AME DAY
Congresso Macroregionale Nord

Desenzano del Garda
23 maggio 2015

Nuove insuline: solo nuove o realmente innovative?

Giorgio Borretta

SC Endocrinologia, Diabetologia e Metabolismo

ASO S. Croce e Carle, Cuneo

Il futuro per le insuline ultra fast acting

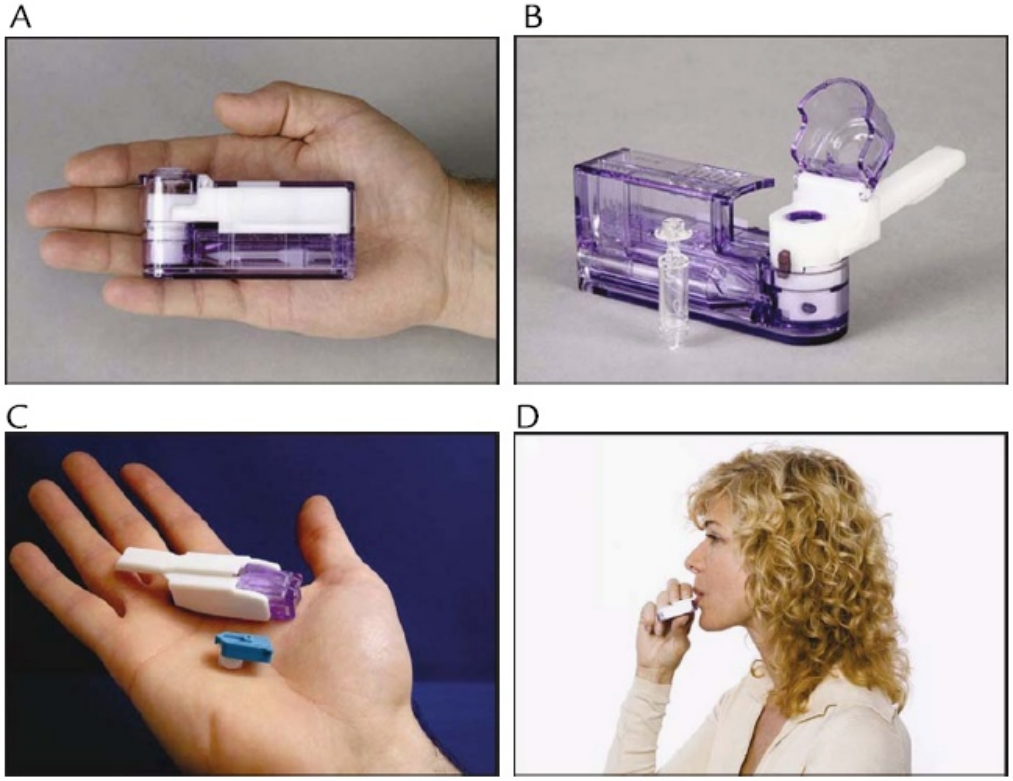
Più veloci
- **Linjeta (Biodel)**

Con aumento di temperatura del sito di infusione
- **InsuLine**

Co-formulate con ialuronidasi
- **Halozyme**

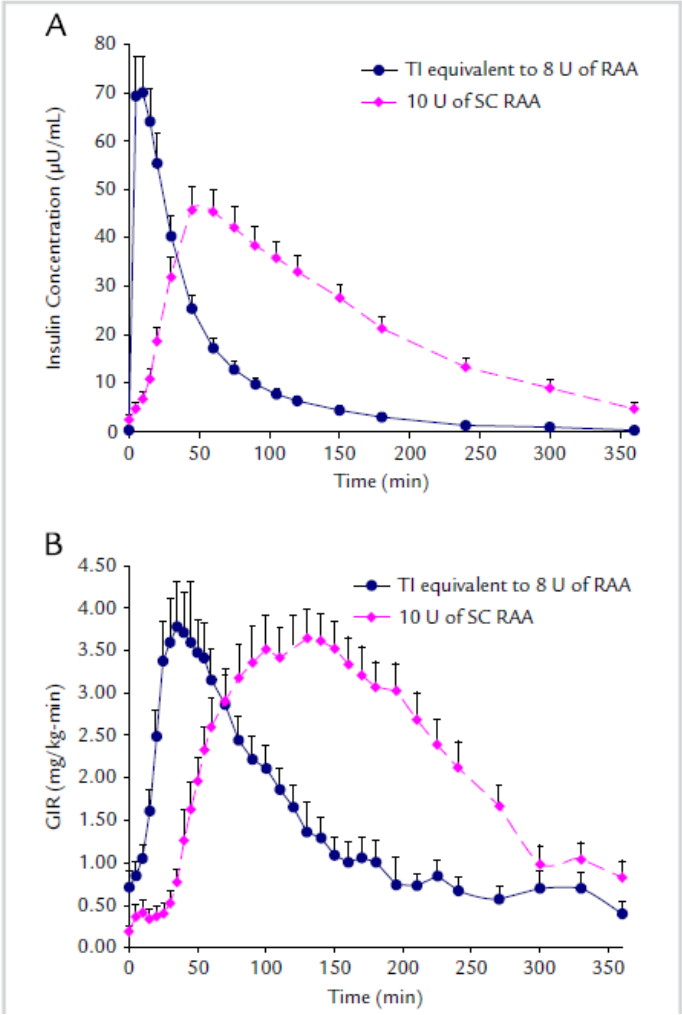
Vie alternative
- **Intradermiche: set di infusione con micro aghi (BD)**
- **Inalatoria: Afrezza**
- **Intra-peritoneale: DiaPort**

AFREZZA



Technosphere® insulin (MannKind Corporation, Valencia, California). (A and B) The original MedTone® inhaler (MannKind). (C and D) The Gen2 device combined with TI into the drug–device combination system called Afrezza® (MannKind).[35] Reproduction of Figure 1 of Neumiller JJ, Campbell RK. Technosphere® Insulin. An Inhaled Prandial Insulin Product. Biodrugs 2010;24 (3):165-172. Copyright: 3412630859531, Springer.

AFREZZA


A
TI equivalent to 8 U of RAA
10 U of SC RAA
Insulin Concentration (μU/mL)
0
10
20
30
40
50
60
70
80
0
50
100
150
200
250
300
350
Time (min)
B
TI equivalent to 8 U of RAA
10 U of SC RAA
GIR (mg/kg-min)
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
0
50
100
150
200
250
300
350
Time (min)

AFREZZA

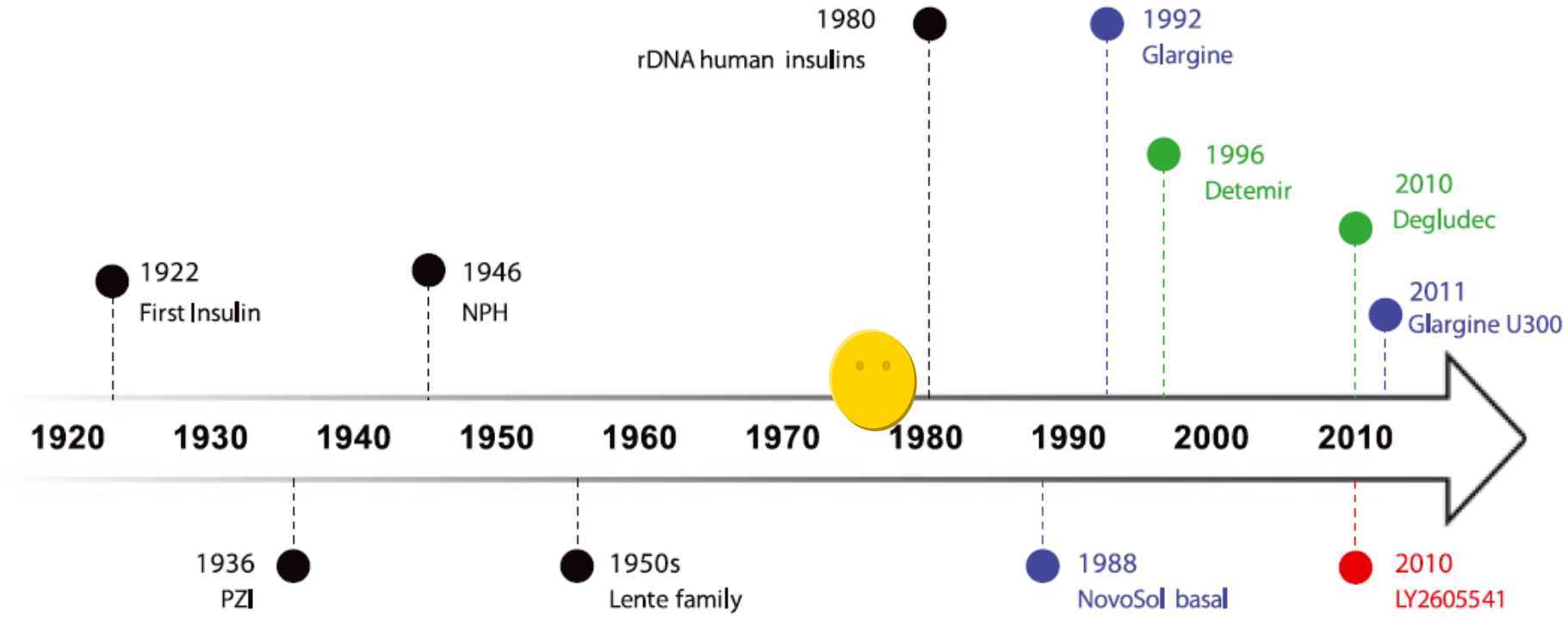
WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- **Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA.** ***[see Warnings and Precautions (5.1)]*****.**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD.** ***[see Contraindications (4)]*****.**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients** ***[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*****.**

Basal insulin analogues in the management of diabetes mellitus: what progress have we made?

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2014; 30: 104–119.

Timeline for the development of novel human insulin analogues.



Change in isoelectric point towards neutral pH

Acylation of insulin with fatty acids C14-C16

PEGylated insulin

In Search of Improved Pharmacokinetic/Pharmacodynamic Profiles

Why We Need Better Basal Insulins

- Poor glycemic control is prevalent
  - 44-63% not achieving treatment goal
- Poor control increases risk of complications and escalates costs worldwide
- Regimen complexity, injection frequency, and weight gain can impede patients ability to manage and control BG levels and prevent hypoglycemia
- Fear of hypoglycemia may delay use of insulin or intensified therapy by clinician and patient

Garber AJ. *Diabetes Obes Metab*. 2014;16:483-491.[15]

Limitazioni delle attuali insuline basali

- **Durata d'azione**
  - Gli analoghi dell'insulina a lunga durata d'azione attualmente disponibili **non durano sempre 24 ore**[1]

- **Variabilità e prevedibilità**
  - Sebbene di gran lunga inferiore rispetto ad NPH, esiste ancora una **variabilità** dell'effetto ipoglicemizzante delle attuali insuline (**intra-paziente e inter-paziente**)[1]

- **Flessibilità**
  - Le insuline basali devono essere somministrate ogni giorno alla stessa ora[2] (**mancanza di flessibilità**)

- **Rischio ipoglicemico**
  - Sebbene di gran lunga inferiore rispetto ad NPH, le attuali insuline **non possiedono un profilo d'azione completamente piatto**

1. Evans *et al. Diabetes, Obesity and Metabolism* 2011;13: 677–684; 2. Joshi *et al. SA Fam Pract* 2009;51:97–102;

Desired Properties for A Basal Insulin Product Relative to Existing Therapy

- Clinical needs
  - Easier and safer dose titration without increasing risk of hypoglycemia
  - 1 injection per day
  - Flexibility in timing
- Glycemic control
  - Achieve treatment goals
  - Duration beyond 24 hours
- PK/PD Profile
  - Less variability
  - Consistent delivery of insulin
  - Flat, stable, and prolonged profile

Evans M, et al. *Diabetes Obes Metab.* 2011;13:677-684.[24]

Novel Basal Insulins on the Horizon

- Insulin degludec*
  - Approved for licensing in Mexico, Europe, Japan, Switzerland
- PEGylated insulin lispro*
  - In development
- High-strength insulin glargine (U300)*
  - Under investigation

*This agent has not been approved by the US FDA for use.

Garber AJ. *Diabetes Obes Metab*. 2014;16:483-491.[15]


TRESIBA®
insulin degludec [rDNA origin] injection

Insulin Degludec: Indication

- **4.1 - Therapeutic Indication**
  - Treatment of diabetes mellitus in adults
- **4.2 - Posology**
  - Tresiba is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day.
  - In type 1 diabetes mellitus, Tresiba must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.
  - In patients with type 2 diabetes mellitus, Tresiba can be administered alone, in combination with oral anti diabetic medicinal products as well as in combination with bolus insulin

Adults

Once daily
Same Time
eveyday

T1DM: basal bolus

T2DM: basal bolus & BOT

Insulin Degludec: qualitative and quantitative composition

- 1 mL solution contains 100 units insulin degludec (equivalent to 3.66 mg insulin degludec)
- One pre-filled pen contains 300 units of insulin degludec in 3 mL solution

IDeg 100 U/ mL (U100, 600 nmol/ mL)

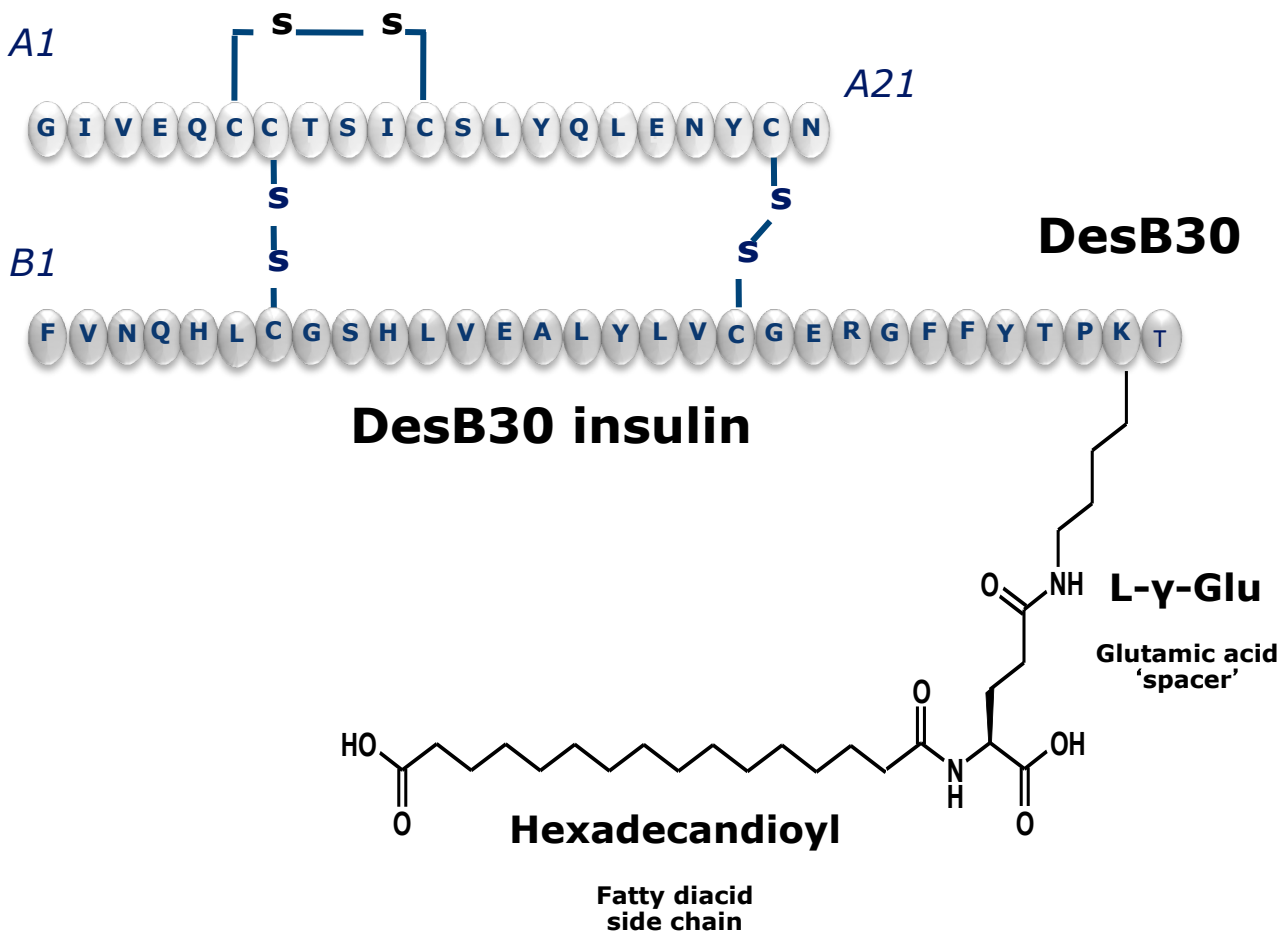
4 Clinical Particulars

- The potency of insulin analogues, including insulin degludec, is expressed in units (U). One (1) unit (U) of insulin degludec corresponds to 1 international unit (IU) of human insulin, 1 unit of insulin glargine or 1 unit of insulin detemir
- In patients with type 2 diabetes mellitus, the recommended daily starting dose is 10 units followed by individual dosage adjustments
- Changing the basal insulin to Tresiba can be done unit-to-unit based on the previous basal insulin dose followed by individual dosage adjustments

1 U Ideg = 1 UI HI = 1 U Idet = 1 U Iglar

Insulin degludec: Rationally designed, beyond sequence modification

***Des**(B30) LysB29(γ-**Glu** Nε-hexa**dec**andioyl) human insulin*

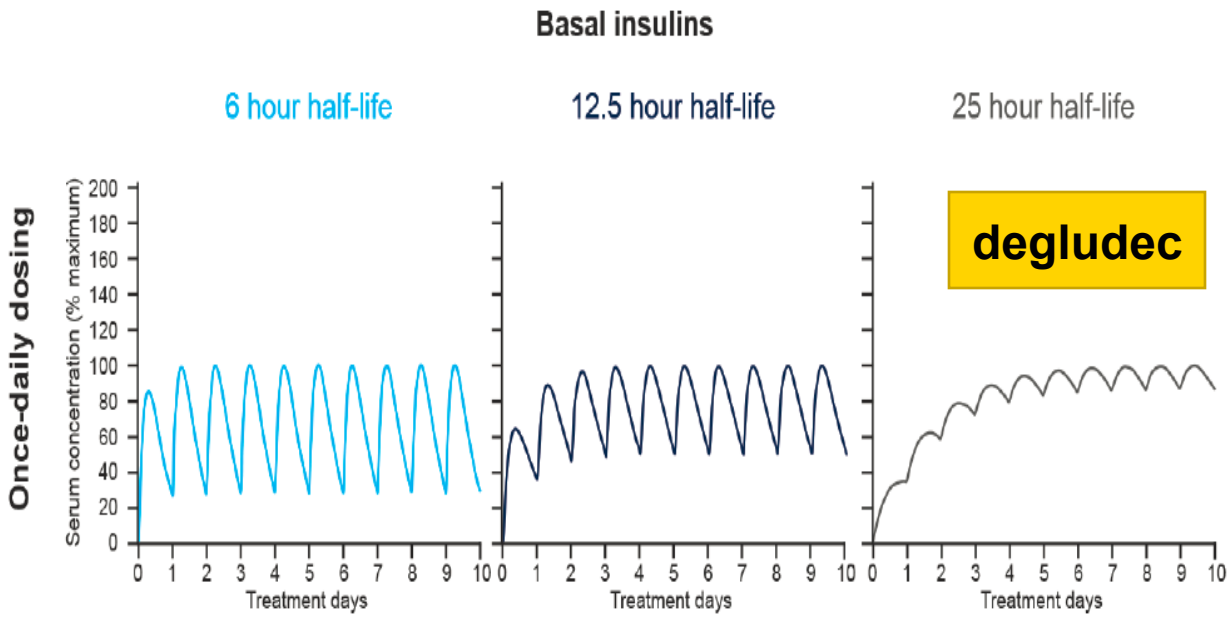


….dopo iniezione

con il rilascio dello Zinco dalle estremità dei multi-esameri

lenta e costante liberazione di monomeri che possono così essere assorbiti….

Insulin degludec: PK & PD



Emivita lunga = migliore qualità del profilo farmacocinetico allo steady state

Pharmacological properties

- **5.1 - Pharmacodynamic properties**
  - *Pharmacodynamic effect:* The duration of action of Tresiba is beyond 42 hours within the therapeutic dose range.
  - Steady state will occur after 2–3 days of dose administration.
  - The insulin degludec glucose-lowering action at steady state shows four times lower day-to-day variability in terms of Coefficients of Variation (CV) for the glucose-lowering effect during 0-24 hours (AUCGIR,τ,SS) and 2–24 hours (AUCGIR2-24h,SS) as **compared to insulin glargine**

Degludec duration of action is beyond 42 hours

Steady state after 2-3 days

Four times lower day-to-day variability

Flexibility

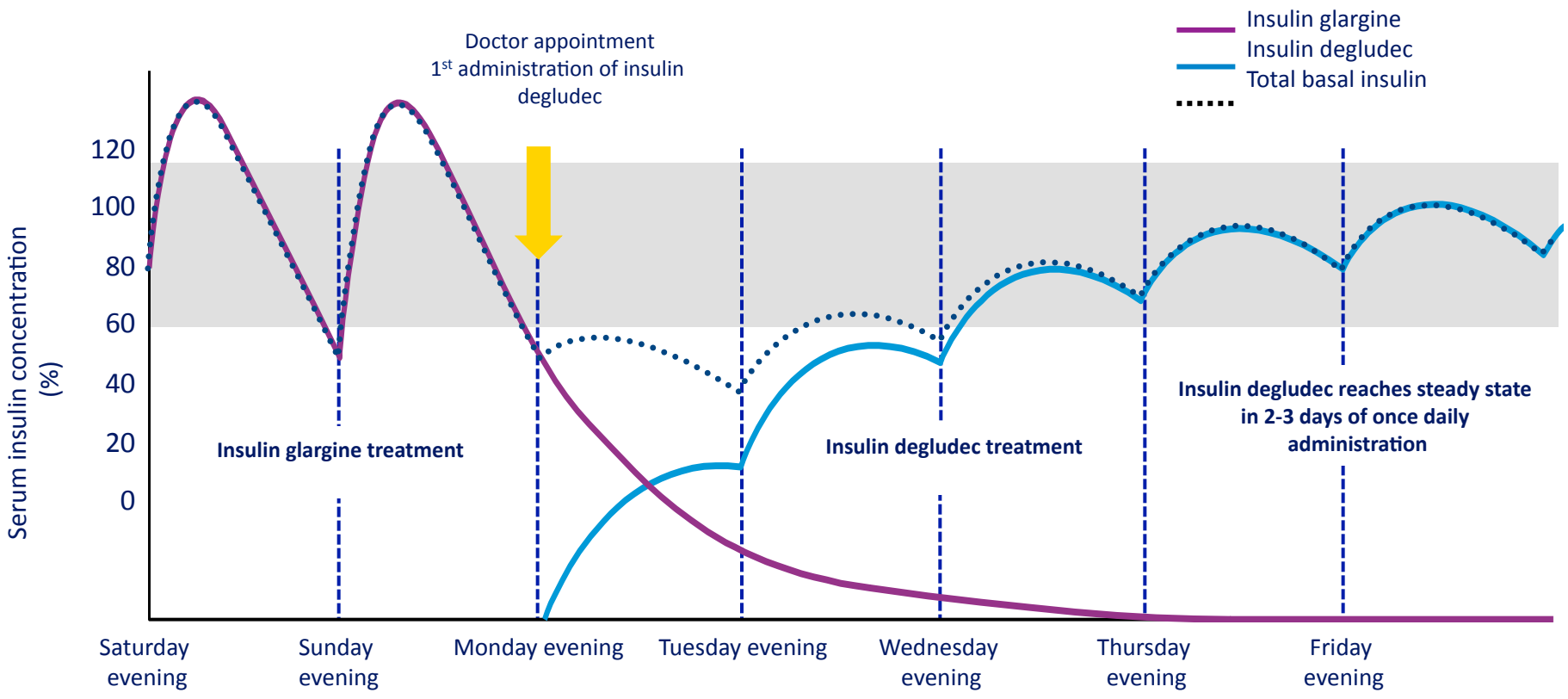
- **4.2 – Flexibility in dosing time**
  - On occasions when administration at the same time of the day is not possible, Tresiba allows for flexibility in the timing of insulin administration
  - A minimum of 8 hours between injections should always be ensured
  - Patients who forget a dose, are advised **to take it upon discovery and then resume their usual once daily dosing schedule**

Flexibility

Minimum interval between 2 doses: 8 hours

«Forgiveness for mistake»

From Glargine to Degludec



In-silico 2-compartment model assuming 1st order kinetics based on documented pharmacokinetic variables and glucose clamp data. Data-on-file.

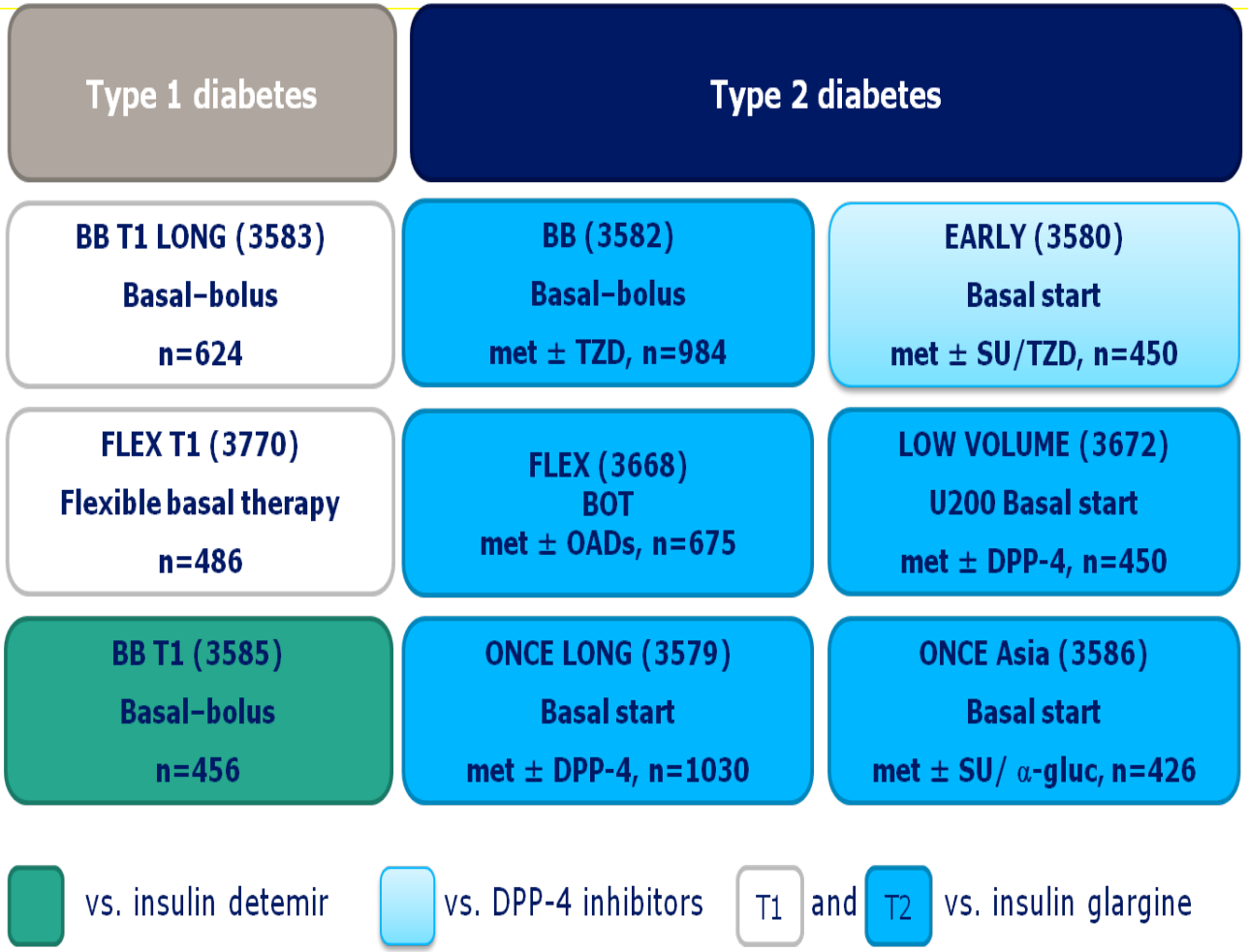
Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial

*Simon Heller, John Buse, Miles Fisher, Satish Garg, Michel Marre, Ludwig Merker, Eric Renard, David Russell-Jones, Areti Philotheou, Ann Marie Ocampo Francisco, Huiling Pei, Bruce Bode, on behalf of the BEGIN Basal-Bolus Type 1 Trial Investigators**

Procedures

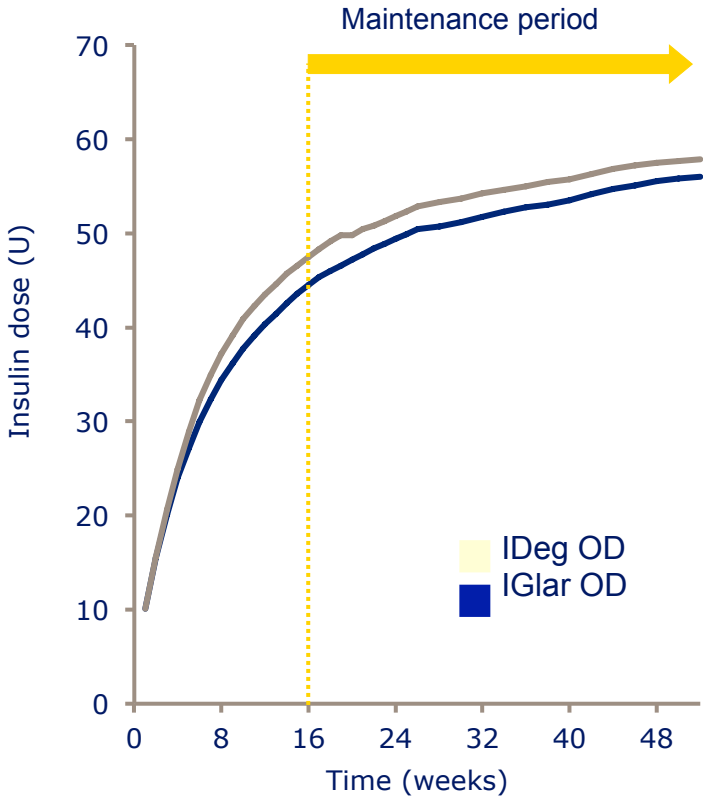
Eligible participants were switched from their long-term basal-bolus insulin therapy to once-daily insulin degludec or insulin glargine with mealtime insulin aspart at randomisation (week 0). If previous basal insulin was used once daily, initial doses were replaced with insulin degludec or insulin glargine in a 1:1 ratio. If more than one daily dose had been taken, the total daily basal dose was calculated and replaced with insulin degludec in a 1:1 ratio, with the recommendation that the dose be reduced by 20–30% for patients in the insulin glargine group, and administered once daily, as per approved prescribing information. Insulin degludec was administered once daily with the main evening meal and insulin glargine was administered according to approved labelling (once daily at any time but at the same time every day throughout the study). Participants switched their pretrial bolus insulin to insulin aspart in a 1:1 ratio. Insulin aspart was taken before

Insulin degludec phase 3a study programme: BEGIN



BEGIN programme: hypoglicaemic events meta-analysis

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



Hypoglycaemia risk reduction IDeg versus IGlar

*Statistically significant, $p<0.05$

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

Pharmacological properties

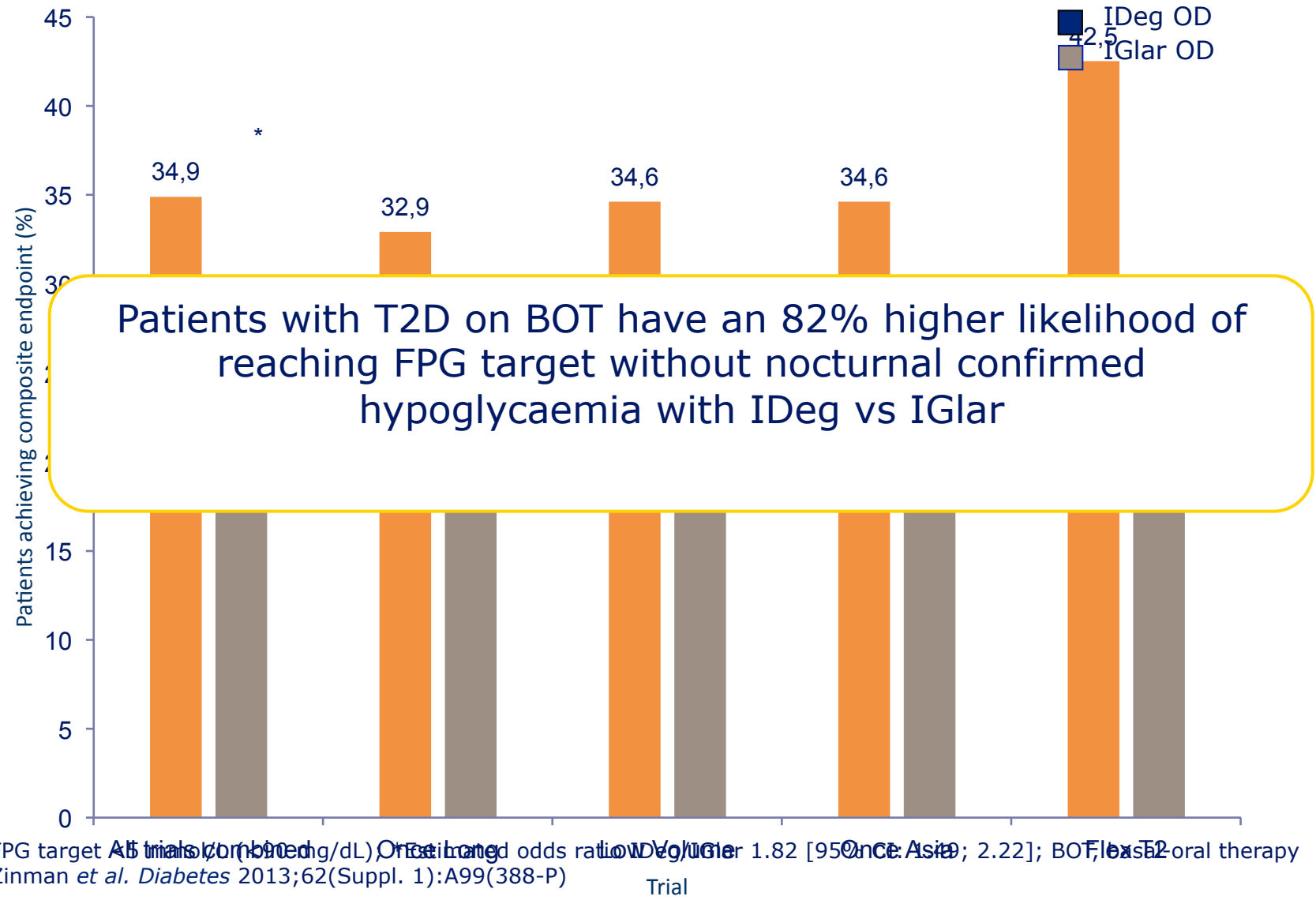
- **5.1 - Pharmacodynamic properties**
  - *Clinical Efficacy and safety:* In a prospectively planned meta-analysis across seven treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, Tresiba was superior in terms of a lower number of treatment emergent confirmed hypoglycaemic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

Hypoglycemia meta-analysis

Degludec superior vs glargine in terms of confirmed and nocturnal hypoglycaemia

Lower FPG and reduction in hypoglycaemia with Degludec vs glargine

Achieving FPG target without nocturnal hypoglycaemia in T2D with BOT



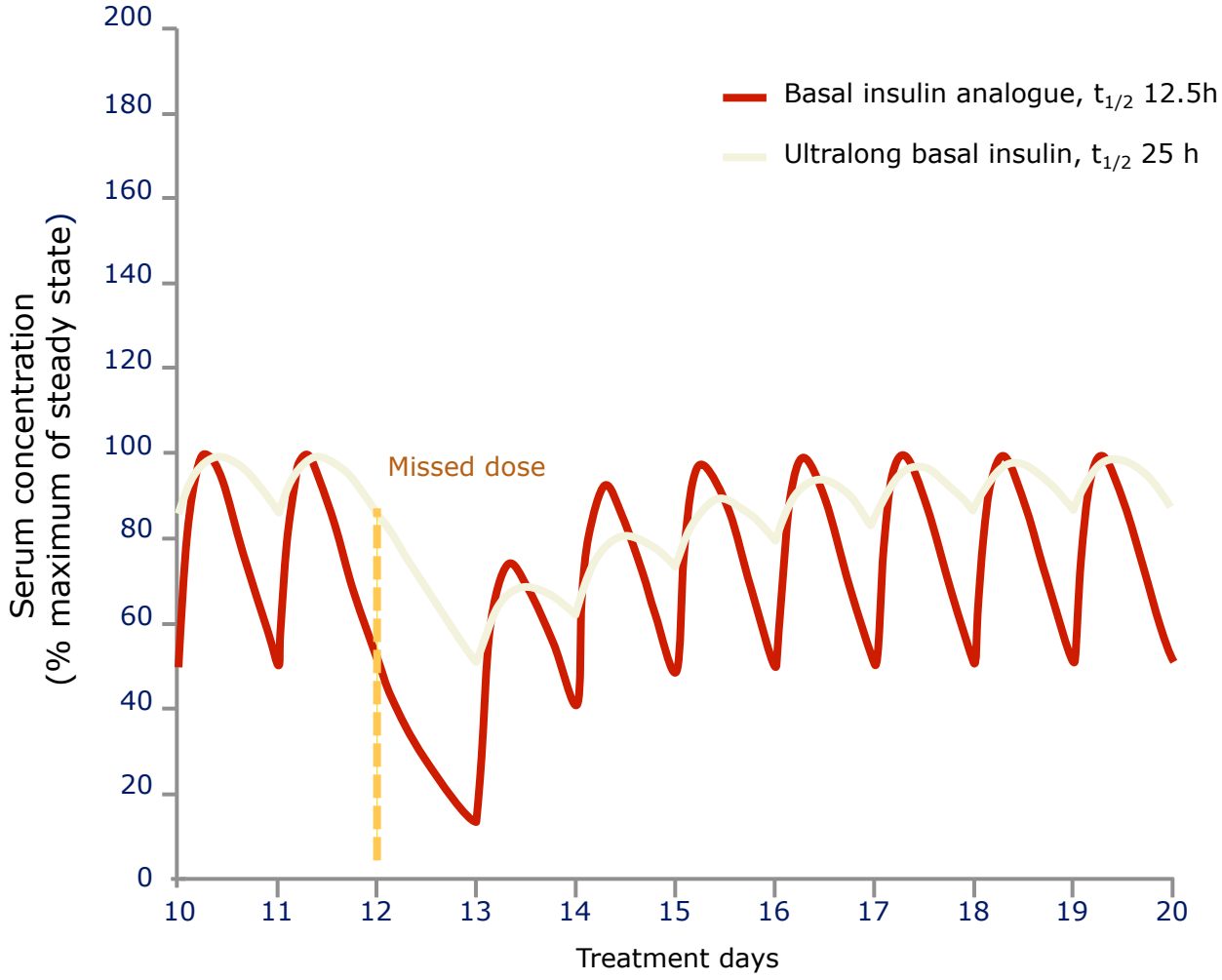
Patients with T2D on BOT have an 82% higher likelihood of reaching FPG target without nocturnal confirmed hypoglycaemia with IDeg vs IGlar

All trials combined: Treatment odds ratio IDeg/IGlar 1.82 [95% CI: 1.49; 2.22]; BOT, basal oral therapy

FPG target < 5 mmol/l (<90 mg/dL), nocturnal confirmed hypoglycaemia

Zinman *et al. Diabetes* 2013;62(Suppl. 1):A99(388-P)

Basal insulin with an ultra-long duration of action: Consequences of a missed dose



These data are for illustrative purposes only

Special populations

- **4.2 – Special populations**
  - *Elderly (≥ 65 years old):* Tresiba can be used in elderly patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).
  - *Renal and hepatic impairment:* Tresiba can be used in renal and hepatic impaired patients. Glucose-monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).
  - *Paediatric population:* The safety and efficacy of Tresiba in children and adolescents below 18 years of age have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

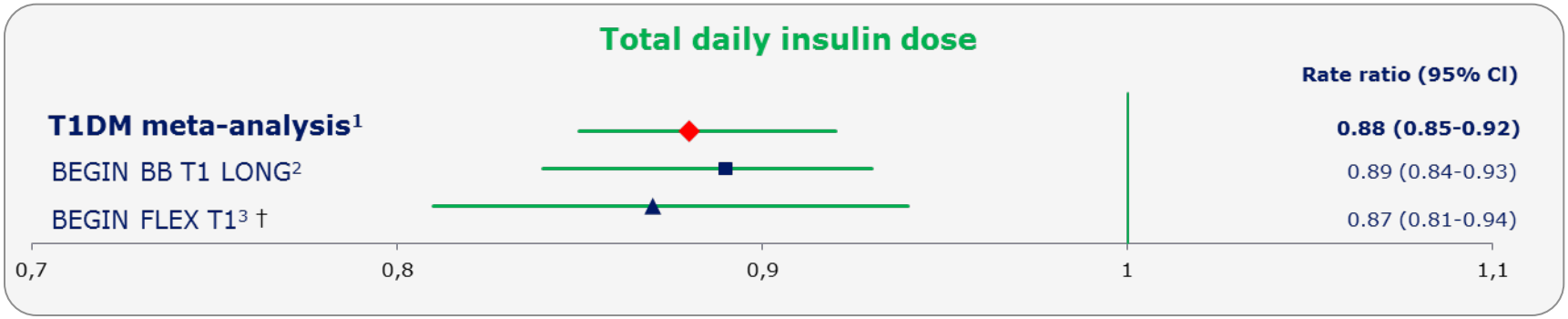
OK in elderly patients

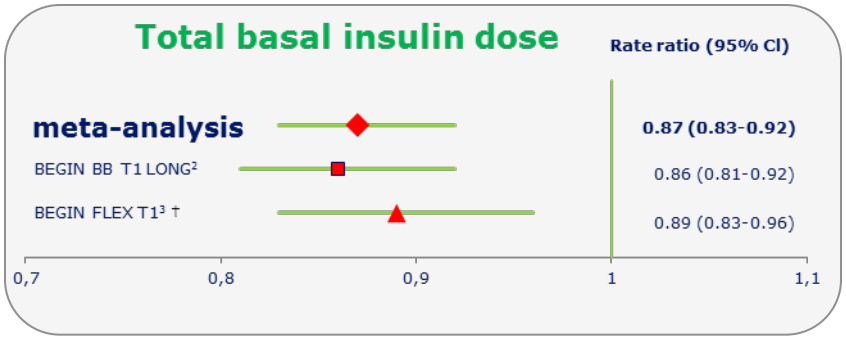
OK in nephropatic & hepatopatic patients

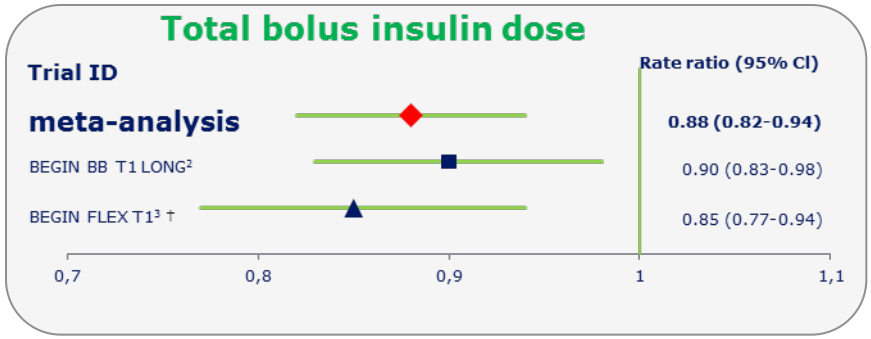
NO in pediatric patients
Ongoing trials

Total daily dose

- For **T1DM patients**, the total daily dose of IDeg was significantly 12% lower than IGlar ($p<0.0001$)[1]
- When analysed separately, significantly 13% lower daily basal and 12% lower bolus doses were observed with IDeg compared with insulin glargine[1]





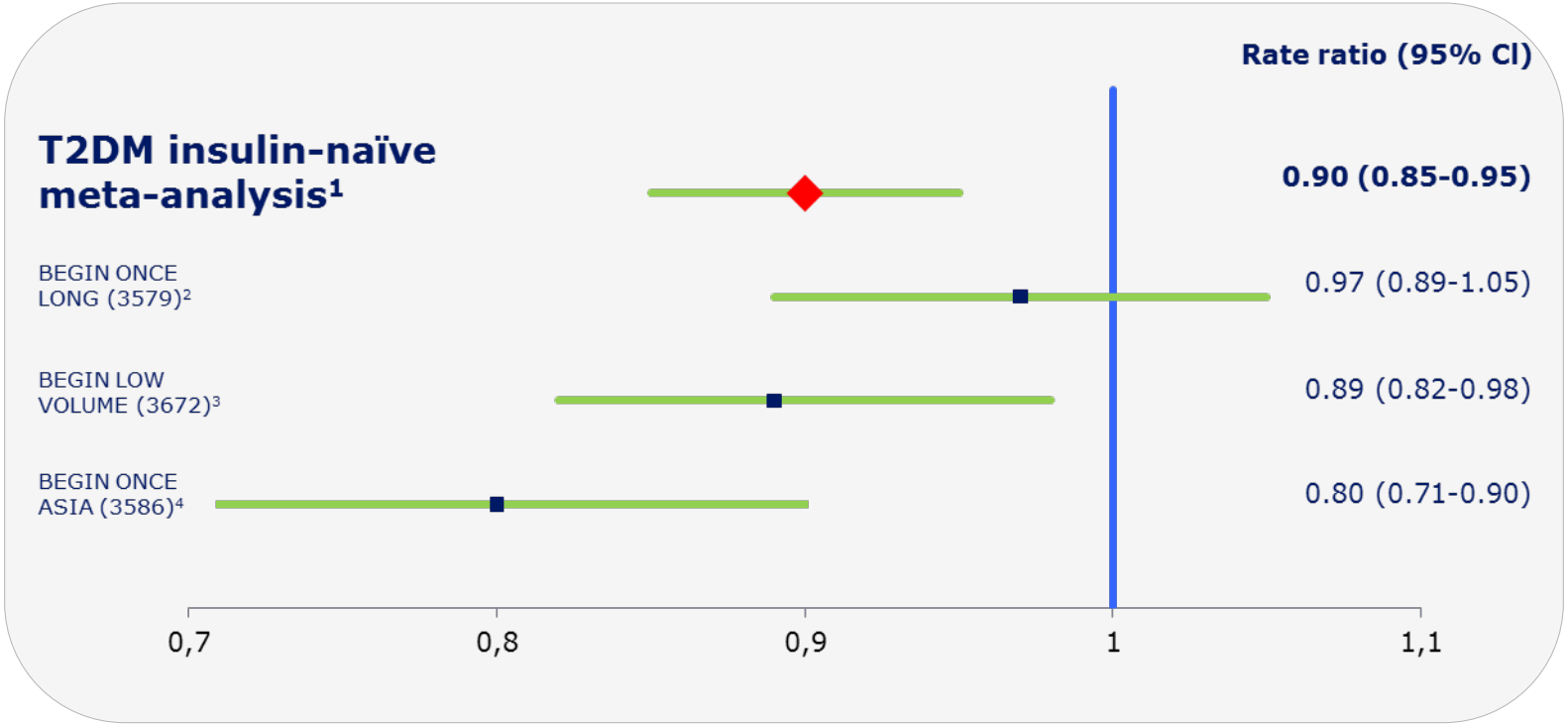


†Ratios deviate from those in the reference Table 2 as the publication analyses all IDeg patients together (incl. forced flexible dosing arm); ratios here are IDeg standard dosing arm only.

1. Data on file, DOF-MA-IDeg-24APR2013-001, Novo Nordisk A/S. 2. Heller et. al. *Lancet* 2012; 379:1489-97. 3. Mathieu et.al. *J Clin Endocrinol Metab* 2013;98(3): 1154-62

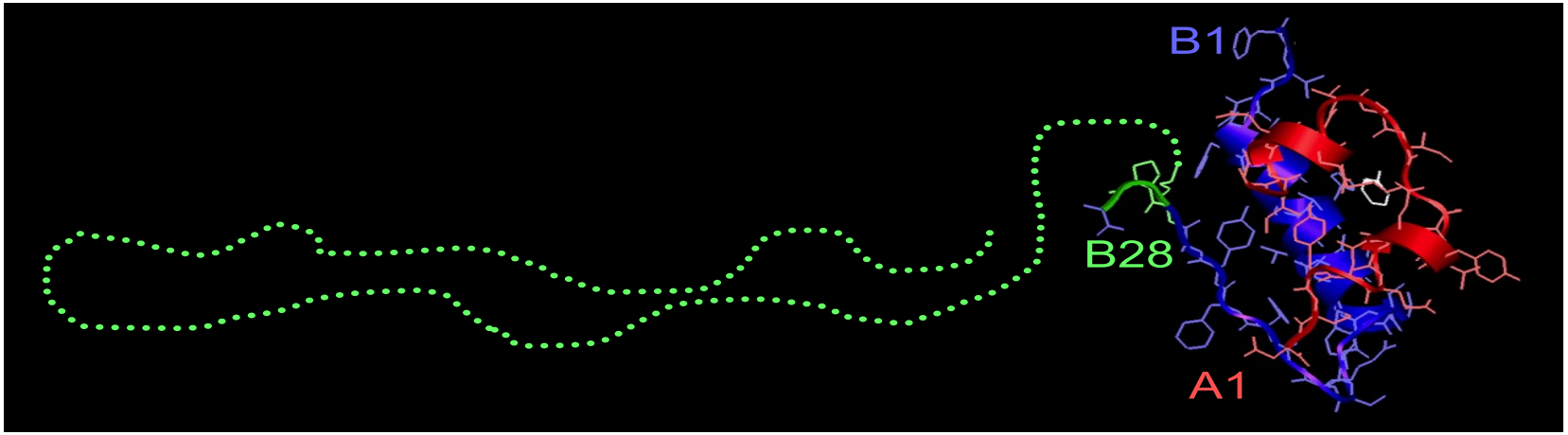
Total daily dose

- For **insulin-naïve T2DM patients**, the total daily dose was 10% lower with IDeg than IGlar (p=0.0004)[1]



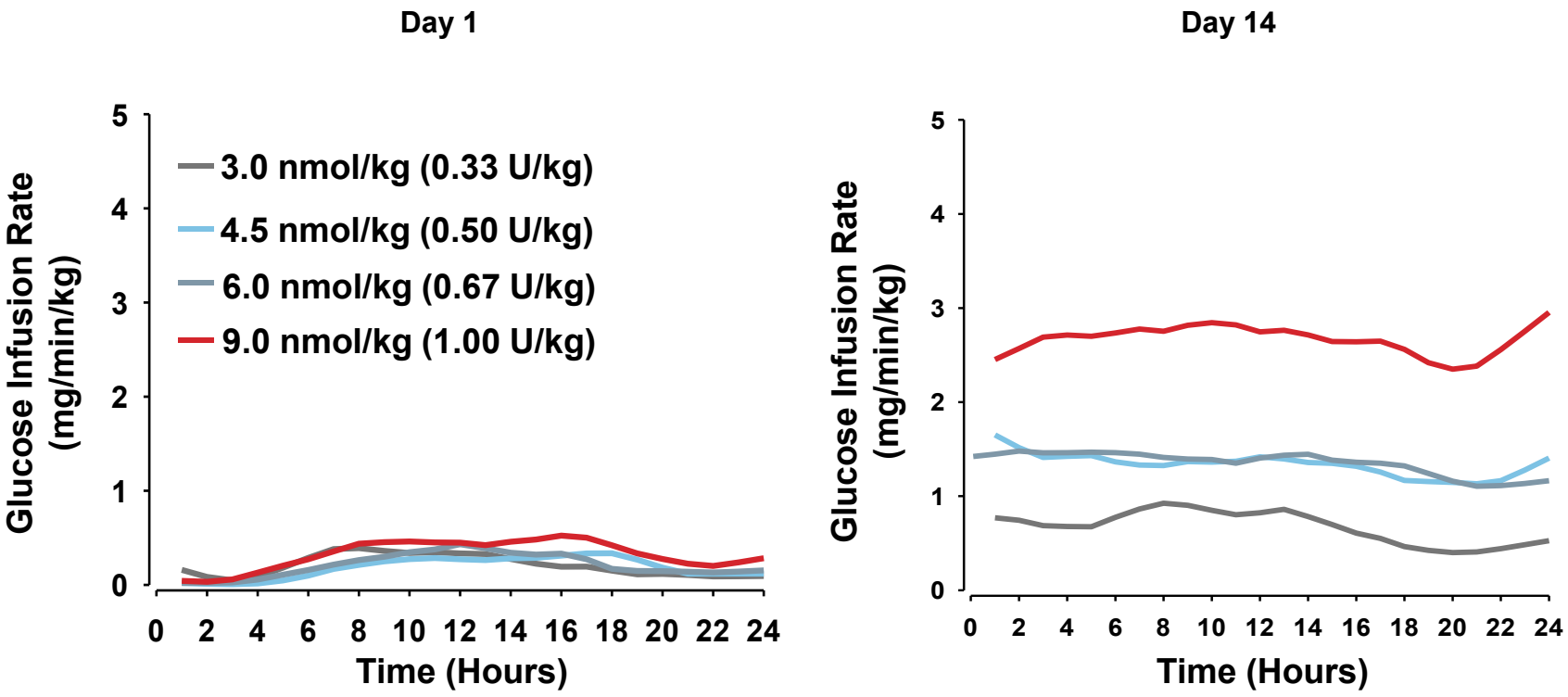
1. Data on file, DOF-MA-IDeg-24APR2013-001, Novo Nordisk A/S. 2. Zinman et al. *Diabetes Care*. 2012; 35(12):2464-71 (+ supplementary online data).
3. Gough et.al., *Diabetes Care* 2013; May 28. [Epub ahead of print]. 4. Onishi et.al. *Journal of Diabetes Investigation* 2013; DOI: 10.1111/jdi.12102 [Epub ahead of print]
(+ supplementary online information).

BIL : A Novel Basal Insulin - LY2605541



- PEGylated insulin lispro with a large molecular profile
- PEG “tail” alters insulin PK by reducing both absorption and clearance with dis tinctive, advantageous pharmacologic characteristics
  - Slow absorption from the injection site
  - Slow elimination from the body
  - Long duration of action
  - More physiologic balance of hepatic/peripheral activity (potential benefits of redu ced “insulinization” of the periphery, and minimal or no weight impact)

PK and GD of BIL in Patients with T2DM: Mean LOESS-fitted Glucose Infusion Rate Profiles of BIL



Sinha et al. *Diabetes Obes Metab* 2014;16(4):344-50.

Pegylated Lispro* vs Glargine in Adults With T2D at 12 Weeks

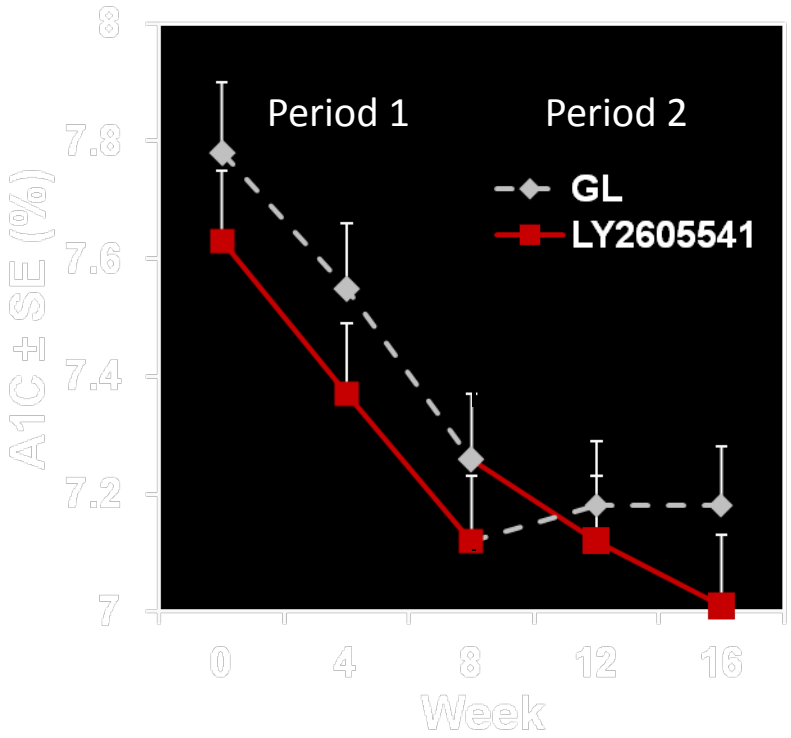
- Patients with T2D, 12 weeks
- After adjusting for baseline rates, nocturnal hypoglycemia was 48% lower in the pegylated lispro group (*P* = .021)

Outcome	PEGL QD (n = 195; 0.59 U/kg)	GLAR QD (n = 93; 0.60 U/kg)	*P* Value
ΔHbA_{1C}, %	–0.7	–0.7	NS
ΔWeight, kg	–0.6	0.3	.001
Overall hypoglycemia, EPY	1.34	1.52	.804
Nocturnal hypoglycemia, EPY	0.25	0.39	.178
Severe hypoglycemia, episodes	0	0	

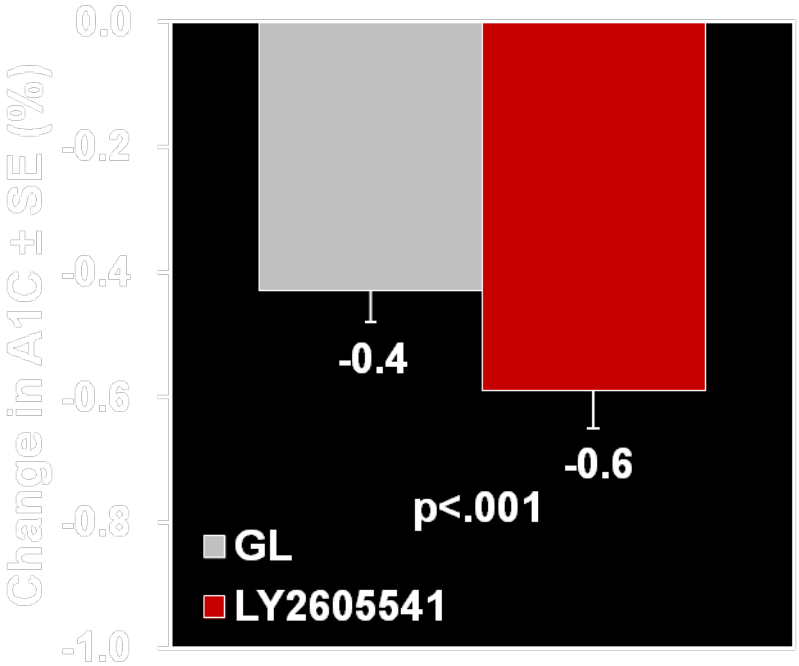
EPY = events/patient year; 2-period = phase 2 crossover trial.
*PEGylated insulin lispro is not FDA approved for clinical use.
Hypoglycemia, plasma glucose ≤ 70 mg/dL or severe per ADA definition.
Bergenstal RM, et al. *Diabetes Care*. 2012;35:2140-2147.[30]

T1D Phase 2 LY2605541 vs. GL: Change in A1C

Mean A1C Throughout 16-week Crossover Study



Mean Change from Baseline in A1C Over 8 Weeks[1]

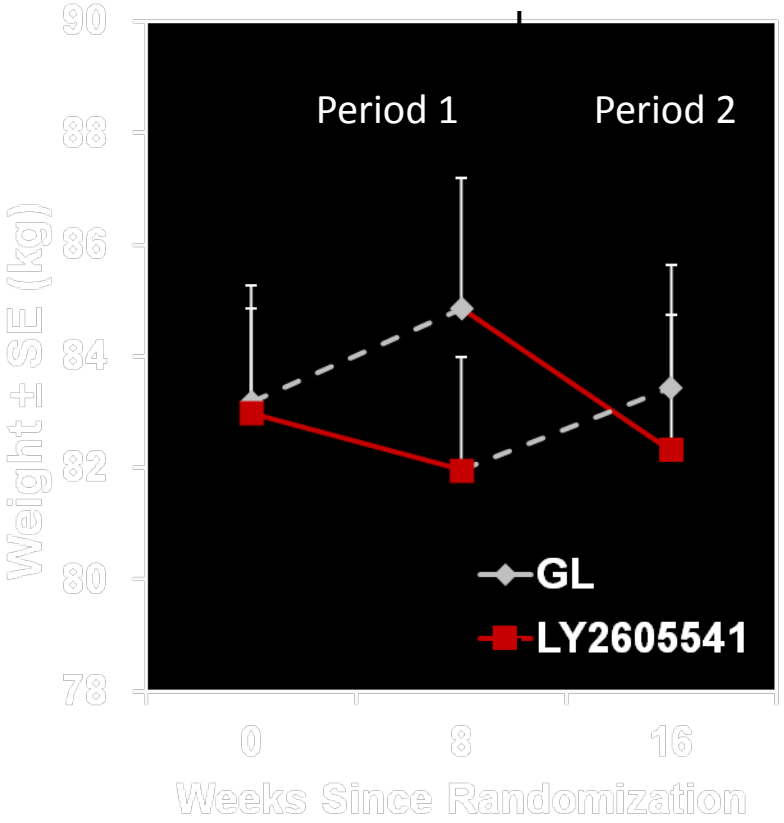


Rosenstock et al. *Diabetes Care*. 2013 Mar;36(3):522-8. doi: 10.2337/dc12-0067. Epub 2012 Nov 27

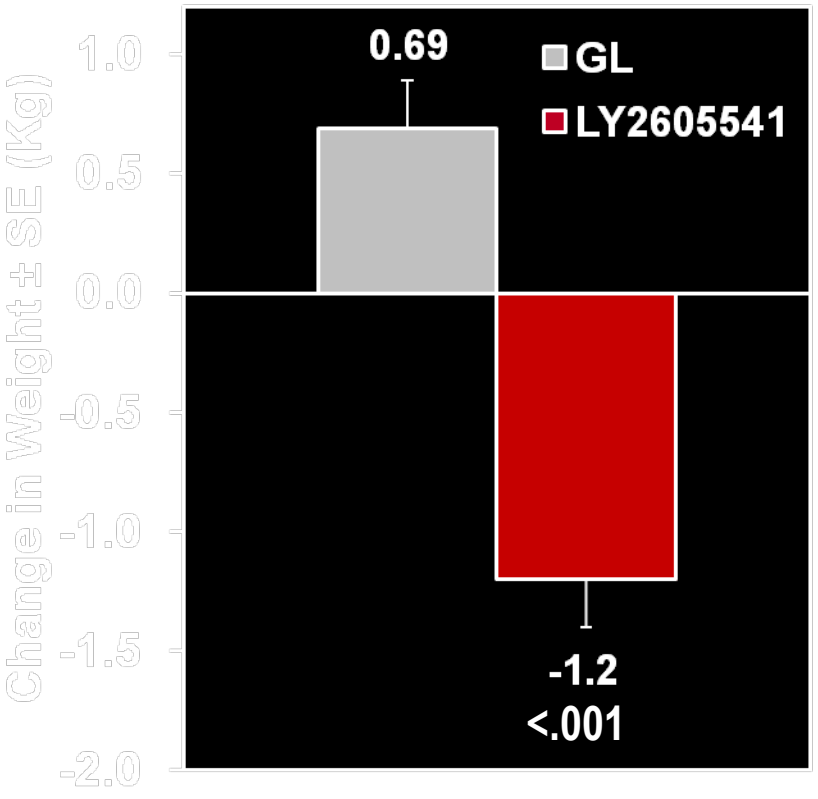
1. Rosenstock et al. *Diabetes* 2012;61(Suppl 1):A212-A344. Abstract# 1026-P.

T1D Phase 2 LY2605541 vs. GL: Change in Weight

Mean Weight Throughout 16-week Crossover Study



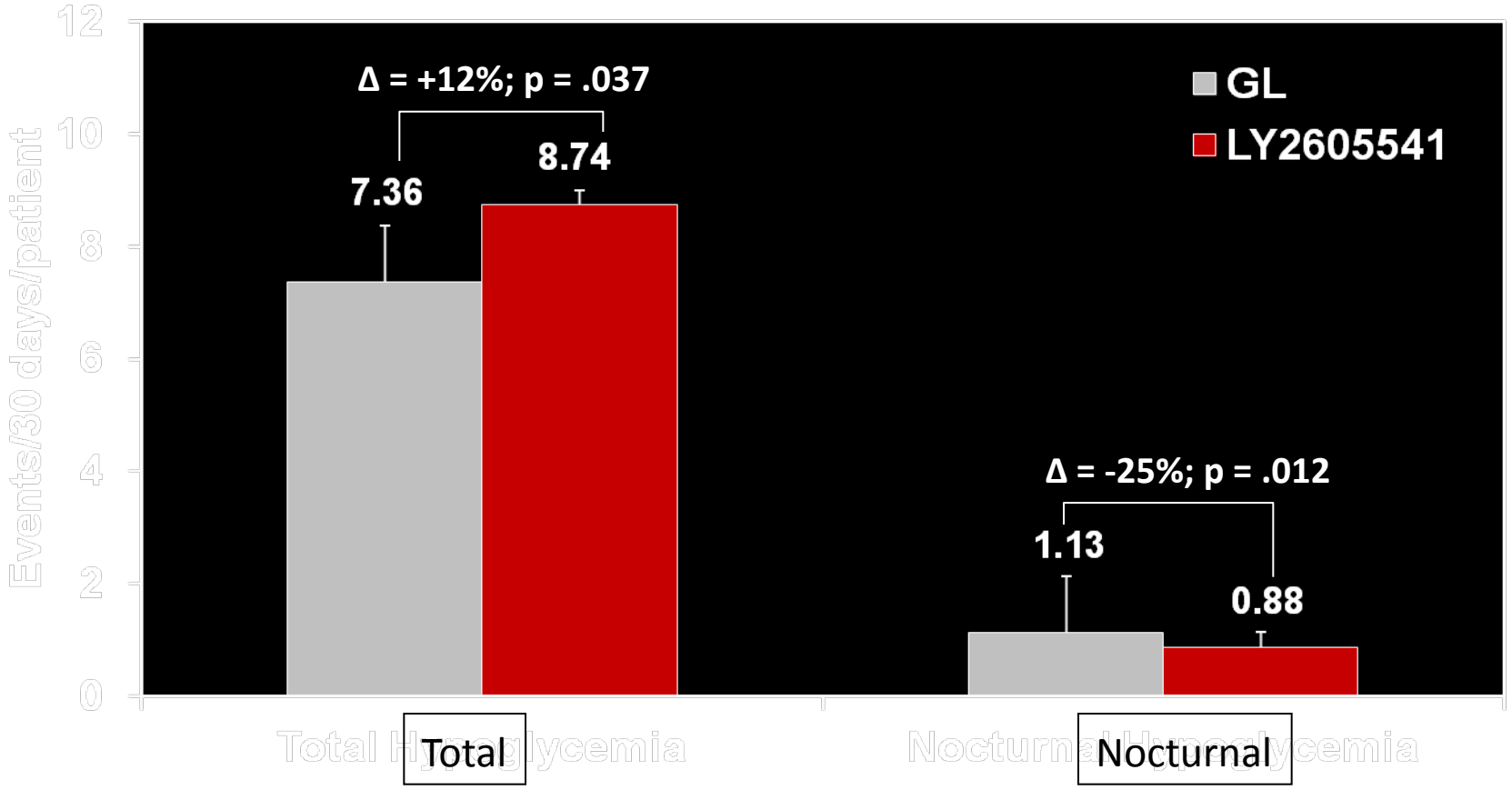
LS Mean Change in Weight Over 8 Weeks[1]



Rosenstock et al. *Diabetes Care*. 2013 Mar;36(3):522-8. doi: 10.2337/dc12-0067. Epub 2012 Nov 27

1. Rosenstock et al. *Diabetes* 2012;61(Suppl 1):A212-A344. Abstract# 1026-P.

T1D Phase 2 LY2605541 vs. GL: Rates of Total and Nocturnal Hypoglycemia



- Severe hypoglycemia incidence similar between groups (6 events with LY2605541 [5 patients] and 6 events with glargine [3 patients])

Rosenstock et al. *Diabetes Care*. 2013 Mar;36(3):522-8. doi: 10.2337/dc12-0067. Epub 2012 Nov 27

Basal Insulin Peglispro Demonstrates Preferential Hepatic Versus Peripheral Action Relative to Insulin Glargine in Healthy Subjects

Robert R. Henry,[1,2] Sunder Mudaliar,[1,2]
Theodore P. Ciaraldi,[1,2]
Debra A. Armstrong,[1] Paivi Burke,[1]
Jeremy Pettus,[2] Parag Garhyan,[3]
Siak Leng Choi,[4] Scott J. Jacober,[3]
Mary Pat Knadler,[3] Eric Chen Quin Lam,[4]
Melvin J. Prince,[3] Namrata Bose,[2]
Niels Porksen,[3] Vikram P. Sinha,[3] and
Helle Linnebjerg[3]

Diabetes Care 2014;37:2609–2615 | DOI: 10.2337/dc14-0210

OBJECTIVE

We evaluated the endogenous glucose production (EGP) and glucose disposal rate (GDR) over a range of doses of basal insulin peglispro (BIL) and insulin glargine in healthy subjects.

RESEARCH DESIGN AND METHODS

This was a single-center, randomized, open-label, four-period, incomplete-block, crossover study conducted in eight healthy male subjects. Subjects had 8-h euglycemic clamps performed with primed, continuous infusions of BIL (5.1 to 74.1 mU/min) in three dosing periods and insulin glargine (20 or 30 mU/m^2/min) in a

CONCLUSIONS

The novel basal insulin analog BIL has relative hepatopreferential action and decreased peripheral action, compared with insulin glargine, in healthy subjects.

290 pmol/L, respectively, and increased accordingly with increases in dose. Suppression of EGP and stimulation of GDR were observed with increasing concentrations of both insulins. At insulin concentrations where EGP was significantly suppressed, insulin glargine resulted in increased GDR. In contrast, at comparable suppression of EGP, BIL had minimal effect on GDR at lower doses and had substantially less effect on GDR than insulin glargine at higher doses.

CONCLUSIONS

The novel basal insulin analog BIL has relative hepatopreferential action and decreased peripheral action, compared with insulin glargine, in healthy subjects.

February 23, 2015

Lilly Announces Update on Regulatory Submission Timing for Basal Insulin Peglispro

INDIANAPOLIS, Feb. 23, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced a delay in the submission of basal insulin peglispro (BIL) to regulatory agencies beyond the first quarter of 2015. The delay includes filings with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency.

Lilly will delay submission in order to generate additional clinical data to further understand and characterize the potential effects, if any, of changes in liver fat observed with BIL treatment in the Phase III trials. Lilly intends that ongoing clinical trials will continue as planned. In the clinical development program to date, in which more than 6,000 patients with type 1 and type 2 diabetes were treated for up to 18 months (approximately 3,900 patients treated with BIL), no drug-induced liver impairment or Hy's Law cases have been observed.

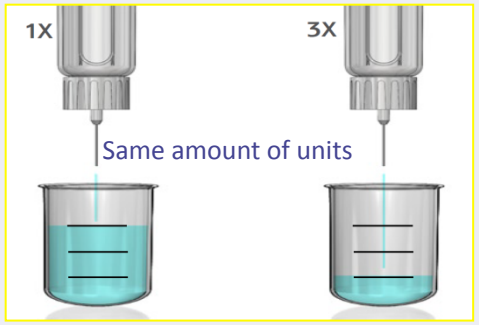
"Lilly believes in the potential of BIL and its novel mechanism of action. The development of BIL remains important to us and we are committed to further evaluating the safety and efficacy of this investigational treatment for people with diabetes," said Enrique Conterno, President, Lilly Diabetes. "While we are disappointed with the delay, we feel it is important to gain a better understanding of the potential effects of BIL on the liver before asking regulators to review the drug for approval. Our priority is delivering safe and innovative medicines to meet the needs of people living with diabetes, and that's what we aim to accomplish with this additional work."

The length of the delay cannot be determined until clinical trial plans have been developed. However, the company anticipates the submission is likely to occur after 2016. Lilly is working to determine next steps, including potential consultations with regulators. Information regarding future submission timing will be provided following these activities.

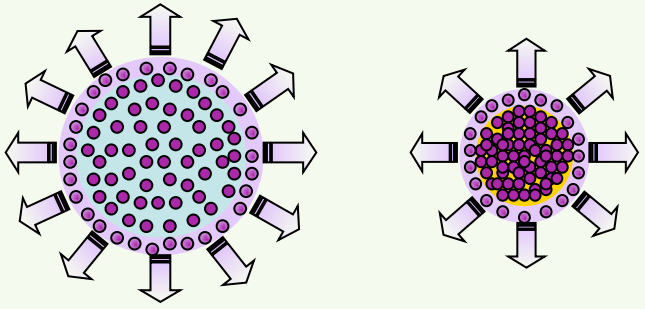
Investigational new insulin glargine Gla-300 (300 U/mL)

Gla-300 is a new long-acting basal insulin with a more even and prolonged PK/PD profile vs Gla-100®

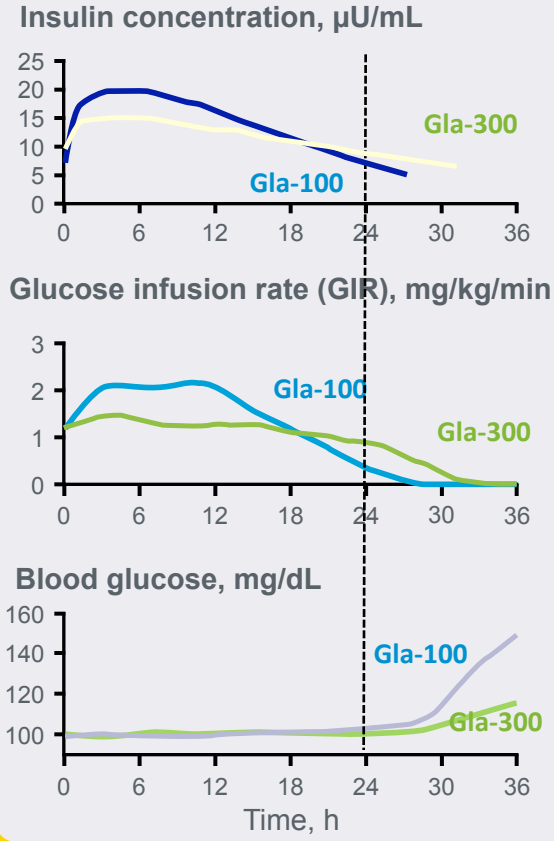
Reduction of volume by 2/3



Reduction of depot surface by 1/2



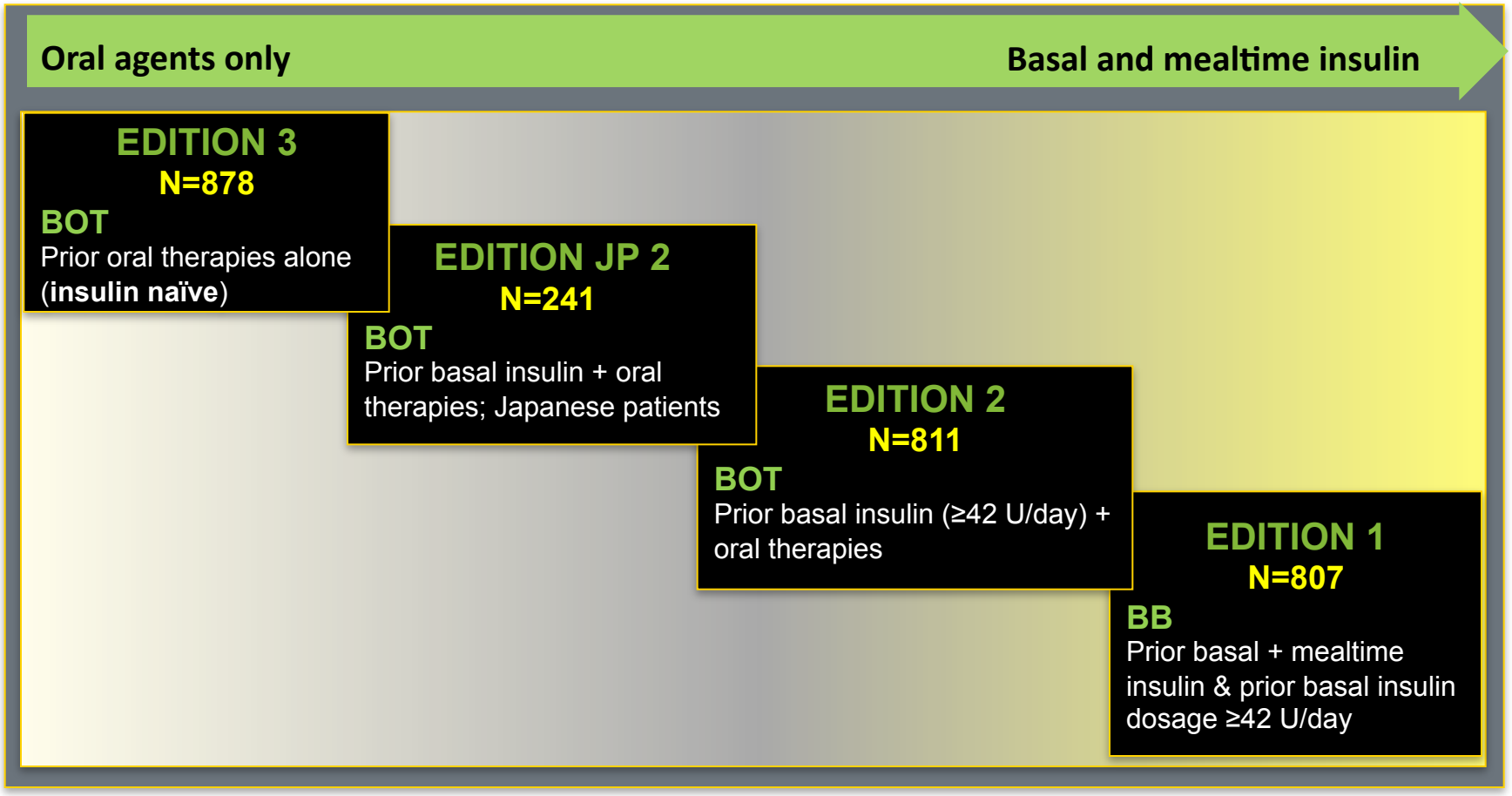
More even and prolonged PK/PD profile



Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6; Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

EDITION program in T2DM

Testing Gla-300 vs Gla-100 across the spectrum of treatment

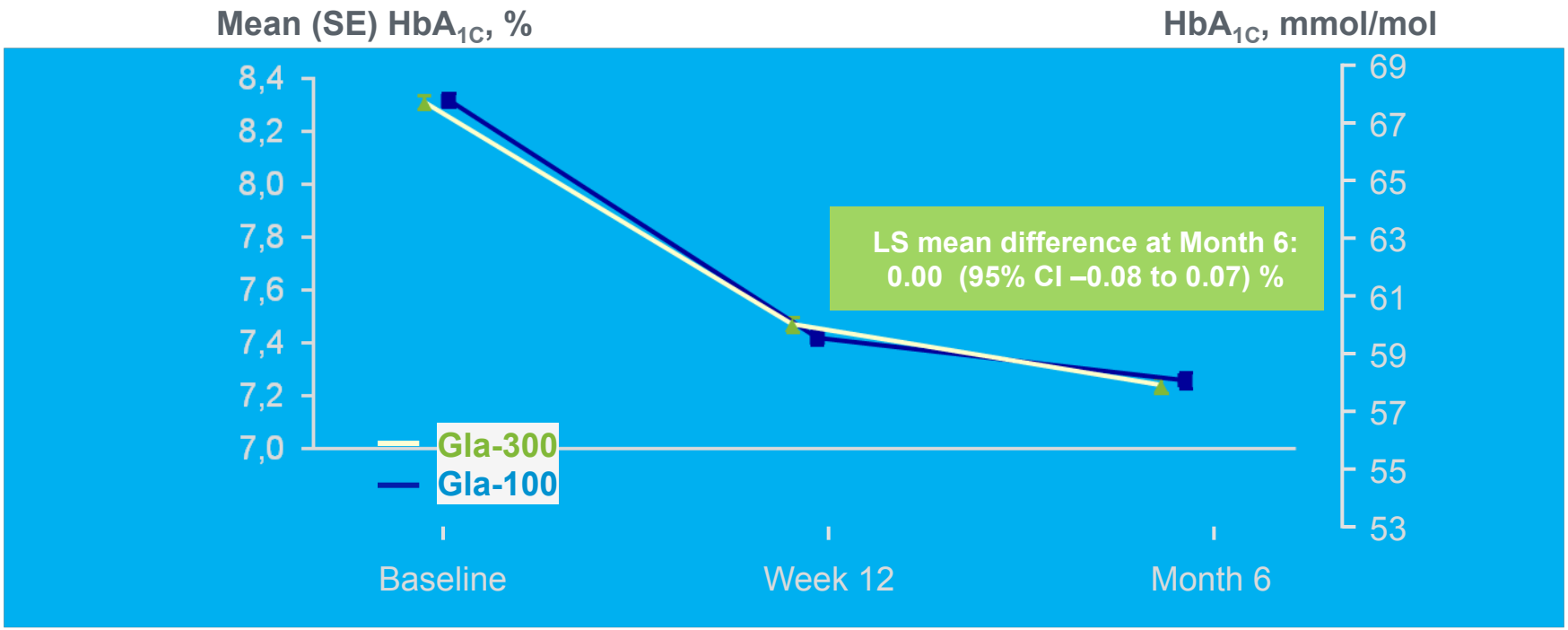


Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014 Sep 5. pii: DC_140990 [Epub ahead of print]; Bolli GB et al. Poster presentation at EASD 2014; Abstract 947; Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976

Pooled Analysis of EDITION Program T2DM Studies: EDITION 1, 2 & 3

Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

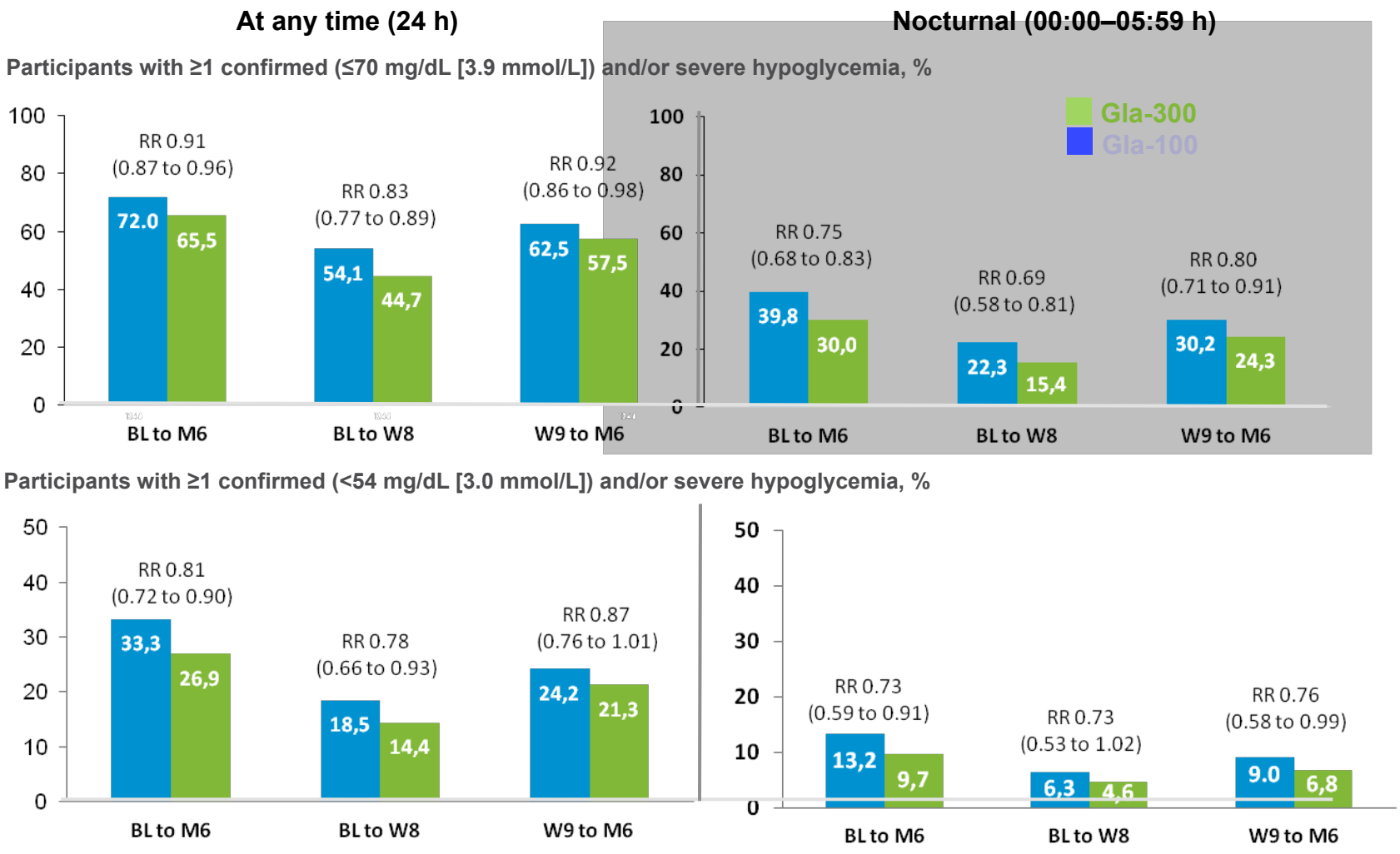
Similar reductions in HbA_{1C} and FPG



- At Month 6, FPG decreased similarly in both groups
  - LS mean (SE) change was −2.0 (0.1) mmol/L with Gla-300 and −2.3 (0.1) mmol/L with Gla-100
  - LS mean difference 0.2 (0.1) mmol/L

Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

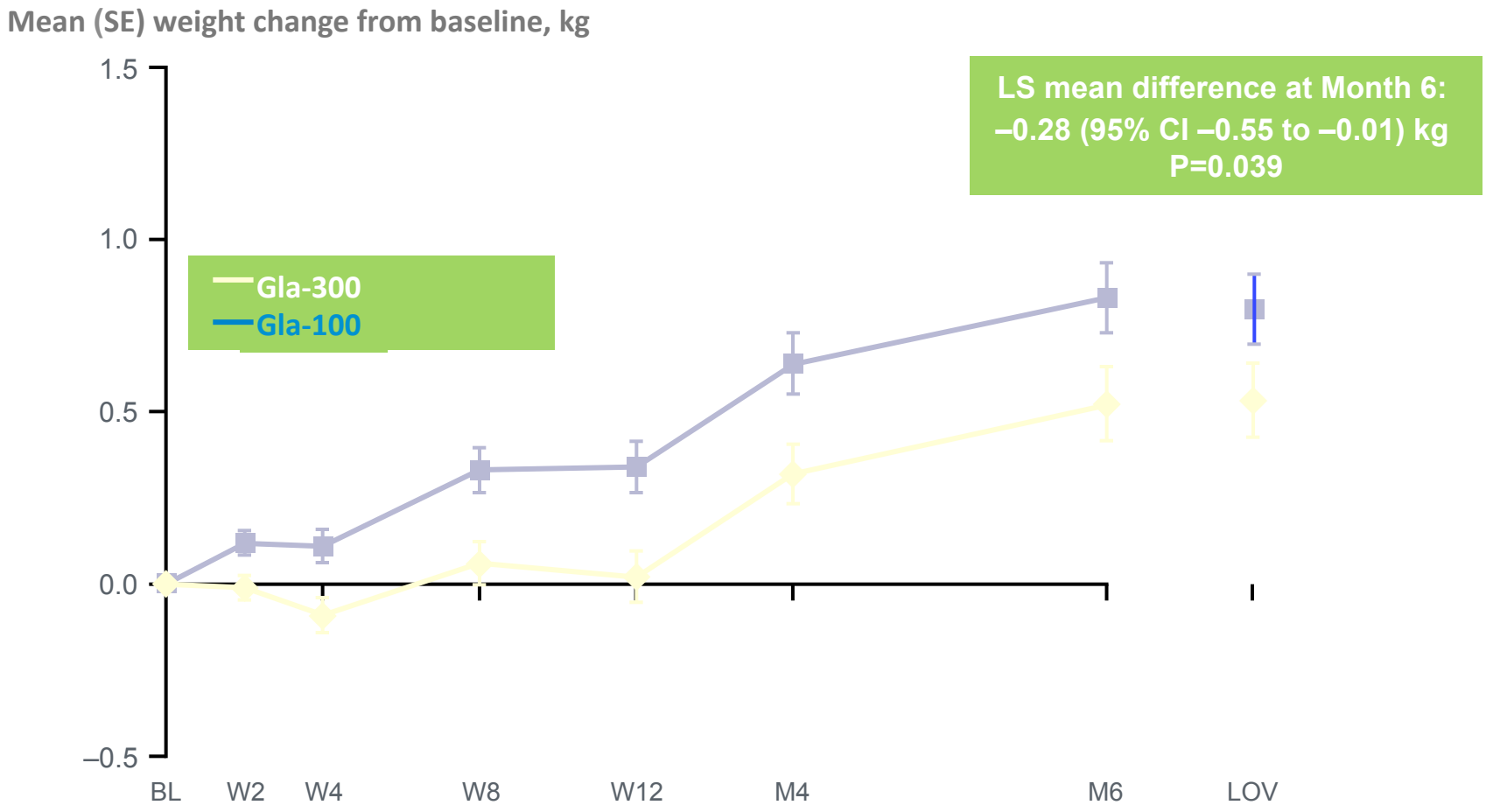
Generally lower confirmed and/or severe hypoglycemia with Gla- 300 vs Gla-100 at any time (24 h) and at night



Relative risk (95% CI)

Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

Small but significant difference in weight gain with Gla-300 vs Gla-100



Ritzel R et al. Poster presentation at EASD 2014; Abstract 963 Available at: http://www.easdvirtualmeeting.org/resources/18908 Accessed September 2014

Benefits of Newer Basal Insulins

- Ultra-long-acting insulin analogs
  - Duration up to 42 hours
- Flat, stable glucose-lowering profile
- Lower within patient day-to-day variability in glucose-lowering effect
- Similar glycemic control compared with available basal insulins
- Flexible timing of injection time, without compromising efficacy or safety
- Less nocturnal hypoglycemia
- Reduced weight gain
- Smaller doses with concentrated insulin
- More “forgiveness” if timing of injection changes or missed dose

Garber AJ. *Diabetes Obes Metab*. 2014;16:483-491.[15]

Insuline Biosimilari (non generiche)

Per i biosimilari viene richiesto che la sequenza aminoacidica sia identica e la farmacodinamica simile

La somiglianza non garantisce identità: *durata di azione ed antigenicità possono essere diversi*

Punti di differenza

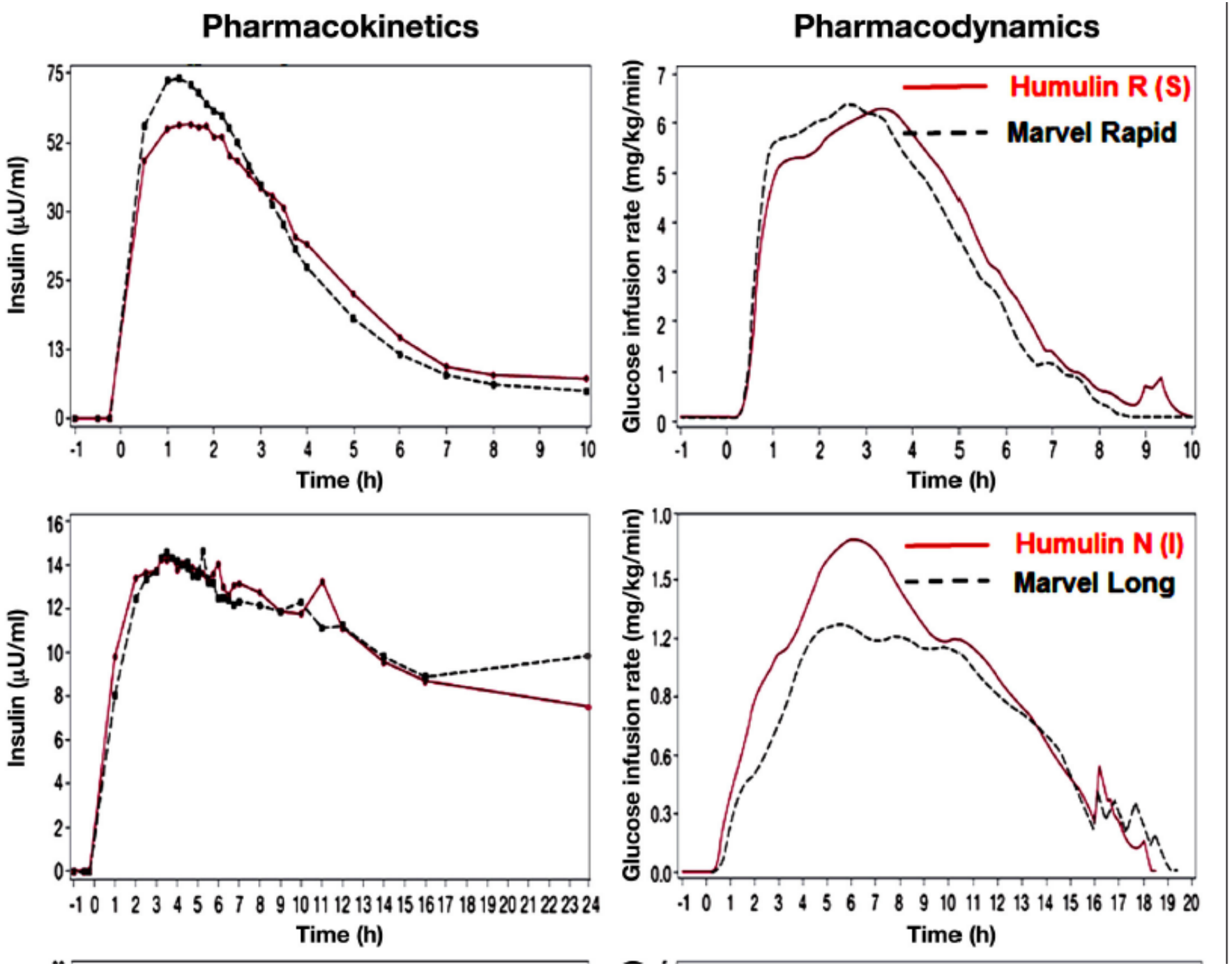
- le cellule della manifattura
- le tecniche di estrazione dal bioreattore
- la tecnica di purificazione
- la processazione post-fermentativa

In conseguenza possono variare:

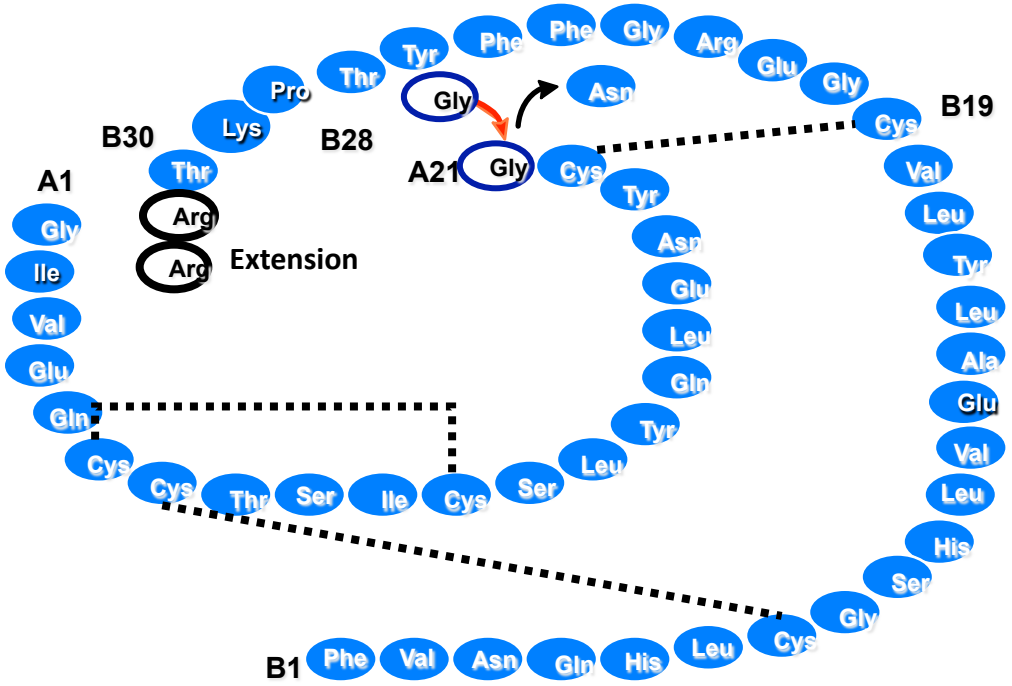
- Composizione
- Attività biologica
- Stabilità di conservazione
- Proprietà di assorbimento
- Antigenicità (differenze di purezza)

Companies Manufacturing Insulins That Might Become Biosimilar Insulins Once They Have Been Subjected to an Official Comparative Analysis with an Approved Reference Product (Regular HI)

Name	Country	Insulin marketed (in the home country)
Wockhardt	India	Regular HI: Wosulin Analog: Glaritus (glargine)
Biocon	India	Regular HI: Insugen Analog: Basalog (glargine)
Bioton	Poland	Regular HI: Gensulin/Biosulin, SciLin
Tonghua DongBao/ Gan&Lee	China	Regular HI: Comonlin Analog: Prandilin (insulin lispro), Basalin (glargine)
MJ Biopharm (Marvel Life Sciences)	India	Regular HI: Biosulin


Pharmacokinetics
Pharmacodynamics
Insulin (µU/ml)
Glucose infusion rate (mg/kg/min)
Time (h)
Humulin R (S)
Marvel Rapid
Humulin N (I)
Marvel Long

BIV-LY3016 is a “new insulin glargine product.”



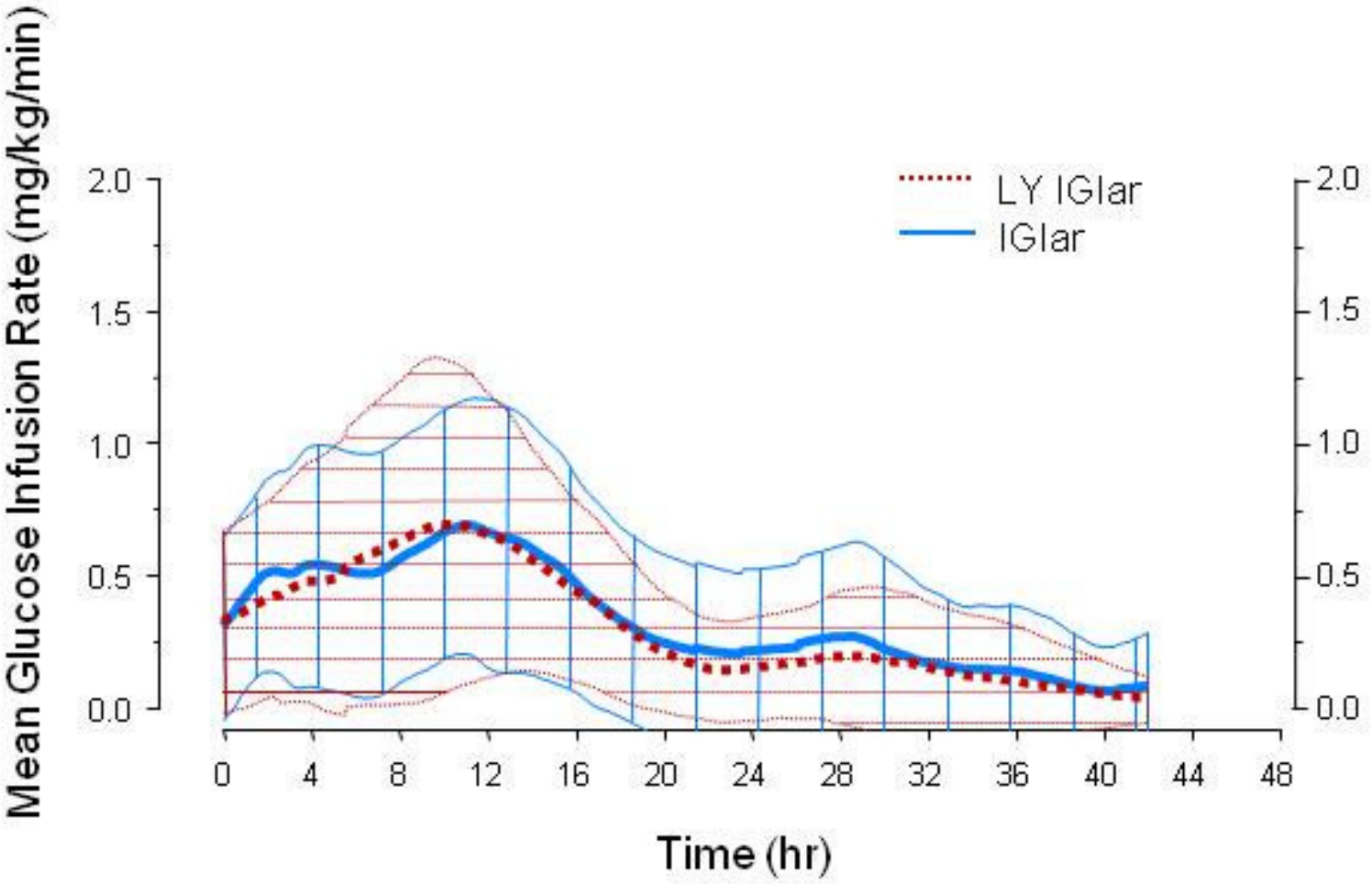
Phase 1 Studies

- PK/PD intra-subject variability in T1DM
- Pilot PK/PD relative bioavailability study, in healthy subjects (n=12 completers; 24 clamps)
- PK/PD bioequivalence in HVs

Phase 3 Studies

- Efficacy non-inferiority and safety, open label in adult T1DM 432 – 550 and T2 (insulin-naïve and existing basal (606 – 792 patients)

LY2963016 VS GLARGINE



LY2963016 VS GLARGINE

outcomes in patients with T1DM or T2DM.

Table 1 Incidence and Effect of Anti-insulin Glargine Antibodies on Clinical Outcomes

			Baseline[a] LY IGlar	Baseline[b] IGlar	Overall[c] LY IGlar	Overall[c] IGlar
Patients with detectable antibodies, n (%)		**T1DM** **T2DM**	45 (17.0) 20 (5.5)	55 (20.6) 13 (3.6)	107 (40.4) 56 (15.3)	105 (39.3) 40 (11.0)
Patients with TEAR, n (%)		**T1DM** **T2DM**	— —	— —	29 (10.9) 14 (3.8)	25 (9.4) 14 (3.8)
Effect of overall TEAR status on clinical outcomes (LSM change[d])	**HbA1c, % (TEAR / no TEAR)**	**T1DM** **T2DM**	— —	— —	-0.38 / -0.25 -1.2 / -1.3	-0.23 / -0.28 -1.7 / -1.3
	Basal Insulin Dose (U/day) (TEAR / no TEAR)	**T1DM** **T2DM**	— —	— —	-0.1 / 3.1 40.2 / 32.0	2.3 / 2.5 67.6 / 31.7
	Total Hypoglycemia Rate (Episodes/30 days) (TEAR / no TEAR)	**T1DM** **T2DM**	— —	— —	-1.1 / -3.0 1.4 / 0.6	-2.5 / -4.1 1.2 / 1.0
Patients with ≥1 Treatment Emergent Allergic Event, n (%)		**T1DM** **T2DM**	— —	— —	20 (7.5) 21 (5.6)	11 (4.1) 27 (7.1)

[a]N=268 T1DM, N=376 T2DM (N numbers reflect maximum sample size; actual sample size may vary slightly from variable to variable due to missing values); 60% of T2DM patients were insulin naïve at baseline
[b]N=267 T1DM, N=380 T2DM (maximum sample size); 60% of T2DM patients were insulin naïve at baseline
[c]Throughout the treatment period unless otherwise specified
[d]From baseline to LOCF endpoint (T1DM, 52 wks; T2DM, 24 wks)
LSM, least squares mean; TEAR, treatment emergent antibody response (defined as patients who were antibody negative at baseline and developed antibody binding values ≥1.26% postbaseline, or patients with detectable antibody levels at baseline with at least a 1% increase in antibody binding value and which is 30% greater than baseline)