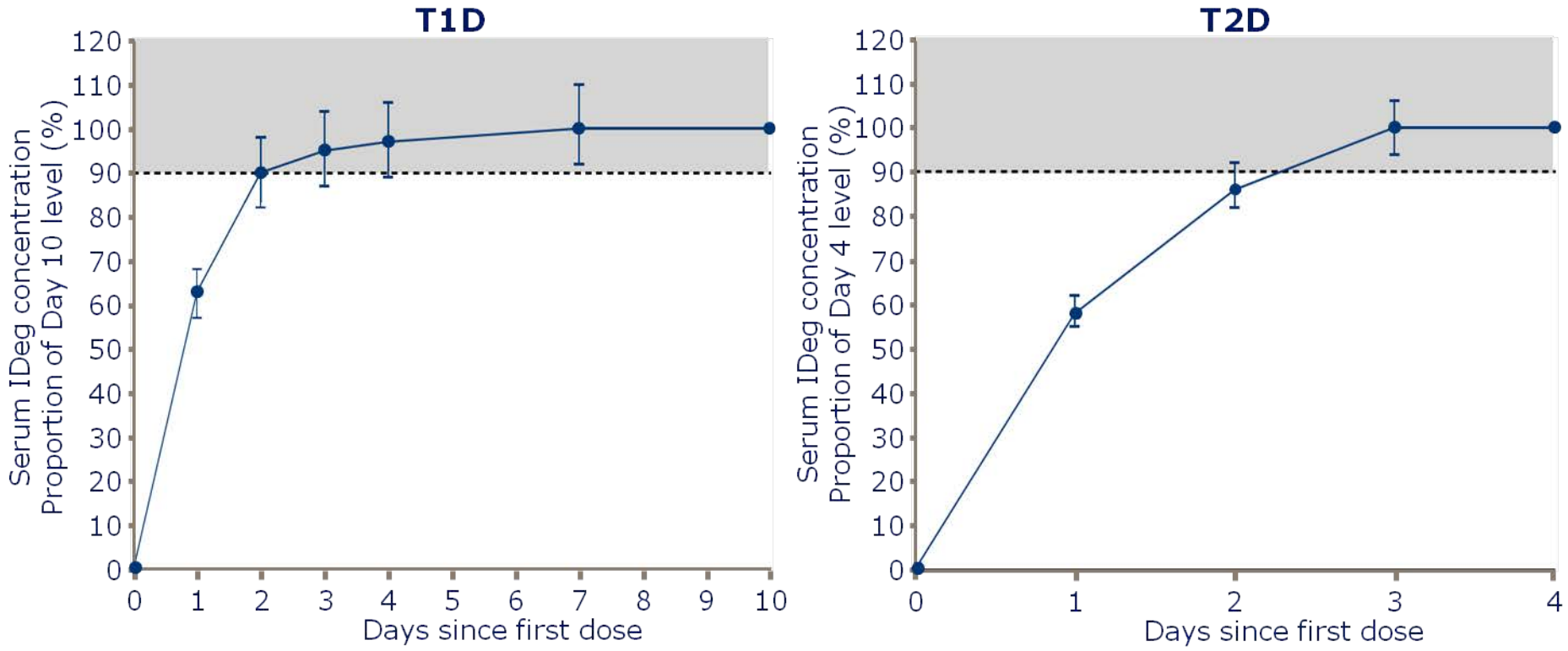
Concentrazione sierica ed emivita di IDeg vs IGlar



	IDeg			IGlar		
	0.4 U/kg	0.6 U/kg	0.8 U/kg	0.4 U/kg	0.6 U/kg	0.8 U/kg
Half-life (hours)	25.9	27.0	23.9	11.8	14.0	11.9
Mean half-life	**25.4**			**12.5**		

Heise et al. IDF 2011:P-1444; Diabetologia 2011;54(Suppl. 1):S425; Diabetes 2011;60(Suppl. 1A):LB11

Degludec : lo steady state è raggiunto entro 2–3 giorni utilizzando una dose giornaliera



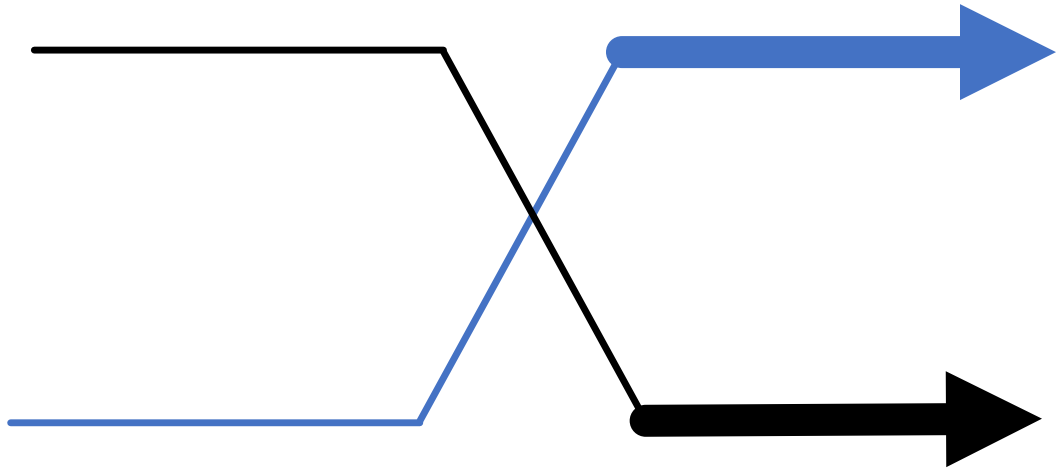
Relative serum IDeg trough concentrations (estimated ratios and 95% CIs) during initiation of once-daily dosing in patients with T1D and T2D

Heise et al. Diabetes 2012;61(Suppl. 1):A259

Insulin Degludec Versus Insulin Glargine in Type 1 and Type 2 Diabetes Mellitus: A Meta-Analysis of Endpoints in Phase 3a Trials

- Conclusions: Compared with glargine, degludec is associated with equivalent HbA1c control and significantly lower nocturnal hypoglycemia rates. In T1DMB/B degludec is also associated with significantly greater reductions in FPG and lower total doses of insulin versus glargine.

Diabetes Ther DOI 10.1007/s13300-014-0076-9



SWITCH 1

Reduced risk of hypoglycaemia with insulin degludec vs. insulin glargine U100 in a T1D population: A randomised double-blind crossover trial

Clinical trial.gov identifier: NCT02034513

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

SWITCH 1: reduced hypoglycemia with insulin degludec (IDeg) versus insulin glargine (IGlar), both U100, in patients with T1D at high risk of hypoglycemia: a randomized, double-blind, crossover trial

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2. **Timothy S Bailey**
   AMCR Institute Inc., Escondido, CA, USA
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4. **Janusz Gumprecht**
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   Novo Nordisk A/S, Søborg, Denmark
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   Novo Nordisk A/S, Søborg, Denmark
8. **Mark Warren**
   Physicians East, Greenville, SC, USA

Introduction

- Insulin degludec (IDeg) is a basal insulin with a unique mode of protraction and a duration of action greater than 42 hours.[1-2]
- The phase 3a development program included two trials in patients with type 1 diabetes (T1D), which demonstrated HbA_{1c} non-inferiority of IDeg to insulin glargine U100 (IGlar) with lower rates of nocturnal confirmed hypoglycemia.[4-6]
- Potential limitations of the phase 3a data included: the lack of blinding, inclusion of non-symptomatic hypoglycemia, exclusion of patients with at least one risk factor for hypoglycemia, and no recording of the timing of IGlar administration.
- SWITCH 1 was designed to confirm the hypoglycemia benefit previously seen, address these limitations, and assess the safe switch to IDeg from other insulins.

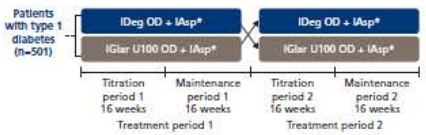
Aims

- Primary: To demonstrate non-inferiority in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycemia episodes for IDeg + insulin aspart (IAsp) versus IGlar+IAsp during the maintenance period (after 16 weeks of treatment). If non-inferiority was confirmed then superiority was assessed based on the upper limit of the 95% confidence interval (CI).
- Secondary: To demonstrate non-inferiority in terms of severe or BG-confirmed symptomatic nocturnal hypoglycemia in the maintenance period, and to confirm superiority with respect to the proportion of patients with severe hypoglycemic episodes in the maintenance period. If non-inferiority was confirmed then superiority was assessed based on the upper limit of the 95% CI.

Methods

- This was a 2× 32-week randomized, double-blind, two-period, crossover, multicenter, treat-to-target phase 3b clinical trial conducted in patients with T1D (Figure 1).
- Patients were randomized 1:1 to morning or evening administration throughout the trial of IDeg or IGlar once daily, both with IAsp 2- to 4-times daily at mealtimes, for 32 weeks, followed by crossover to IGlar or IDeg.
- Eligible patients had at least one of the following hypoglycemia risk factors:
  - ≥1 severe hypoglycemic episodes within the last year
  - Moderate chronic renal failure (glomerular filtration rate 30–59 mL/min/1.73 m^2)
  - Hypoglycemic symptom unawareness
  - Diabetes duration >15 years
  - Episode of hypoglycemia within the last 12 weeks (according to ADA definition: (≤70 mg/dl. ≦3.9 mmol/l.)).
- Blinding was ensured by using a vial and syringe for the basal insulin; the starting dose of basal insulin and bolus insulin (algorithm users) was reduced by 20% at randomization and crossover.
- Titration of basal insulin was according to the trial algorithm (target: 71–90 mg/dL: lowest of three consecutive measurements). Titration of bolus insulin (target: 71–108 mg/dL) was either according to the algorithm or based on the meal carbohydrate content, depending on experience.
- Confirmation of non-inferiority in HbA_{1c} reduction was a prerequisite for conducting the hypoglycemia analyses.
- Confirmed symptomatic hypoglycemia was defined by a BG <56 mg/dL (<3.1 mmol/L) with symptoms and nocturnal hypoglycemia was any episode occurring between 00:01 and 05:59, both inclusive. Severe hypoglycemia was defined in accordance with ADA guidelines (ADA 2013) and all reported episodes of severe hypoglycemia were adjudicated by an independent external committee.

Figure 1 Trial design.



*IAsp was administered 2- to 4-times a day as part of a full basal-bolus regimen.
IAsp, insulin aspart; IDeg, insulin degludec; IGlar U100, insulin glargine; OD, once daily

- *P*-values were derived using a Poisson model with a logarithm of the exposure time (100 years) as offset; estimates were adjusted for treatment, period, sequence, and dosing time as fixed effects, and patient as a random effect. McNemar's test was used to analyze the secondary confirmatory endpoint of proportion of patients experiencing severe hypoglycemia.

Results

- Baseline characteristics are shown in Table 1.
- In total, 501 patients were randomized and 500 were exposed to trial product, with 395 (78.8%) completing both treatment periods.

Efficacy

- The pre-requisite of achieving HbA_{1c} non-inferiority in both treatment periods was met (Figure 2); estimated treatment difference (ETD) in treatment period 1: 0.03 %-points $[-0.10; 0.15]_{95\%\ CI}$; in treatment period 2, the ETD was 0.11%-points $[-0.00; 0.23]_{95\%\ CI}$.
- Mean HbA_{1c} at the end of treatment period 1 was 6.92% (IDeg) versus 6.78% (IGlar), and at the end of treatment period 2 was 6.95% (IDeg) versus 6.97% (IGlar) (Figure 2).
- Mean FPG for both groups also decreased during treatment period 1. In treatment period 2, the mean FPG for those switching to IDeg continued to decrease; however, the mean FPG for those switching to IGlar increased slightly.

Hypoglycemia (Figure 3, Table 2)

- Non-inferiority and superiority for the primary endpoint was achieved (significant 11% lower rate of severe or BG-confirmed symptomatic hypoglycemia with IDeg versus IGlar) in the maintenance periods. To avoid one episode of severe or BG-confirmed symptomatic hypoglycemia, one patient would need to be treated for 4 months with IDeg instead of IGlar.
- Non-inferiority and superiority were also achieved for the secondary endpoint of the number of severe or BG-confirmed symptomatic nocturnal hypoglycemic episodes in the maintenance periods (significant 36% reduction) for IDeg versus IGlar. To avoid one episode of severe or BG-confirmed symptomatic nocturnal hypoglycemia, one patient would need to be treated for 1 year with IDeg instead of IGlar.
- Severe hypoglycemia was significantly reduced by 35% in the maintenance period. To avoid one episode of severe hypoglycemia, three patients would need to be treated for 1 year with IDeg instead of IGlar.
- Similar results were seen for the full treatment period.
- IDeg was superior to IGlar regarding a lower proportion of patients experiencing severe hypoglycemia during the maintenance (p=0.0016) and total (p=0.0090) treatment periods.

Table 1 Baseline characteristics.

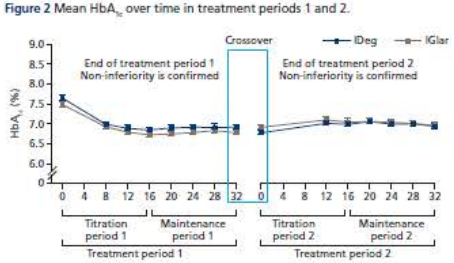
Characteristic	Total
Full analysis set (FAS), n (%)	501
Male, %	53.7
Race, White/Black/Asian/Other, n (%)	92.2/6.4/0.4/1.0
Ethnicity, Hispanic or Latino, n (%)	51 (10.2)
Age, years	45.9 (14.2)
Weight, kg [lb]	80.5 (17.4) [177.5 (38.3)]
BMI, kg/m^2	27.5 (4.8)
Duration of diabetes, years	23.4 (13.4)
HbA_{1c}, %	7.6 (1.0)
FPG, mg/dl. [mmol/L]	169.8 (79.6) [9.4 (4.4)]
eGFR (mL/min/1.73 m^2)	90.0 (21.1)
Insulin treatment at screening	
Continuous subcutaneous insulin infusion (CSII)	97 (19.4)
Basal OD + 2–4 bolus injections	224 (44.7)
Basal BID + 2–4 bolus injections	179 (35.7)

BID, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; OD, once daily.

Safety

- At the end of treatment period 1, mean IDeg dose increased from 29 U to 39 U and mean IGlar dose from 24 U to 36 U. At the end of treatment period 2, mean IDeg dose increased from 36 U to 37 U and mean IGlar dose from 39 U to 41 U. A *post hoc* analysis confirmed a 3% significantly lower basal insulin dose with IDeg versus IGlar.

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



IDeg, insulin degludec; IGlar, insulin glargine.

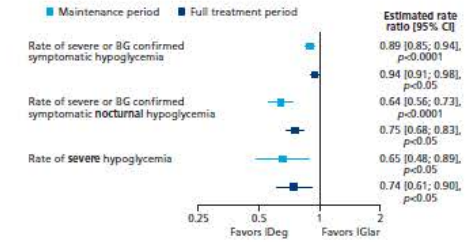
Table 2 Hypoglycemia summary.

Definition	IDeg		IGlar	
	Incidence n (%)	Rate/100 PYE	Incidence n (%)	Rate/100 PYE
Maintenance period				
Severe or BG-confirmed symptomatic hypoglycemia	323 (77.3)	2200.9	337 (79.9)	2462.7
Severe or BG-confirmed nocturnal symtomatic hypoglycemia	137 (32.8)	277.1	182 (43.1)	428.6
Severe hypoglycemia	43 (10.3)	69.1	72 (17.1)	92.2
Full trial period				
Severe or BG-confirmed symptomatic hypoglycemia	377 (83.0)	2044.2	398 (86.5)	2168.0
Severe or BG-confirmed symptomatic nocturnal hypoglycemia	210 (46.3)	281.2	248 (53.9)	371.9
Severe hypoglycemia	90 (19.8)	86.4	119 (25.9)	104.8

BG, blood glucose; IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient-year of exposure.

- Mean total daily insulin dose (basal plus bolus) increased from 53 U to 69 U for IDeg and from 46 U to 63 U for IGlar in treatment period 1, and from 63 U to 64 U for IDeg and from 69 U to 69 U for IGlar at the end of treatment period 2. A *post hoc* analysis confirmed a 3% significantly lower total insulin dose with the IDeg versus IGlar arm.
- Weight changes were comparable between IDeg and IGlar in treatment period 1 and treatment period 2 (2.6 vs. 2.7 kg and 0.7 vs. 0.0 kg, respectively).
- Adverse event rates and serious adverse event rates were similar between treatment groups (356.8 events/100 patient-years vs. 358.5 events/100 patient-years and 39.0 events/100 patient-years vs. 45.1 events/100 patient-years for IDeg and IGlar, respectively).
- The most common adverse events were nasopharyngitis, upper respiratory tract infections, and hypoglycemia.
- One fatality occurred in the IDeg group (respiratory fume inhalation disorder) and three in the IGlar group (one acute coronary syndrome, one cardiac death, one pneumonia).

Figure 3 Forest plot showing the rates of the respective hypoglycemia endpoints in both the maintenance and overall treatment periods.



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.

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. Heller *et al. Lancet* 2012;379:1489–97.
5. Bode *et al. Diabet Med* 2013;30:1293–97.
6. Mathieu *et al. J Clin Endocrinol Metab* 2013;98:1154–62.

Conclusions

- **In this double-blind crossover trial in patients with T1D, IDeg was non-inferior in terms of a reduction in HbA_{1c} and achieved superiority for both the primary and confirmatory secondary hypoglycemia endpoints compared with IGlar.**
- **For the maintenance period, results show:**
  - **11% lower rate of severe or BG-confirmed symptomatic hypoglycemia**
  - **36% lower rate of severe or BG-confirmed symptomatic nocturnal hypoglycemia**
  - **35% lower rate of severe hypoglycemia.**
- **Similar significant benefits were also seen in the full treatment period.**
- **The proportion of patients with severe hypoglycemic episodes was significantly lower for IDeg versus IGlar in both the maintenance and full treatment periods.**
- **There was no apparent difference between IDeg and IGlar for the standard efficacy parameters or in terms of adverse events.**
- **SWITCH 1 demonstrates a significant hypoglycemia benefit with IDeg versus IGlar and provides reassurance that in a T1D population, there were no safety concerns in switching to IDeg from any other basal insulin regimen, or from continuous subcutaneous insulin infusion.**

Objective

Primary objective:

- To demonstrate non-inferiority in the rates of severe or BG-confirmed symptomatic hypoglycaemia episodes for IDeg OD + IAsp vs. IGlar U100 OD + IAsp during the maintenance period (after 16 weeks of treatment)
  - If non-inferiority was confirmed then superiority was assessed based on the upper limit of 95% CI

Secondary objectives:

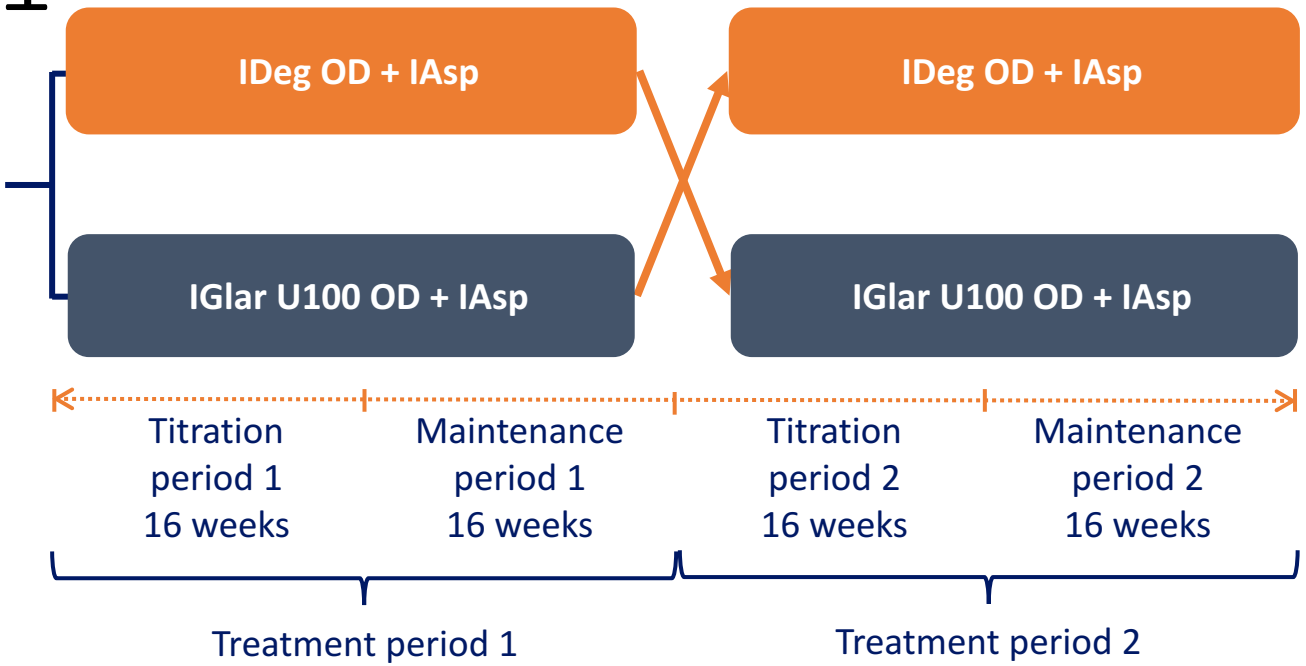
- To demonstrate non-inferiority in terms of severe or BG-confirmed symptomatic **nocturnal** hypoglycaemia in the maintenance period, and to confirm superiority with respect to the proportion of patients with severe hypoglycaemic episodes in the maintenance period
  - If non-inferiority was confirmed then superiority was assessed based on the upper limit of 95% CI

BG, blood glucose; CI, confidence interval; IAsp, insulin aspart; IDeg, insulin degludec; IGlar U100, insulin glargine U100; OD, once daily

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

Trial design: SWITCH 1

Patients with type 1 diabetes (n=501)



Patient characteristics inclusion criteria

- Age ≥18 years
- T1D ≥52 weeks
- Basal–bolus regimen (NPH or IDet OD/BID + 2–4 injections bolus insulin) or CSII ≥26 weeks
- HbA_{1c} ≤10%
- BMI ≤45 kg/m^2

Trial information

- Double-blind
- Crossover
- Treat-to-target
- Randomised 1:1 to morning or evening dosing administration
- 20% dose reduction at randomisation and at switch for all patients in both arms

BID, twice daily; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; IDet, insulin detemir; NPH, neutral protamine Hagedorn; T1D, type 1 diabetes

Lane *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 (basal)

- Once-daily administration morning **or** evening (randomised 1:1)
- Starting dose:
  - Treatment period 1: 20% reduction of basal pre-trial dose
  - Treatment period 2: 20% reduction of basal dose at end of treatment period 1
- Vial and syringe

Iasp (bolus)

- 2–4 injections/day
- Starting dose:
  - Treatment period 1: 20% reduction of pre-trial bolus dose
  - Treatment period 2: 20% reduction of bolus dose at end of treatment period 1
- FlexPen®

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

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
• Diabetes duration for ≥15 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

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

Baseline characteristics

Characteristic	Total
Full analysis set (FAS), n	**501**
Male, %	**53.7**
Race, White/Black/Asian/Other, n (%)	**92.2/6.4/0.4/1.0**
Ethnicity, Hispanic or Latino, n (%)	**51 (10.2)**
Age, years	**45.9** (14.2)
Weight, kg/lb	**80.5** (17.4)/**177.5** (38.3)
BMI, kg/m^2	**27.5** (4.8)
Duration of diabetes, years	**23.4** (13.4)
HbA_{1c}, %	**7.6** (1.0)
FPG, mg/dL [mmol/L]	**169.8** (79.6) [**9.4** (4.4)]
eGFR (mL/min/1.73 m^2)	**90.0** (21.1)

Values are mean (SD) unless otherwise stated
FPG, fasting plasma glucose; SD, standard deviation
Lane *et al.* Presented at the American Diabetes Association, 76th Annual Scientific Sessions, 10–14 June 2016, New Orleans, LA, USA

Treatment at screening

	Total	
	n	%
Insulin treatment regimen	501	100.0
Continuous subcutaneous insulin infusion (CSII)	97	19.4
Basal OD + 2–4 bolus injections	224	44.7
Basal BID + 2–4 bolus injections	179	35.7

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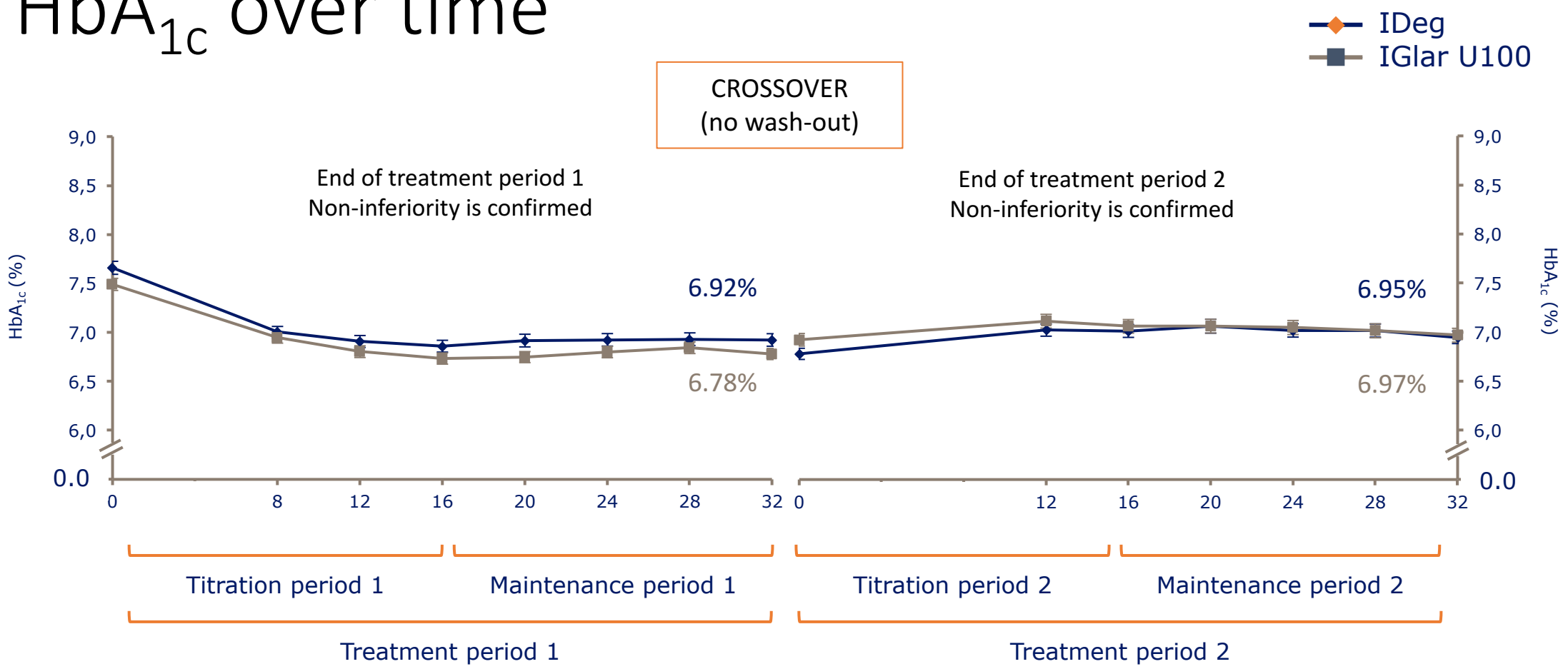
HbA_{1c} over time



Mean±SEM
Comparisons: Estimates adjusted for multiple covariates
SEM, standard error of the mean

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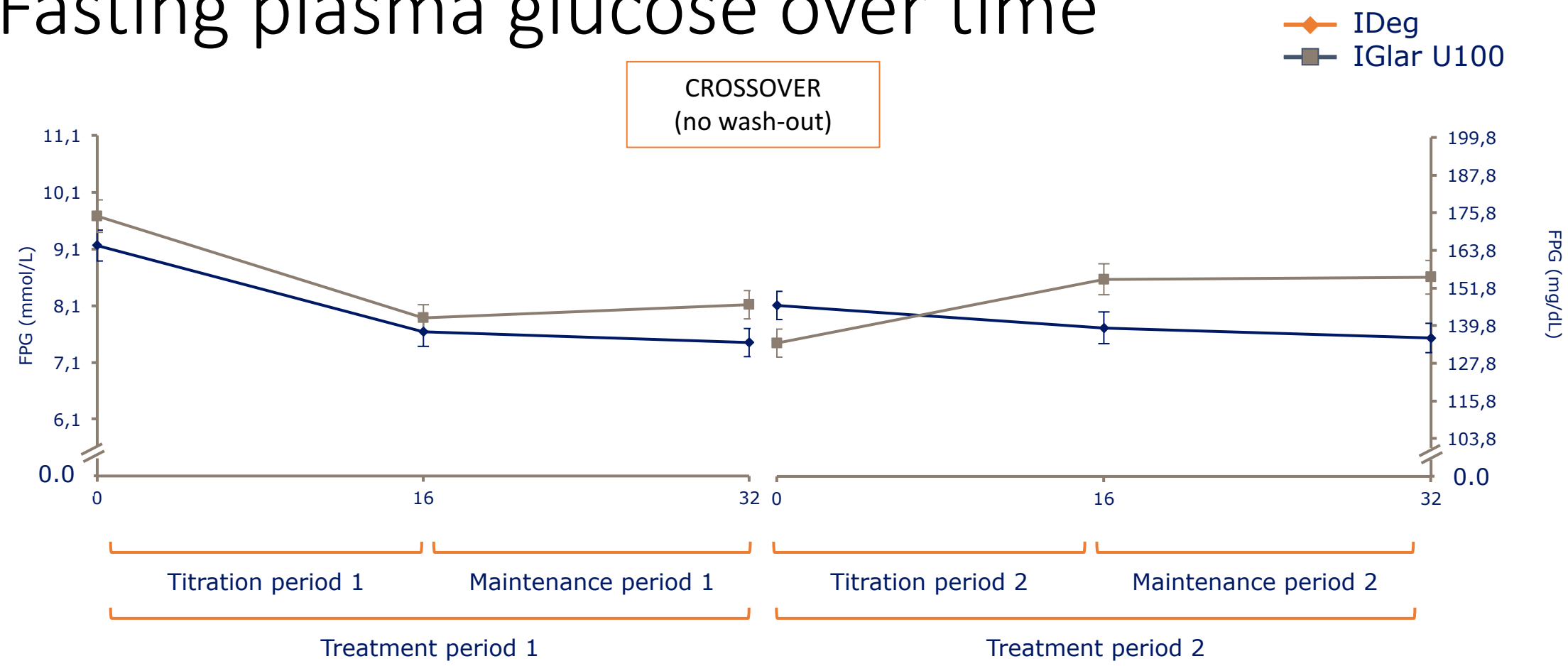
Fasting plasma glucose over time



Mean±SEM

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

Daily insulin doses by treatment period

	Treatment period 1 (32 weeks)		Treatment period 2 (32 weeks)	
U	**IDeg**	**IGlar U100**	**IDeg**	**IGlar U100**
Basal				
Baseline	29	24	36	39
End of treatment period	39	36	37	41
Total (including bolus)				
Baseline	53	46	63	69
End of treatment period	69	63	64	69

U, units

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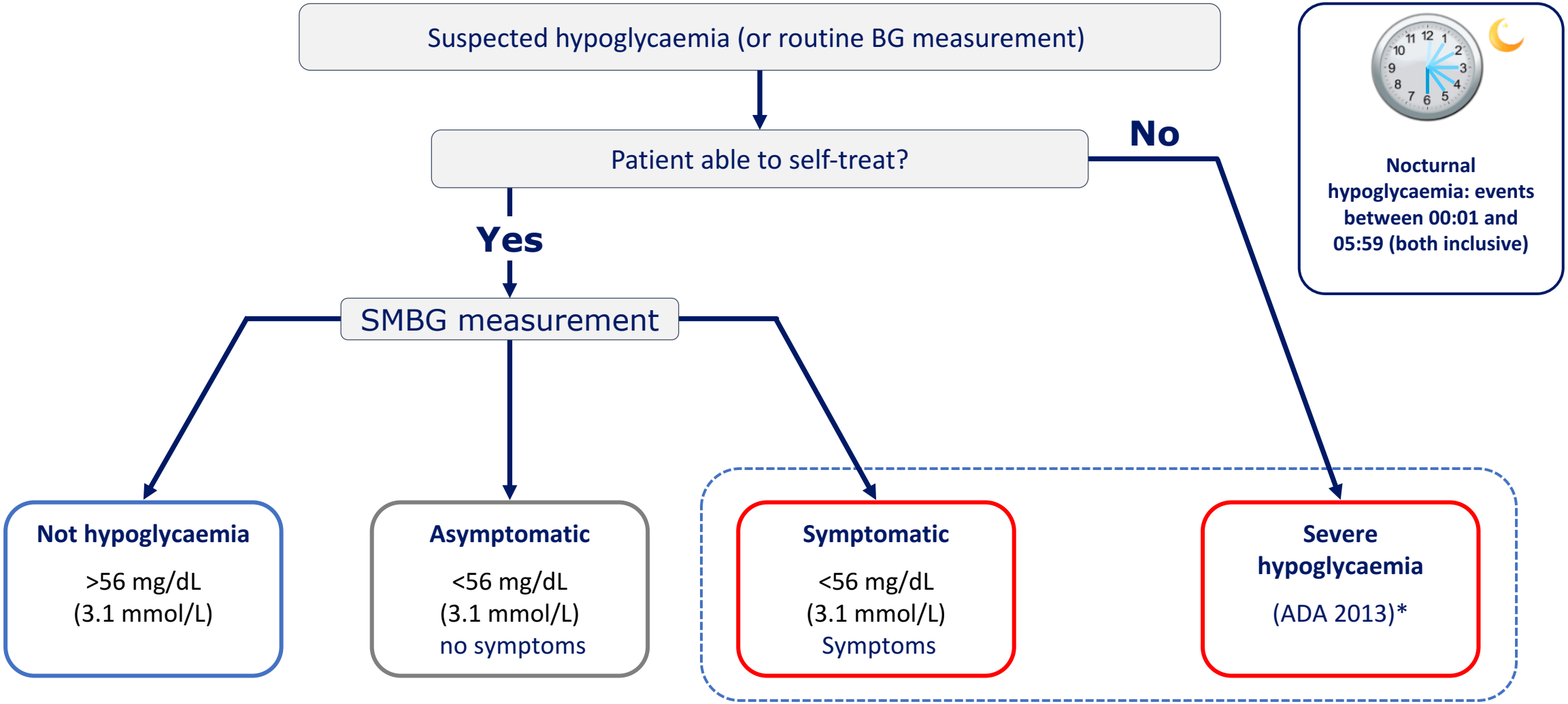
SWITCH hypoglycaemia classification



*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

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Clinical interpretation of the hypoglycaemia evidence: maintenance period

Type of event	Risk reduction (significance)	To avoid one severe or BG-confirmed symptomatic hypoglycaemic episode, you would need to treat:
Severe or BG-confirmed symptomatic hypoglycaemia	11%, *p*<0.0001 (in favour of IDeg)	1 patient for 4 months
Severe or BG-confirmed symptomatic **nocturnal** hypoglycaemia	36%, *p*<0.0001 (in favour of IDeg)	1 patient for 1 year
Severe hypoglycaemia	35%, *p*<0.05 (in favour of IDeg)	3 patients for 1 year

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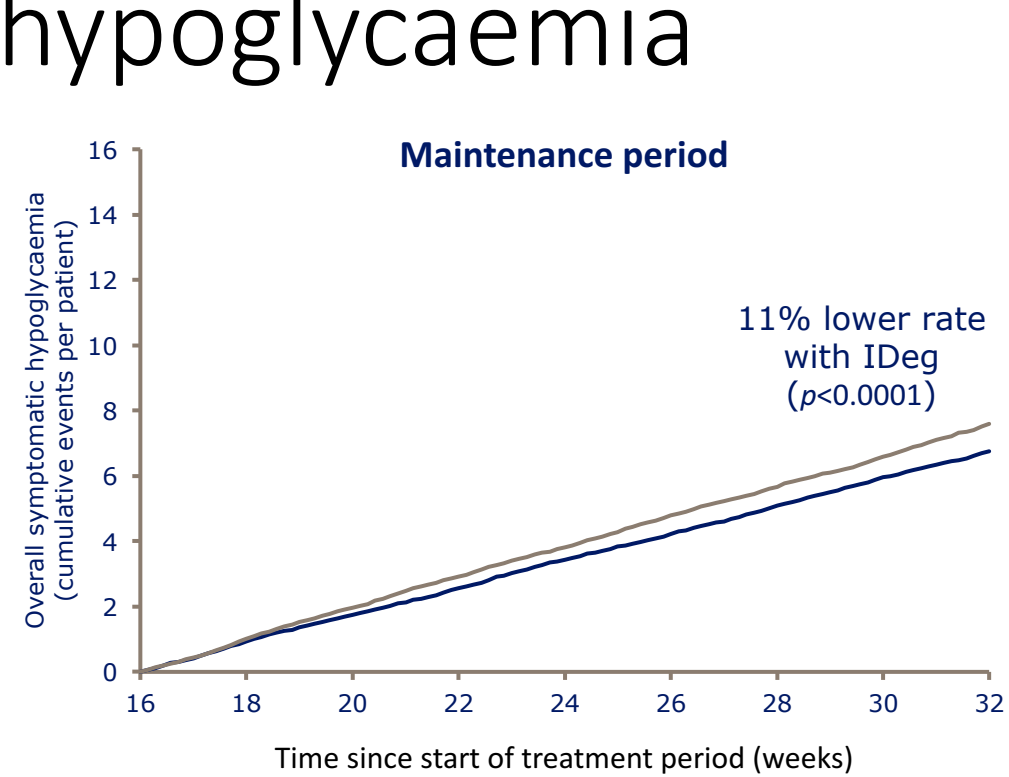
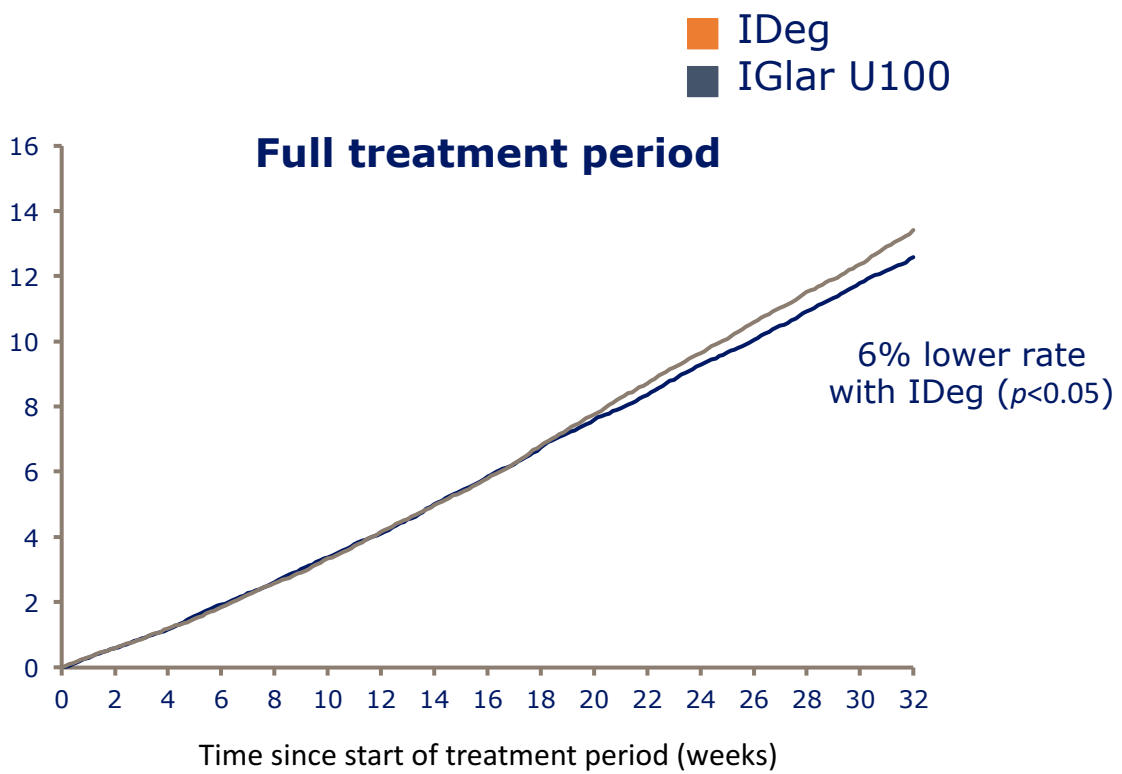
Severe or BG-confirmed symptomatic hypoglycaemia





IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
77.3%	2200.9	79.9%	2462.7

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
83.0%	2044.2	86.5%	2168.0

Comparisons: Estimates adjusted for multiple covariates

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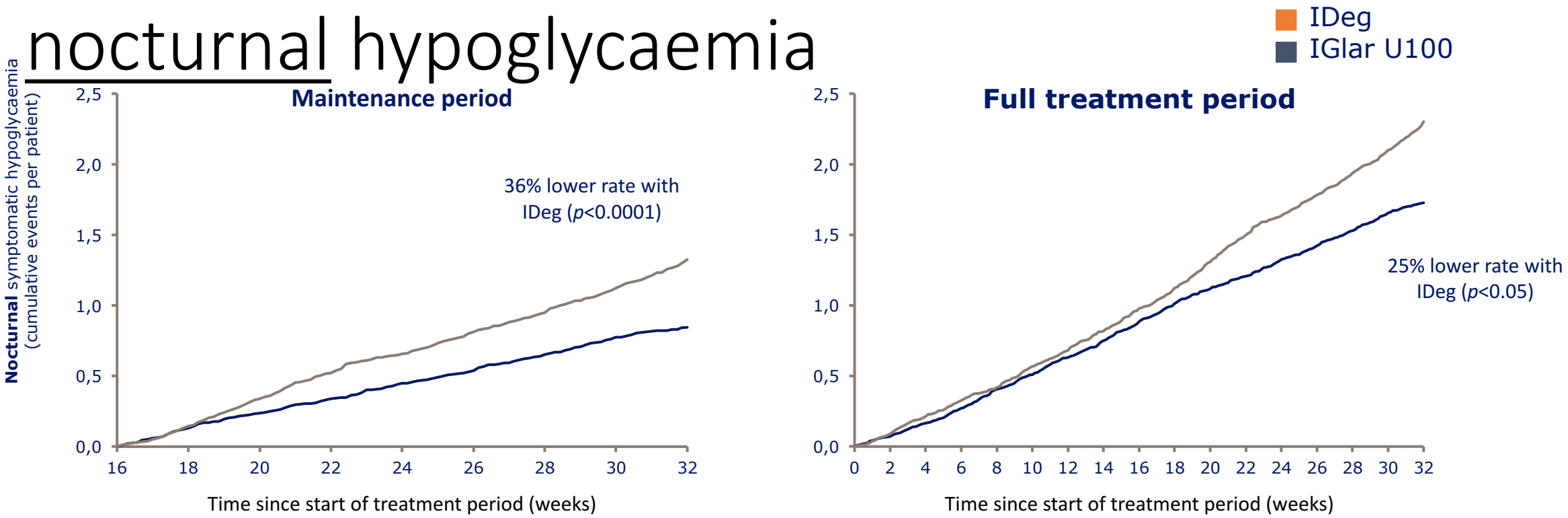
Severe or BG-confirmed symptomatic nocturnal hypoglycaemia



IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
32.8%	277.1	43.1%	428.6

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
46.3%	281.2	53.9%	371.9

Comparisons: Estimates adjusted for multiple covariates

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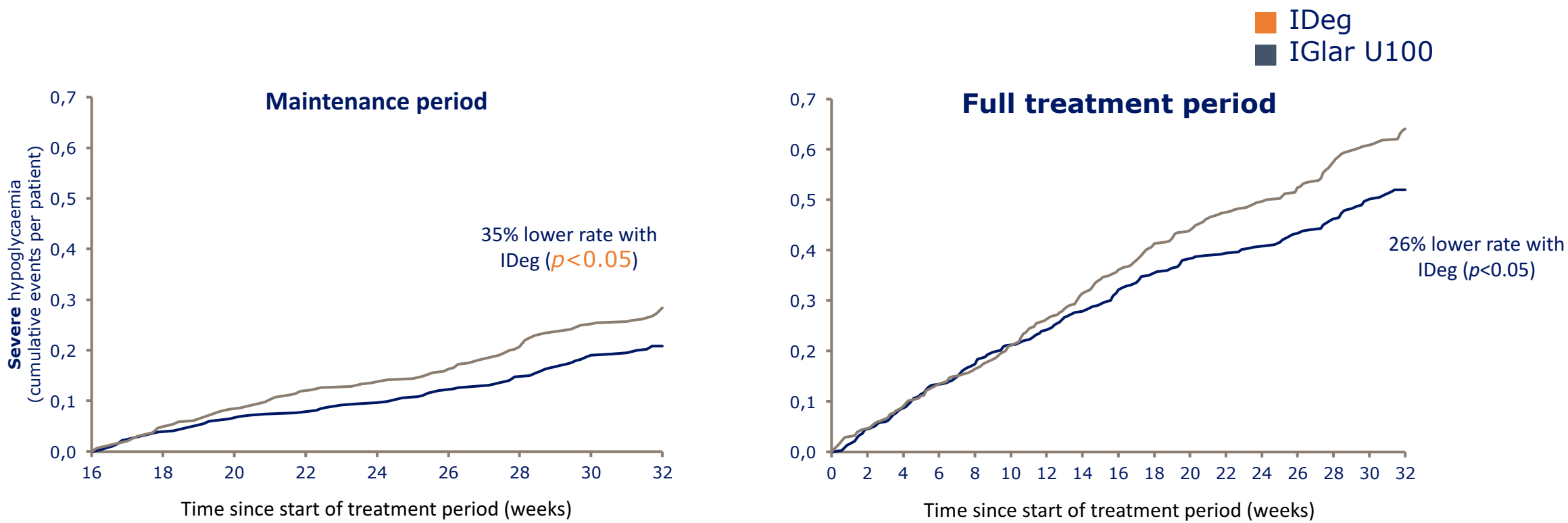
Severe hypoglycaemia



IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
10.3%	69.1	17.1%	92.2

IDeg		IGlar U100	
Proportion (% patients)	**Rate** (episodes/ 100 PYE)	**Proportion** (% patients)	**Rate** (episodes/ 100 PYE)
19.8%	86.4	25.9%	104.8

Comparisons: Estimates adjusted for multiple covariates

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Hypoglycaemia: full treatment period

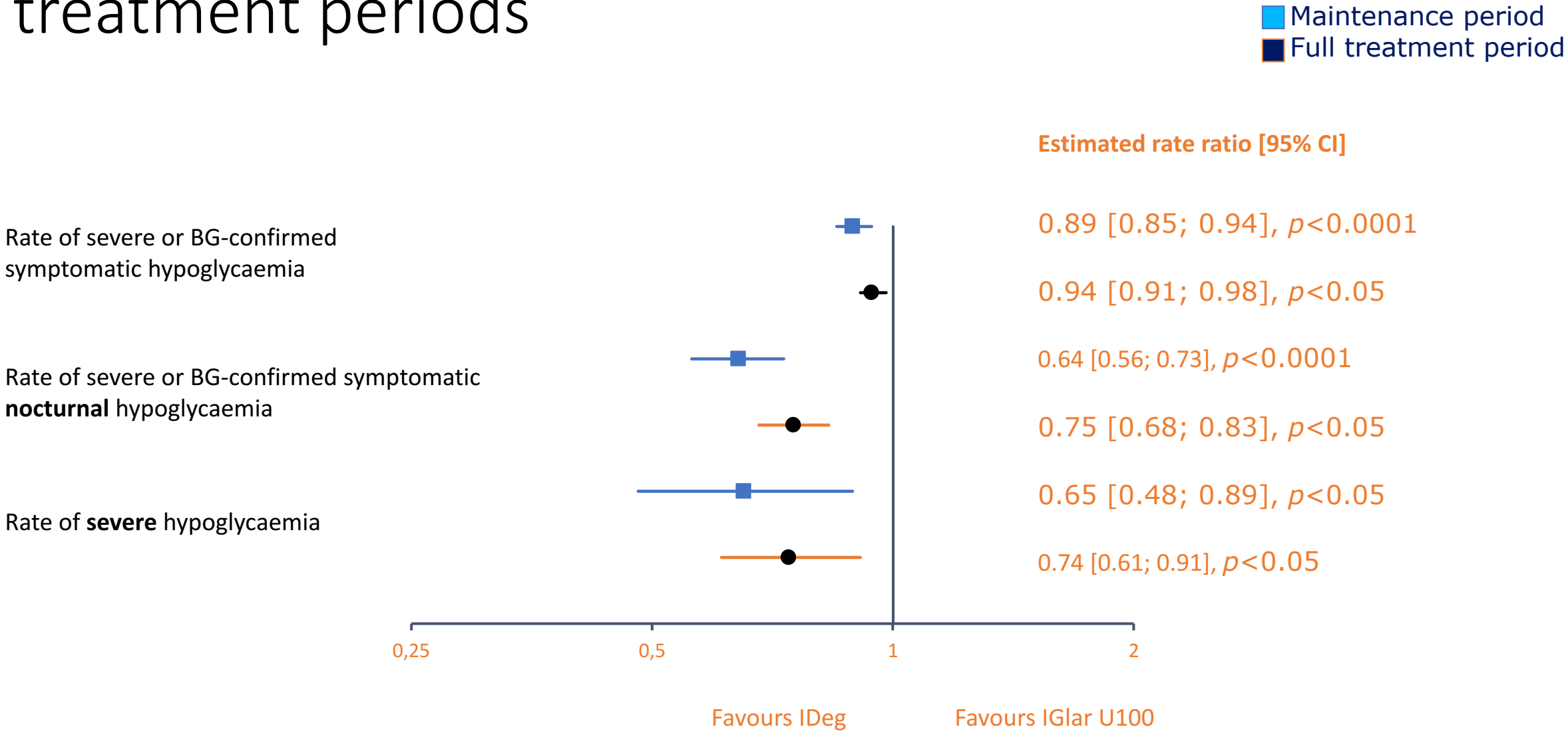
	IDeg		IGlar U100		IDeg vs. IGlar U100	
	Proportion % patients (# patients)	Rate episodes/ 100 PYE	Proportion % patients (# patients)	Rate episodes/ 100 PYE	Rate ratio	ΔRisk
Severe or BG-confirmed symptomatic	83.0% (377)	**2044.2**	86.5% (398)	**2168.0**	0.94*	**–6%**
Severe or BG-confirmed symptomatic nocturnal	46.3% (210)	**281.2**	53.9% (248)	**371.9**	0.75*	**–25%**
Severe†	19.8% (90)	**86.4**	25.9% (119)	**104.8**	0.74*	**–26%**

*$p<0.05$

†All episodes of severe hypoglycaemia were confirmed by external adjudication committee

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

Hypoglycaemia: maintenance and full treatment periods



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Conclusion

Hypoglycaemia

In the maintenance period for IDeg vs. IGlar U100:

- Significantly lower rate (11%) of severe or BG-confirmed hypoglycaemia
- Significantly lower rate (36%) of severe or BG-confirmed **nocturnal** hypoglycaemia
- Significantly lower rate (35%) of **severe** hypoglycaemia
- Significantly lower **proportion** of patients with **severe** hypoglycaemic episodes

Similar benefits were seen in the full treatment period

Other endpoints

- The glycaemic control with IDeg, in terms of HbA_{1c}, was shown to be non-inferior to IGlar U100
- There was no apparent difference between IDeg and IGlar U100 for the standard efficacy parameters, except for a significant difference in FPG in favour of IDeg
- No safety issues were identified with IDeg
- SWITCH 1:
  - Demonstrates a significant hypoglycaemia benefit with IDeg vs. IGlar U100
  - Provides reassurance that there were no safety concerns in switching to IDeg from any other basal insulin regimen, or from CSII

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

Insulina glargine 300 U

NUOVA FORUMLAZIONE DI GLARGINE 100 U/mL

Insulina Glargine 300: i messaggi dagli studi

Quale è la differenza tra Gla-300 e Gla-100?

Volume di iniezione più piccolo per Gla-300 vs Gla-100[1]

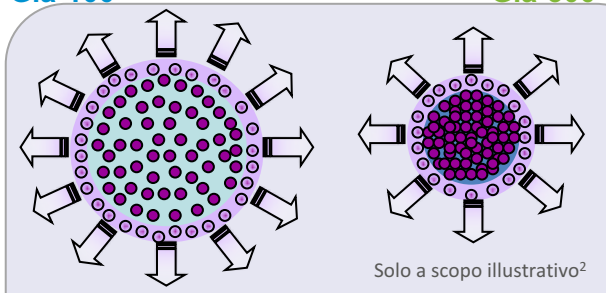
Riduzione del volume di 2/3[1]

Gla-100 Gla-300

Un depot SC più piccolo e compatto con Gla-300 vs Gla-100[1,2]

Area di superifice più piccola[1,2]

Gla-100 Gla-300



Solo a scopo illustrativo[2]

Differente cinetica di assorbimento: rilascio più lento e graduale[1-4]

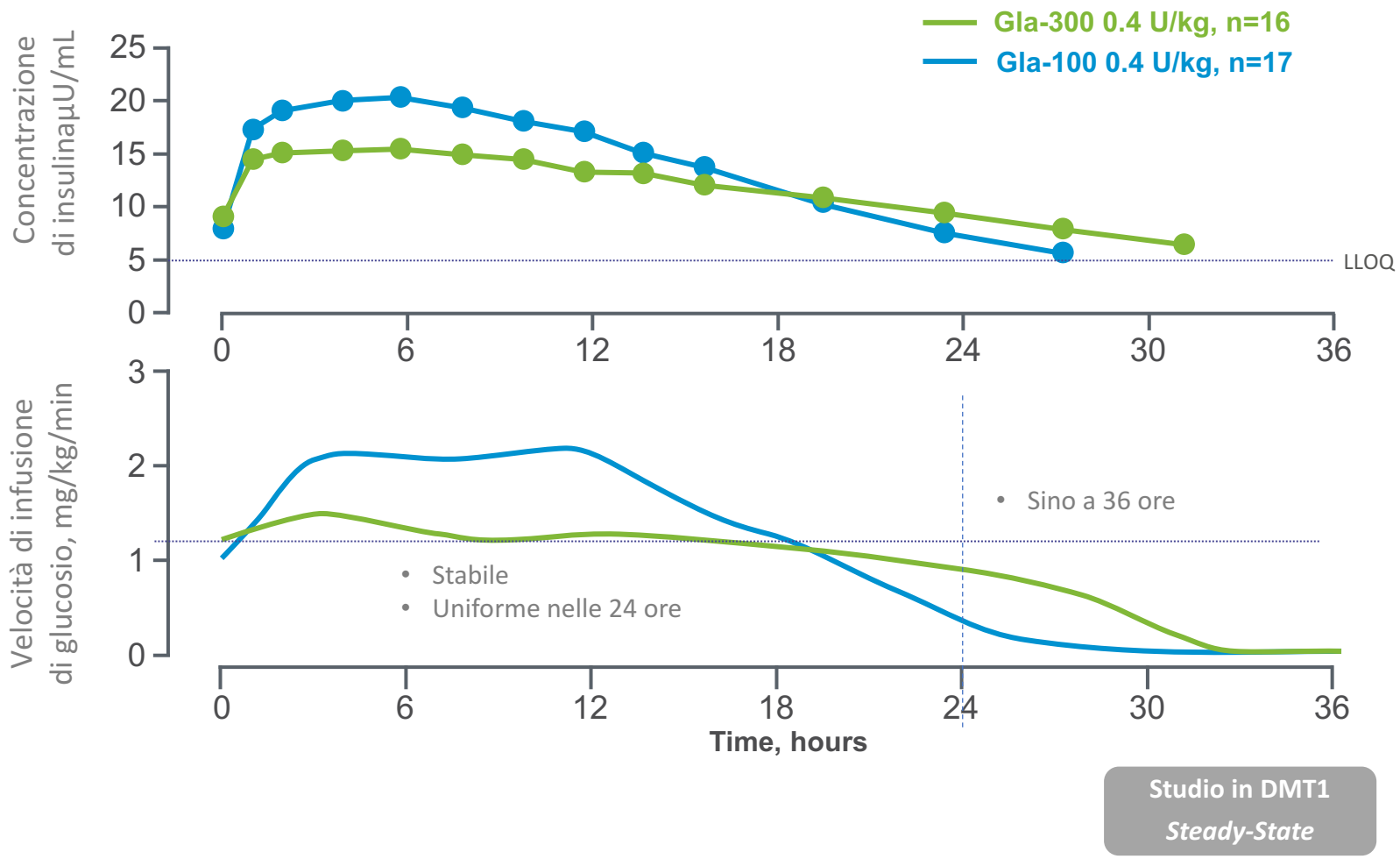
Gla-300 mostra un profilo PK/PD differente vs Gla 100: durata di azione più stabile e prolungata, oltre le 24 ore[4]

- Il metabolismo di insulina glargine è lo stesso indipendentemente dalla somministrazione di Gla-100 o Gla-300; il metabolita M1 è stato confermato come la principale parte attiva circolante nel sangue[3]

PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous

1. Pettus J, et al. Diabetes Metab Res Rev. 2015 Oct 28. doi: 10.1002/dmrr.2763. [Epub ahead of print]; 2. Adapted from Sutton G et al. Expert Opin Biol Ther. 2014;14:1849-60; 3. Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; 4. Becker RH et al. Diabetes Care. 2015;38:637-43

Insulina Glargine 300: Presenta un profilo farmacocinetico e farmacodinamico più costante e prolungato rispetto a insulina glargine 100 U/ml



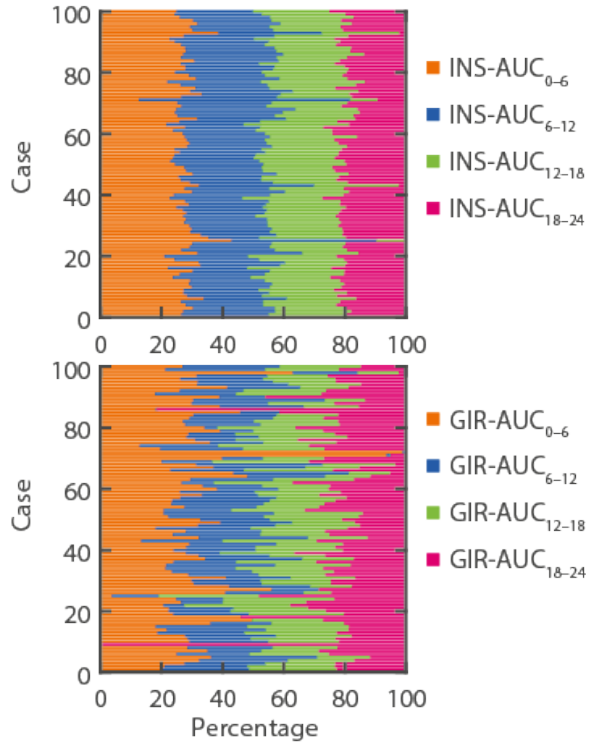
PROFILO PIU' COSTANTE E PROLUNGATO

LLOQ, lower limit of quantification; PD, pharmacodynamic; PK, pharmacokinetic; T1DM, type 1 diabetes mellitus
Becker RH et al. Diabetes Care. 2015;38:637-43

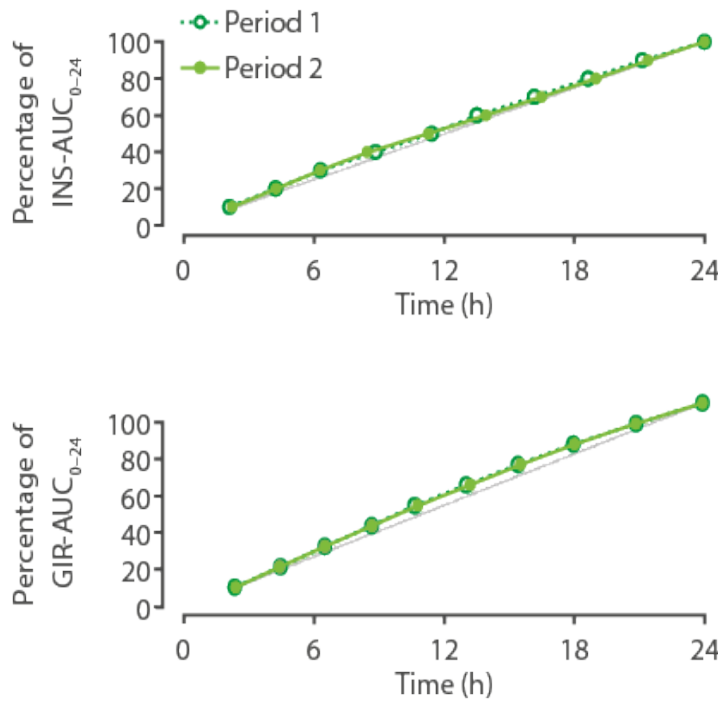
Low within-day variability

Exposure and activity was nearly evenly distributed over 24 h

Percentage of INS-AUC$_{0–24}$ and GIR-AUC$_{0–24}$ per 6-hour time period, by case



Median time to percentage cumulative U300 exposure (INS) and activity (GIR) by treatment period



Grey line represents a perfectly even distribution

Becker RH et al. Poster presentation at EASD 2014; Abstract 953 Available at: http://www.easdvirtualmeeting.org/resources/18262 Accessed September 2014

VARIABILITA’ PK/PD : RIASSUNTO

RIDOTTA VARIABILITA’ GLICEMICA

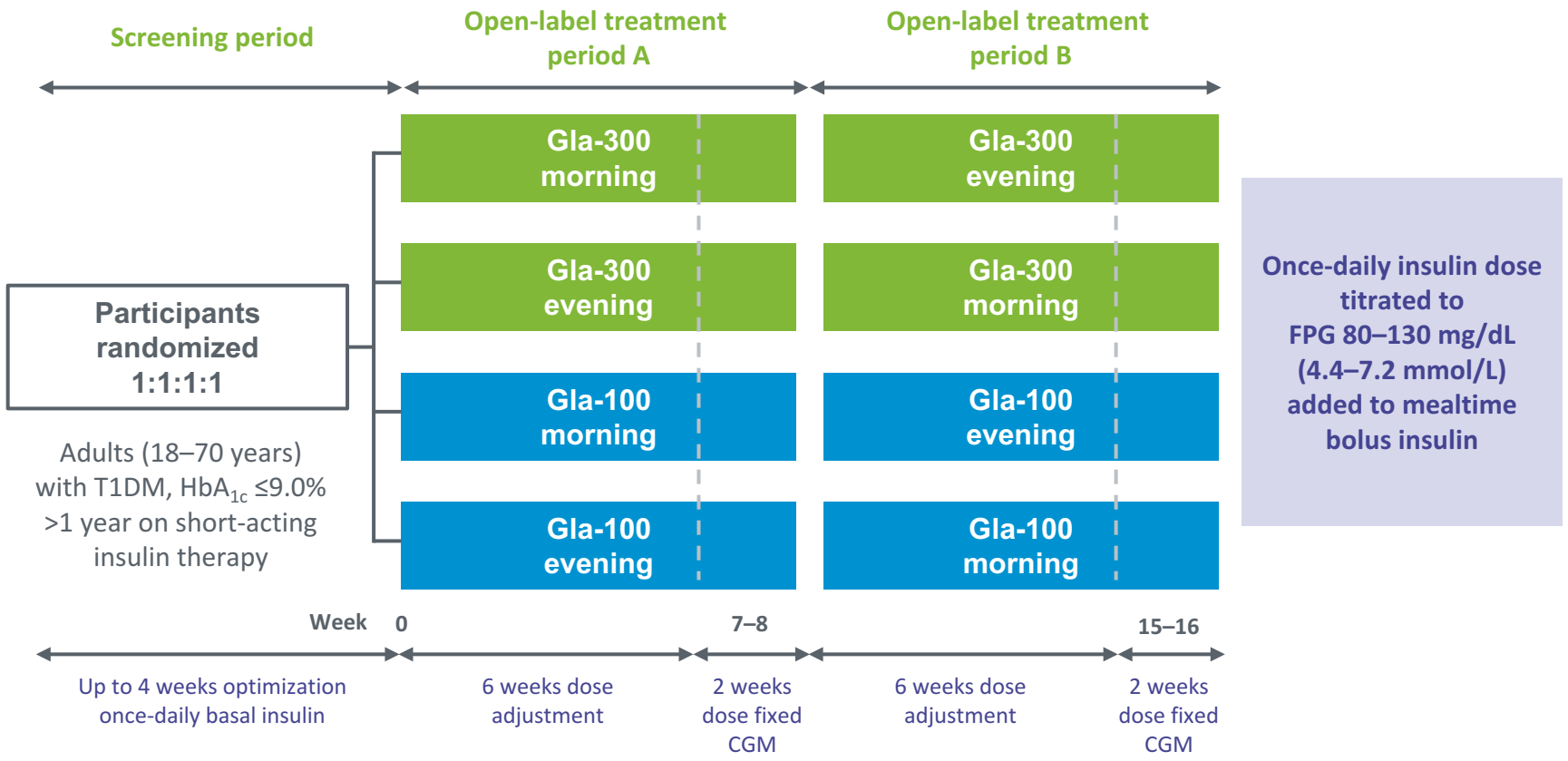
- In questo studio di calmp euglicemico allo steady-state su 50 partecipanti con T1DM che hanno utilizzato una dose terapeutica si è dimostrato:
  - Un profilo PK e PD più costante e prolungato, con una esposizione ed attività insulinica oltre le 24 ore
  - **Il profilo costante PK/PD si declina in una bassa fluttuazione all’interno del giorno ed una alta riproducibilità tra giorni.**

Becker RH et al. Poster presentation at EASD 2014; Abstract 953
Available at: http://www.easdvirtualmeeting.org/resources/18262 Accessed September 2014

CGM study in T1DM patients (PDY 12777)

Evaluating glucose control with once-daily morning or evening injections of Gla-300 or Gla-100

- Multicenter, 16-week, Phase 2, parallel group, 2-period crossover study (N=59)

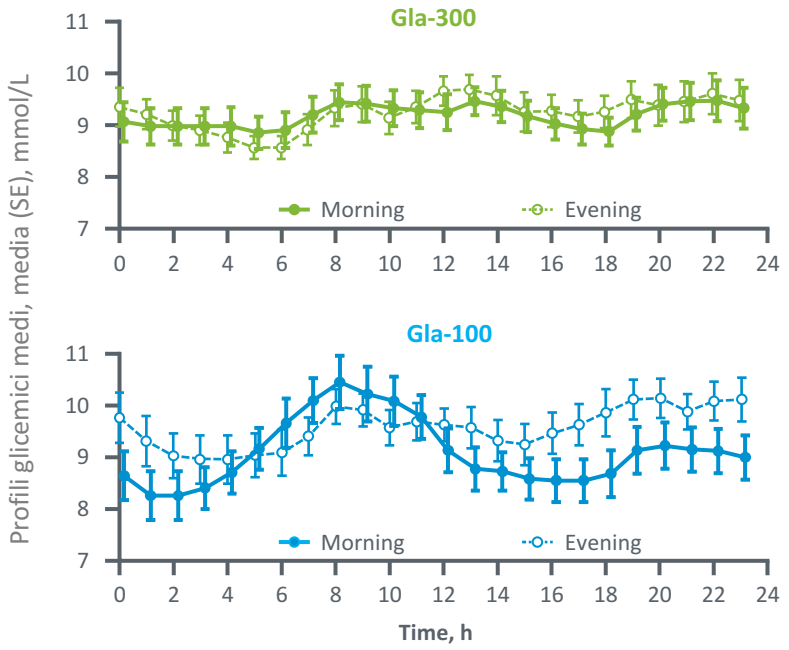


Bergenstal RM et al. Poster presentation at EASD 2014; Abstract 949;
Bergenstal RM et al. Diabetes Tech Ther. 2015;17(Suppl1):A16-17 (abstract no. 39)

Un profilo glicemico più stabile con Gla-300 vs Gla-100
Studio di monitoraggio glicemico in continuo (CGM) nel DMT1 (PDY12777)

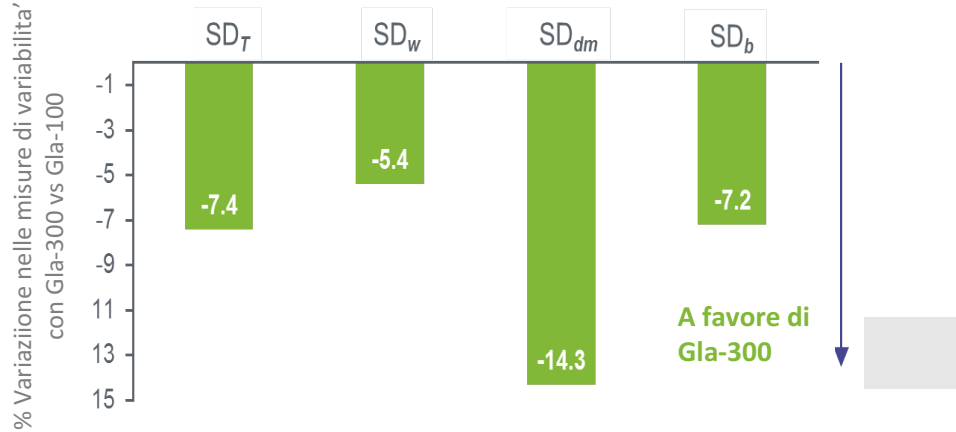
RIDOTTA VARIABILITA' INTRA-SOGGETTO

Profili glicemici più costanti con Gla-300 vs Gla-100, indipendentemente dal momento di iniezione (mattina o sera)



Average 24-h glucose profiles during the last 2 weeks of each treatment period (continuous glucose monitoring population; pooled data period A + B)

Tutte le misure di variabilità intra-soggetto intra-giornaliere e tra-giorni risultano numericamente inferiori per I soggetti trattati con Gla-300 vs Gla-100



Valori assoluti; media(SE) (mg/dL)	SD_T Variabilità deviazione standard totale	SD_w Variabilità intra-giornaliera	SD_{dm} Variabilità tra le medie giornaliere	SD_b Variabilità tra giorni (stessa ora)
Gla-100	76.1 (2.7)	61.4 (1.8)	41.4 (2.5)	71.3 (2.9)
Gla-300	70.5 (2.4)	58.1 (2.1)	35.5 (1.7)	66.2 (2.3)
P-value	0.1259	0.2286	0.052	0.1568

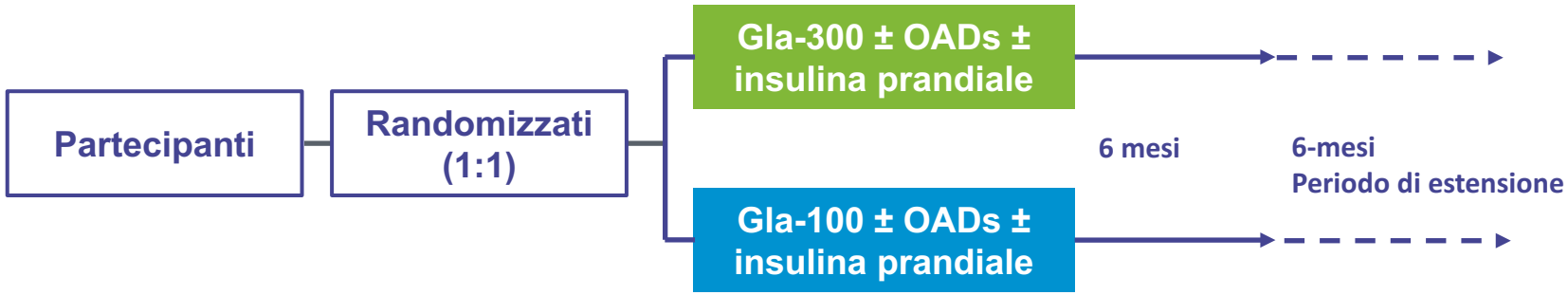
- Studio CGM di fase II, a gruppi paralleli, crossover con Gla-300 vs Gla-100 somministrato la mattina o la sera in 59 soggetti con DMT1

Bergenstal RM et al. Oral presentation at ATTD 2015. Diabetes Tech Ther. 2015;17(Suppl 1):A16-17 (abstract no. 39);
Bergenstal RM et al. Poster presentation at EASD 2014; Abstract 949

Insulina Glargine 300: i messaggi dagli studi

Programma di studi EDITION: obiettivi e disegno[1-6]

- **OBIETTIVO**: valutare l'efficacia clinica e la sicurezza di Gla-300 vs Gla-100
- Randomizzazione 1:1, in aperto, gruppi paralleli, studi multicentrici di fase 3
- Programma di studi EDITION è stato costruito con un simile disegno di studi per confermare i risultati degli studi di fase II (PK/PD)



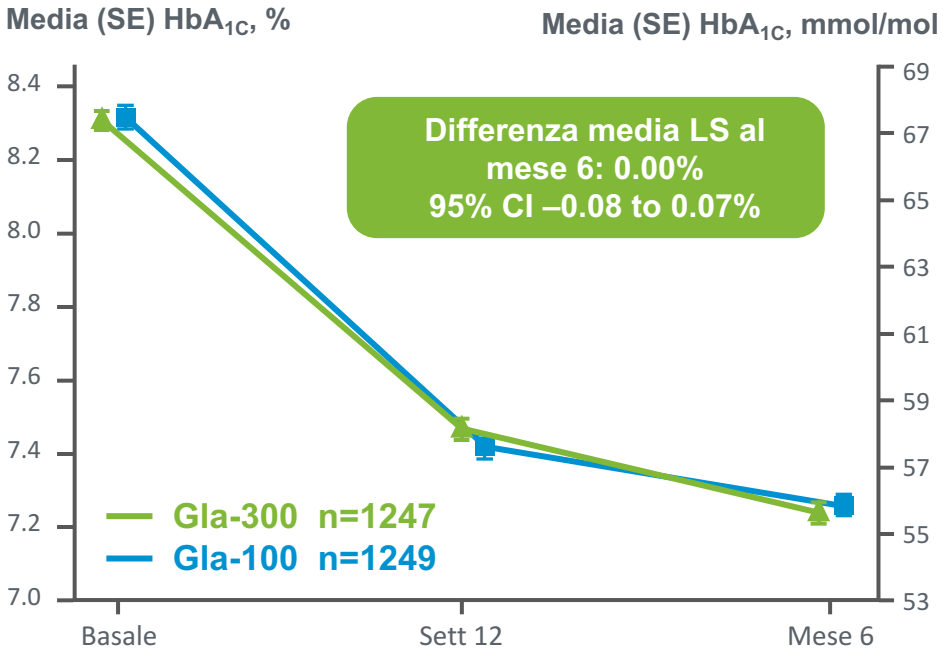
Endpoint primario (tutti gli studi): non-inferiorità a Gla-100 nella riduzione di HbA_{1C} a 6 mesi

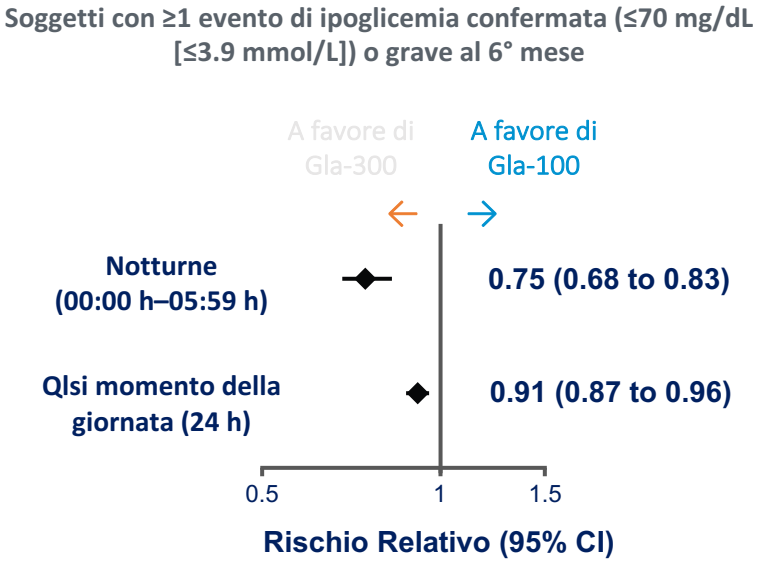
HbA_{1C}, glycated hemoglobin A_{1C}; OADs, oral antihyperglycemic drugs; 1. Riddle MC et al. Diabetes Care. 2014;37:2755-62; 2. Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; 3. Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; 4. Terauchi Y et al. Diabetes Obes Metab. 2016;18:366-74; 5. Home PD et al. Diabetes Care. 2015;38:2217-25; 6. Matsuhisa M et al. Diabetes Obes Metab. 2016;18:375-83

Insulina Glargine 300: i messaggi dagli studi

RIDUZIONE IPOGLICEMIE

Riduzione sovrapponibile di HbA_{1C} con meno ipoglicemie e minor incremento di peso con Gla-300 vs Gla-100 al mese 6





EDITION 1+2+3 DMT2
Meta-analisi a livello paziente, M6

- Minor incremento di peso con Gla-300 vs Gla-100: differenza media LS −0.28 kg (95% CI −0.55 to −0.01; P=0.039)

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
CI, confidence interval; HbA_{1C}, glycated hemoglobin A_{1C}; LS, least squares; SE, standard error; T2DM, type 2 diabetes mellitus
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015;17:859-67

Insulina Glargine 300: i messaggi dagli studi

FLESSIBILITA'

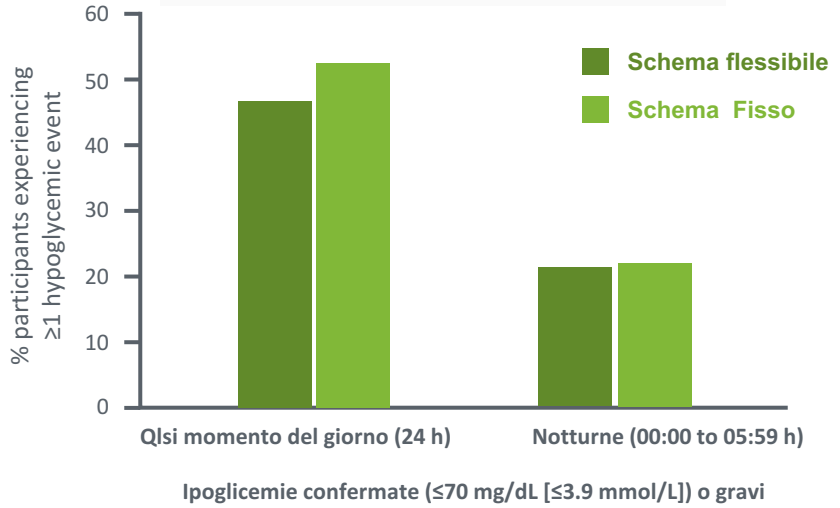
Flessibilità del momento di somministrazione con Gla-300

- **DMT1: iniezione mattutina o serale**
  - **In EDITION 4, l'iniezione mattutina o serale di Gla-300 non ha evidenziato diffferenze clinicamente rilevanti nel miglioramento di HbA_{1C} o nelle ipoglicemie[1] (ulteriormente confermato anche dallo studio CGM nel DMT1)[2]**
- **Nei sotto-studi EDITION 1 e 2 nel DMT2 (Mesi 6–9) la somministrazione di Gla-300 con schema flessibile* non ha mostrato alcun impatto sul controllo glicemico e incidenza di ipoglicemie[3]**

Dati cumulativi sotto-studi EDITION 1 e 2
(popolazione mITT)

	Schema flessibile n=99	Schema fisso n=95
HbA_{1C},%		
Mese 6, media (SD)	7.30 (0.93)	7.30 (0.96)
Mese 6–9, variazione media LS (SE)	0.05 (0.06)	0.00 (0.07)
Differenza media LS (95% CI)	0.05 (–0.13 to 0.23)	

Dati cumulativi sotto-studi EDITION 1 e 2
(popolazione di sicurezza)



*Momento di somministraione flessibile: iniezione 1 volta al giorno in intervalli di **24 ± 3 h**

CGM, continuous glucose monitoring; CI, confidence interval; HbA_{1C}, glycated hemoglobin A_{1C}; LS, least squares; mITT, modified intention-to-treat; SD, standard deviation; SE, standard error; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; 1. Home PD et al. Diabetes Care. 2015;38:2217-25; 2. Bergenstal RM et al. Diabetes Technol Ther 2015;17:A16–A17; 3. Adapted from Riddle M et al. Diabetes Technol Ther. 2016;18:252-7

FLESSIBILITA’

Grazie al profilo più stabile, insulina glargine 300 U/mL consente uno schema di somministrazione flessibile[1]

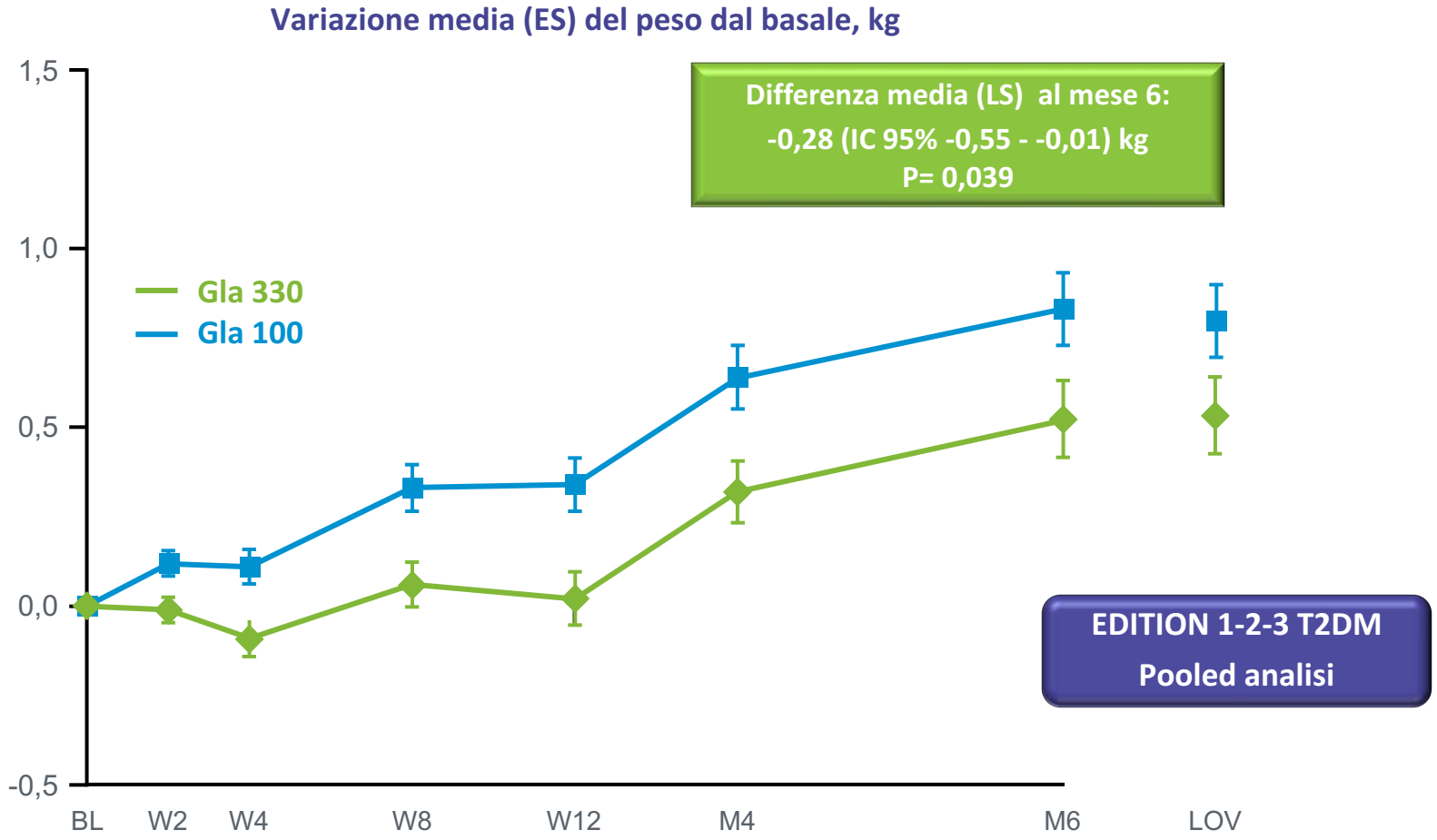
- quando necessario i pazienti possono assumere Glargine U300 fino a 3 ore prima o dopo l’orario di somministrazione abituale

- flessibilità di somministrazione al mattino o alla sera

1. Shiramoto M et al, Diabetes Obes Metab 2015; 17: 254-60. 2. Toujeo, Riassunto delle caratteristiche del prodotto.

Differenza lieve, ma significativa dell'aumento di peso

VARIAZIONE PESO CORPOREO

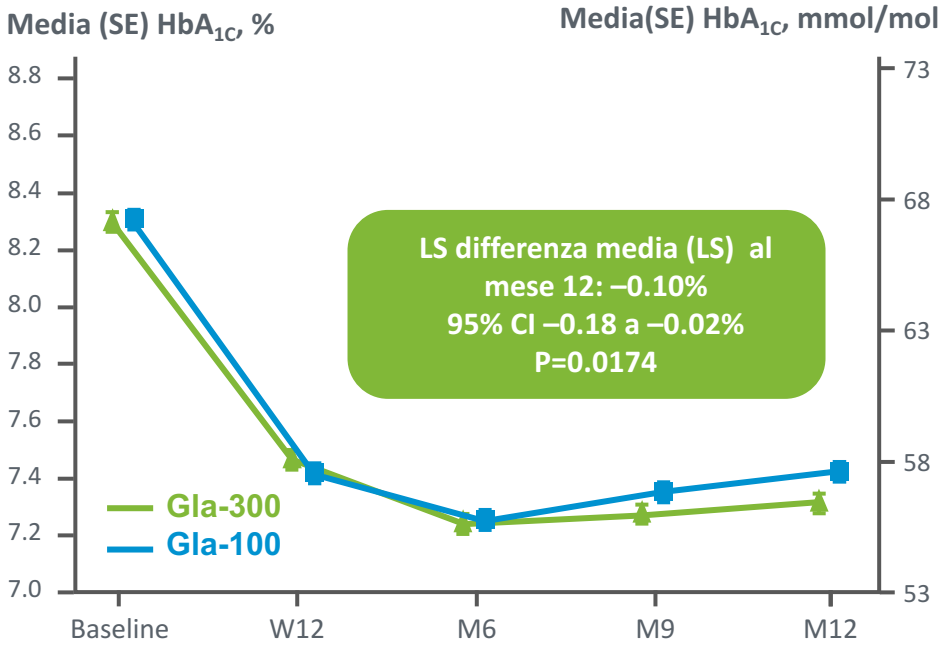


Ritzel R et al. Diabetes Obes Metab. 2015

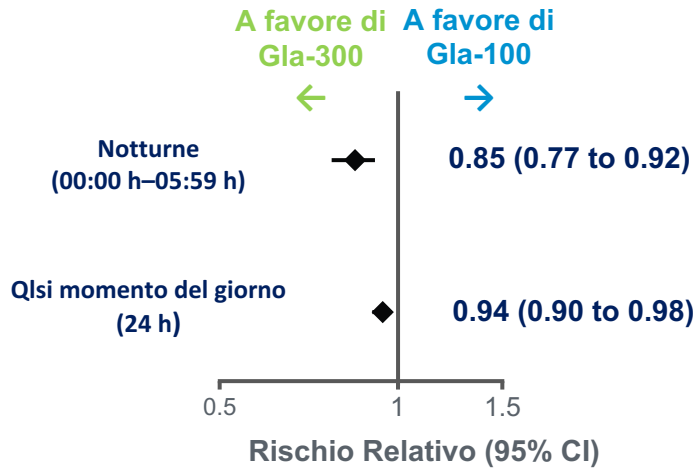
Insulina Glargine 300: i messaggi dagli studi

BENEFICI A LUNGO TERMINE

Riduzione di HbA_{1C} con un minor numero di ipoglicemie e minor incremento di peso con Gla-300 vs Gla-100 dopo 12 mesi



Soggetti con ≥1 evento di ipglicemia confermato (≤70 mg/dL [≤3.9 mmol/L]) o grave al mese 12



EDITION 1+2+3 T2DM
Meta-analisi a livello paziente, M12

- 3.2% soggetti con Gla-300 e 3.6% con Gla-100 avevano ≥1 evento ipoglicemico grave in ogni momento del giorno (24 h) (rischio relativo 0.89; 95% CI 0.59 to 1.35)
- Minor incremento di peso con Gla-300 vs Gla-100: differenza media LS −0.40 kg (95% CI −0.71 a −0.09; P=0.0117)

CI, confidence interval; HbA_{1C}, glycated hemoglobin A_{1C}; LS, least squares; M, month; T2DM, type 2 diabetes mellitus; W, week
Adapted from Ritzel R et al. Poster presentation at ADA 2015; Abstract 1030-P

Insulina Glargine 300: i messaggi dagli studi

- Nuova formulazione, con profilo cinetico-dinamico più costante ed uniforme e **un'attività insulinica sino a 36 ore**

- Controllo glicemico con **ridotto rischio di ipoglicemie**
  - **sia notturne che in ogni momento della giornata**
  - **particolarmente durante le prime 8 settimane, periodo critico per la titolazione**
  - oltre il periodo notturno standard predefinito (00.00-06.00)

- **Flessibilità di somministrazione (+/- 3 ore, al mattino o alla sera)**

- Minor incremento del peso corporeo

- Possibilità di raggiungere un miglior controllo glicemico nel lungo termine grazie alla riduzione delle ipoglicemie

MECCANISMI D'AZIONE QUADRO GLUCIDICO

QUOTA ASSORBITA

- Aumento trascrizione messageri deputati a Ins R
- Attivazione AMPK (Met)
- Aumento espressione recettori GLUT 4 e GLUT 1 (Met/Pio)
- Riduzione trascrizione recettori PPAR γ sugli adipociti (Pio)

QUOTA NON ASSORBITA

- Inibizione parziale α glucosidasi intestinale (Acb)
- Stimolo secrezione GLP-1 (DPP IV Inb)
- Modulazione microbiota intestinale in senso insulino sensibile (Met)

MECCANISMI D'AZIONE QUADRO LIPIDICO

QUOTA ASSORBITA

- Aumento trascrizione messageri deputati a LDL R
- Riduzione trascrizione messaggeri PCSK9 sugli epatociti
- Riduzione trascrizione recettori PPAR γ e α sugli adipociti

QUOTA NON ASSORBITA

- Inibizione parziale assorbimento colesterolo per sequestro Sali biliari
- Aumento escrezione colesterolo

Clinical Nutrition xxx (2015) 1–5

Contents lists available at ScienceDirect

Clinical Nutrition

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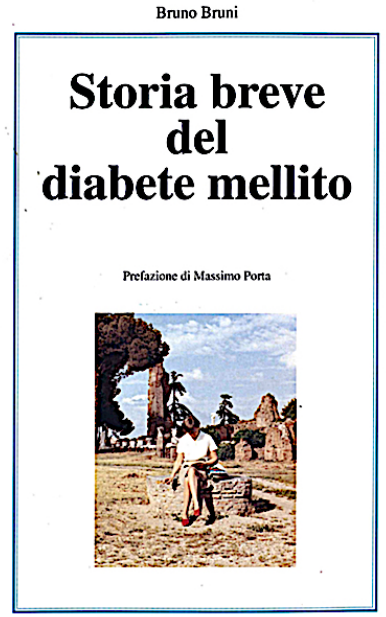
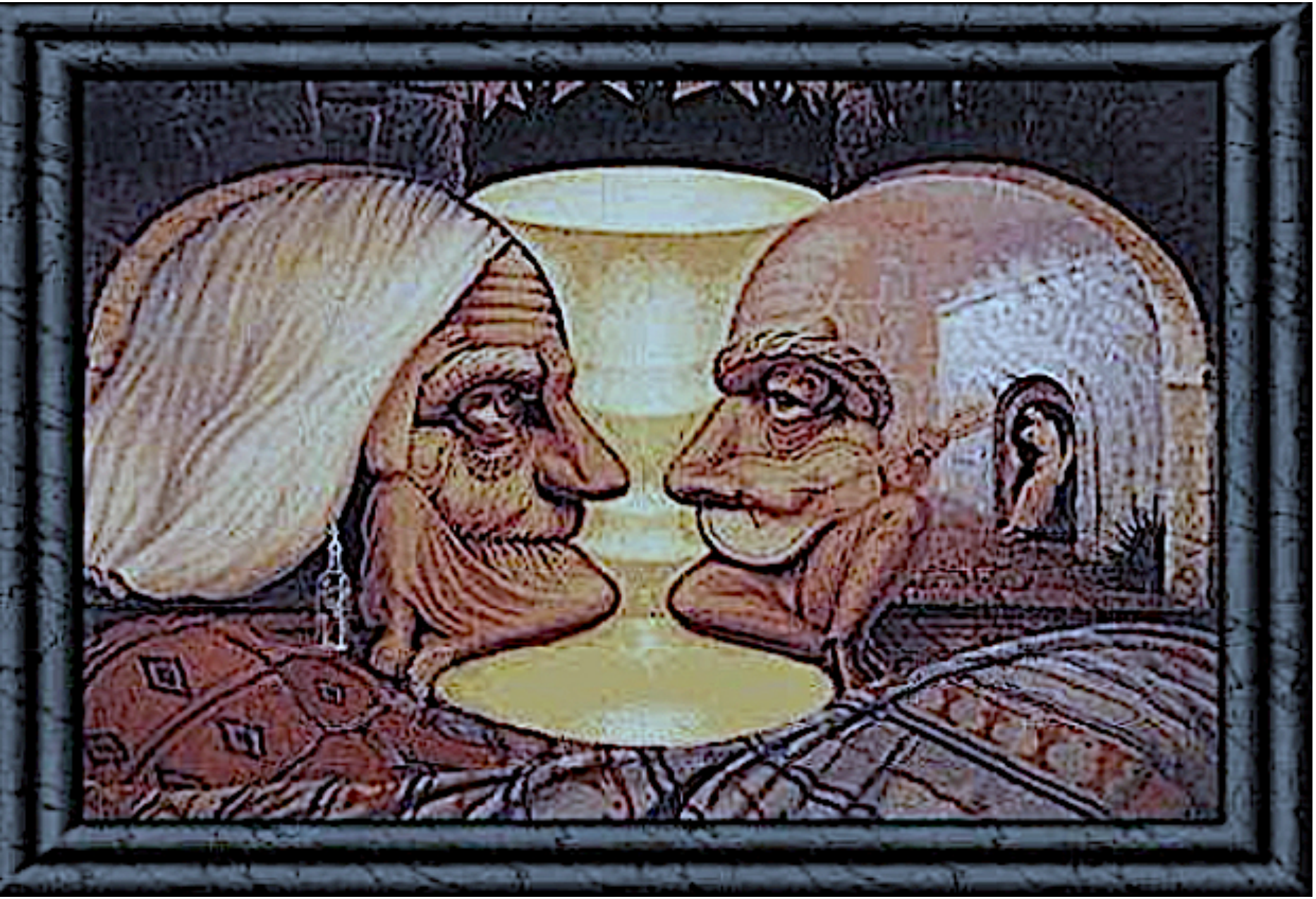
Original article

The role of a fixed *Berberis aristata*/*Silybum marianum* combination in the treatment of type 1 diabetes mellitus

- “…….One of my clinical colleagues describes the problem of the variable insulin action with the statement: “The variability of insulin action appears to be the pestilence of insulin therapy” (Prof. E.A. Chantelau,1993).”
- LUTZ HEINEMANN, DIABETES TECHNOLOGY & THERAPEUTICS Volume 4, Number 5, 2002



- Abbiamo ed avremo ancora di più a disposizione Insuline per schemi terapeutici basal-bolus ragionevolmente sicuri ed efficaci nel Diabete tipo 1
- Questi parametrici del controllo glicemico sono tutti favorevolmente modificati:
  - Varibilità glicemica
  - Ipoglicemia
  - Glicemia al risveglio
  - HBa1c
- E non vi ho parlato troppo di Microinfusori ……..



Grazie per l’attenzione

Prof. Bruno Bruni