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PALERMO, 17-19 NOVEMBRE 2016

NUOVISSIME TERAPIE

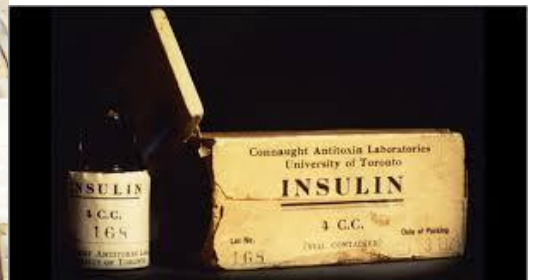
Insuline ultrarapide: CSII vs basal bolus

Giorgio Grassi

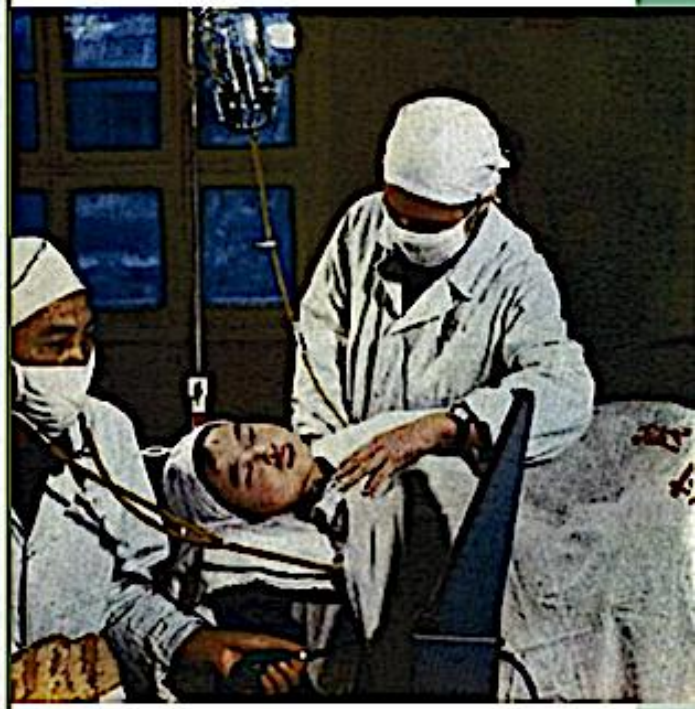
Endocrinologia Diabetologia e Metabolismo

Città della Salute e della Scienza

Torino



"Tenendo alta la grande bandiera rossa del pensiero del Presidente Mao Tse-Tung e manifestando la superiorità del sistema socialista sotto la guida appropriata del nostro partito, abbiamo ottenuto la sintesi totale dell'insulina bovina... per tutti i diversi stadi della nostra ricerca abbiamo seguito scrupolosamente gli insegnamenti del Presidente Mao-Tse-Tung: eliminando le superstizioni, analizzando le contraddizioni, rendendo omaggio alla pratica e riassumendo spesso le esperienze"



Insulin in the SC space……

- The time–action profiles of RAIAs do not match the rapid surge observed with physiologic insulin secretion, which is essential to suppress the rise in post-meal blood sugar. Analogs with faster and consistent insulin action profiles are essential to optimize insulin therapy for people with diabetes.
- Unlike the β-cell, which secretes insulin directly into the portal venous circulation, the AP infuses insulin into the SC space, which leads to a substantial delay of insulin absorption

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

Moving toward the ideal insulin for insulin pumps

Advances in insulin formulations have been important for diabetes management and achieving optimal glycemic control. Rapid-acting insulin analogs provide a faster time–action profile than regular insulin and are approved for use in pumps. **However, the need remains for therapy to deliver a more physiologic insulin profile**. New insulin formulations and delivery methods are in development, with the aim of accelerating insulin absorption to accomplish ultra-fast-acting insulin time–action profiles.

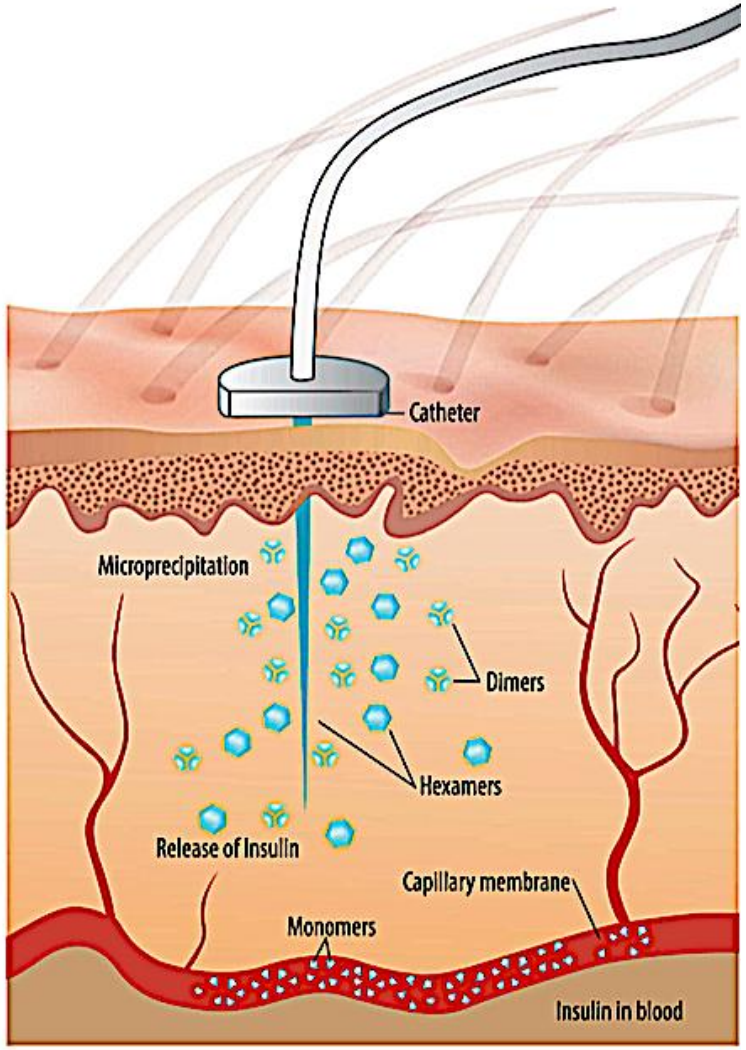


Figure 1. Hexameric insulin dissociation into dimers and monomers following subcutaneous infusion of rapid-acting insulin analogs.

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

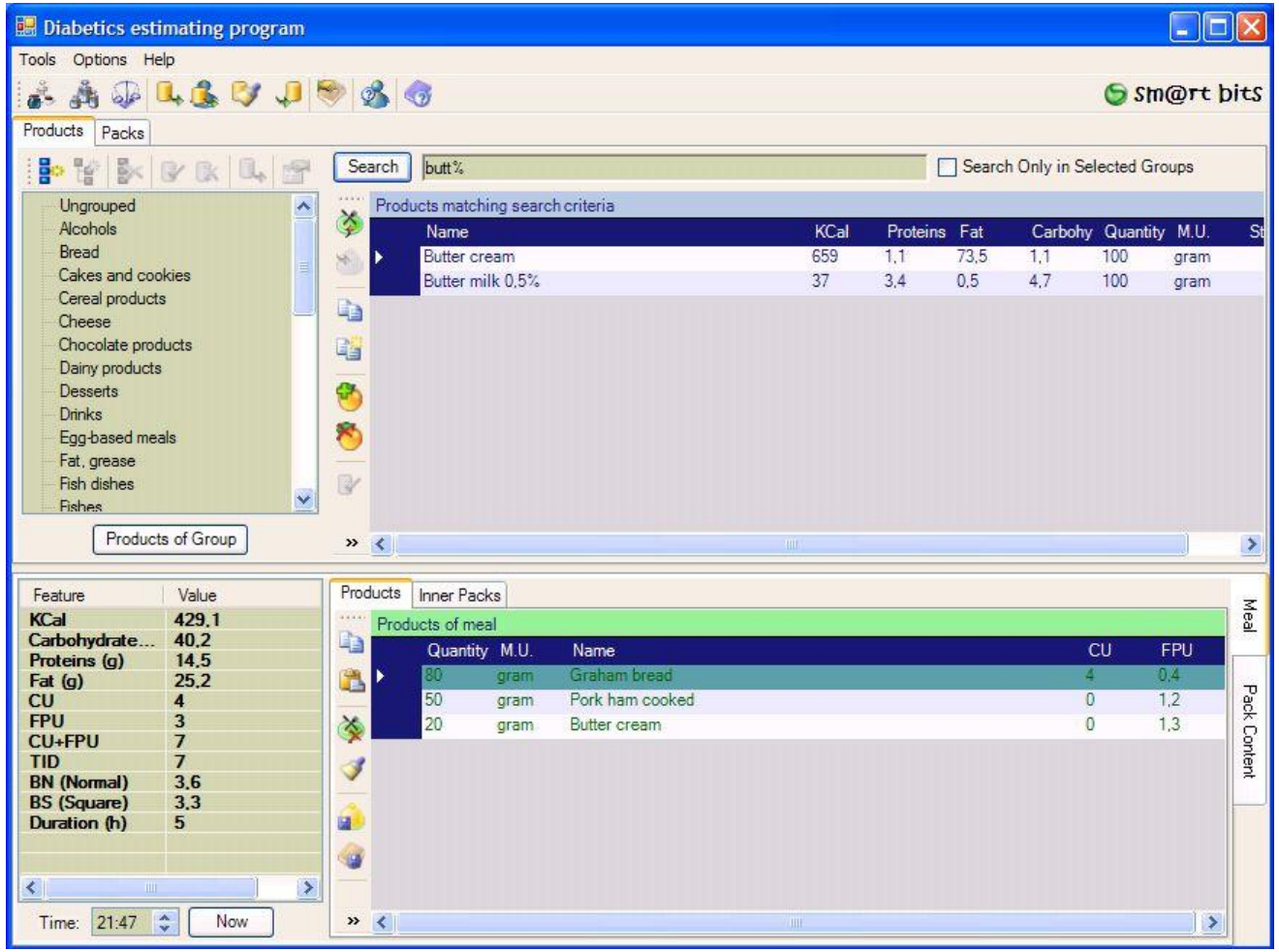
"Tamborlane phenomenon."

- Other factors that have been shown to lead to altered insulin action are temperature of the injection site; mixing RAIAs with long-acting insulins; and the age of insulin infusion site.[Diabet Care. 2010;33:1009– 1012. Curr Med Res Opin. 2014;30:753–760]
- The Yale insulin PK/PD study group demonstrated that the PK/ PD properties of RAIAs vary according to the age of the infusion site (i.e., from 1 to 4 days).[Diabet Care. 2009;32:240–244]
- **Surprisingly, the peak plasma insulin level was increased and the time-to-peak concentration was decreased during the fourth day of infusion site use compared with the first day**

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

CSII tecnologie per un bolo ed una erogazione basale più efficace ed adattabile

Bolus calculator



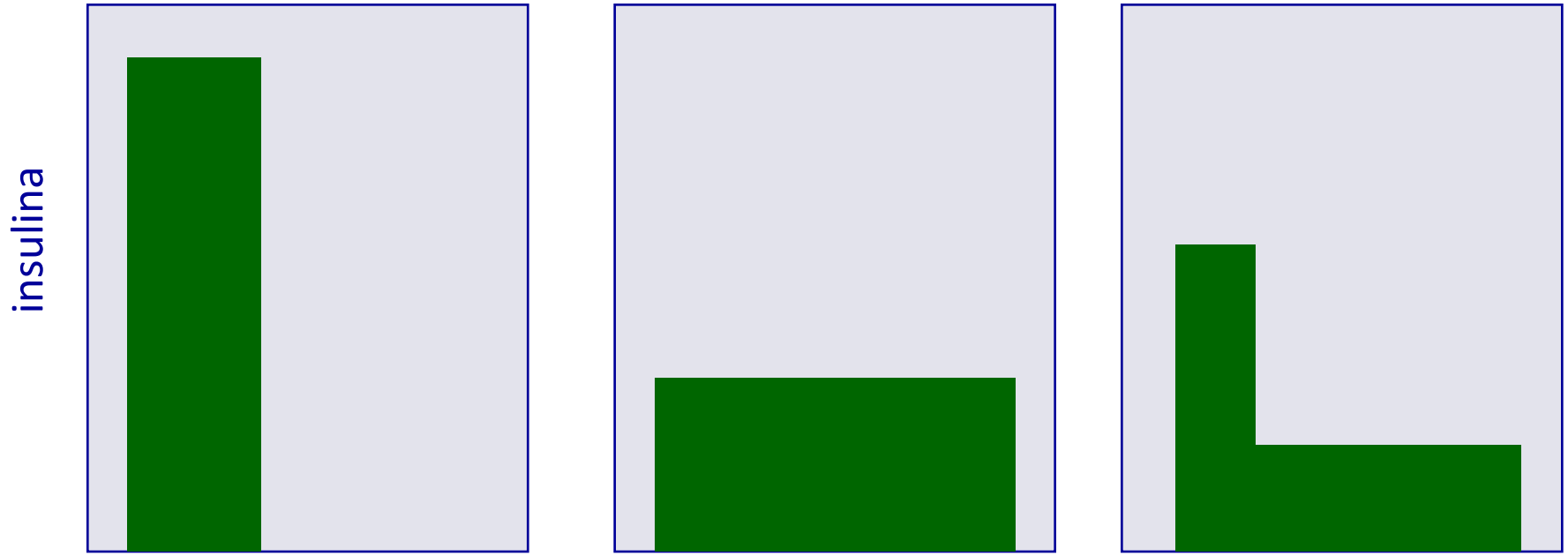
- The main advantage of the presented software is that it facilitates calculations of carbohydrate and fat protein exchange in meals.
- calculating data for insulin pumps and the injection (according to the author's method of Prof. MD, PhD, Ewa Pańkowska, Institute of Mother and Child of Warsaw)

Tipologie di boli

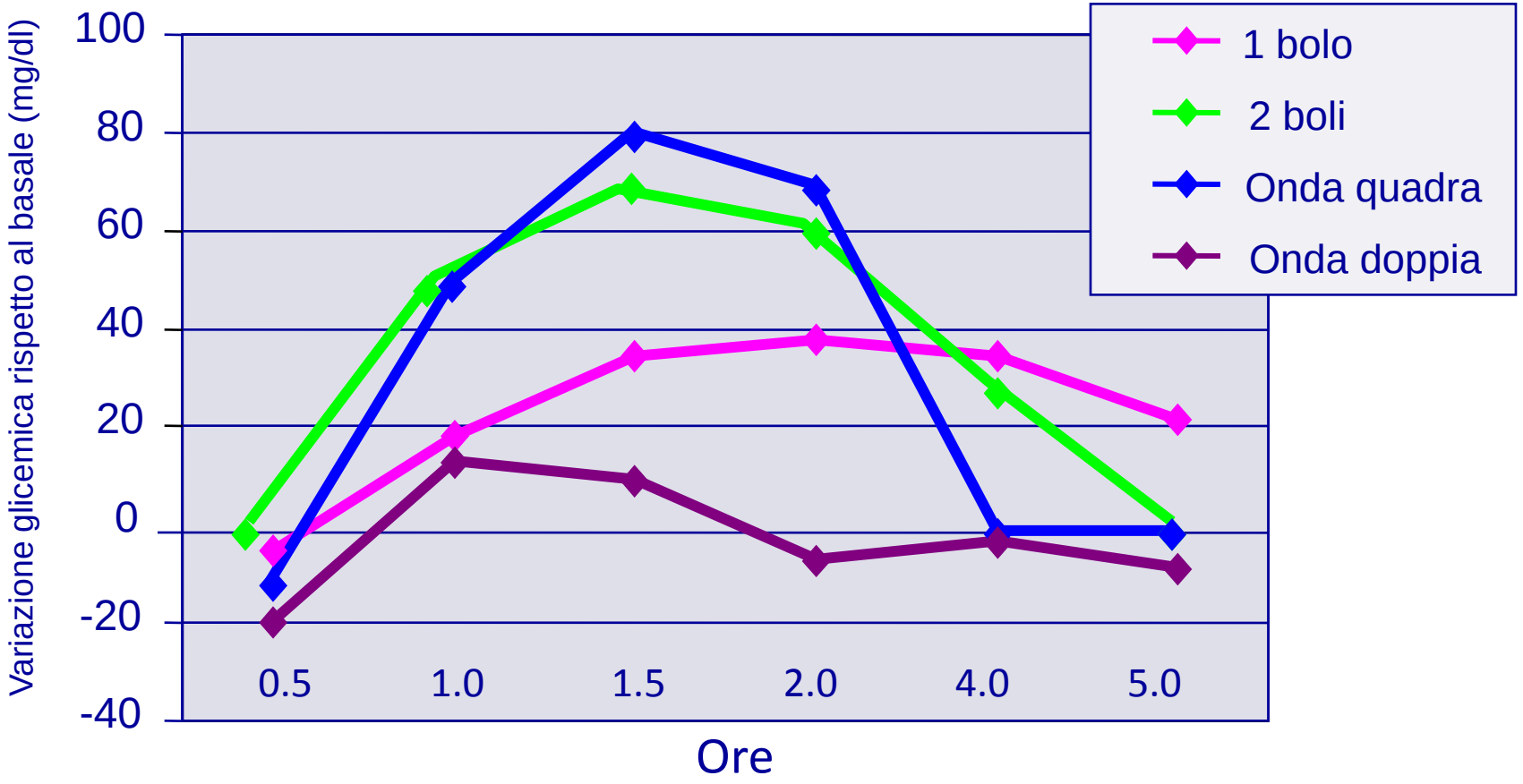
normale:
erogazione immediata

ad onda quadra (prolungato):
erogazione in un arco di tempo
più esteso, da 15’ a 12 ore

ad onda doppia:
erogazione combinata



Confronto di diversi tipi di boli con pasto ricco in Carboidrati & Grassi

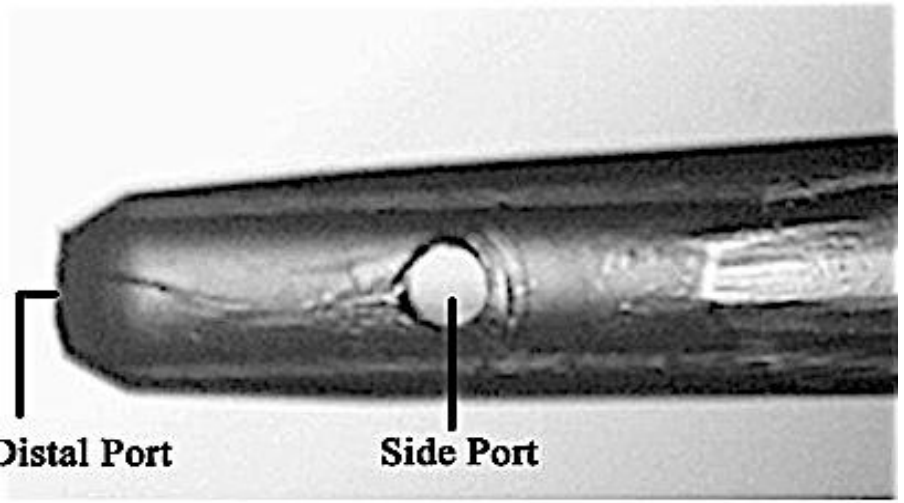


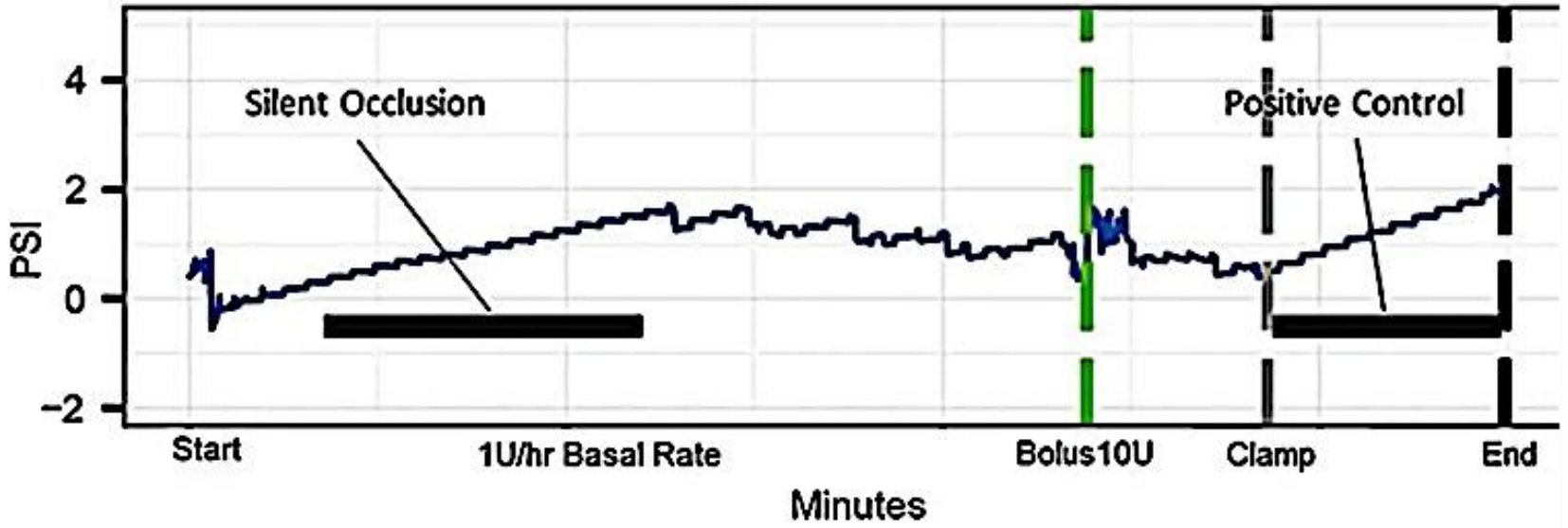
Chase HP et al: Diabetic Medicine 2002;19:317-321

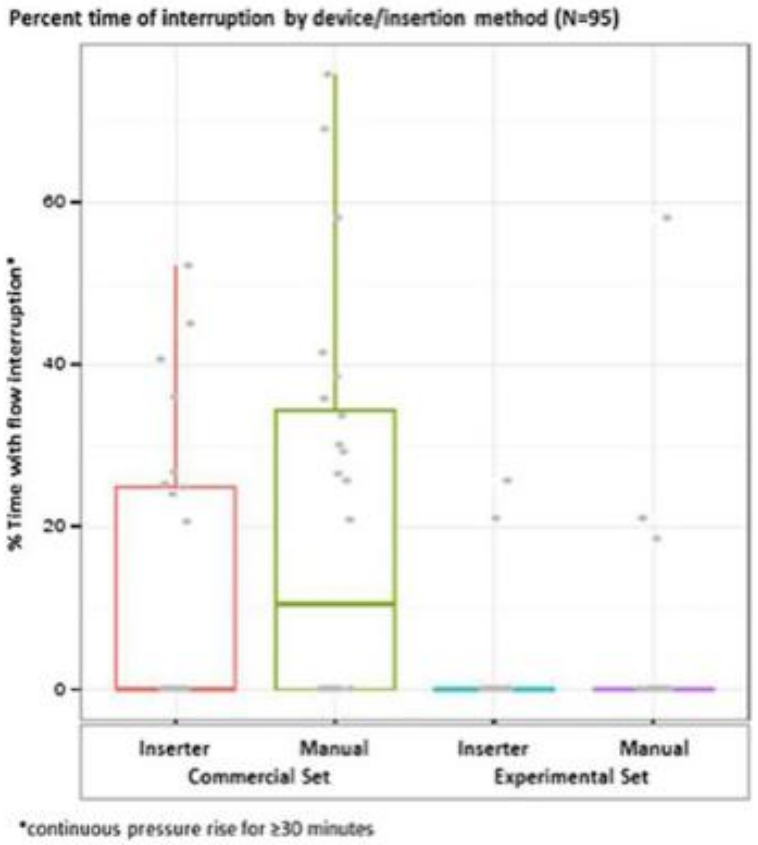
Insulin Infusion Set: The Achilles Heel of Continuous Subcutaneous Insulin Infusion (*J Diabetes Sci Technol 2012;6(4):954-964*)

- Pickup Survey of 91 adult CSII patients revealed set problems in a majority of them:
  - kinking in 64.1% of subjects
  - blockage in 54.3%. Blockage was associated with > 3 days of use of infusion sets
- Diabetes Technology & Therapeutics 2014; 16:145-9.

Infusion-set: Reduced Silent Occlusions with a Novel Catheter Infusion Set







Unexplained and unresponsive hyperglycemia during CSII that occurs without triggering an occlusion alarm raises the concern that ‘‘silent’’ occlusions may be occurring.

DIABETES TECHNOLOGY & THERAPEUTICS Volume 18, Number 3, 2016

Lag Setting del Bolo

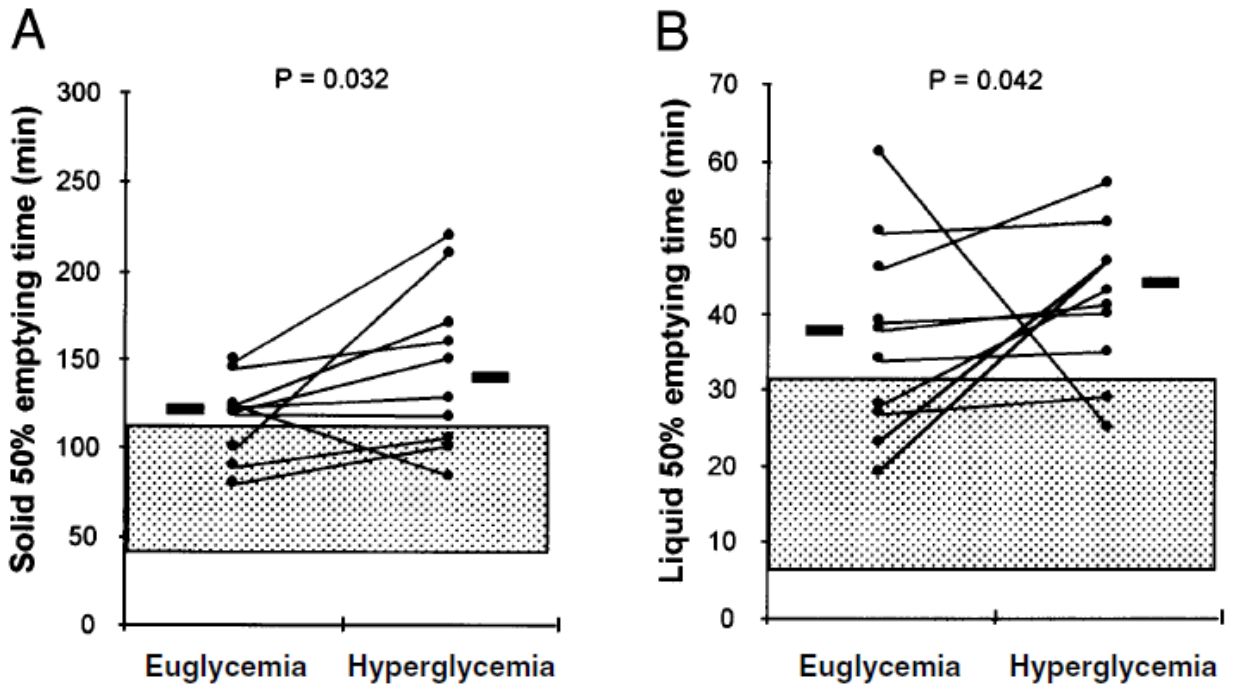


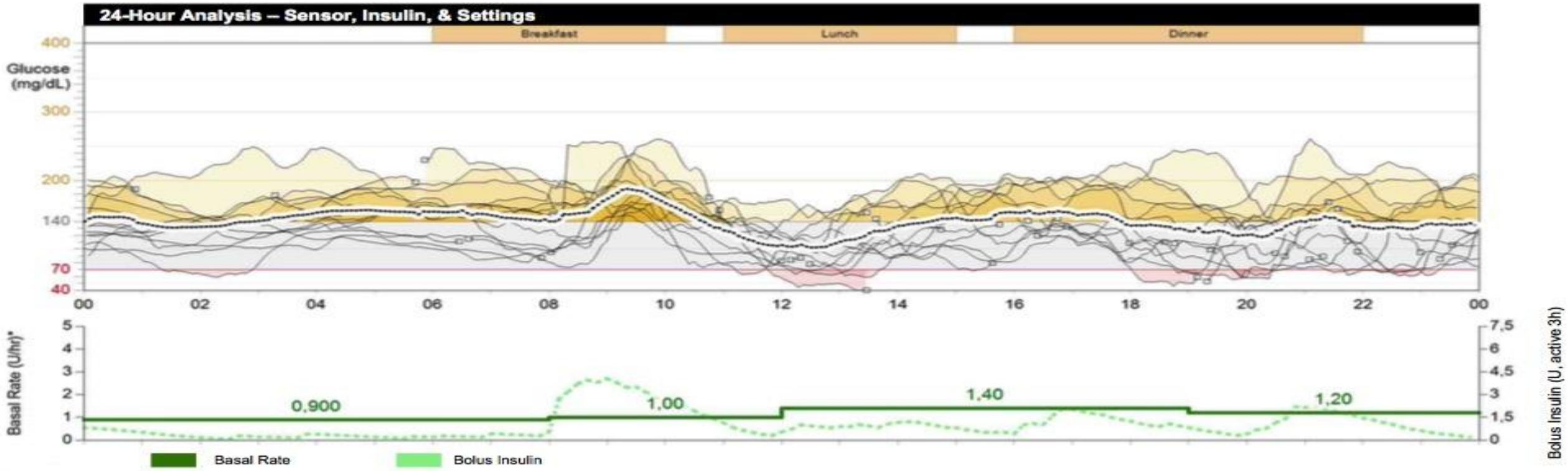
Figure 1—*Solid gastric emptying (A) and liquid gastric emptying (B) in 10 type 1 diabetic patients during euglycemia and hyperglycemia. Mean values are indicated by the solid bars. The ranges in healthy subjects are shown by the shaded areas. From Fraser et al. (13).*

- Ritardare di **15, 30, 45 o 60 minuti** l'inizio dell'erogazione del bolo insulinico

- **4 differenti velocità** di erogazione del bolo
  - Molto lento (3 Units/min = 20 sec/Unit)
  - Lento (6 Units/min = 10 sec/Unit)
  - Moderato (9 Units/min = 6.7 sec/Unit)
  - Standard (12 Units/min = 5 sec/Unit)

DC 1994;17:901

Predictive LGS in real-Life



La reale protezione dall'ipoglicemia

La tecnologia **SmartGuard™** sul sistema MiniMed™ aiuta a proteggere dall'ipoglicemia.

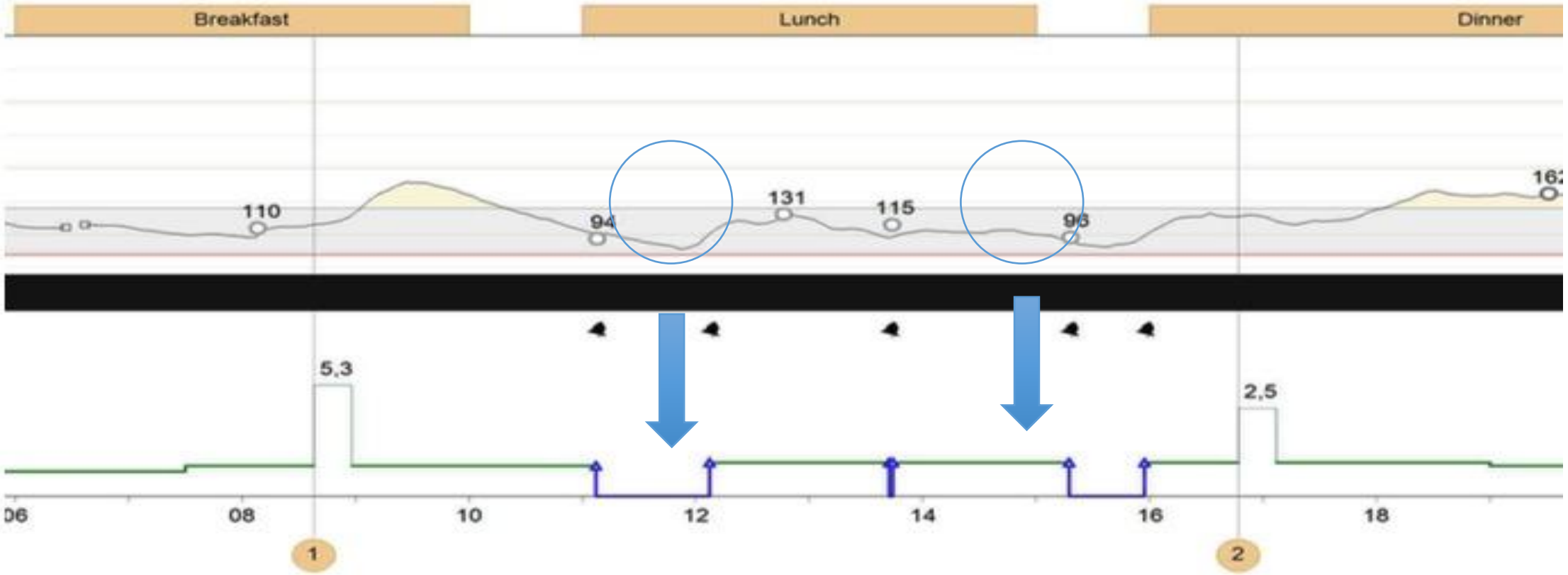
Come funziona:

1 PREVEDE
quando i livelli di glucosio

2 BLOCCA
l'erogazione di insulina per prevenire

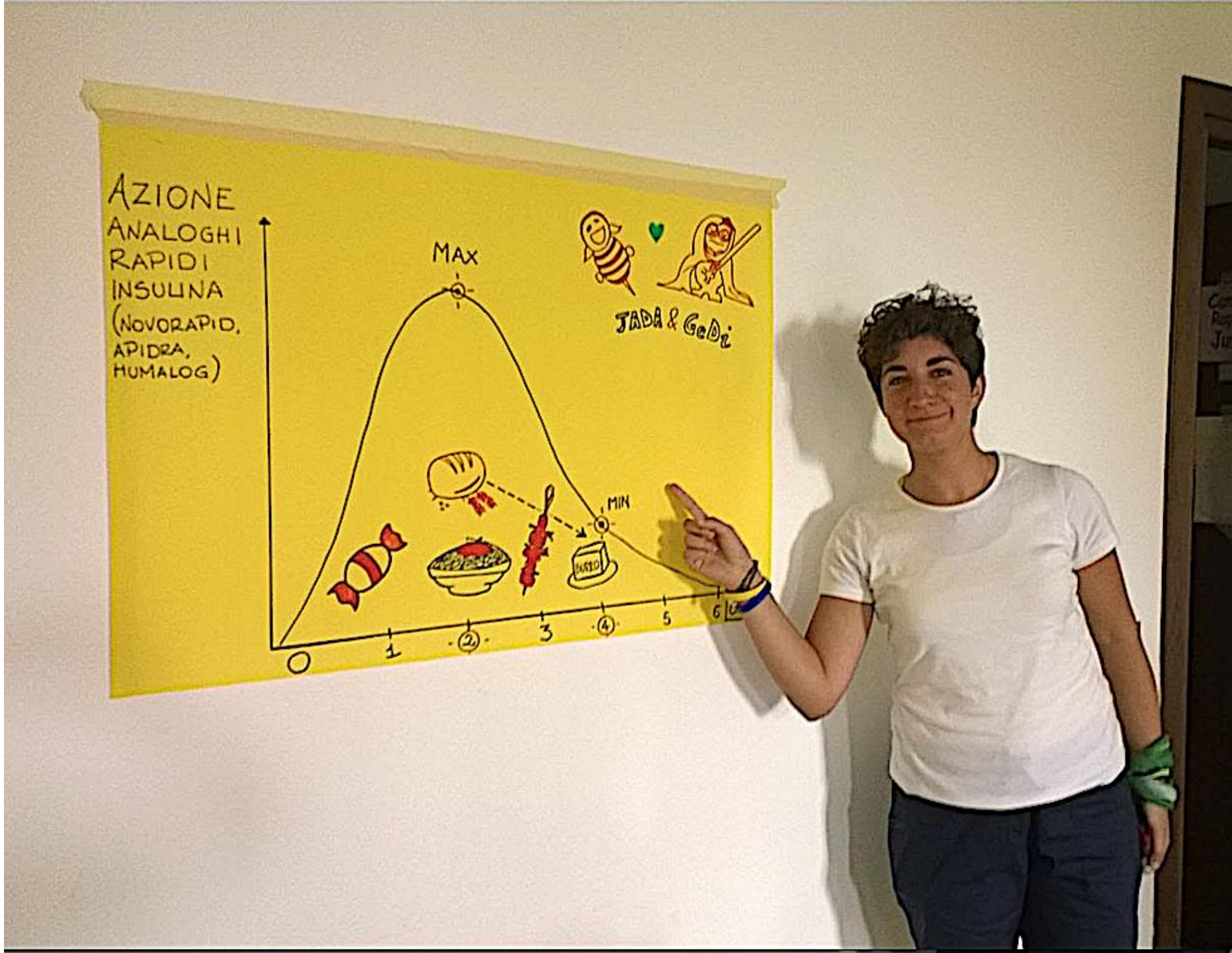
3 RIAVVIA
l'erogazione di insulina quando i livelli di glucosio sono tornati

Predictive LGS in real-Life



Insulina prandiale: il presente

Educazione Terapeutica: I corsi



Designing an ultra-fast insulin

Administration

- Sprinkler needle
- Pulmonary

Formulation

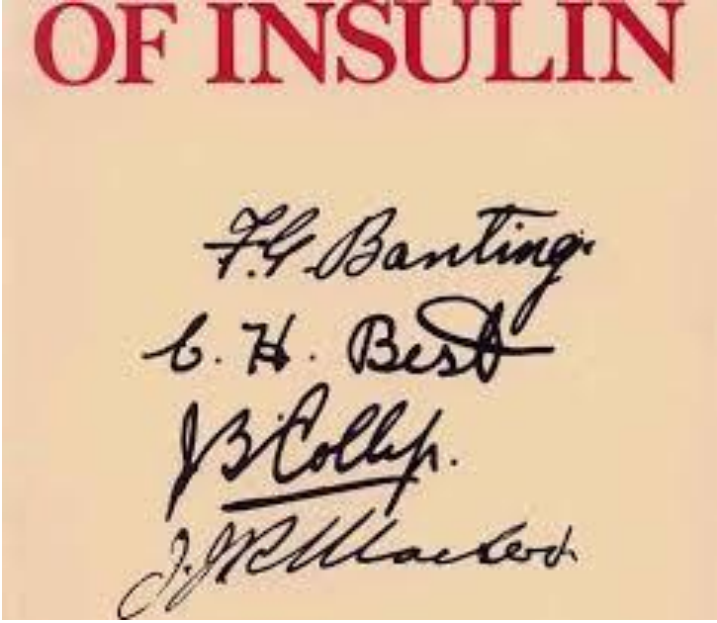
- **Additives, for example:**
  - **EDTA/citric acid**
  - **Magnesium**
  - **Bio-chaperone**
  - **Niacinamide**
  - **Other**

Injection site

- Application of heat
- Hyaluronidase

EDTA, ethylenediamine tetra-acetic acid

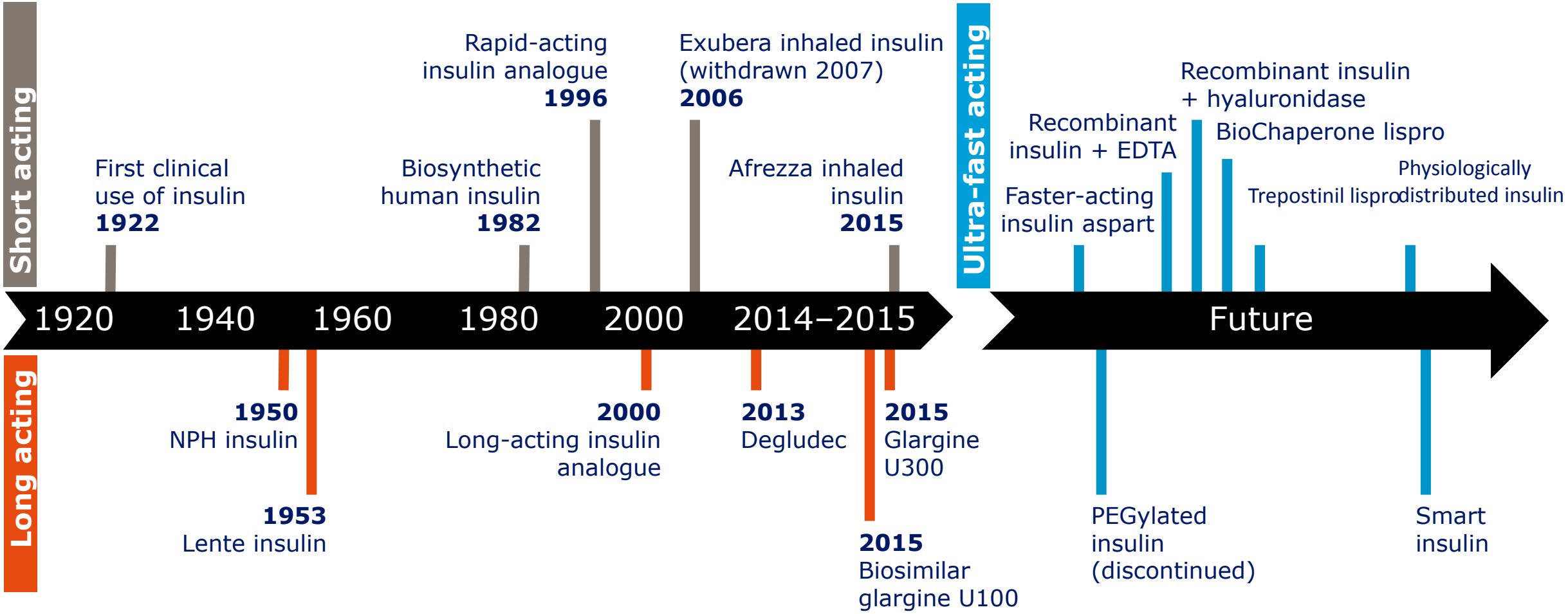
Clinical pharmacology results



Formulation

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

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

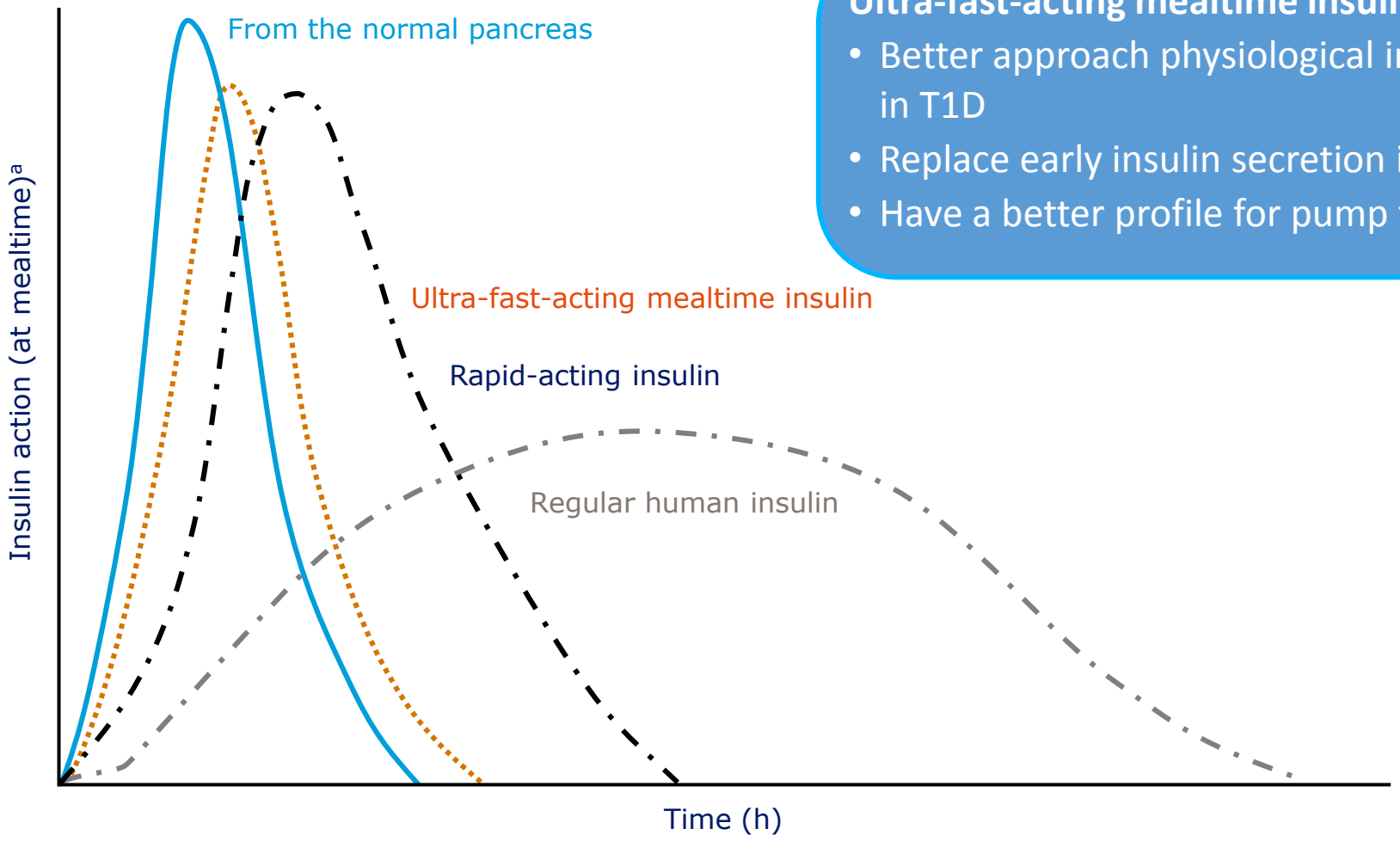


Adapted from Cahn A et al. *Lancet Diabetes Endocrinol* 2015;3:638–652.
Eli Lilly Patent Application 12 Nov 2015; Eli Lilly Press Release 4 Dec 2015; Novo Nordisk Capital Markets Day R&D update 19 Nov 2015

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

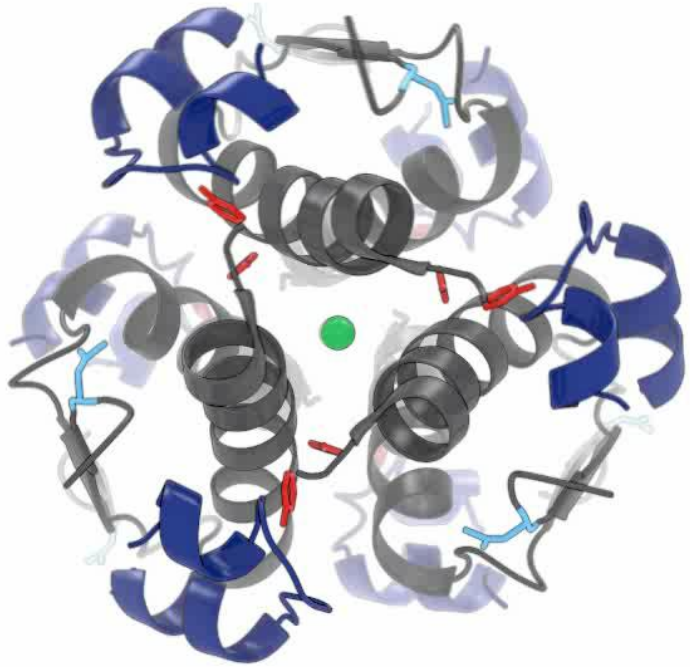
Ultra-fast-acting mealtime insulin should:

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



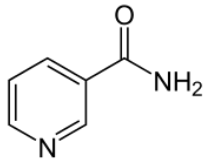
[a]Schematic representations. T1D, type 1 diabetes; T2D, type 2 diabetes.Adapted from Home PD. Diabetes Obes Metab 2015;17:1011–20.

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



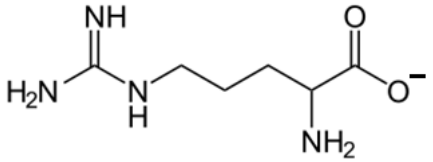
Insulin aspart

Niacinamide: absorption modifier



Vitamin B3

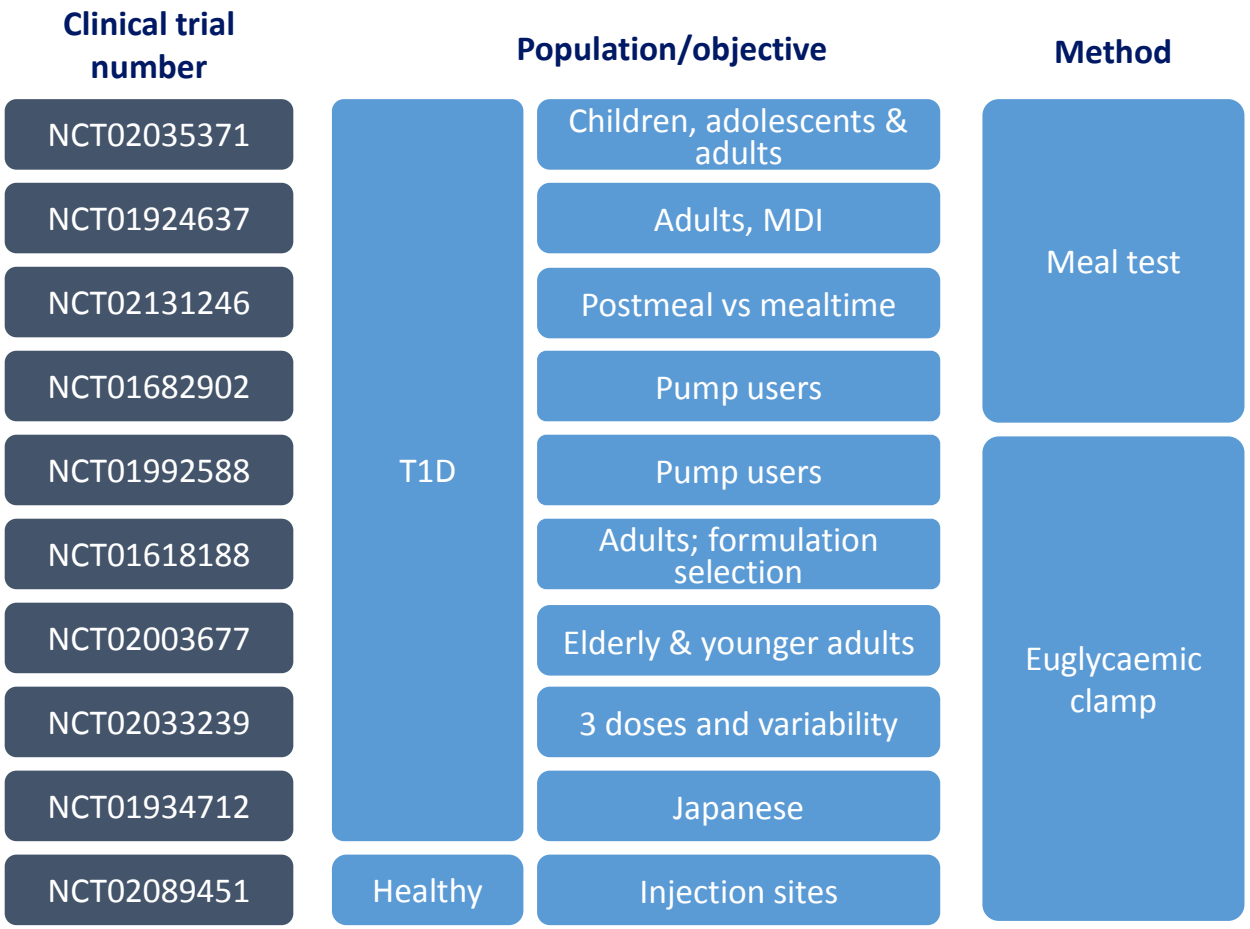
L-Arginine: added for stability



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

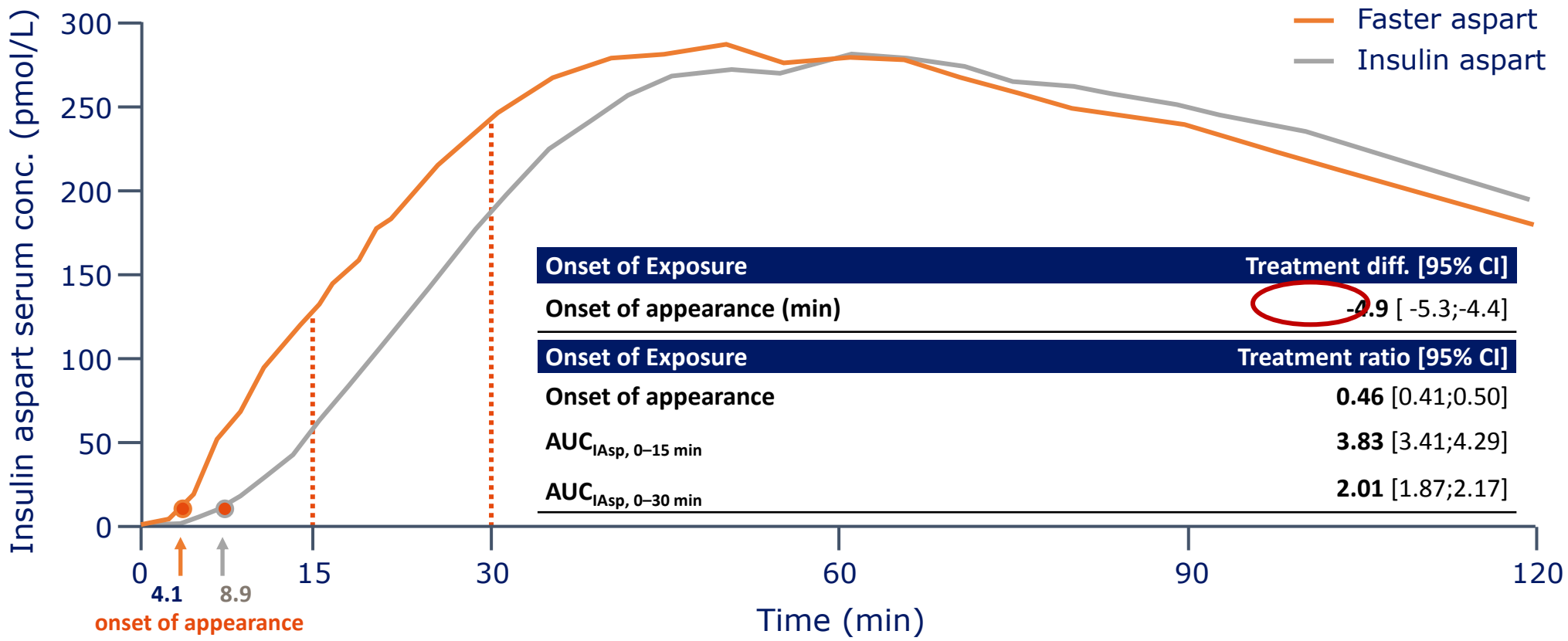
PK: 6 studies (218 subjects)

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

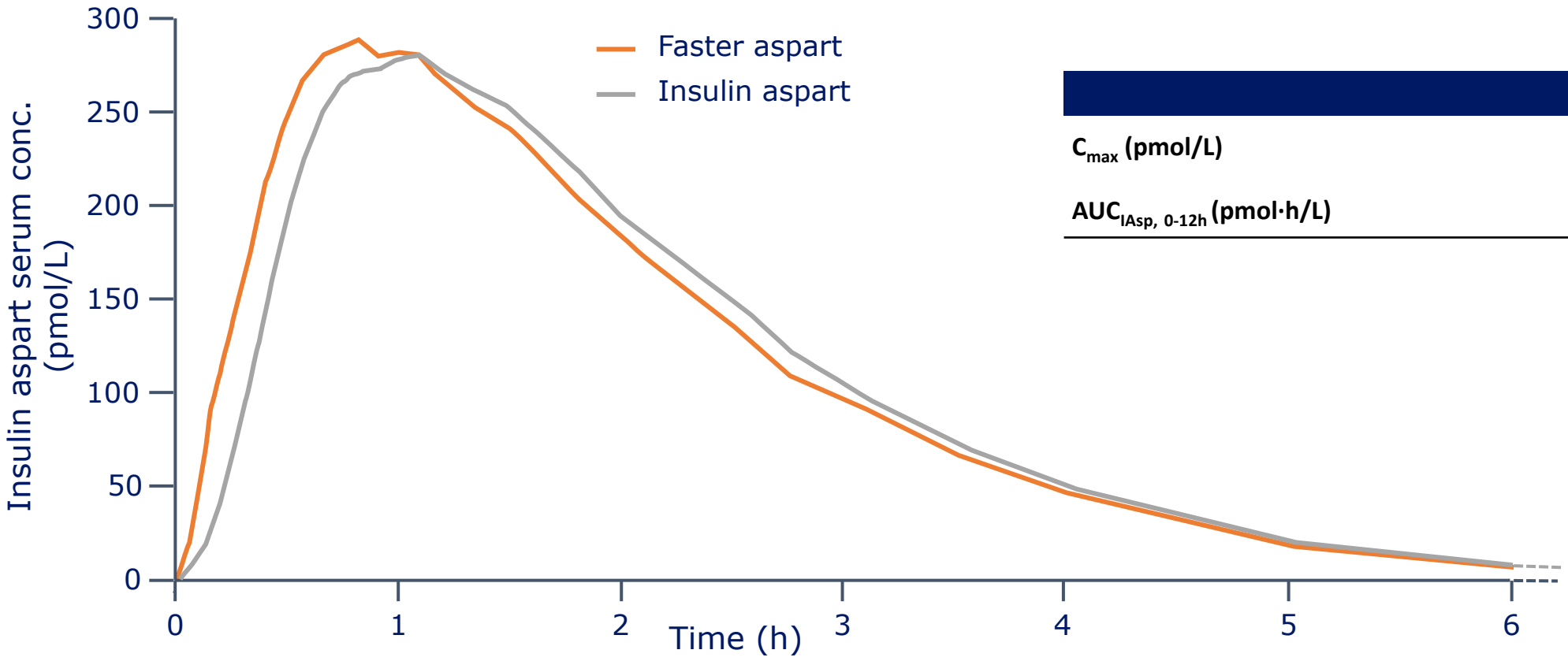
Two-fold higher insulin exposure within the first 30 minutes

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

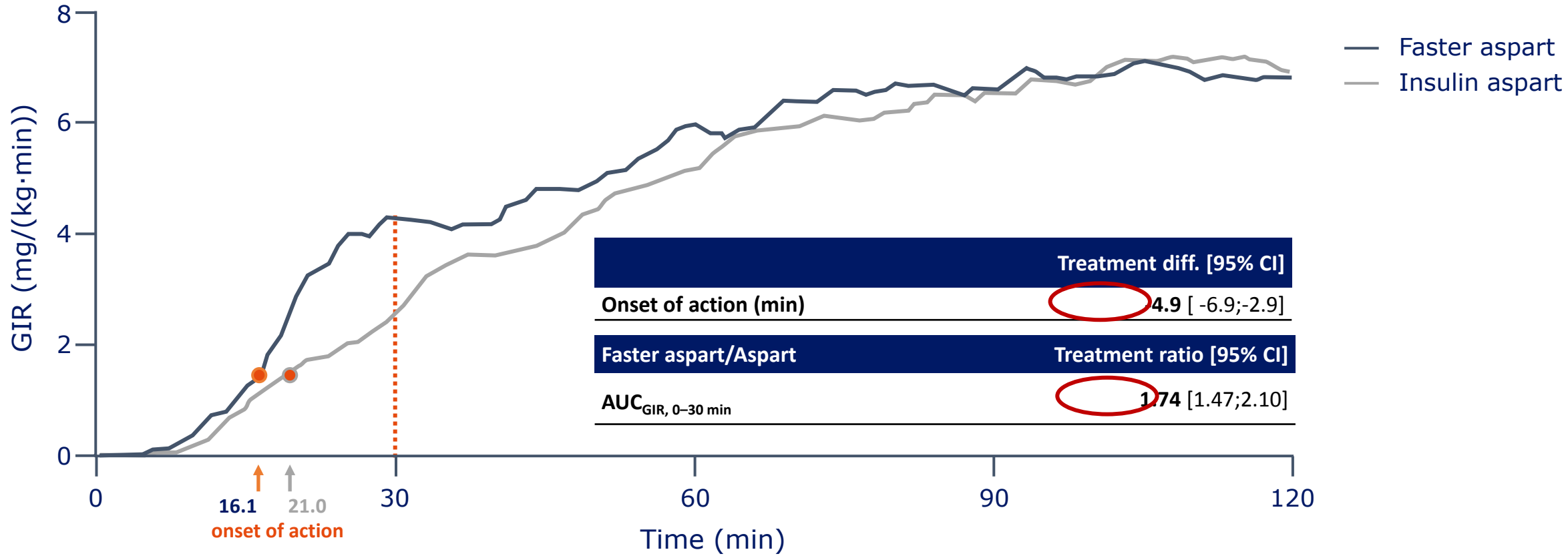
C_{max} ratio p=0.085

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



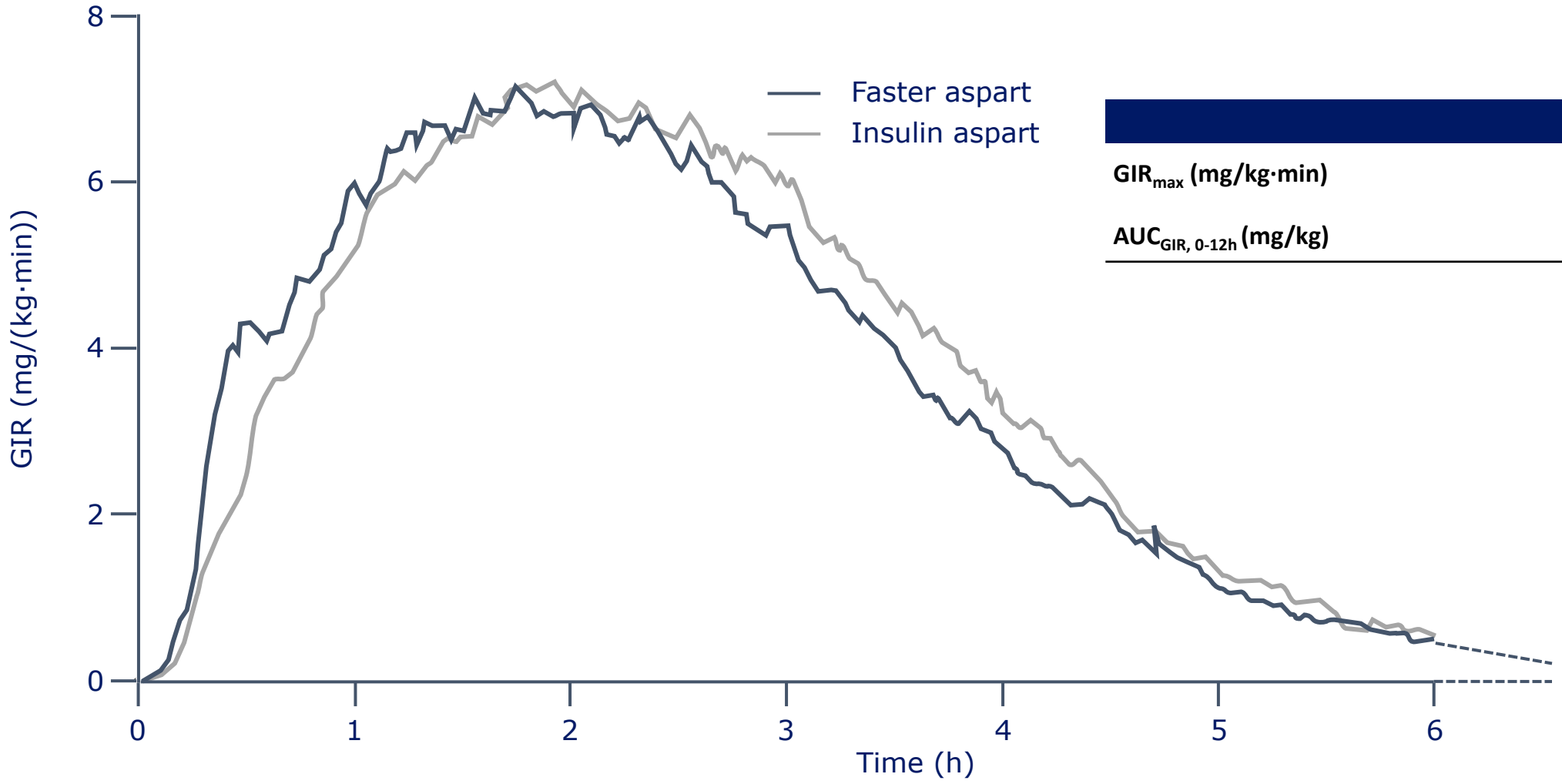
>50% greater insulin action within the first 30 minutes

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



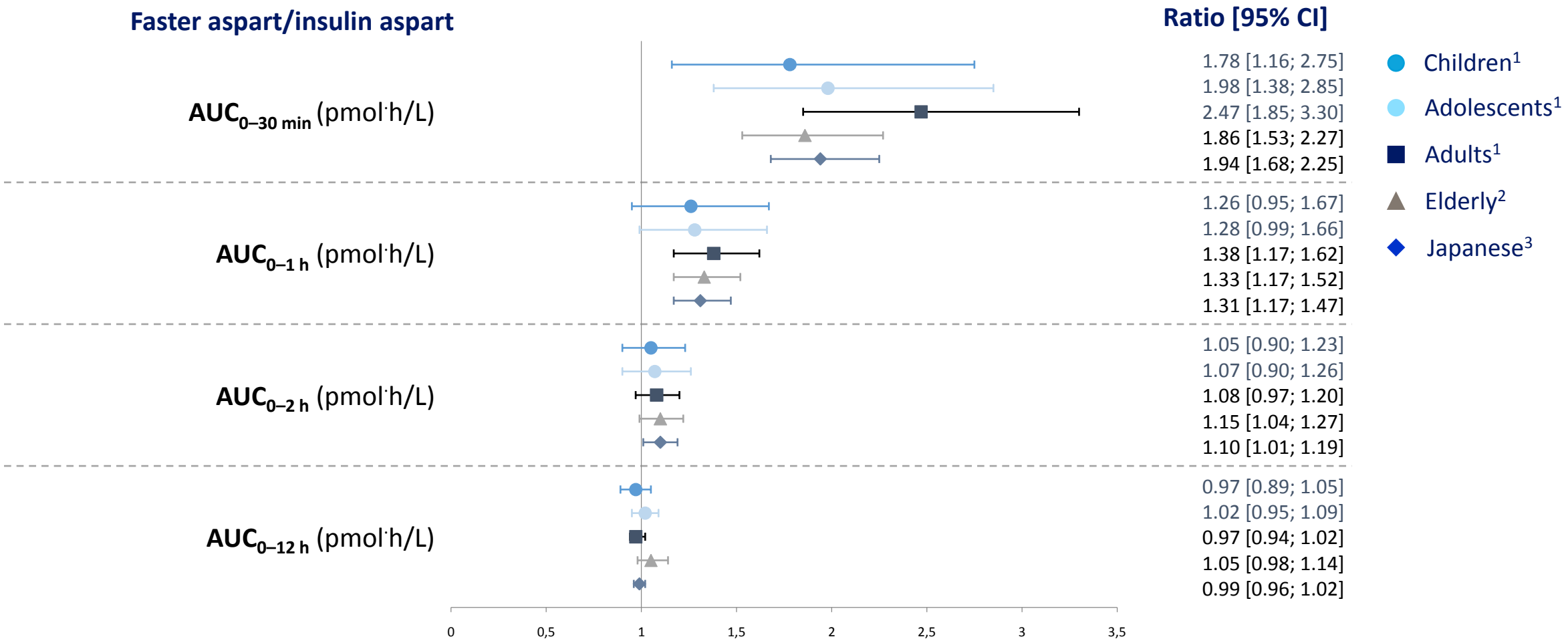
	Ratio [95%CI]
GIR_{max} (mg/kg·min)	**1.01** [0.96;1.05]
$AUC_{GIR,\ 0\text{-}12h}$ (mg/kg)	**0.98** [0.94;1.03]

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

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

Insulin exposure in special populations with T1D

Greater early insulin exposure consistently observed with faster aspart vs. insulin aspart

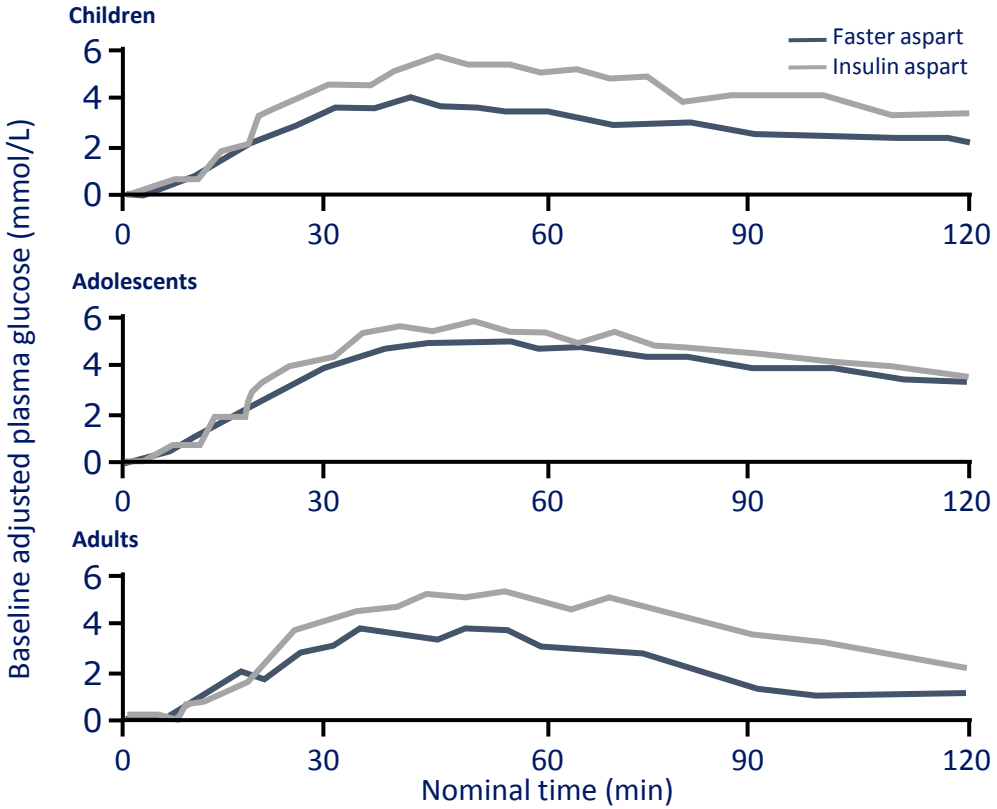


AUC, area under the curve; CI, confidence interval; T1D, type 1 diabetes

1. Danne *et al. Diabetes* 2015;64(S1):976-P; 2. Heise *et al. Diabet Obes Metab* 2015;17:682–8; 3. Shiramoto *et al. Diabetes* 2015;64(S1):983-P

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

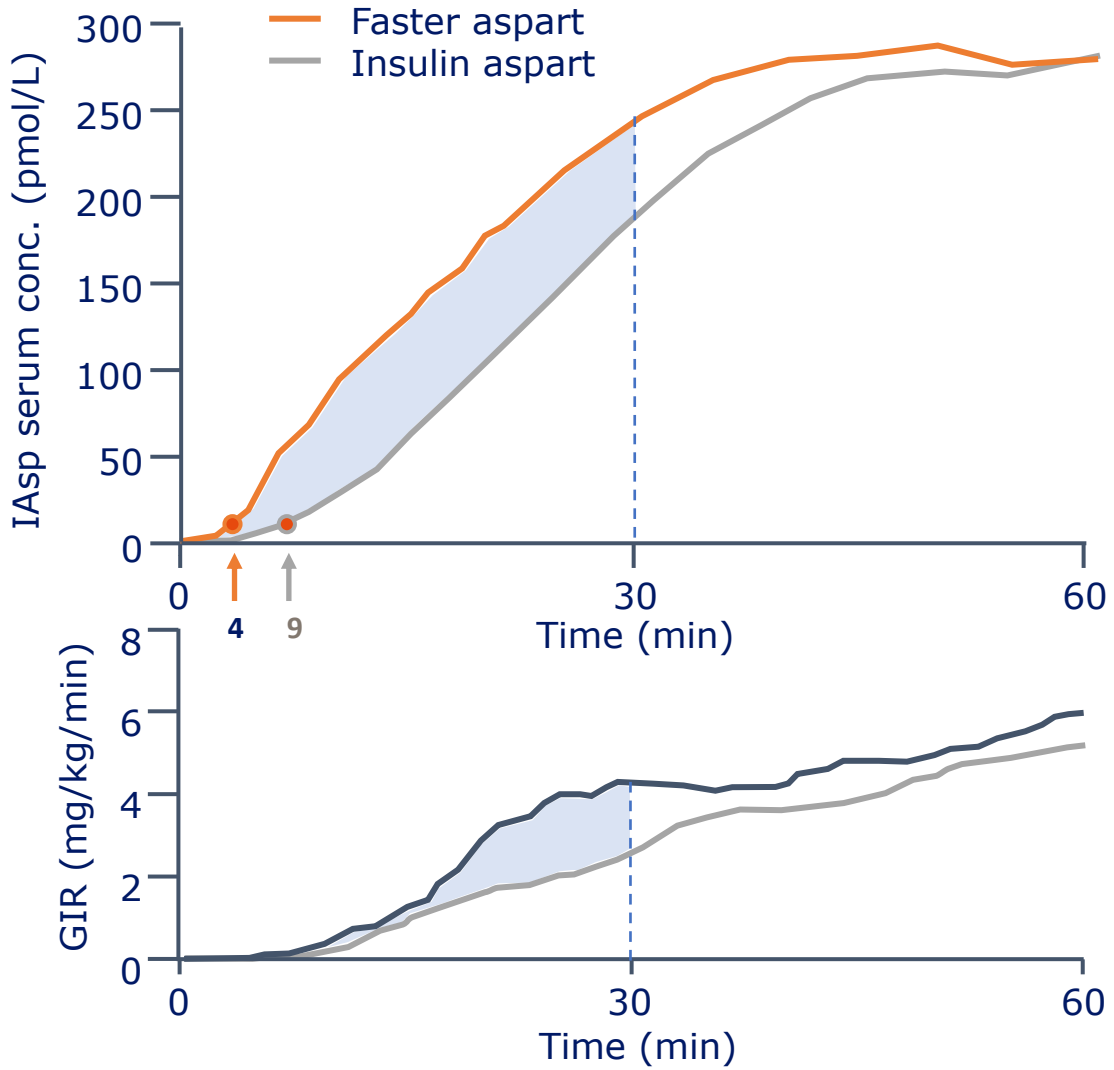
What do we know about faster aspart via s.c. injection (PK/PD)?

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

ump data


120


4:0
PM
OLUS HISTORY
2MAR 3:25A
6.1U
CH: 0 BG:---
MiniMed
ESC
ACT


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

CSII trials (overview)

Trial 3890: PK/PD pump trial

Trial 3930: Exploratory pump trial with meal test

onset® 4 : Confirmatory pump compatibility and safety trial

PD, pharmacodynamics; PK, pharmacokinetic; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

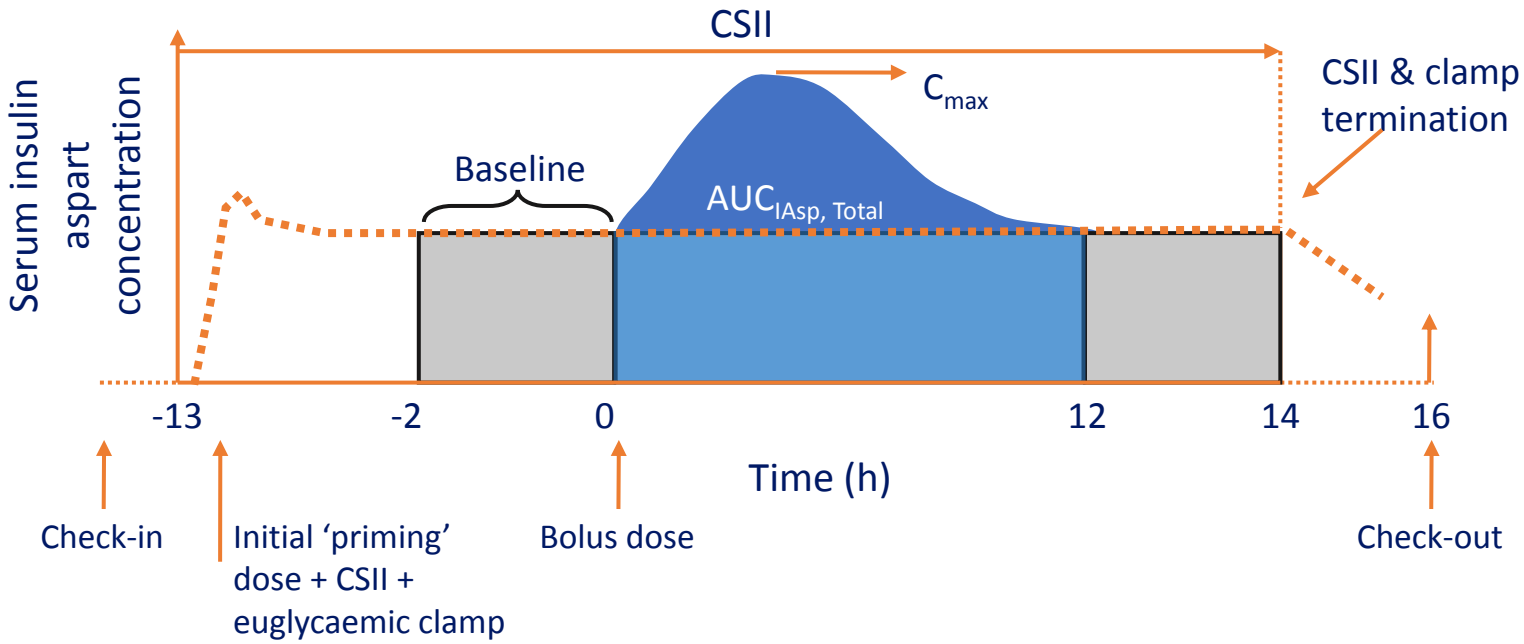
PK and PD Study

- Randomised, double-blind trial in 48 subjects with type 1 diabetes (mean ± SD age: 46.3±8.6 y; HbA1c: 7.4±0.6%); euglycemic clamp
- Two-period, crossover trial: faster aspart vs insulin aspart
- Insulin pump (MiniMed Paradigm® Veo™ 754 [Medtronic])

Doses:

- Priming dose – 0.08 U/kg BW
- Basal rate – 0.02 U/kg BW/h
- Bolus dose – 0.15 U/kg BW

- Maximum bolus infusion time is 5 min

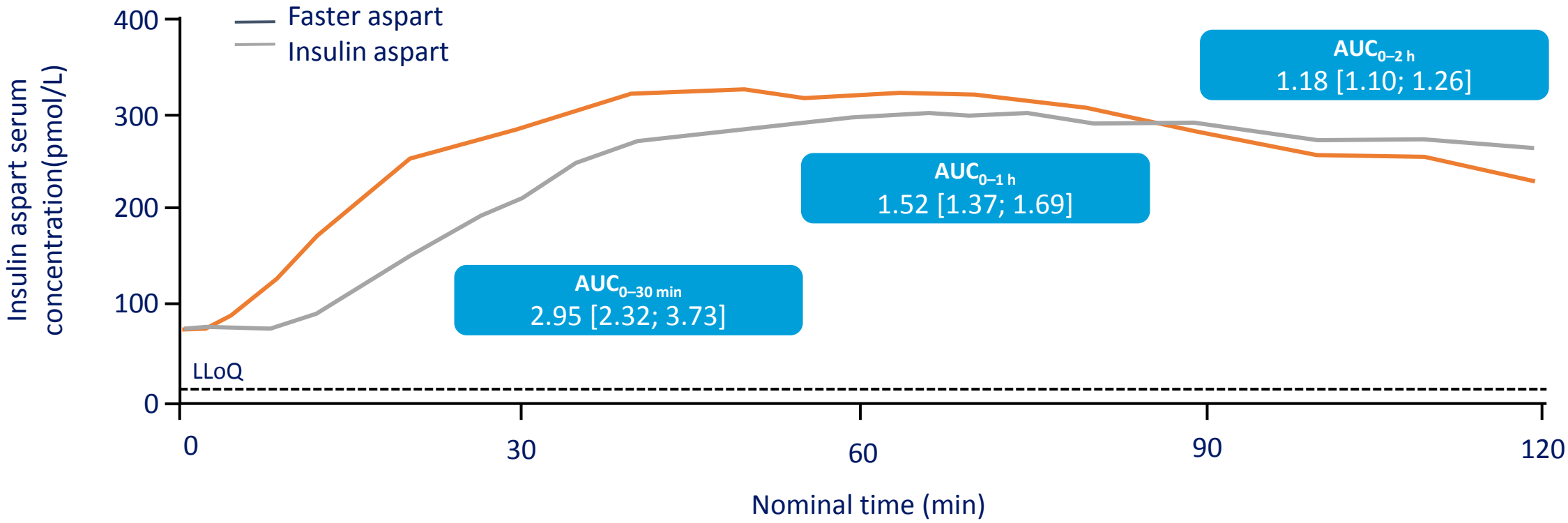


A second formulation of faster aspart [R] was tested in this exploratory study, but was discontinued in favour of faster aspart [Q] and not reported here.

AUC, area under the curve; BW, body weight; CSII, continuous subcutaneous insulin infusion

Heise T *et al. Diabetes* 2015;64(S1):Abstract 1005-P

PK results (CSII)

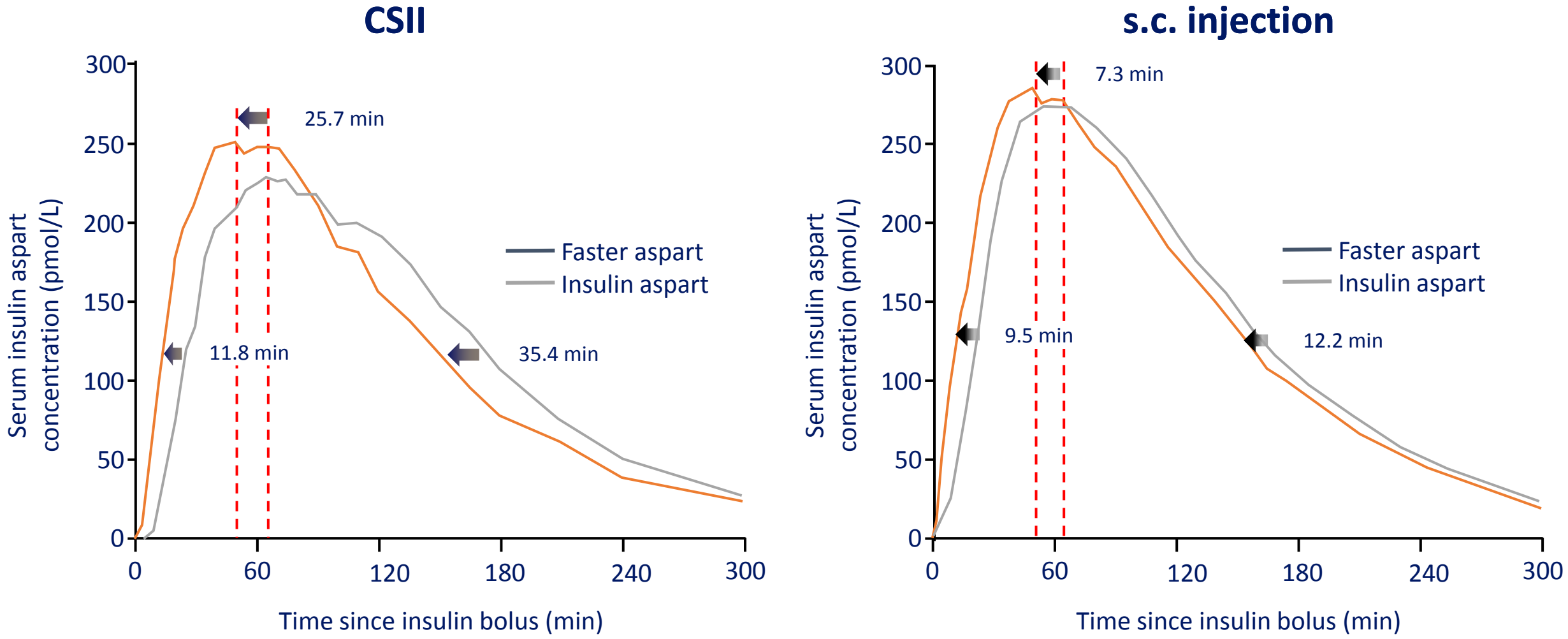


- ~3-fold higher insulin exposure within the first 30 min with faster aspart vs. insulin aspart

Treatment ratios (faster aspart/insulin aspart) and 95% CI.
AUC, area under the curve; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; LLoQ, lower limit of quantification
Heise T *et al. Diabetes* 2015;64(S1):Abstract 1005-P

PK summary: CSII *vs* s.c. injection

Indirect comparison

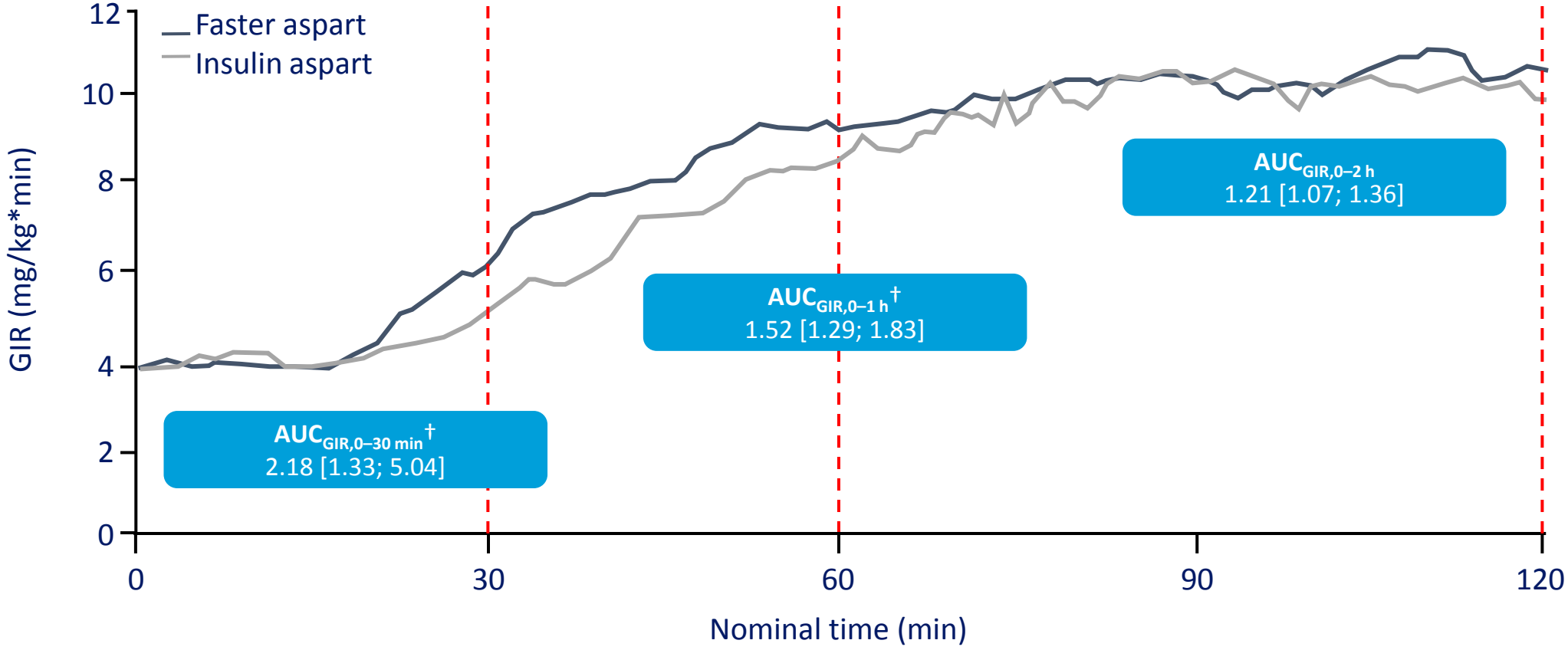


CSII, continuous subcutaneous insulin infusion; s.c., subcutaneous insulin infusion

Heise T *et al. Diabetes* 2015;64(S1):Abstract 1005-P. Heise T et al. *Diabetes* 2016;65(S1):A239.

PD results (CSII)

Greater early glucose-lowering effect with faster aspart vs. insulin aspart



- More than 100% greater insulin action within the first 30 min
- Similar total and maximum glucose-lowering effect

Treatment ratios (faster aspart/insulin aspart) and 95% CI. †Calculated using Fieller's method.
AUC, area under the curve; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; GIR, glucose infusion rate; PD, pharmacodynamics

Heise T *et al. Diabetes* 2015;64(S1):Abstract 1005-P

Comparing faster aspart and insulin aspart in CSII

14-day exploratory crossover trial

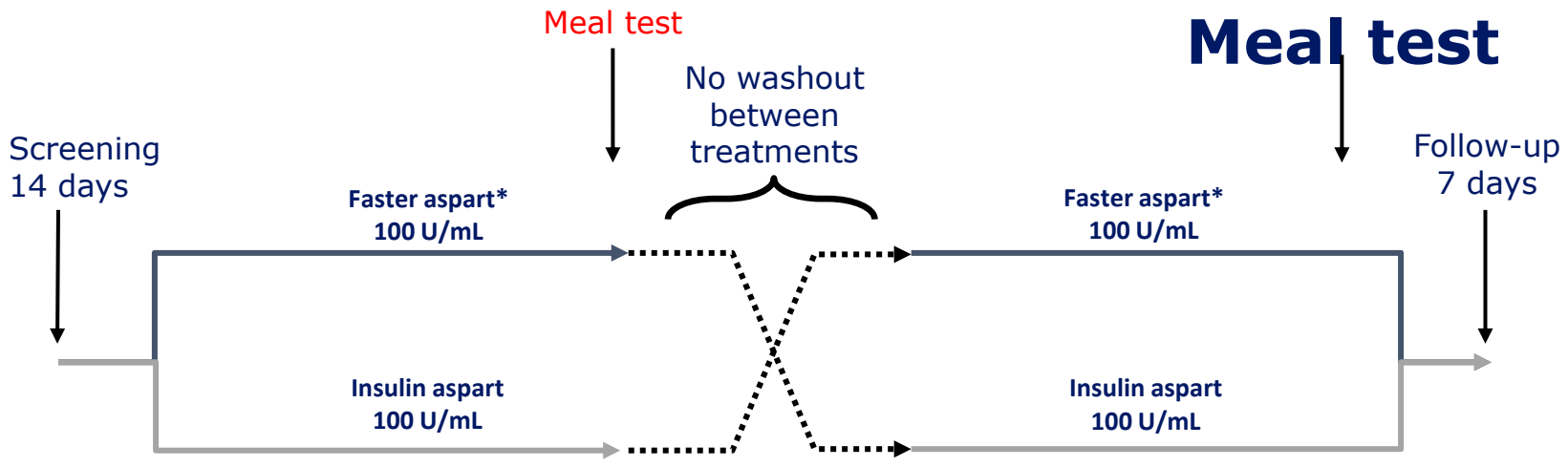
A double-blind, randomised, crossover, active-controlled trial comparing 14 days of continuous subcutaneous insulin infusion (CSII) of faster aspart with CSII of insulin aspart in 43 adults with T1D

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

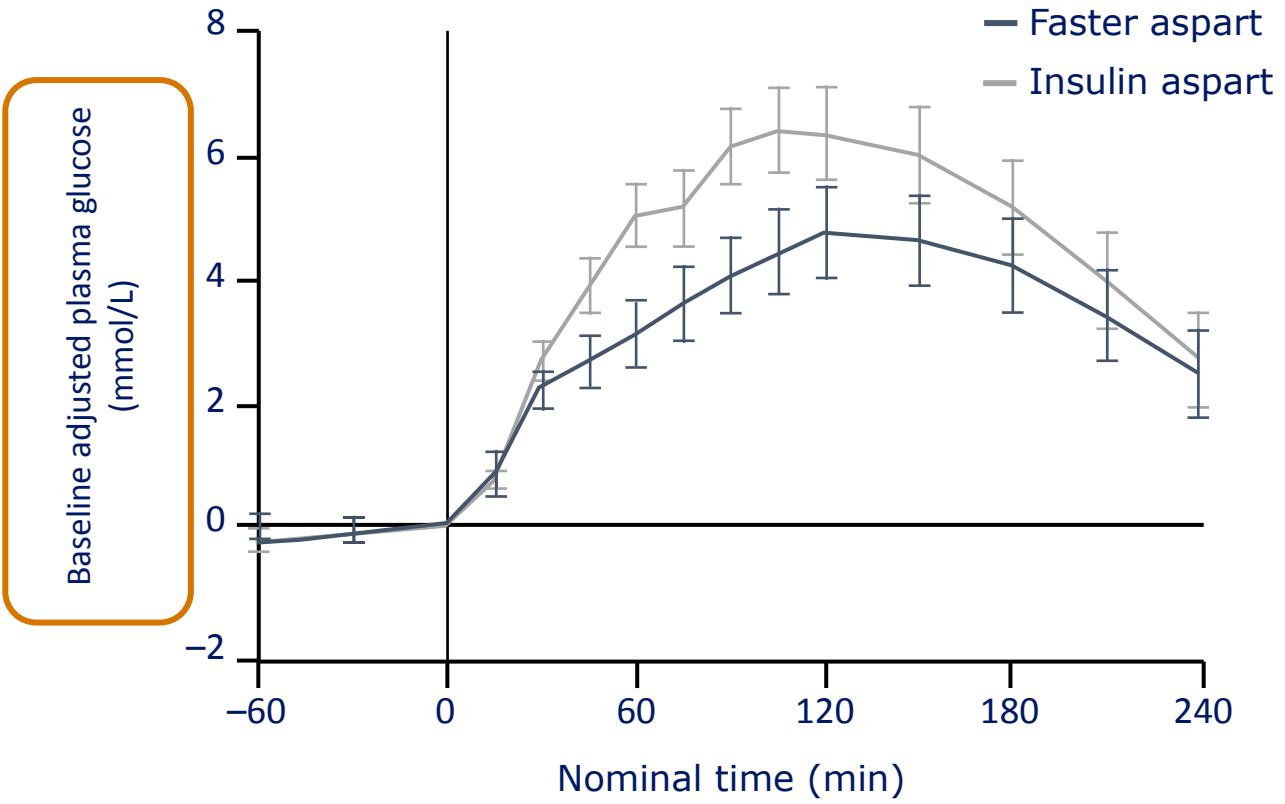
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; PG, plasma glucose; T1D, type 1 diabetes

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

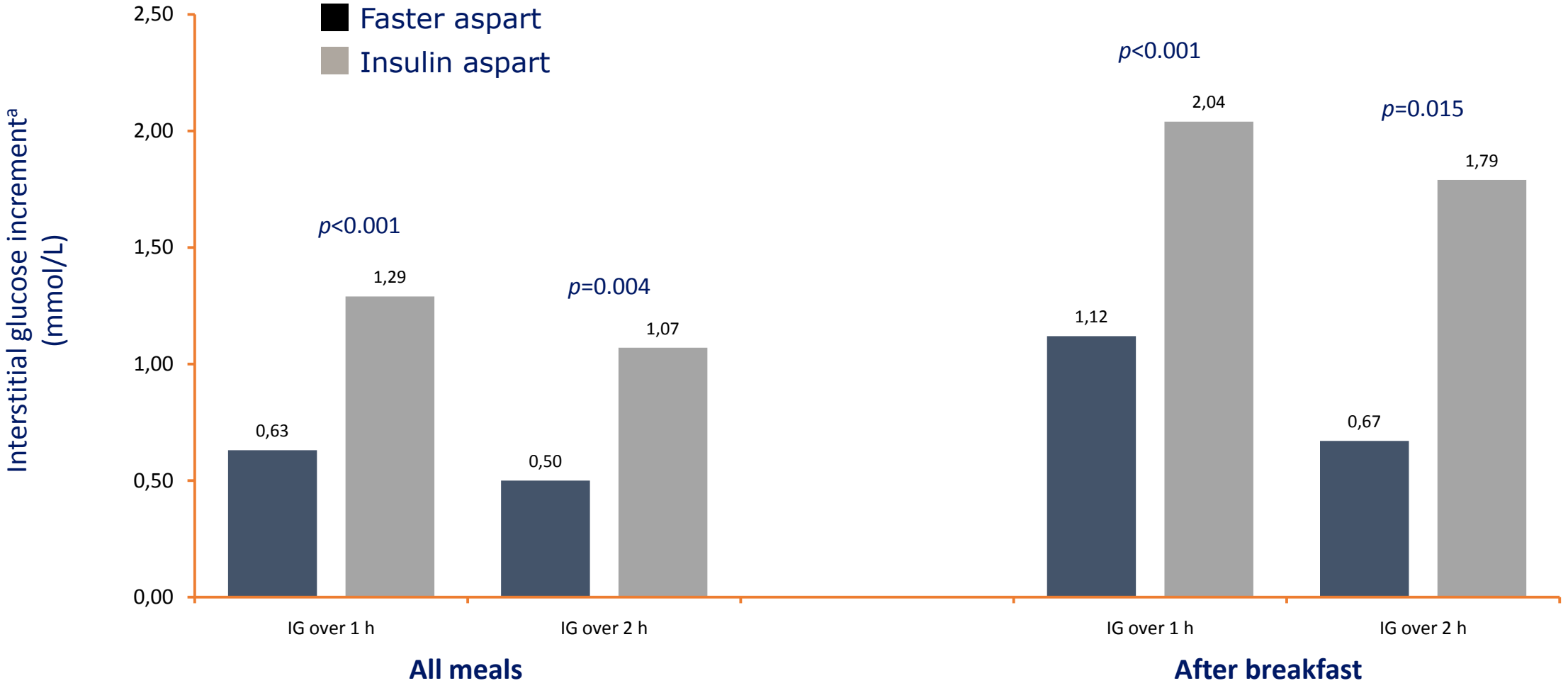
Faster aspart showed a significantly greater post-meal glucose-lowering effect after a standardised meal test with regard to 2-hour PPG response

[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.

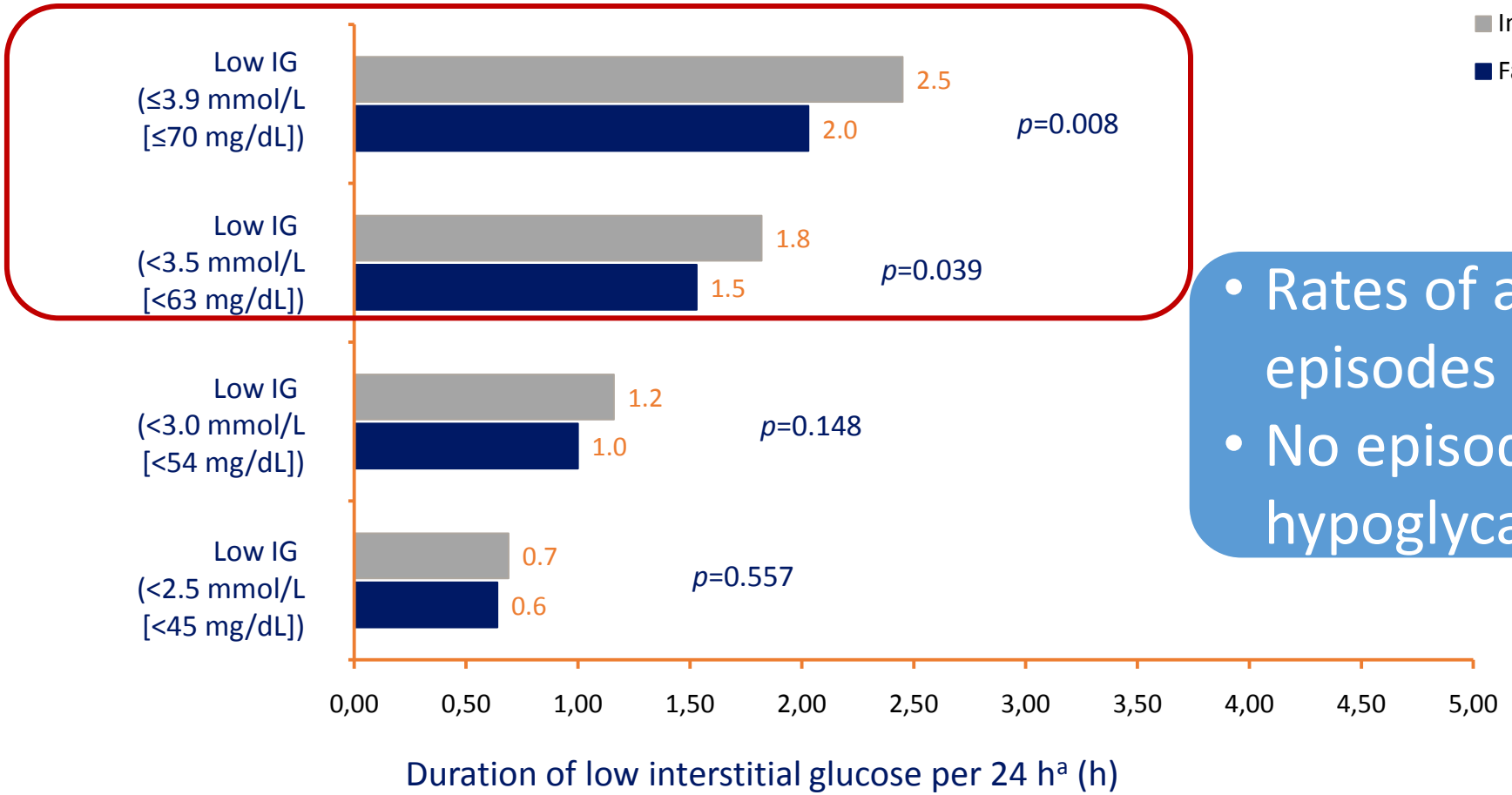
Post-prandial IG increments after 1 and 2 hours



[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

Overview of the phase 3a (onset®) programme for faster aspart

	Patients enrolled	Primary objective and study treatments	Study design and randomised subjects
onset® 1 study 3852	T1D basal–bolus	Non-inferiority HbA_{1c} faster aspart (mealtime and postmeal) vs insulin aspart, all with detemir	n=1143 26-week + 26-week extension RCT partially double-blind
onset® 2 study 3853	T2D basal + metformin +/- other OAD	Non-inferiority HbA_{1c} faster aspart vs insulin aspart, both with glargine U100	n=689 26-week RCT double-blind
onset® 3 study 4049	T2D basal + metformin +/- other OAD	Superiority HbA_{1c} basal–bolus (faster aspart) vs basal (both with previous basal insulin)	n=236 18-week RCT open-label
onset® 4 study 3931	T1D insulin pumps	Pump compatibility faster aspart vs insulin aspart	n=37 6-week RCT double-blind

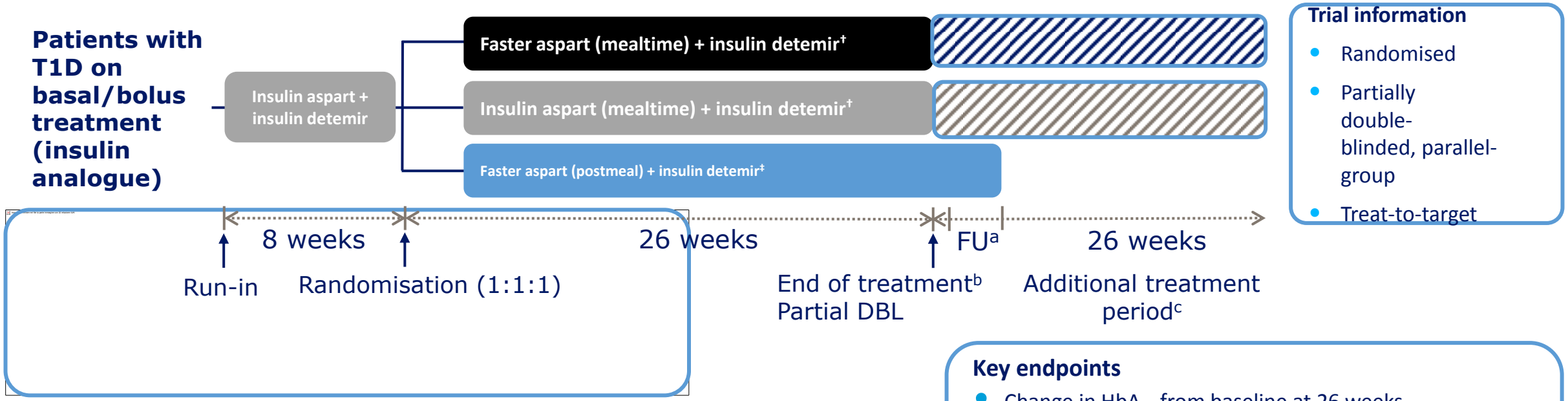
HbA_{1c}, glycosylated haemoglobin; T1D, type 1 diabetes; T2D, type 2 diabetes; RCT, randomised controlled trial; OAD, oral antidiabetic drug

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 endpoints

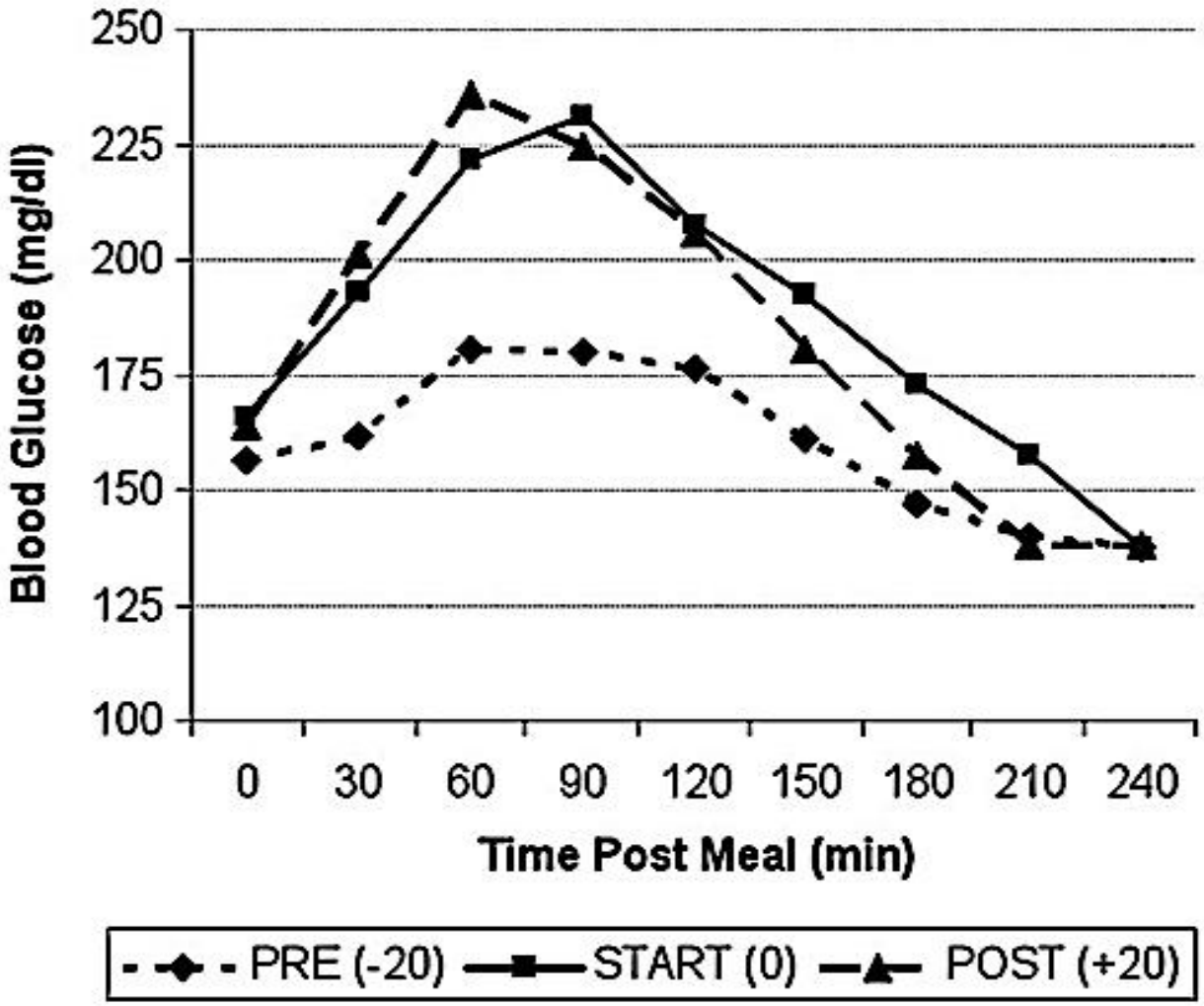
- Change in HbA_{1c} from baseline at 26 weeks
- PPG regulation (based on meal test)
- Body weight regulation
- Number of hypoglycaemic episodes
- Number of treatment-emergent AEs

†Double-blind arm; ‡Open-label arm; [a]Follow-up (7–30 days). [b]Primary endpoint. [c]Results 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

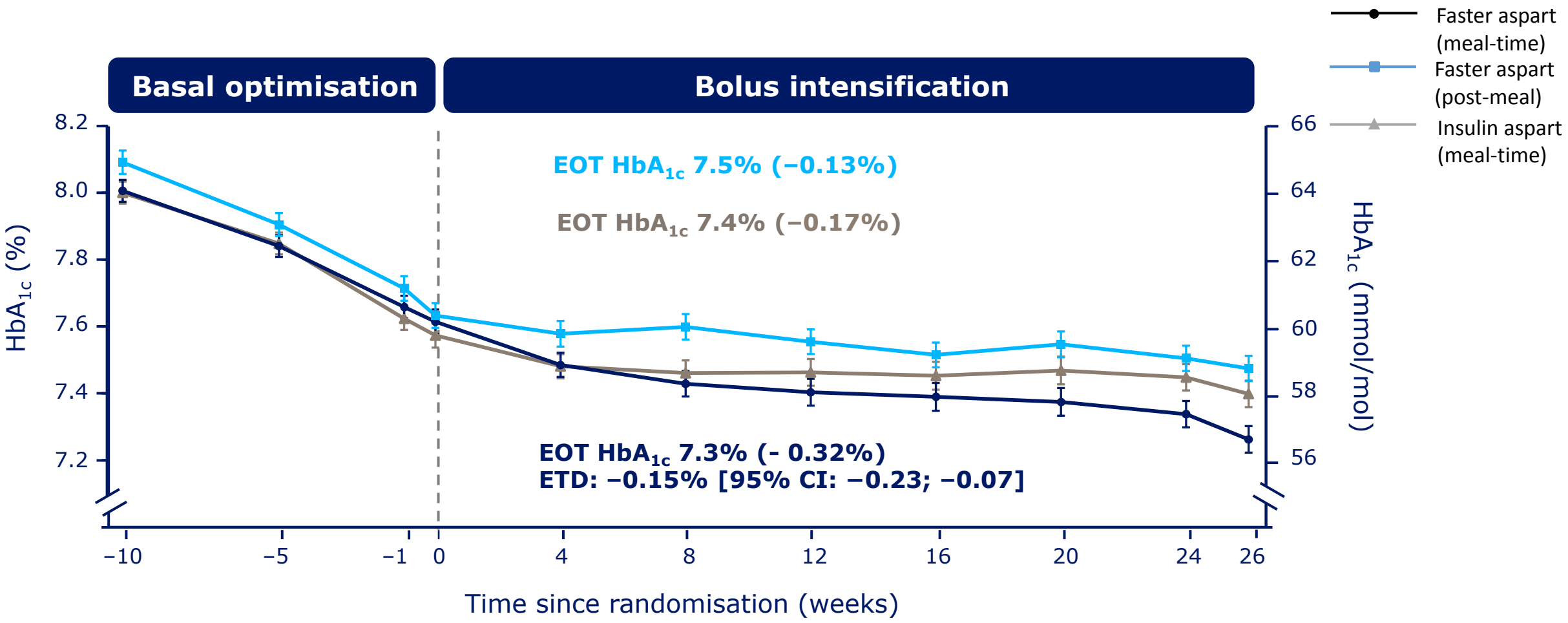
Russell-Jones D *et al*. *Diabetes* 2016;65(S1):A77

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)

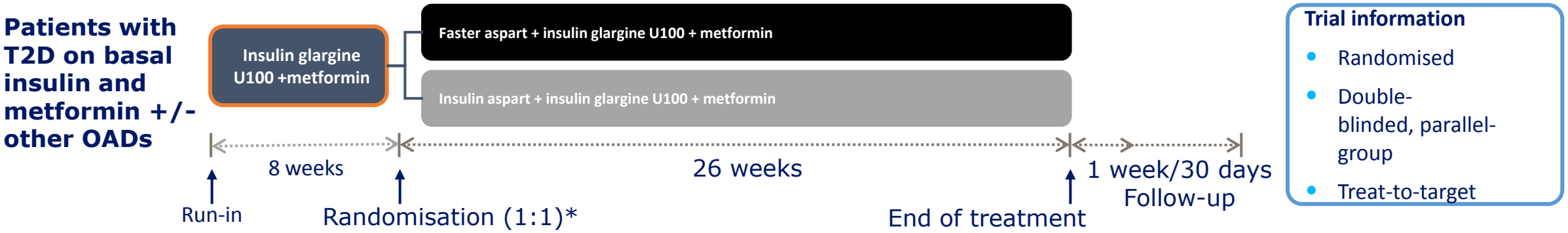
The overall safety profile for faster aspart and insulin aspart was similar and as expected for insulin aspart

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

Efficacy and safety of faster-acting insulin aspart (faster aspart) versus insulin aspart, combined with insulin glargine and metformin, in adults with type 2 diabetes

NN1218-3853 (onset® 2)

onset® 2: Trial design



Trial information

- Randomised
- Double-blinded, parallel-group
- Treat-to-target

Key inclusion criteria

- T2D ≥6 months and age ≥18 years
- OD insulin detemir, insulin glargine U100 or NPH ≥3 months
- Current treatment ≥3 months with unchanged dosing:
  - Metformin (≥1000 mg) or metformin (≥1000 mg) + SU/glinide/DPP-4 inhibitors and/or AGIs
- HbA_{1c} 7.0–9.5% (metformin only) or 7.0–9.0% (metformin + OAD)
- BMI ≤40.0 kg/m^2

Key endpoints

- HbA_{1c}
- 2-hour PPG increment (meal test)
- Body weight
- Number of treatment-emergent hypoglycaemic episodes
- Number of treatment-emergent AEs

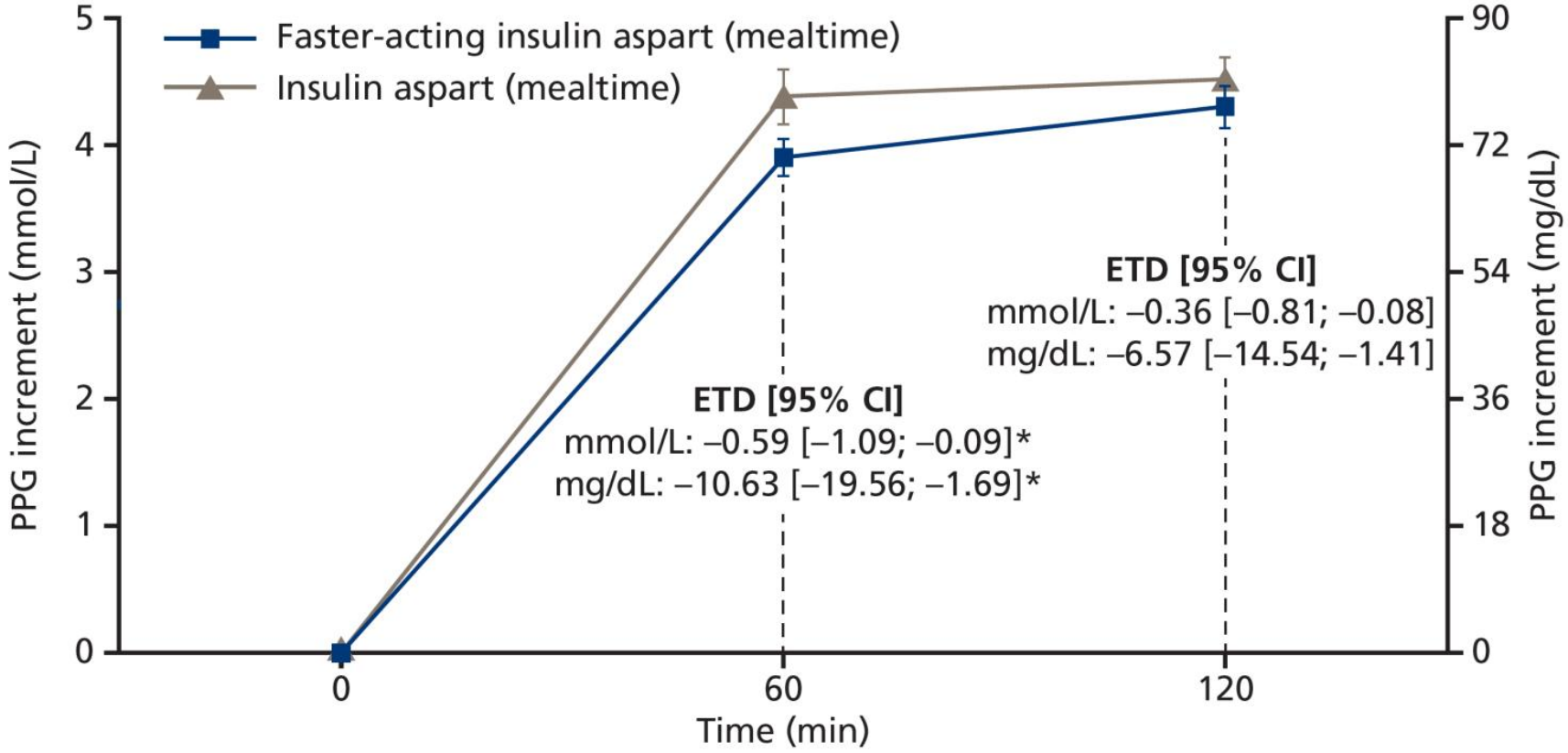
*Randomisation criteria: HbA_{1c} 7.0–9.5% (both inclusive), based on HbA_{1c} measured at visit 9 (week -1).

AE, adverse event; AGI, alpha-glucosidase inhibitor; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FU, follow-up; HbA_{1c}, glycosylated haemoglobin; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drug; OD, once daily; PPG, postprandial plasma glucose; SU, sulphonylurea; T2D, type 2 diabetes

Bowering K et al. Diabetes 2016;65(S1):A63

onset® 2: PPG increment at week 26

Significantly greater reduction at 1 h with faster aspart vs. insulin aspart



Full analysis set; observed data. Error bars: ± standard error (mean). Estimated treatment difference (ETD; faster aspart – IAsp) for PPG increment changes from baseline. *Statistically significant in favor of faster aspart.

Bowering K et al. Diabetes 2016;65(S1):A63

Summary

Faster aspart: onset® 2

Faster aspart effectively improved glycaemic control (EOT HbA_{1c} = 6.6%) in subjects with T2D previously on basal insulin only

- HbA_{1c} reduction: non-inferior to insulin aspart

PPG regulation (meal test):

- 1-h PPG increment significantly improved vs. insulin aspart
  (ETD [95% CI]:−0.59 mmol/L [−1.09;−0.09]; −10.6 mg/dL [−19.6;−1.7])
- 2-h PPG increment† not significantly improved vs. insulin aspart
  (ETD [95% CI]: −0.36 mmol/L [−0.81;0.08]; −6.6 mg/dL [−14.5;1.4])

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

Similar overall safety profile with faster aspart and insulin aspart

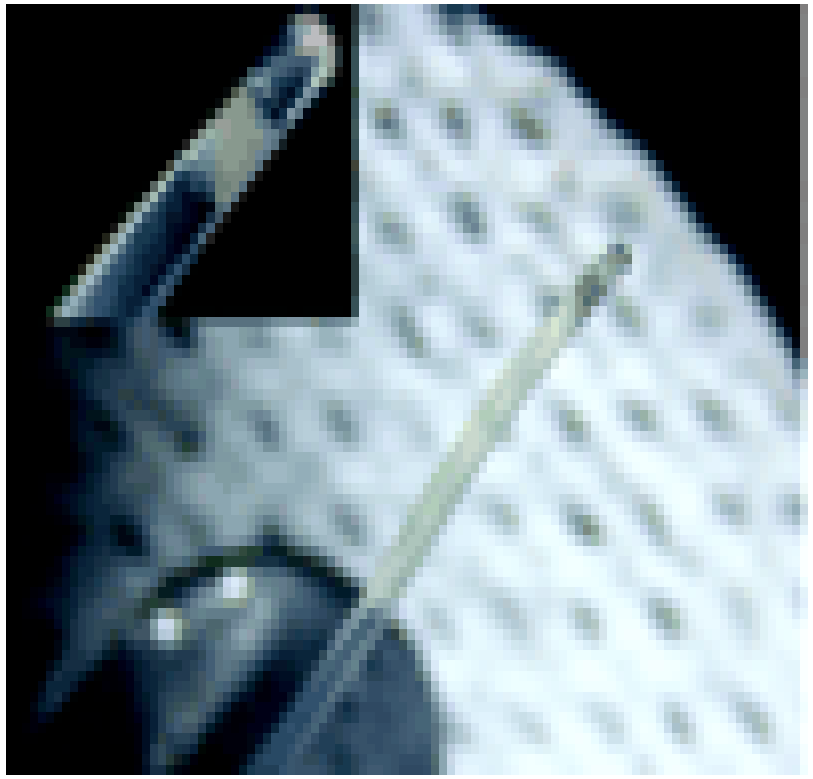
†Confirmatory secondary endpoint

BG, blood glucose; CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference (faster aspart–insulin aspart); PPG, postprandial plasma glucose; T2D, type 2 diabetes

Bowering K et al. Diabetes 2016;65(S1):A63

Efficacy and safety of faster-acting insulin aspart (faster aspart) in a basal–bolus regimen versus basal insulin therapy, both in combination with metformin in adults with type 2 diabetes

NN1218-4049 (onset® 3)



Pump compatibility trial (faster aspart vs insulin aspart)

onset® 4

onset® 4 trial design

Conclusions

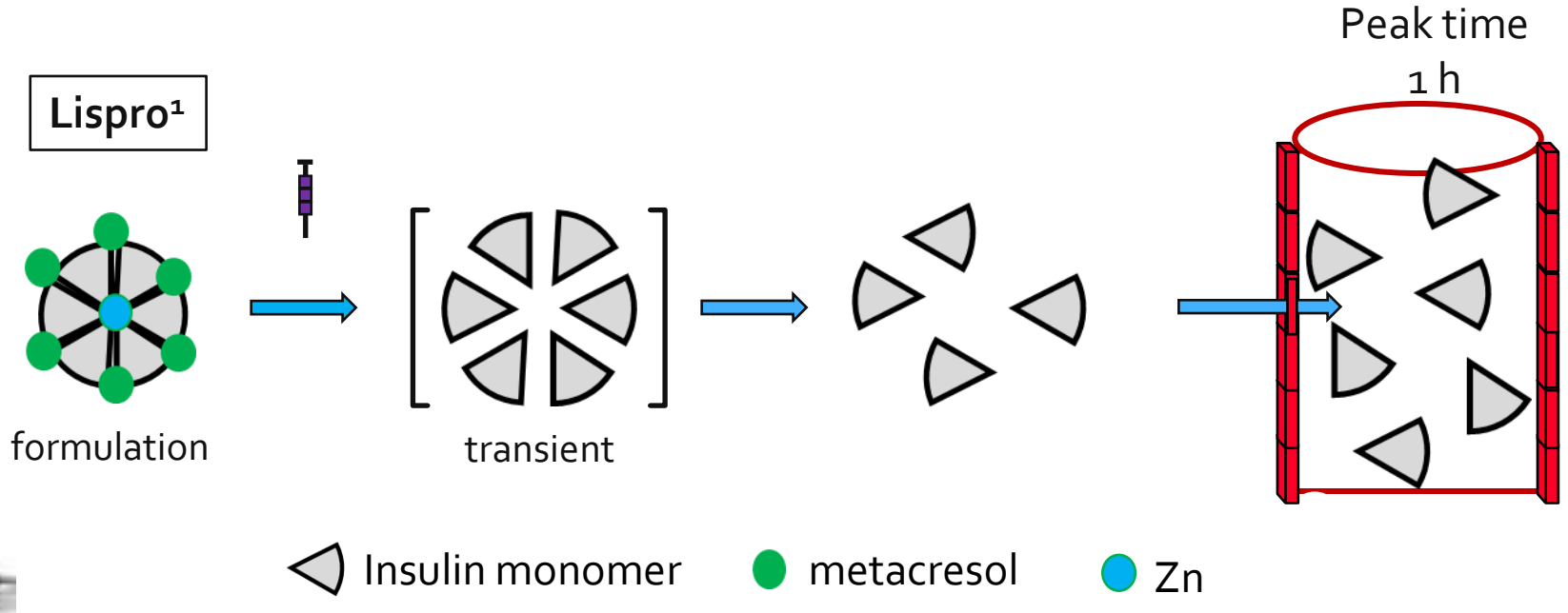
- **Primary endpoint achieved: no differences in pump compatibility as assessed by microscopically confirmed infusion set occlusions**.
- The estimated mean change in HbA_{1c} from baseline to Week 6 favored faster aspart, but was not statistically significantly different from IAsp in this small-scale, 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

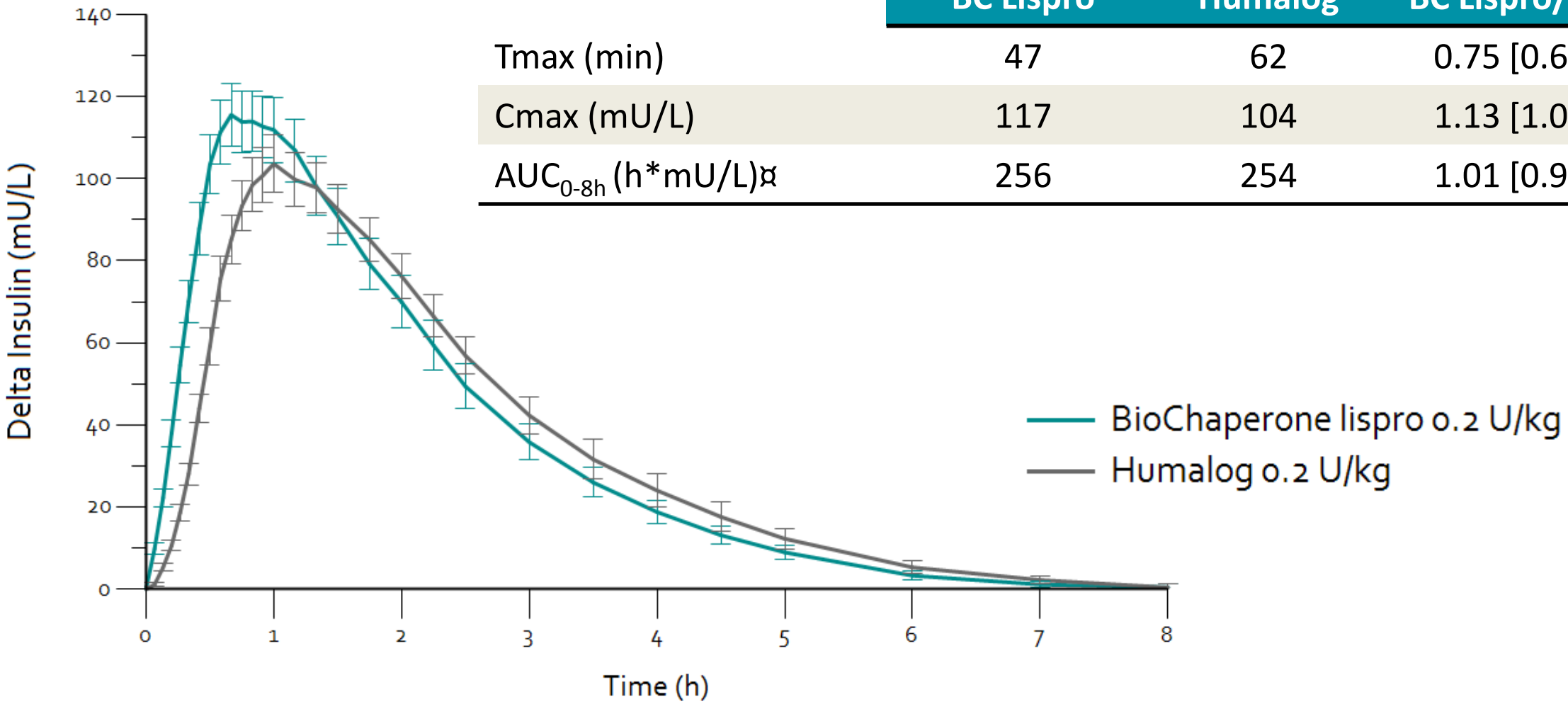
Trial population

- 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

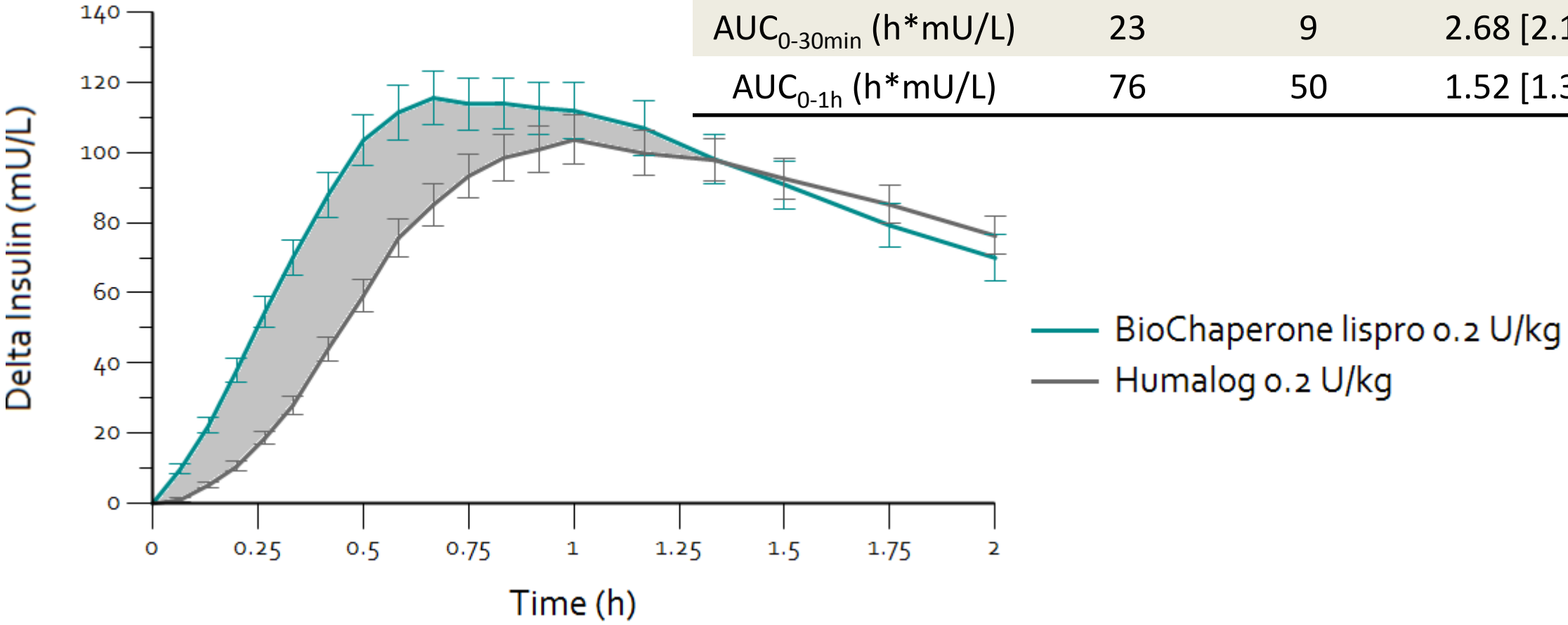
Shorter Tmax, higher Cmax and similar exposure

	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]



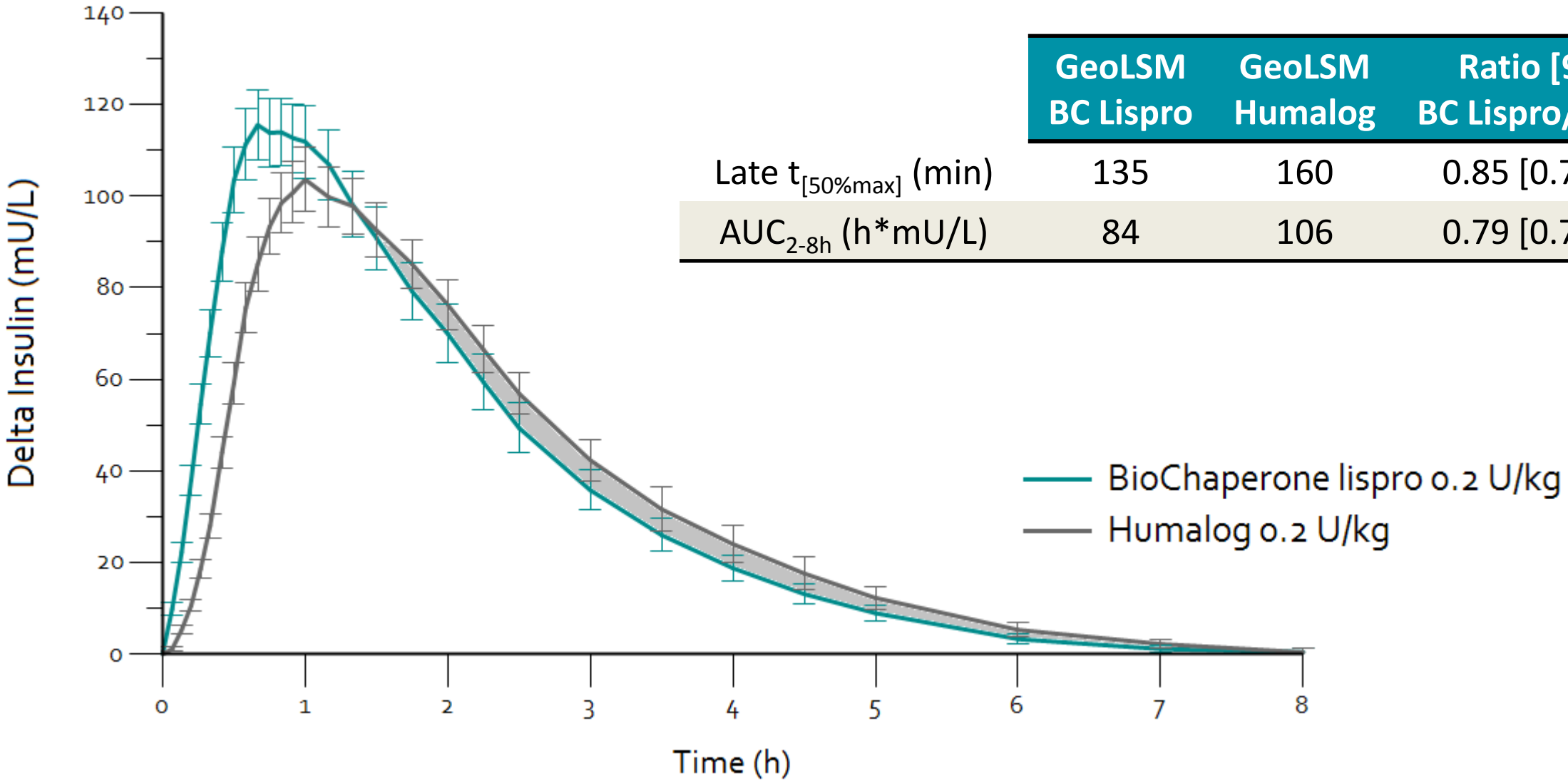
Greater earlier exposure: Faster In

	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]



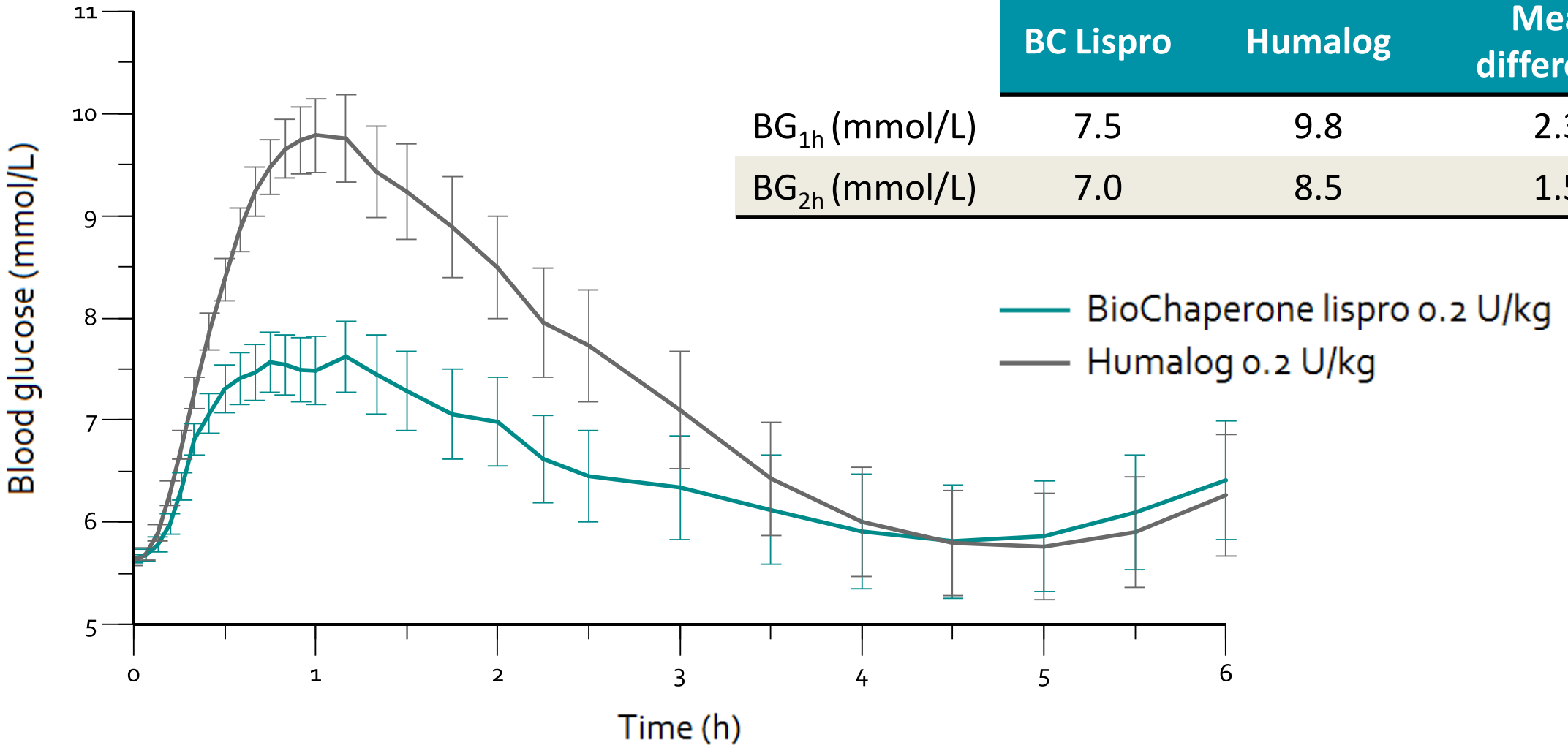
Lower late exposure: Faster-out

	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]



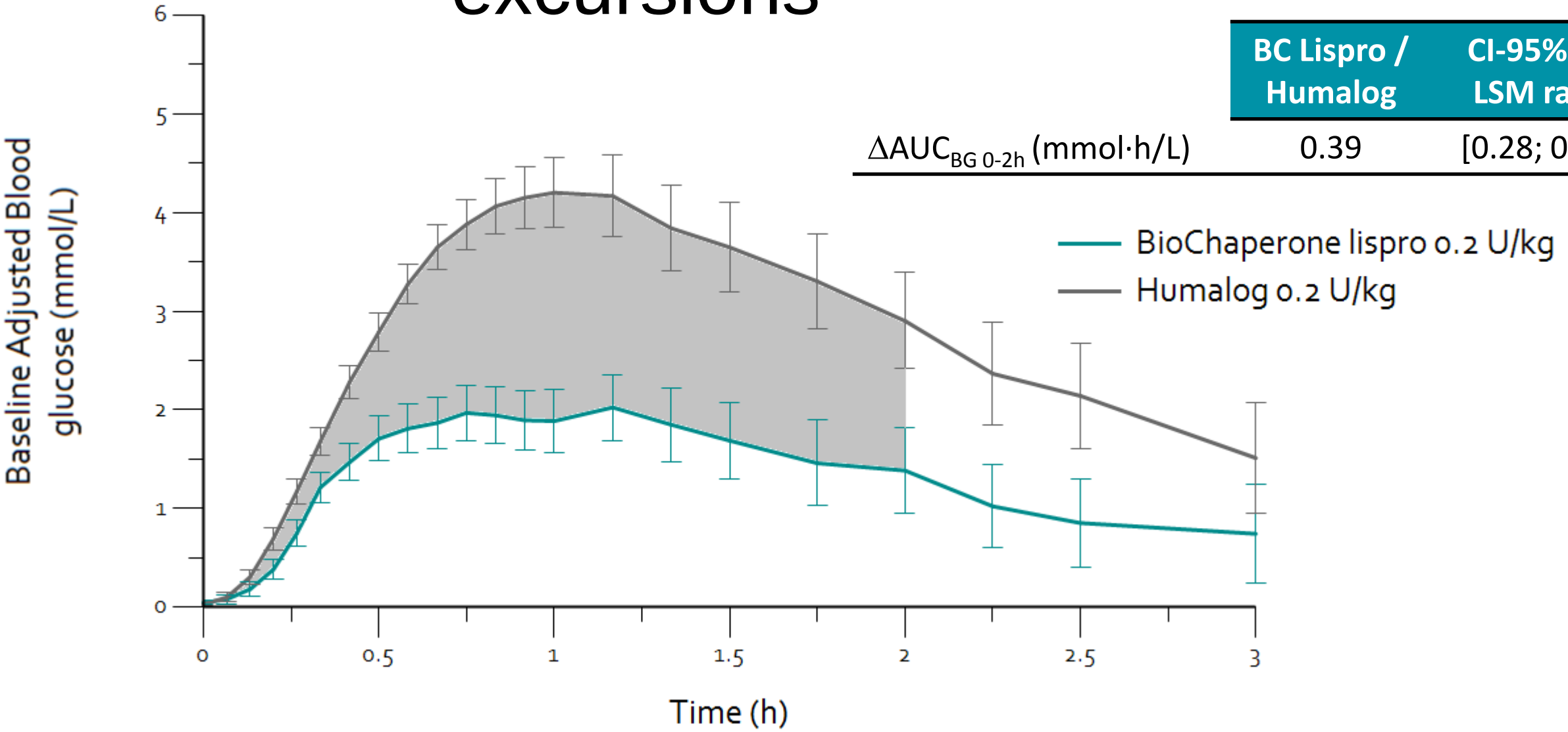
Better post-prandial glucose control

	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

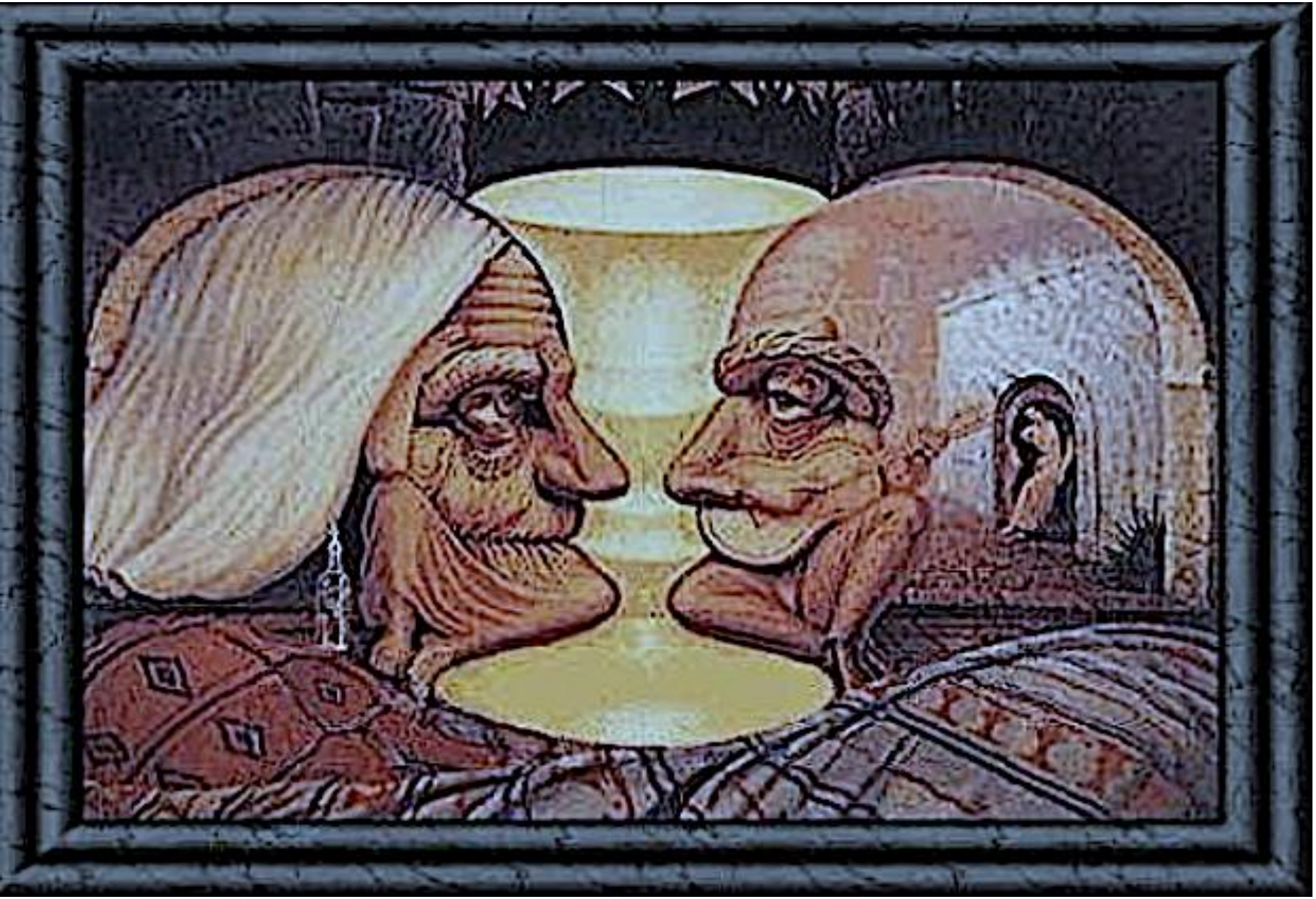
PD Results

	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)



Grazie per l’attenzione