18 Congrés de la Societat Catalana d'Endocrinologia i Nutrició
13 de Noviembre de 2015

Que poden aportar les noves insulines?
Nuevas insulinas basales

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Conflictos de interés

Francisco Javier Escalada

En relación con el tema: Conferencias para Lilly, Novonordisk y Sanofi y **pertenece a comités asesores** de Sanofi.

New Basal Insulin Formulations

- Introducción
- Mecanismo de acción, duración, variabilidad
- Estudios pivotales
  - Control glucémico
    - HbA1c
    - Glucemia basal
  - Hipoglucemias
  - Peso
  - Dosis de insulina
- Seguridad
  - Cardiovascular
  - No cardiovascular

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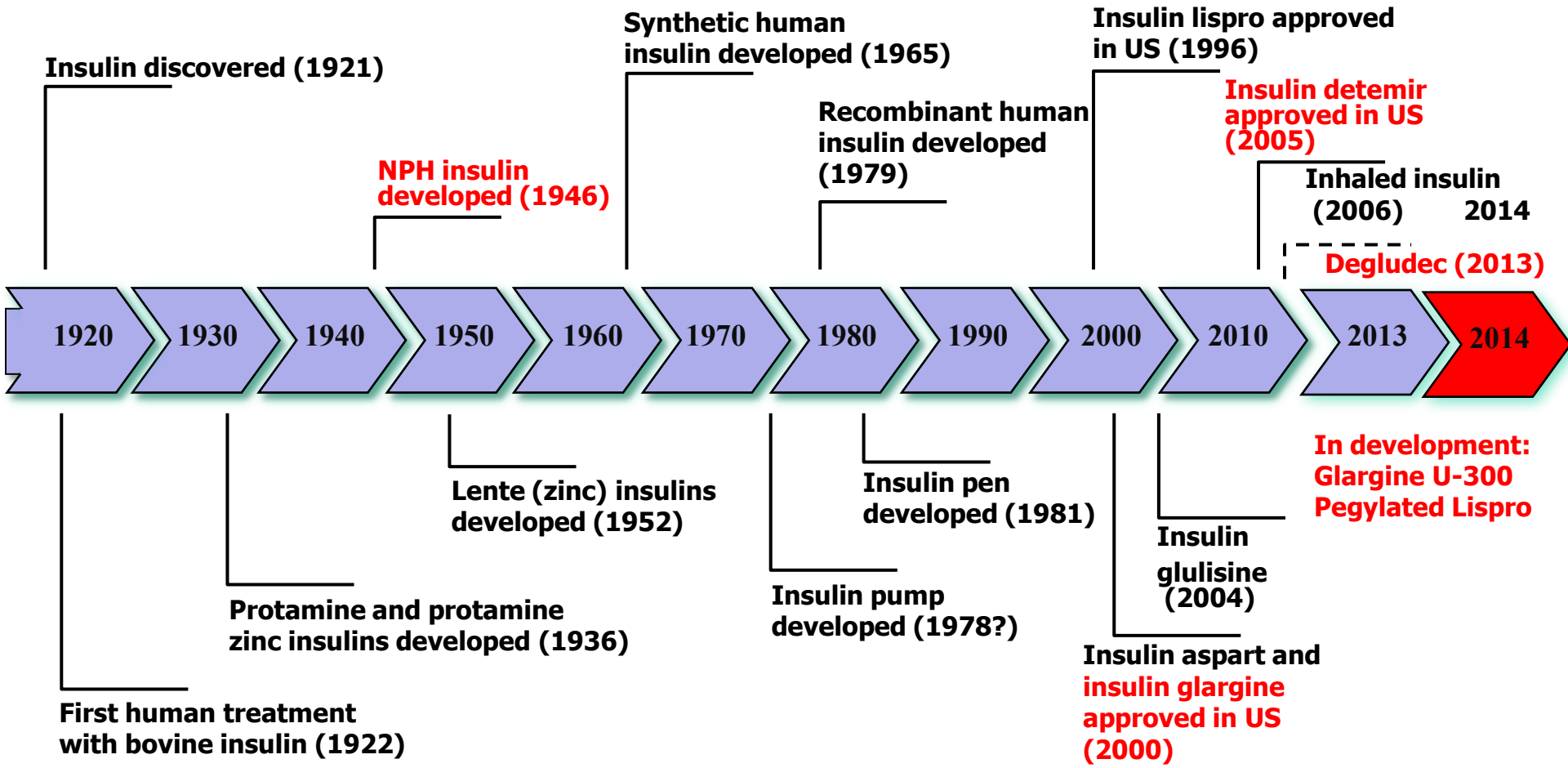
Milestones in Insulin Development

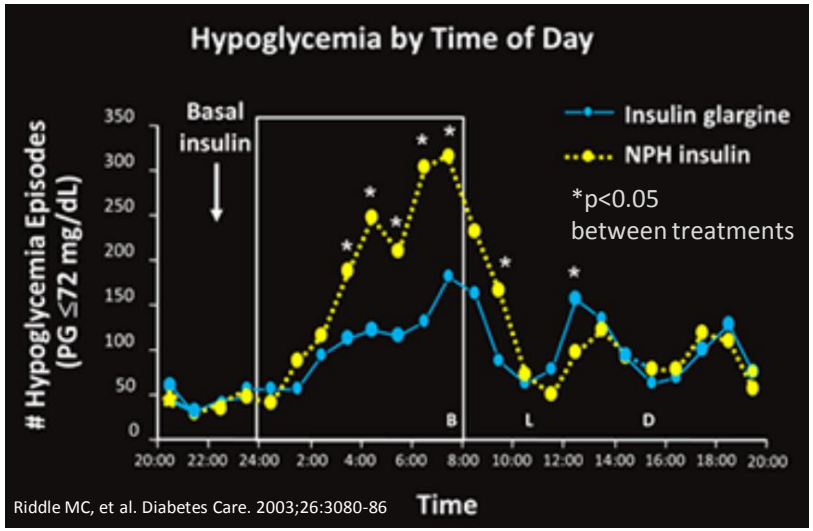


Tattersall RB. In: Pickup JC, Williams G, eds. Textbook of Diabetes. 3rd ed. Blackwell Science: Malden, MA; 2003:1.1-1.22; Drugs@ FDA; http://diabetes.webmd.com/news/20071018/pfizer-quits-inhaled-insulin-exubera.

Characteristics of Available Basal Insulin Analogs

Benefits over NPH

- Longer duration of action
- Less variability
- Less weight gain
- Less hypoglycemia



Simon ACR. *Diabetes Technol Ther.* 2011;13(suppl 1):S103-108. Grunberger G. *Diab Obes Metab*. 2013;15(suppl 1):1-5.

Diabetes, Obesity and Metabolism 15 (Suppl. 1): 1–5, 2013.

The need for better insulin therapy

G. Grunberger

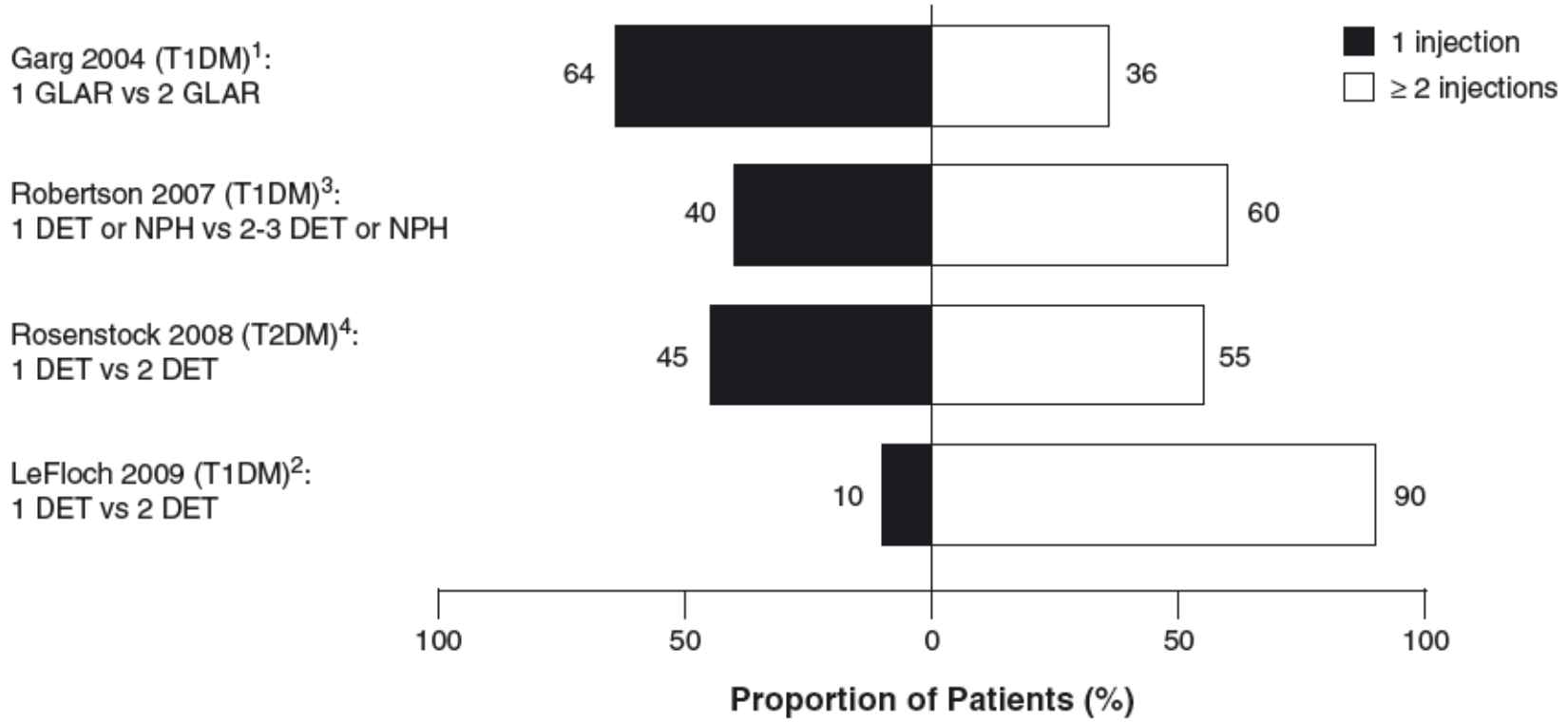
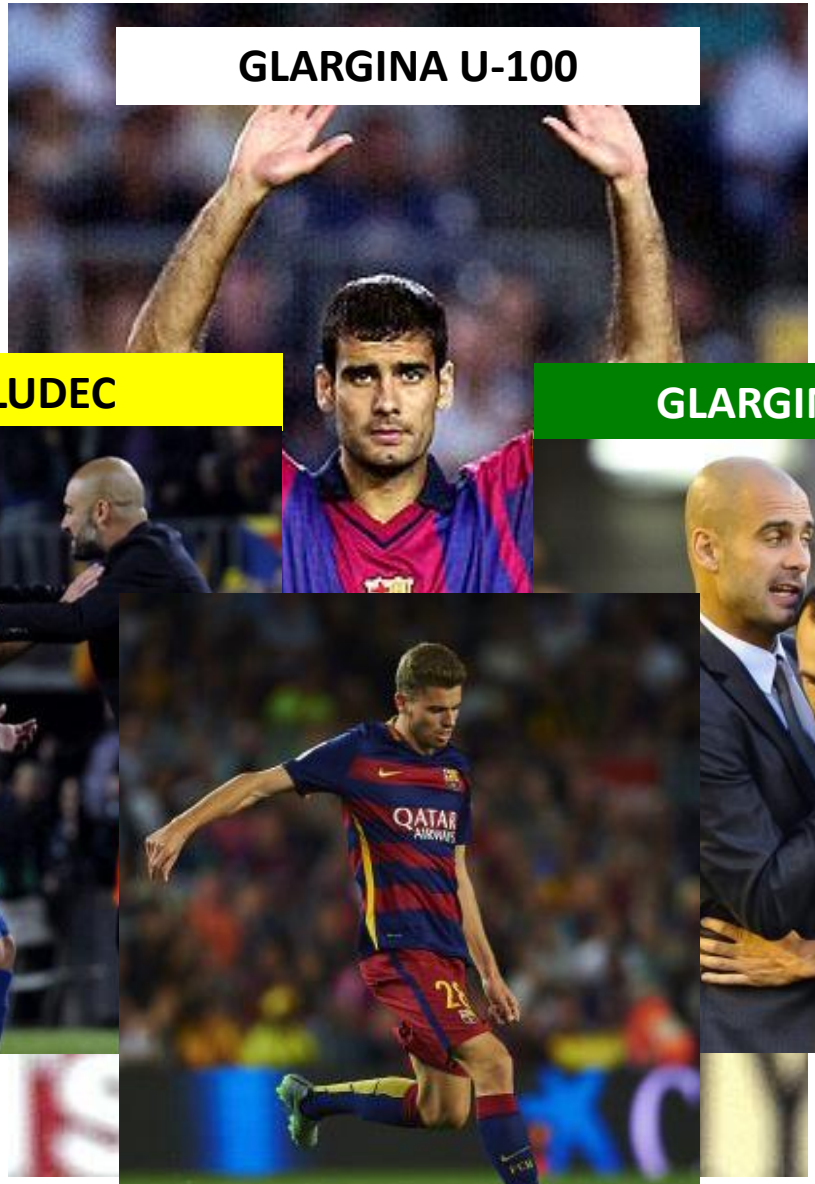


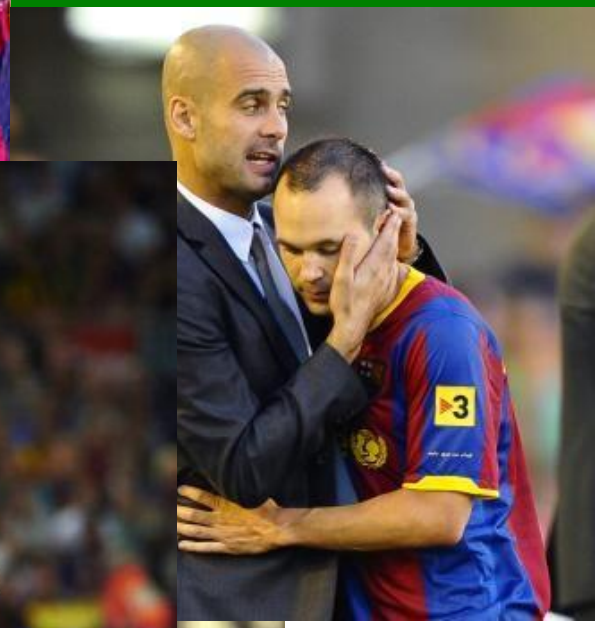
Figure 4. Multiple doses of basal insulin analogues may be needed to attain glycaemic goals. Adapted with permission from Refs. [22,42–44].

GLARGINA U-100



DEGLUDEC

GLARGINA U-300



PEGILADA LISPRO

New Basal Insulin Formulations

- **Glargine U-300**
- **Degludec**
- ***Pegylated Lispro**

No head-to-head trials

Estudios frente a Glargina U-100

* Not FDA Approved

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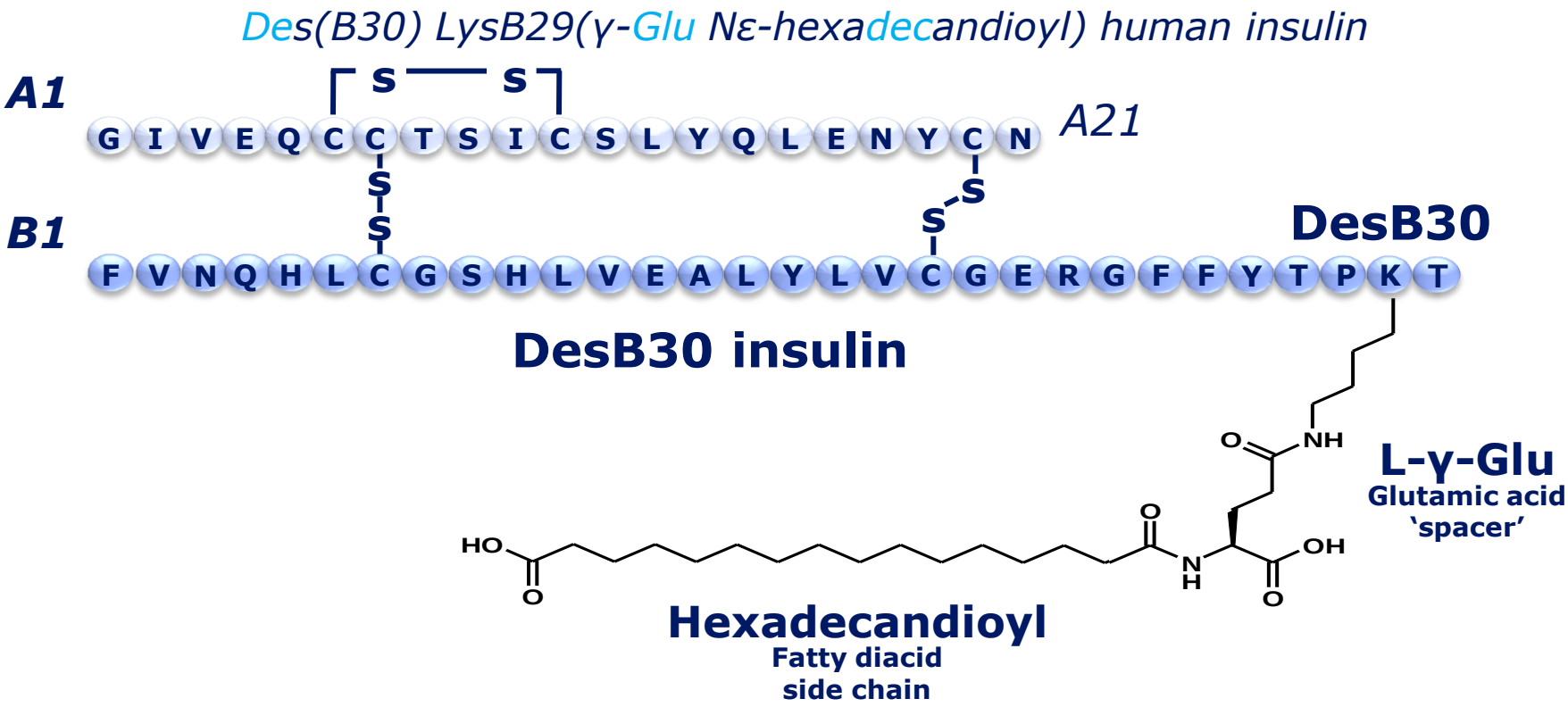
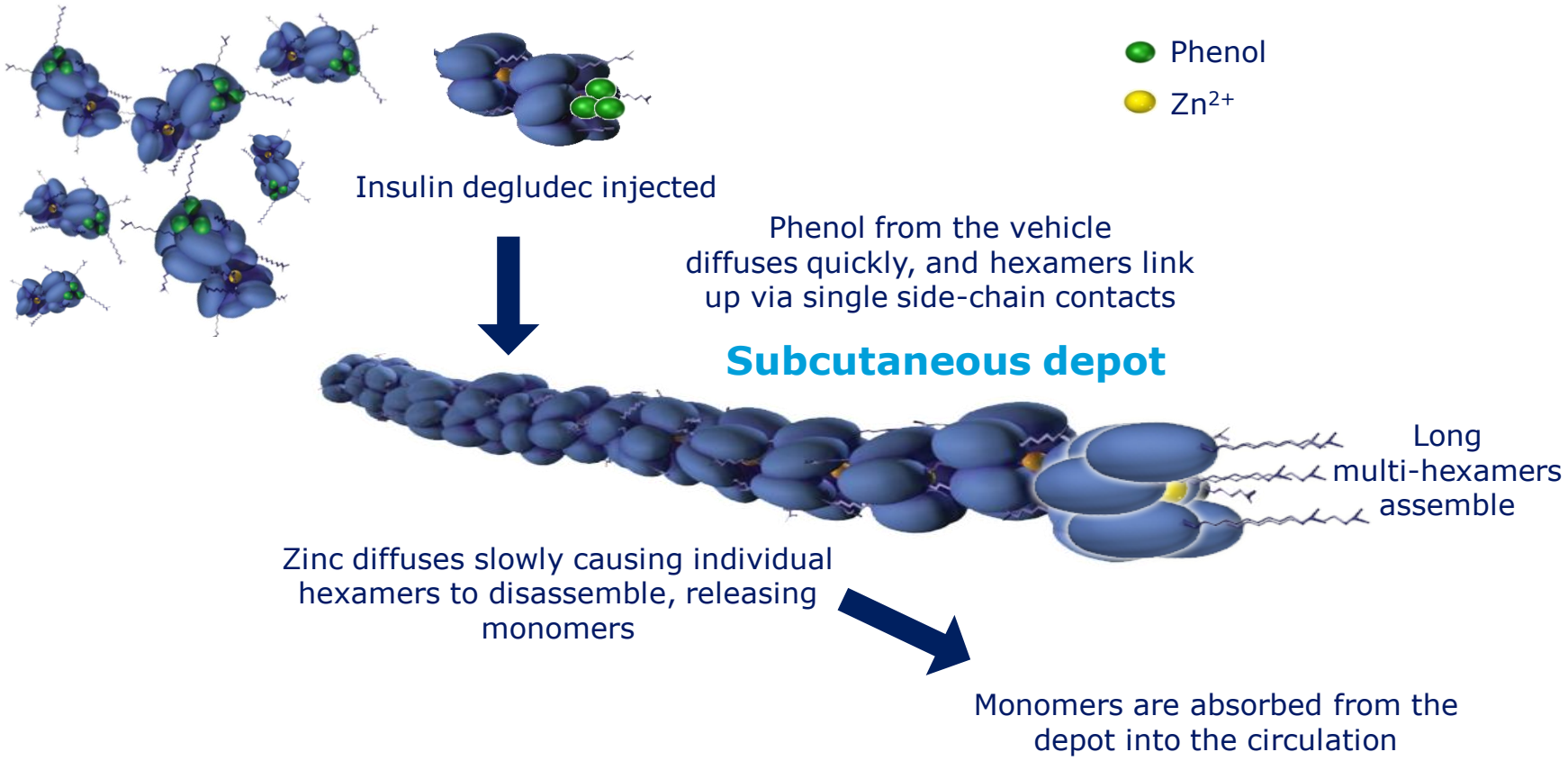
  - Cardiovascular
  - No cardiovascular

Insulin degludec: rationally designed, beyond sequence modification

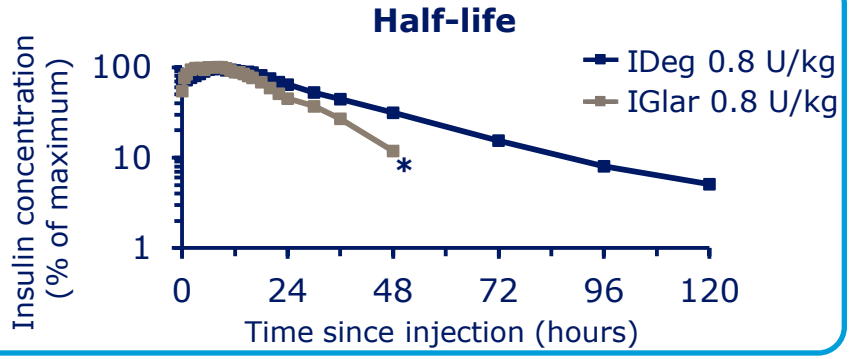


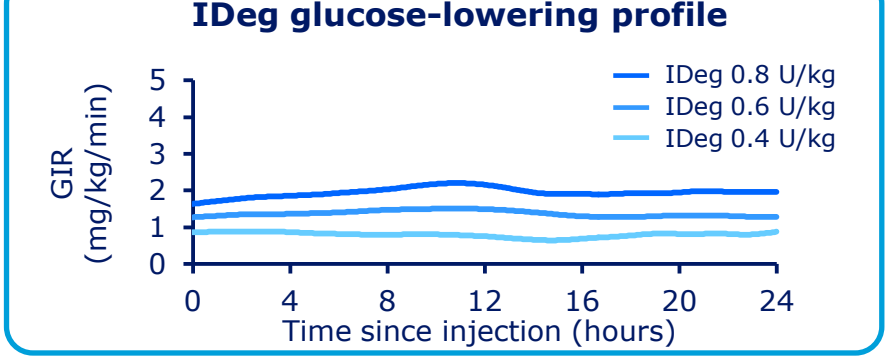
Insulin degludec: from injection to slow release from the subcutaneous depot



Jonassen *et al. Pharm Res* 2012;29:2104–14

IDeg has a flat glucose-lowering profile with a half-life twice as long as IGlar





IDeg half-life (25.4 hours) is twice that of IGlar (12.5 hours)

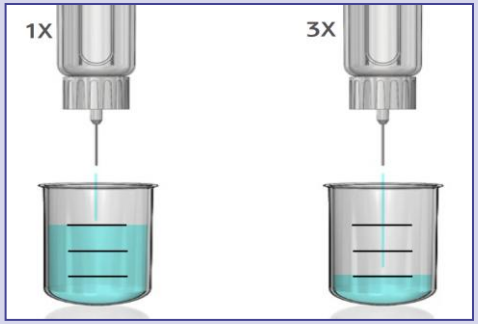
*Insulin glargine was undectable after 48 hours.

CV, coefficient of variation; GIR, glucose infusion rate; IDeg, insulin degludec; IGlar, insulin glargine; T1D, type 1 diabetes

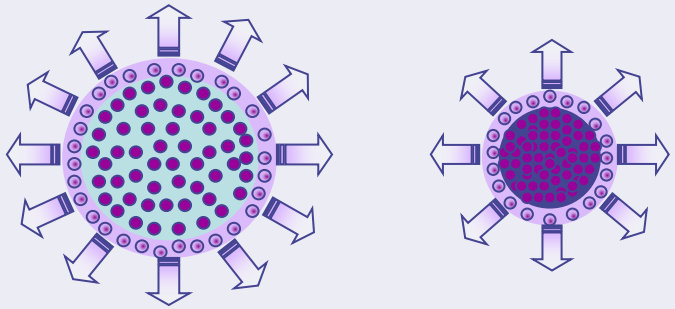
Heise *et al. Diabetes Obes Metab* 2012;14:944–50; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425; Heise *et al. Diabetes Obes Metab* 2012;14:859–64

U300 es una nueva insulina basal de duración prolongada que ofrece beneficios PK/PD adicionales

Reducción de volumen (2/3)



Menor superficie del depot (1/2)

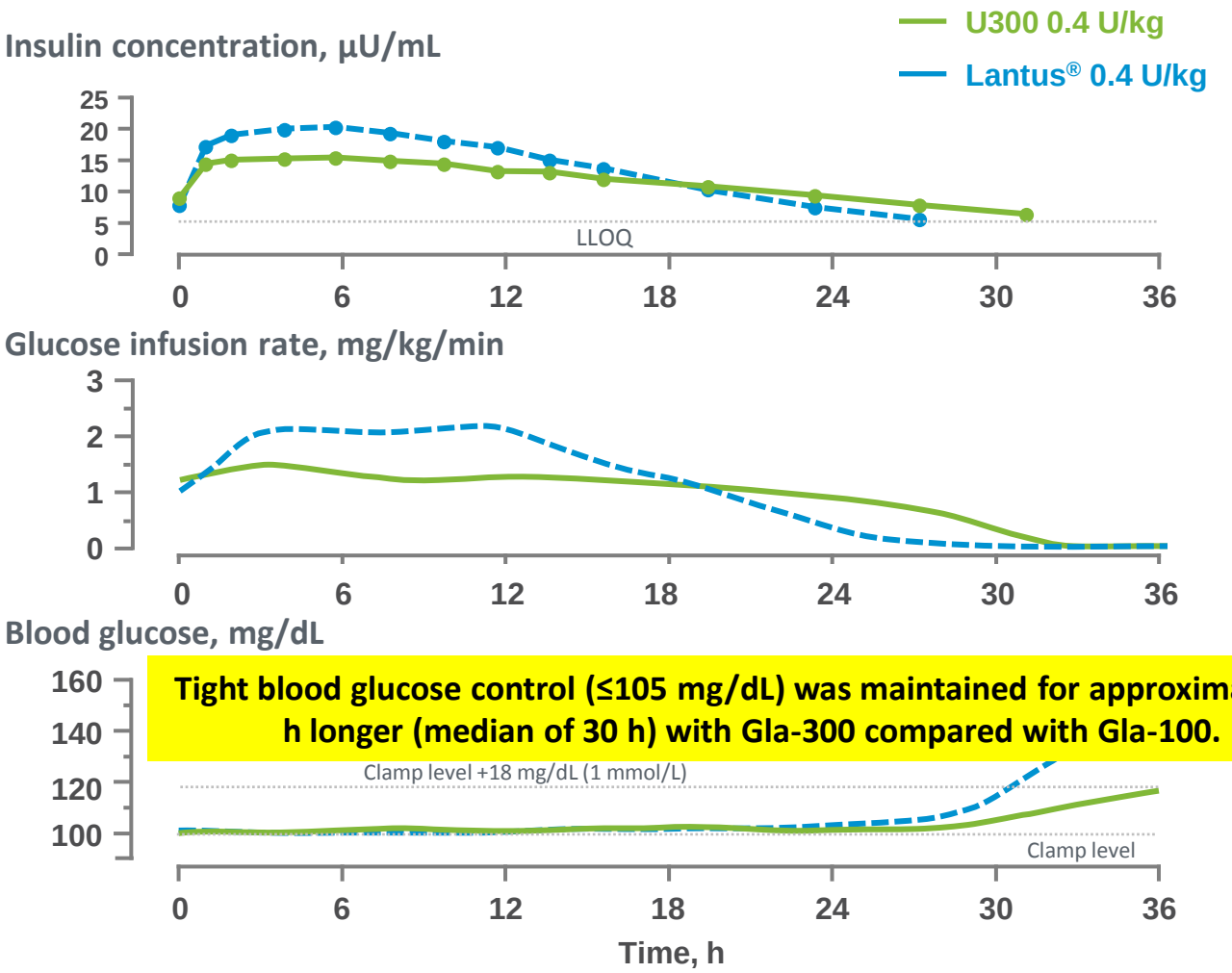


30 U insulina:

- **G-100: 0,3 ml**
- **G-300: 0,1 ml**

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]
PD, pharmacodynamic; PK, pharmacokinetic
Data on file

La liberación más controlada y gradual con U300 vs Lantus resulta en un perfil PK más constante y prolongado y un efecto reductor de la glucosa durante más de 24 horas

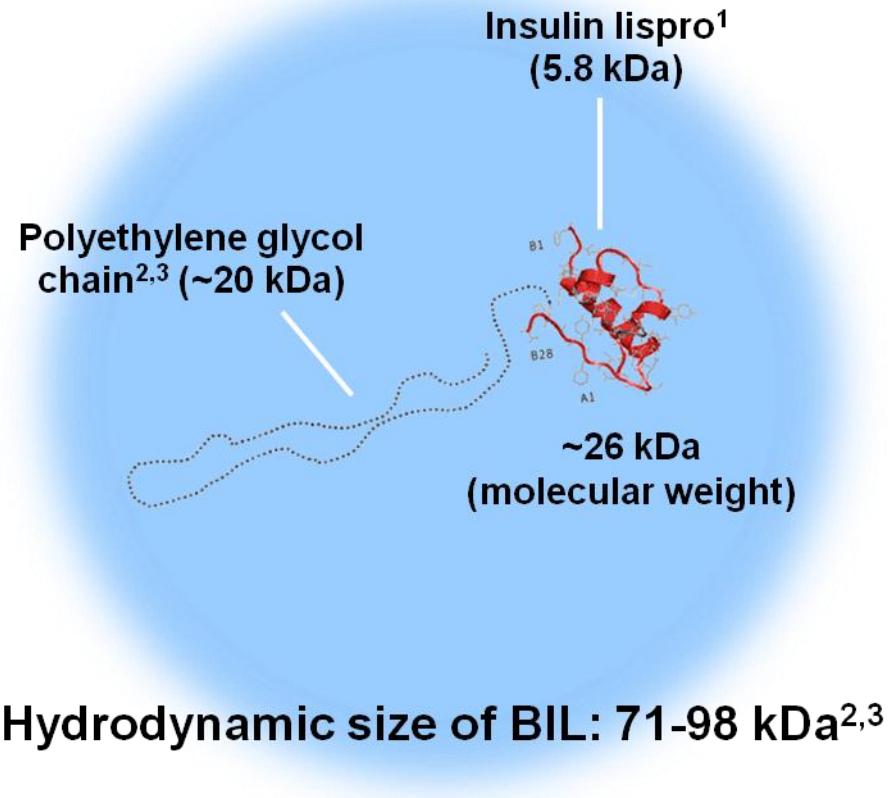


Tight blood glucose control (≤105 mg/dL) was maintained for approximately 5 h longer (median of 30 h) with Gla-300 compared with Gla-100.

Euglycemic clamp study in T1DM in steady state (8 days' treatment)

Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

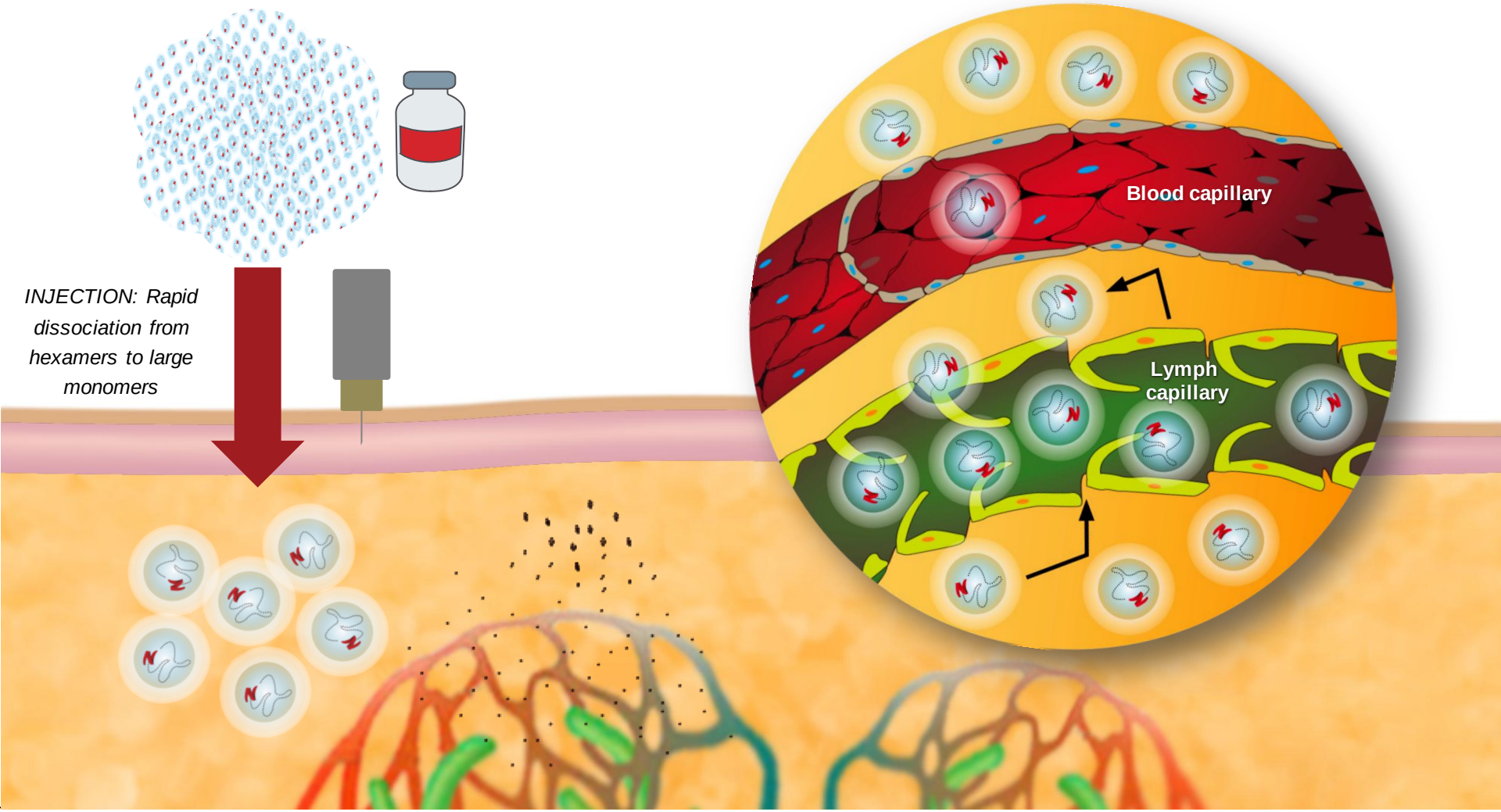
BIL: a novel basal insulin analog with a large hydrodynamic size



For perspective, the hydrodynamic size of BIL is ≥ albumin[4]

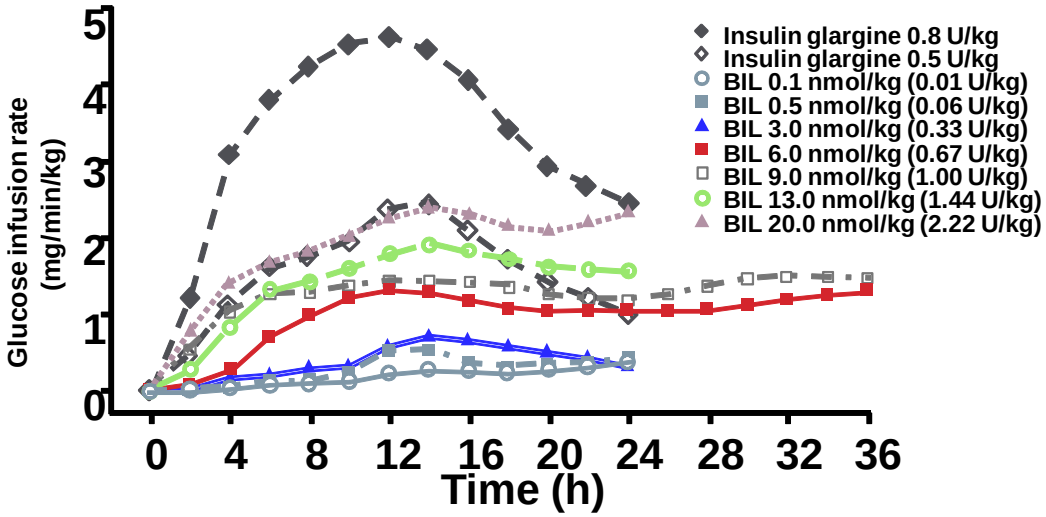
1. Humalog®. US prescribing information 2011; 2. Beals JM et al. *Diabetologia* 2012;55(Suppl):abs 42;
3. Beals JM et al. Oral presentation 42 at the 48th Annual Meeting of the European Association for the Study of Diabetes, Berlin, Germany, October 1-5, 2012; 4. Meloun B et al. *FEBS Lett* 1975;58:134-7

Hypothesis: the large hydrodynamic size of BIL may allow slow absorption of monomers predominantly via the lymphatic system

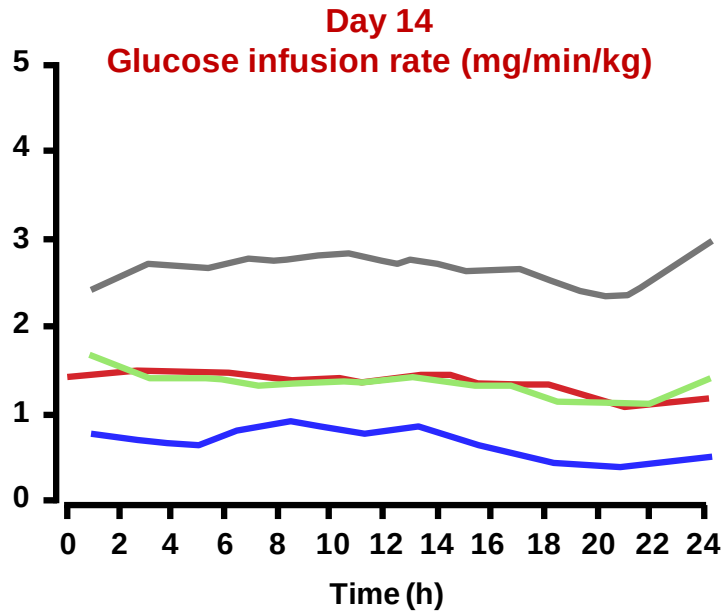


1. Kaminskas LM et al. *J Controlled Release* 2013;168:200-8; 2. Kaminskas LM, Porter CJ. *Adv Drug Del Rev* 2011;63:890-900; 3. Kaminskas LM et al. *J Control Release* 2009;140:108-16; 4. Charman SA et al. *Pharm Res* 2001;18:1620-6

Mean GIR profiles following single and multiple once-daily SC doses of BIL in patients with T2DM



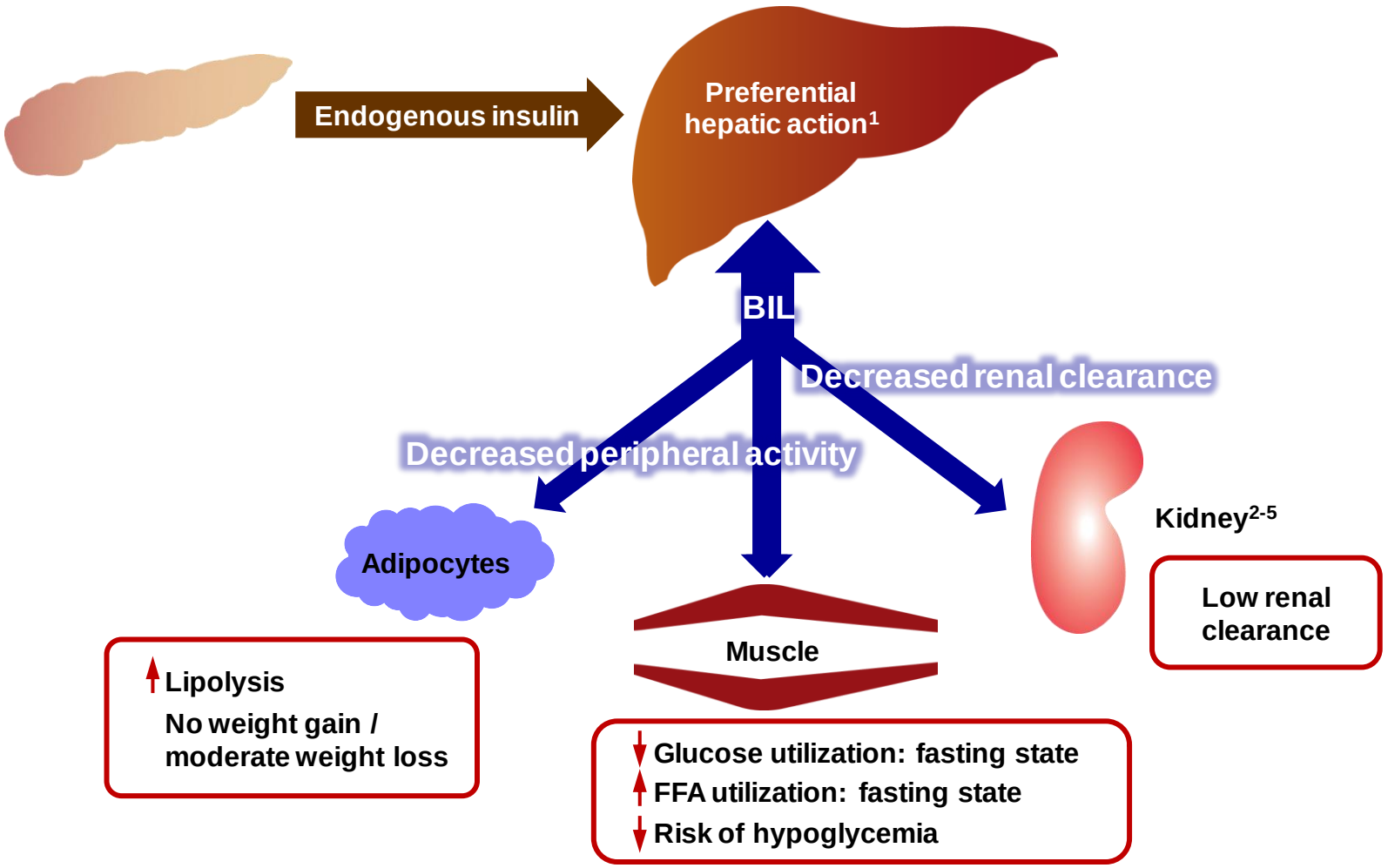
The GIR profiles mirrored the PK profiles following single SC doses of BIL and glargine in healthy subjects[1,2]



The flat GIR profiles at steady state mirrored the flat PK profile at steady state[3]

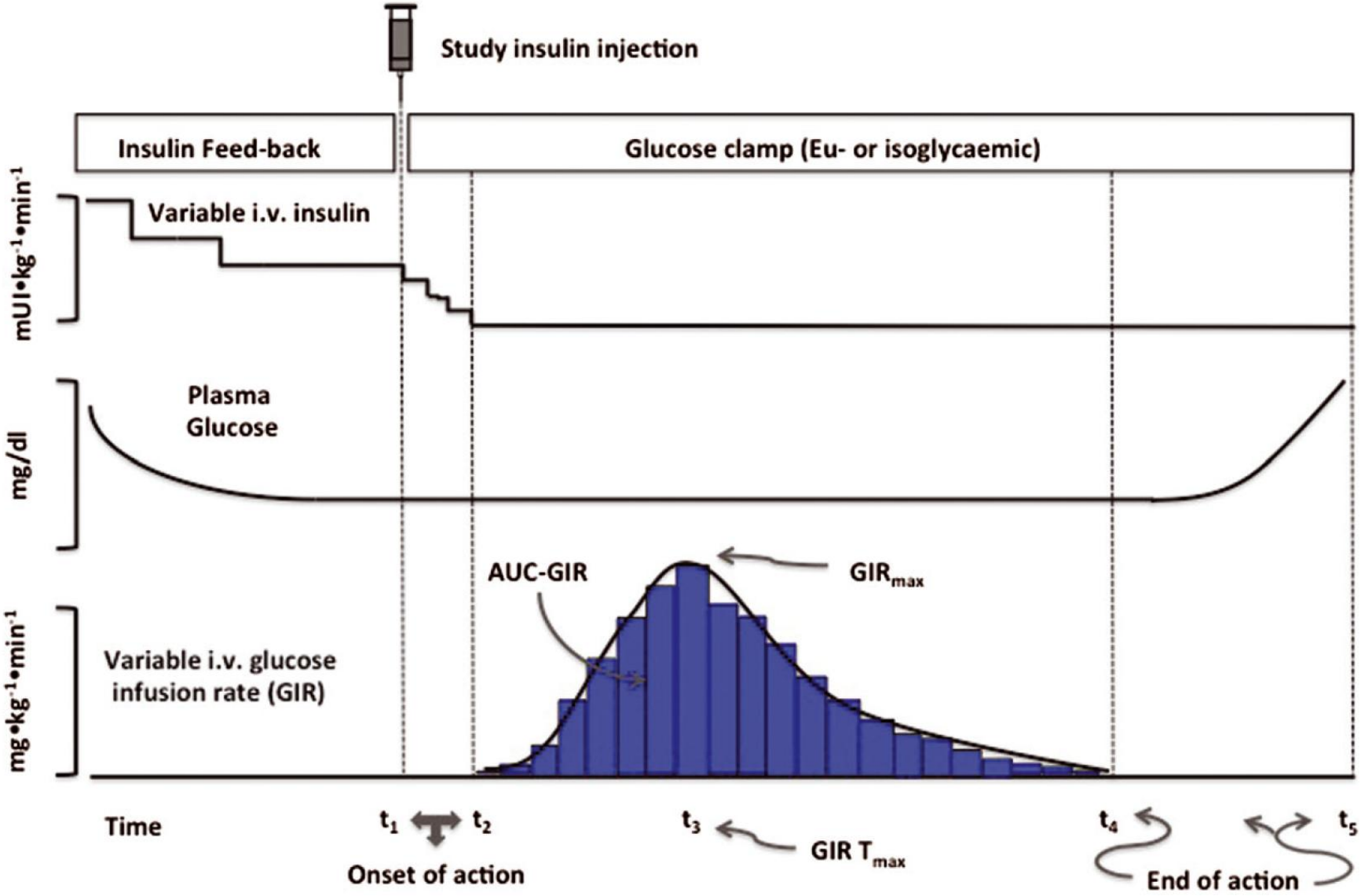
1. Sinha VP et al. *Diabetes* 2012;61(Suppl 1):abs 1063-P; 2. Sinha VP et al. Poster 1063-P presented at ADA, 2012
3. Sinha VP et al. *Diabetes Obes Metab* 2014;16:344-50

Hypothesis: based on preclinical data, BIL may more closely mimic that of endogenous insulin due to a greater hepatic vs peripheral activity profile

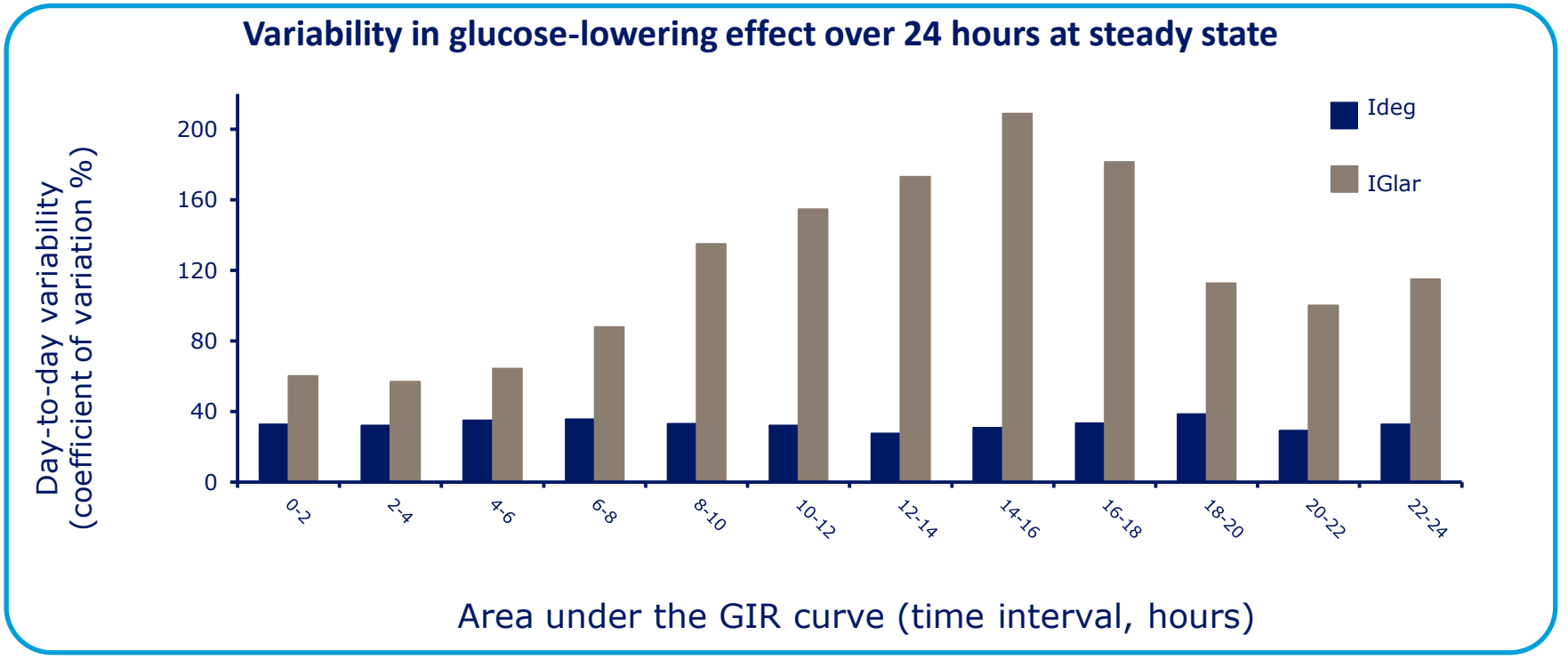


1. Moore MC et al. *Diabetes* 2014;63:494-504; 2. Beals JM et al. *Diabetologia* 2012;55(Suppl):abs 42; 3. Beals JM et al. Oral presentation 42 presented at EASD, 2012; 4. Linnebjerg H et al. *Diabetologia* 2012;55(Suppl):abs 922; 5. Linnebjerg H et al. Poster 922 presented at EASD, 2012

Variability



IDeg has a flat glucose-lowering profile with a four-times lower day-to-day variability



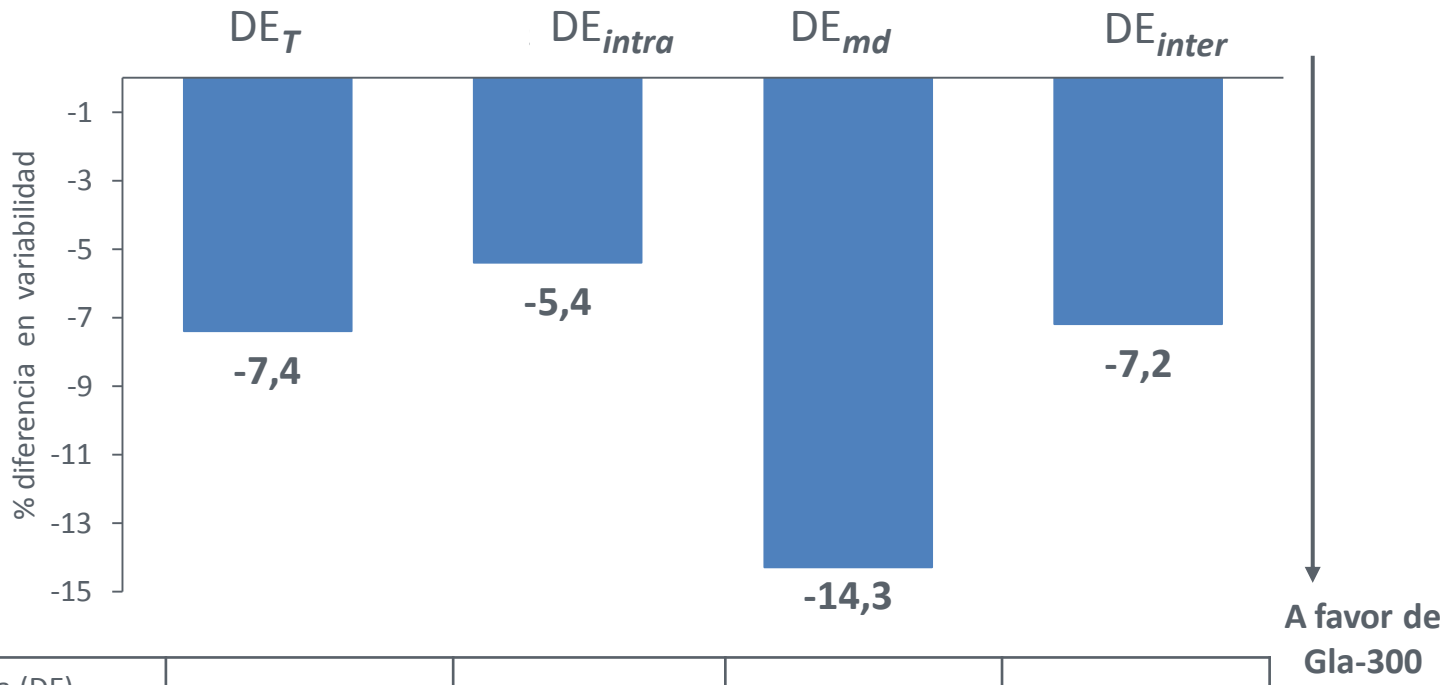
IDeg variability is four-fold lower than IGlar

	Onset of action* (hours)	End of action* (hours)	Duration of action* (hours)	GIR T_{max} (time of peak)	Within-subject variability*,† (CV% of AUC-GIR)
NPH [20,23,24,31]	1–2	14–15	13–16	5–7	68
NPL [35,36,93]	1–2	17–23	16–22	4–7	48
Glargine [20,22,31,42]	1–2	22–27	21–27	4–12	48–99
Detemir [20,22,23,37]	1–2	19–23	16–23	7–9	27
Degludec [42,43]	NR (studied at steady state)	>42	>42	Virtually none	20

Medidas de la variabilidad glucémica: últimas 2 semanas de tratamiento†

Estudio de MCG en T1

Todas las medidas de la variabilidad glucémica intradiaria e interdiaria fueron numéricamente inferiores en los participantes que recibieron Gla-300 que en los que recibieron Gla-100



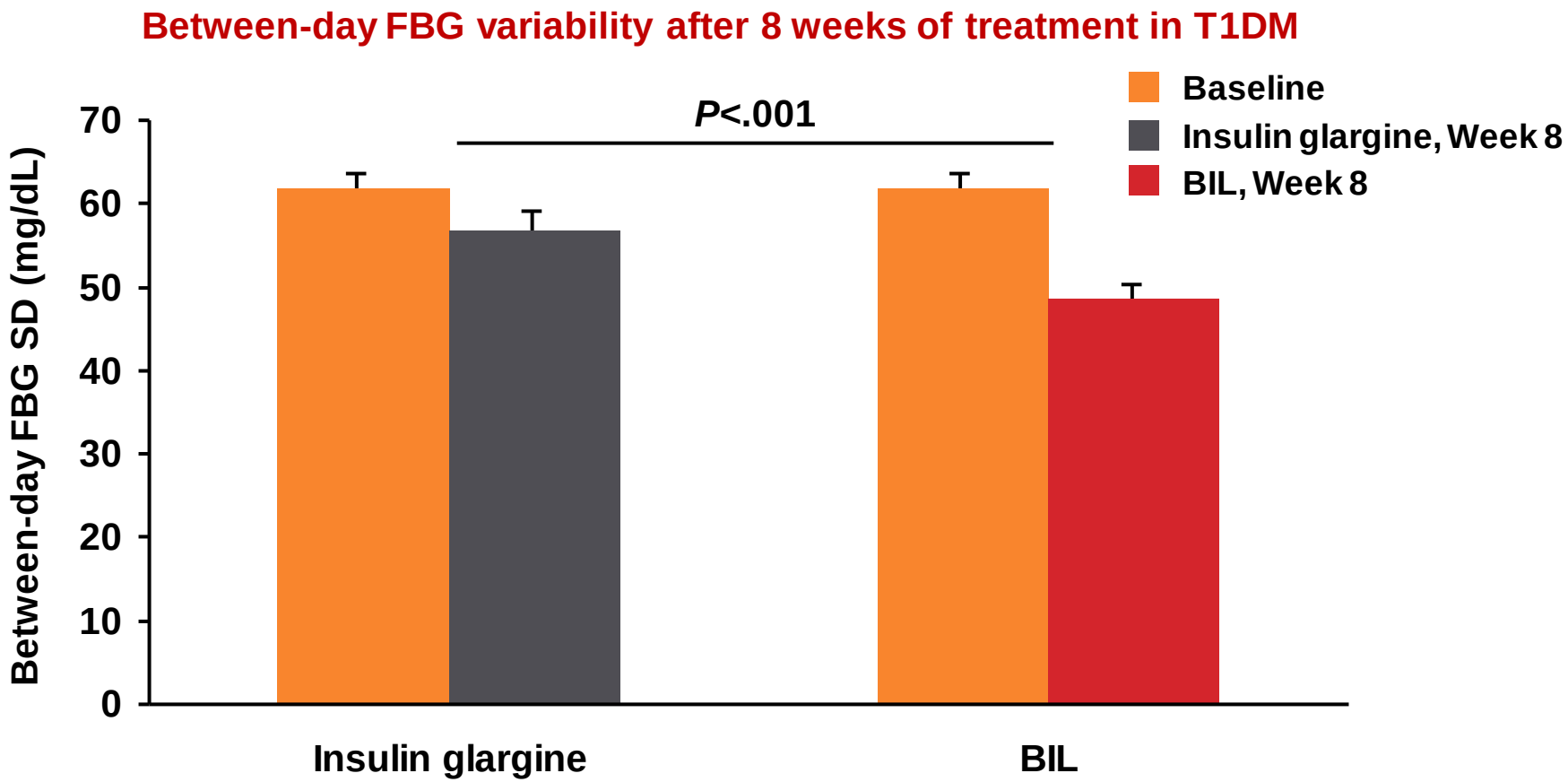
Valor absoluto;media (DE) (mg/dl)	DE$_T$	DE$_{intra}$	DE$_{md}$	DE$_{inter}$
Gla-100	76,1 (2,7)	61,4 (1,8)	41,4 (2,5)	71,3 (2,9)
Gla-300	70,5 (2,4)	58,1 (2,1)	35,5 (1,7)	66,2 (2,3)
Valor de P	0,1259	0,2286	0,052	0,1568

Población con MCG; †Combinada las 2 últimas semanas de tratamiento en cada periodo (semanas 7-8 y semanas 15-16), grupos de inyección combinados por la mañana y por la noche

DE: desviación estándar; DE$_T$: variabilidad de la desviación estándar total; DE$_{intra}$: variabilidad intradiaria; DE$_{md}$: variabilidad entre las medias diarias; DE$_{inter}$: variabilidad interdiaria (para el mismo momento del día)

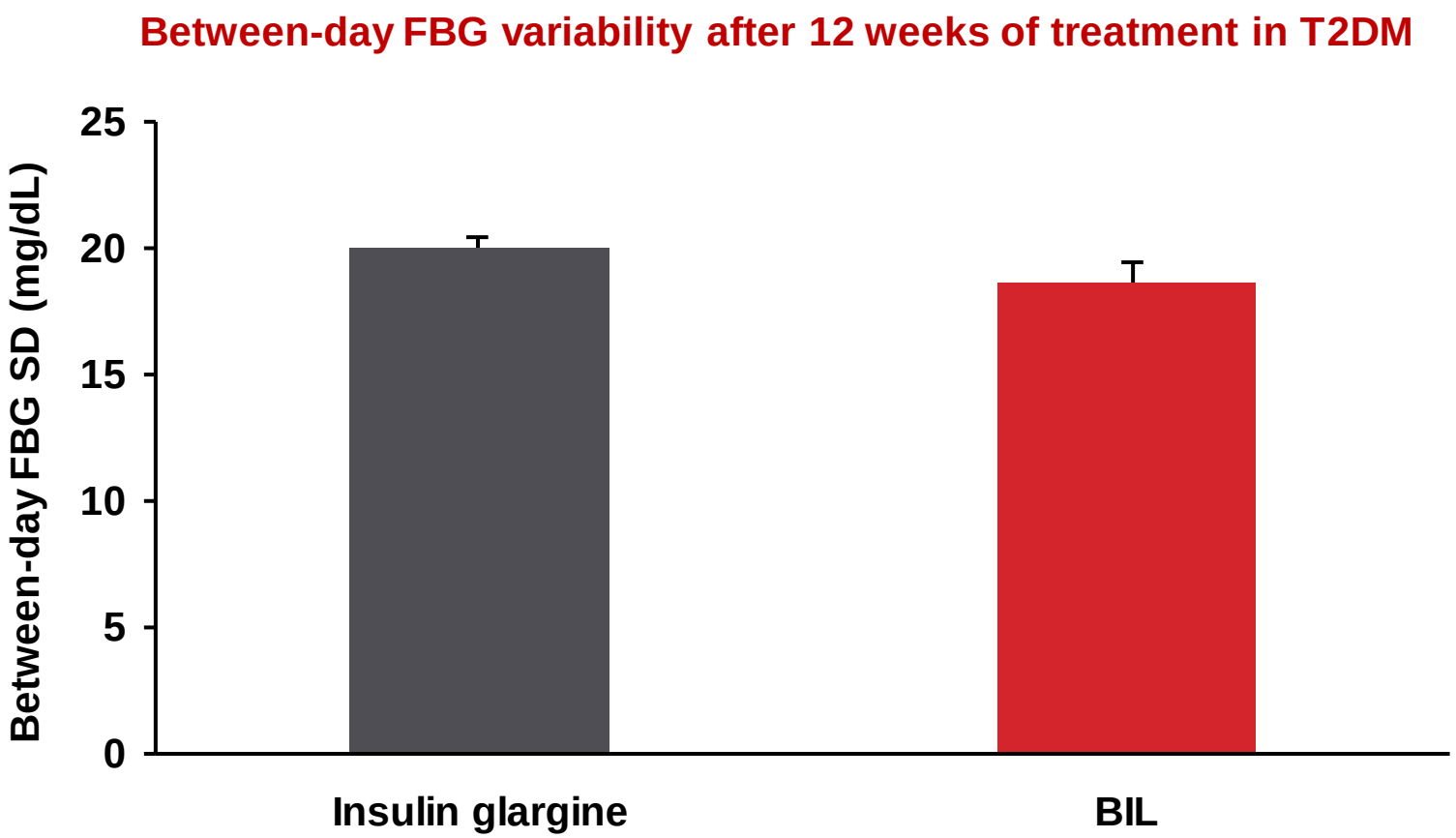
Bergenstal et al. Diabetes Tech Ther 2015; 17 (Suppl1): A16-17 (abstract no. 39).

Between-day FBG variability was significantly lower with BIL compared with insulin glargine in T1DM



Rosenstock J et al. *Diabetes Care* 2013;36:522-8

In T2DM patients, between-day FBG variability was similar for BIL and insulin glargine at the end of treatment



Bergenstal RM et al. *Diabetes Care* 2012;35:2140-7

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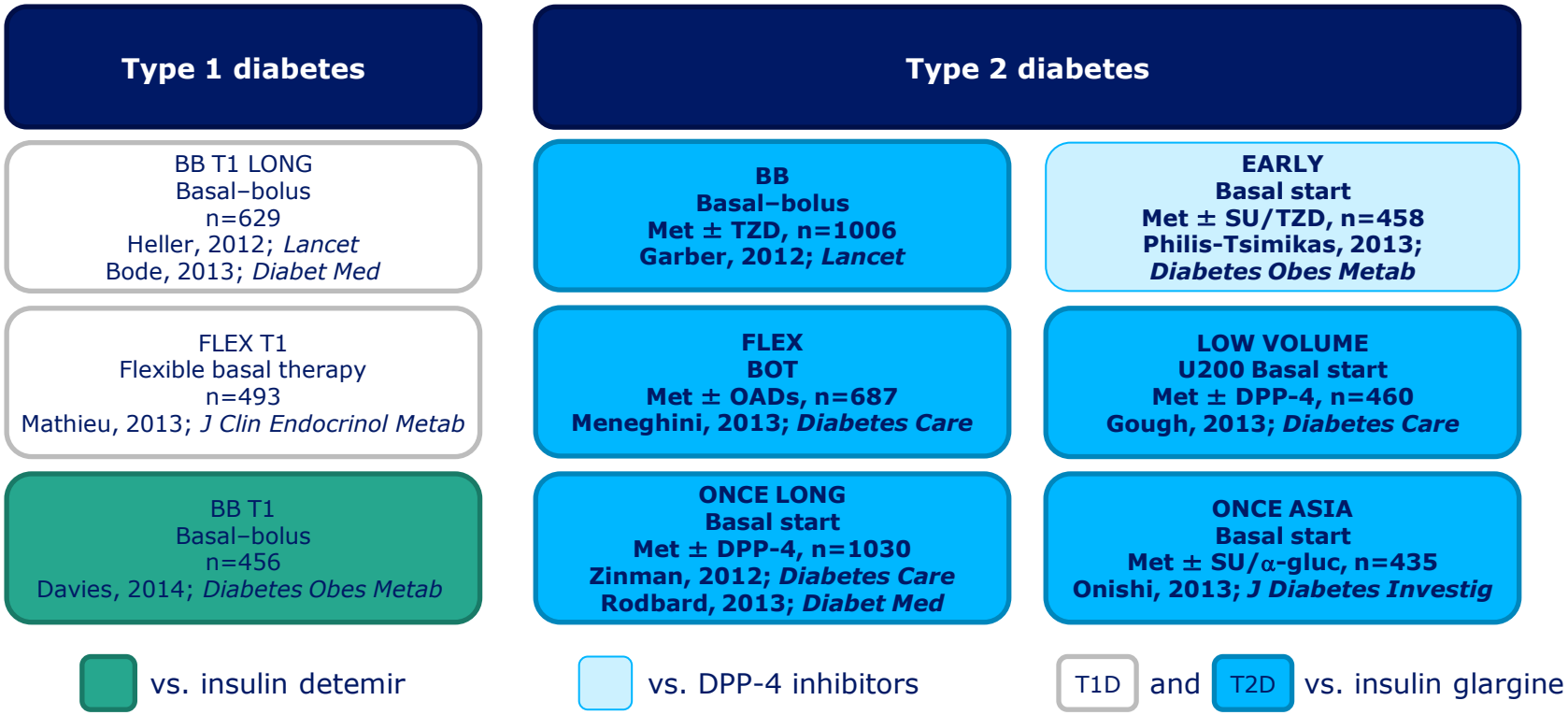
Insulin degludec once daily (BEGIN)

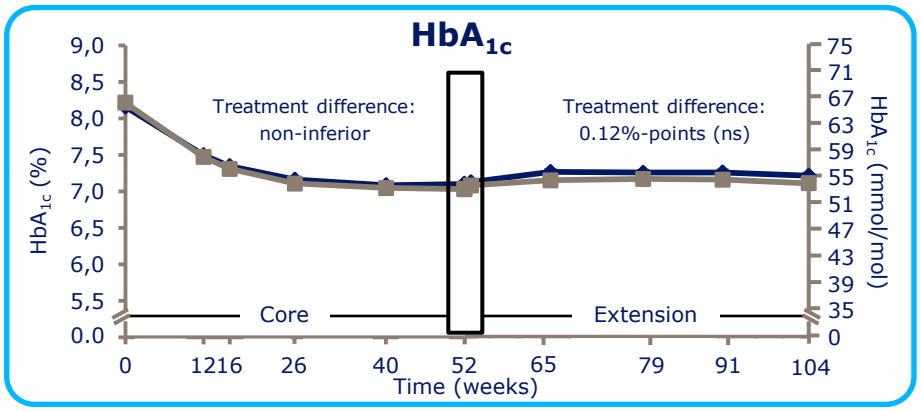
All studies with active comparator

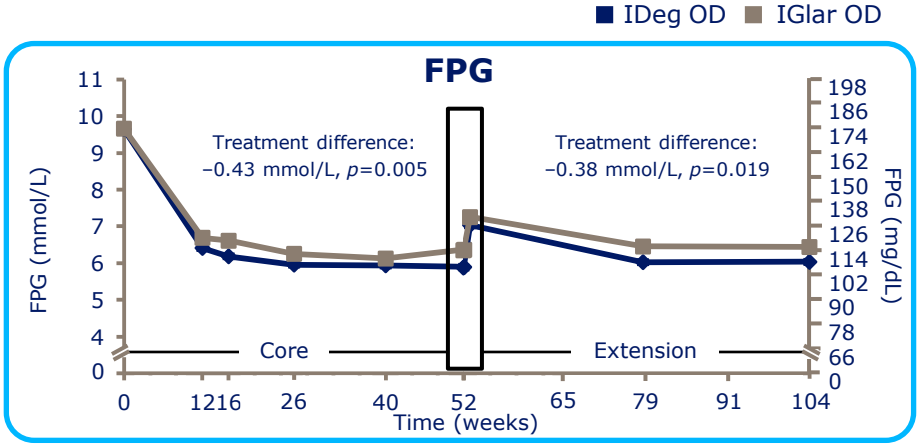


α-gluc, alpha glucosidase inhibitor; BB, basal–bolus; BOT, basal–oral therapy; DPP-4, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione

Insulin-naïve T2D: results

BEGIN ONCE LONG – 2 years





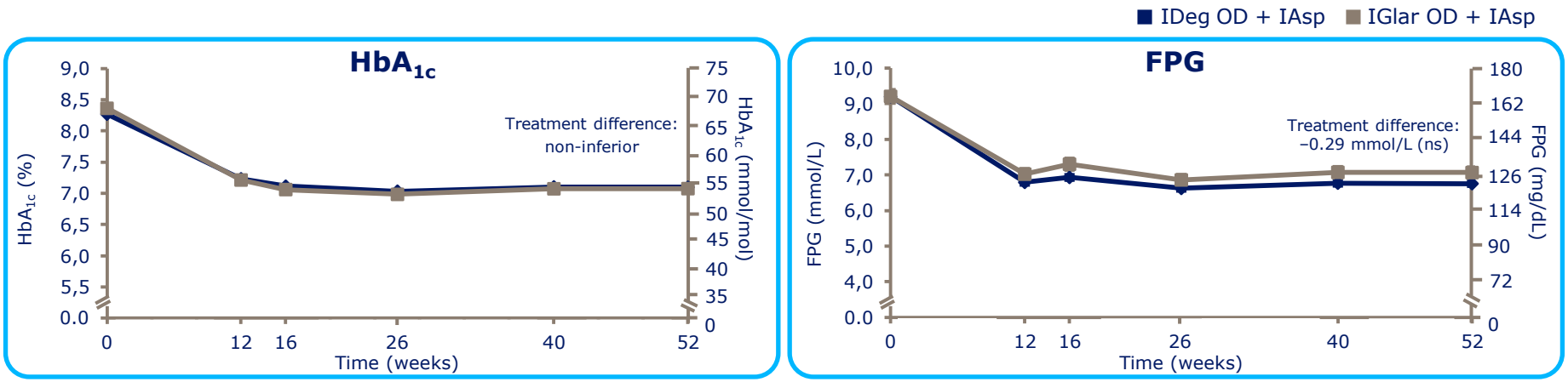
Mejora GB -0.38 mmol/L (6,8 mg/dL) (p=0.019)

Black box denotes both treatment arms switching to NPH for 1 week then resuming IDeg or IGlar to allow for antibody measurement

Zinman *et al. Diabetes Care* 2012;35:2464–71; Rodbard *et al. Diabet Med* 2013;30:1298–304

Basal–bolus in T2D: results

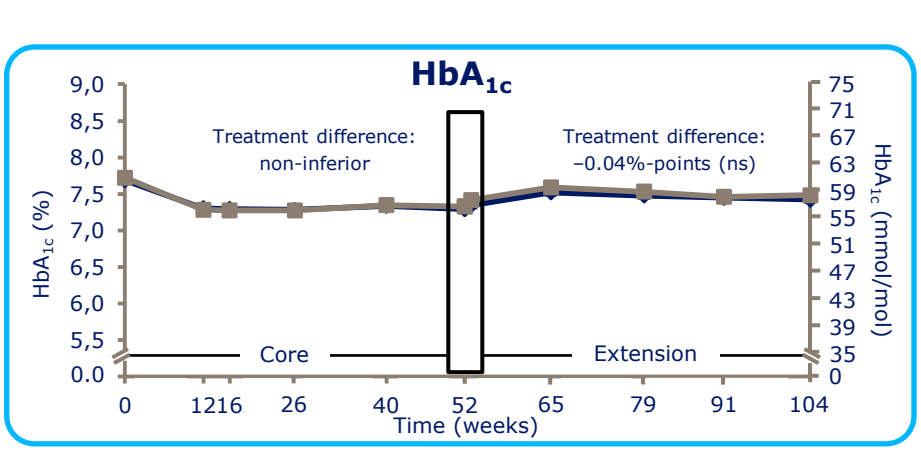
BEGIN BB T2D

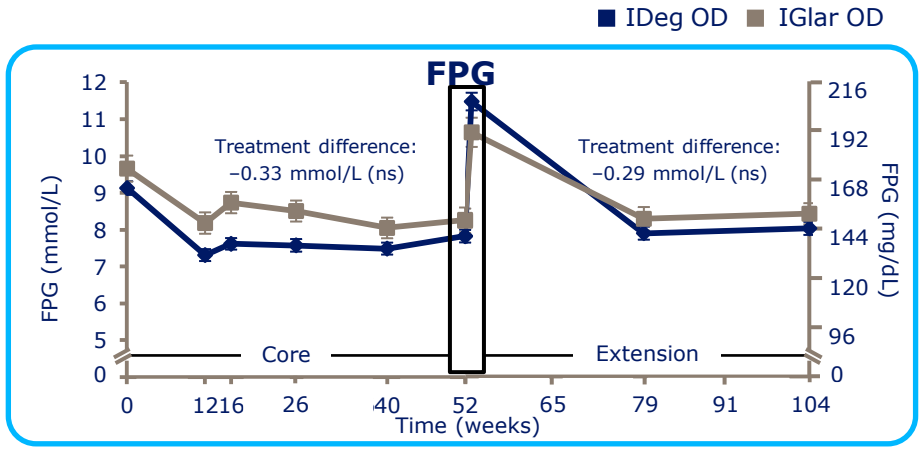


Garber *et al. Lancet* 2012;379:1498–507

Basal–bolus in T1D: results

BEGIN BB T1D – 2 years





Black box denotes both treatment arms switching to NPH for 1 week then resuming IDeg or IGlar to allow for antibody measurement

Heller *et al. Lancet* 2012;379:1489–97; Bode *et al. Diabet Med* 2013;30:1293–7

Phase 3a summary: IDeg vs Iglar

Trial	Population/ comparator	Duration (wks)	Efficacy	
			Non-inf. HbA_{1c}	FPG mmol/L [mg/dL]
ONCE LONG (core and extn)	Insulin naïve, T2D	104	✓	-0.38 [-6.84]
BB	Previously treated with insulin, T2D	52	✓	-0.29 [-5.22]
T1 BB LONG (core and extn)	Type 1	104	✓	-0.29 [-5.22]

extn, extension; non-inf., non-inferior; wks, weeks
* Data depict results for IDeg Flexible vs. IGlar

Insulin degludec significantly better

No significant difference

Programa de estudios EDITION. Glargina U-300 vs Glargina U-100

Análisis de eficacia, tolerancia y seguridad en diferentes poblaciones

EDITION 1	**DM2**	Tto previo: Basal-bolo
EDITION 2	**DM2**	Tto previo: Basal + ADOs
EDITION 3	**DM2**	Tto previo: ADOs (insulin-naïve)
EDITION 4	**DM1**	Tto previo: Basal-bolo

Riddle et al. Diabetes Care 2014;37(10):2755-62; Yki-Jarvinen et al. Diabetes Care 2014 Sep 5. pii: DC_140990. [Epub ahead of print]; Bolli et al (abstract). ADA 2014, Diabetes 2014; Tesauch et al (abstract). ADA 2014, Diabetes 2014; Matsuhisa et al (abstract) ADA 2014, Diabetes 2014.

Análisis agrupado EDITION 1, 2 y 3: Se evaluó el control glucémico y las hipoglucemias durante 6 meses en una amplia población heterogénea con DM2

Diseño de los estudios y características basales

	EDITION 1		EDITION 2		EDITION 3		META-ANALYSIS	
Tratamiento del estudio	U300 vs Lantus® (+AIR+Met)		U300 vs Lantus® (+Met+ADOs*)		U300 vs Lantus® (+Met+ADOs†)		N/A	
Número participantes								
U300	404		404		439		1247	
Lantus®	403		407		439		1249	
Tratamiento hipoglucemiante previo	Insulina Basal + insulina en las comidas + ADOs		Insulina basal + ADOs		Insulin naive + ADOs		N/A	
Criterios de inclusión								
Dosis de insulina	≥42 U		≥42 U				N/A	
HbA_{1C}	7–10%		7–10%		7–11%			
Edad, años	≥18		≥18		≥18			
Media al inicio	**U300**	**Lantus®**	**U300**	**Lantus®**	**U300**	**Lantus®**	**U300**	**Lantus®**
IMC, kg/m^2	36.6	36.6	34.8	34.8	32.8	33.2	34.7	34.8
Edad, años	60.1	59.8	57.9	58.5	58.2	57.2	58.7	58.5
Duración diabetes, años	15.6	16.1	12.7	12.5	10.1	9.6	12.7	12.6
HbA_{1C}, %	8.15	8.16	8.26	8.22	8.51	8.57	8.31	8.32

*Use of sulfonylureas were prohibited within 2 months prior to screening and during the study
†Except sulfonylureas, glinides and other OADs not approved for use with insulin
AIR, análogo de insulina rápida

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

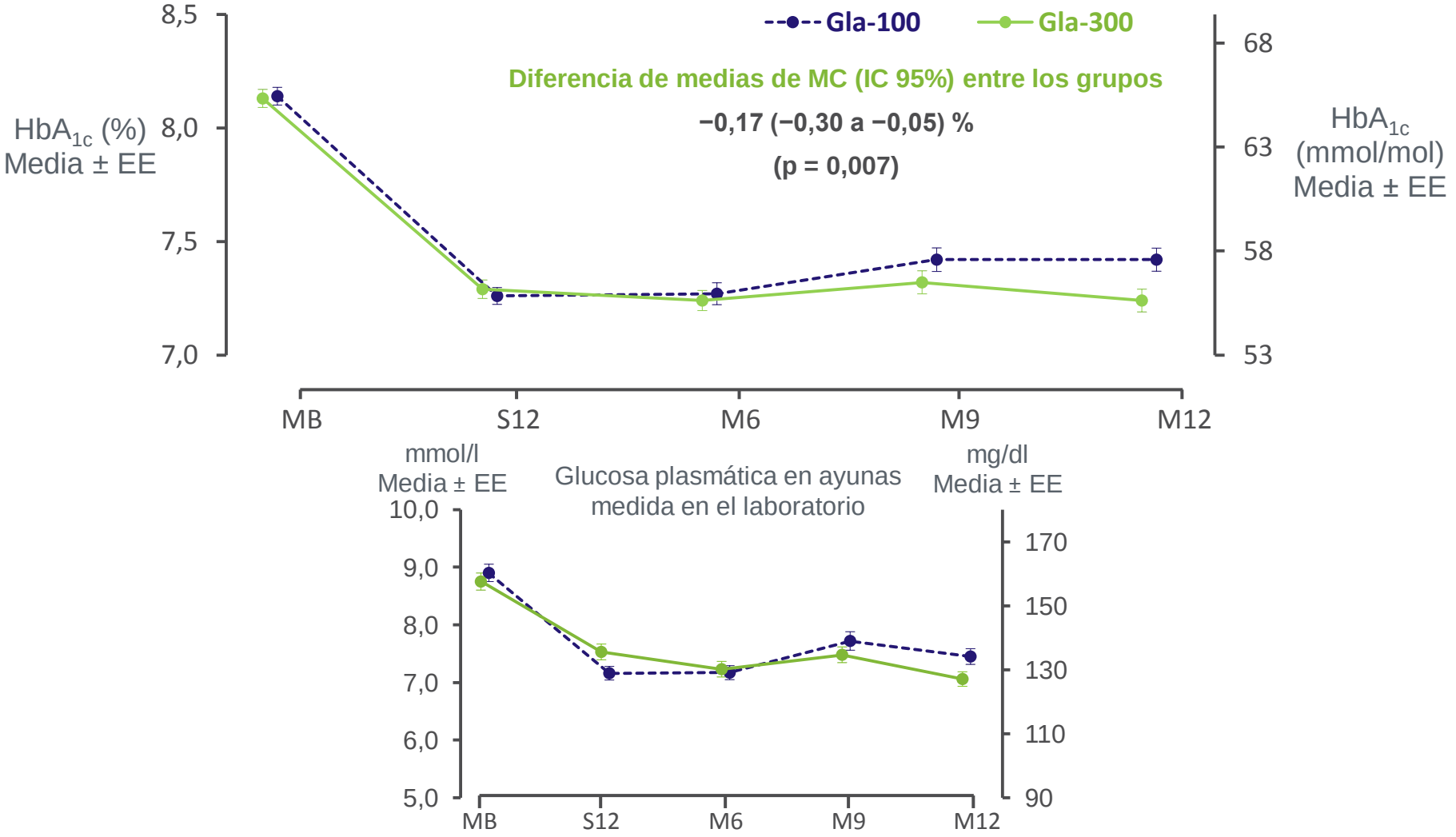
GLARGINA U-300

HbA1c: se alcanzó el criterio de valoración principal en todos los ensayos

Criterio de valoración principal: no inferioridad en el cambio en la HbA1c con Gla-300 frente a Gla-100 en el mes 6

Datos en archivo, informe final del EDITION 1, pág. 72; informe final del EDITION 2, pág. 73; informe final del EDITION 3, pág. 83; informe final del EDITION JP 2, pág. 86; informe final del EDITION 4, pág. 88; informe final del EDITION JP 1, pág. 80 Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; Bolli GB et al. Diabetes Obes Metab. 2015 Jan 14. doi: 10.1111/dom.12438. [Pub. electrónica antes de impresión]; Terauchi Y et al. Presentación en póster en la reunión de la EASD 2014; abstract 976; Home PD et al. Presentación en póster en la reunión de la ADA 2014; abstract 80-LB; Matsuhisa M et al. Presentación en póster en la reunión de la EASD 2014; abstract 975

EDITION 1, 1 año: control glucémico y dosis de insulina



- **Gla-300 produjo reducciones más sostenidas de la HbA_{1c} a los 12 meses comparado con Gla-100**

Población ITm (Gla-300, n = 404; Gla-100, n = 400)

MB, momento basal; IC, intervalo de confianza; MC, mínimos cuadrados; M6, mes 6; M9, mes 9; M12, mes 12; EE, error estándar; S12, semana 12

The BIL Phase 3 program

Primary end point in all studies: change from baseline in HbA_{1c}

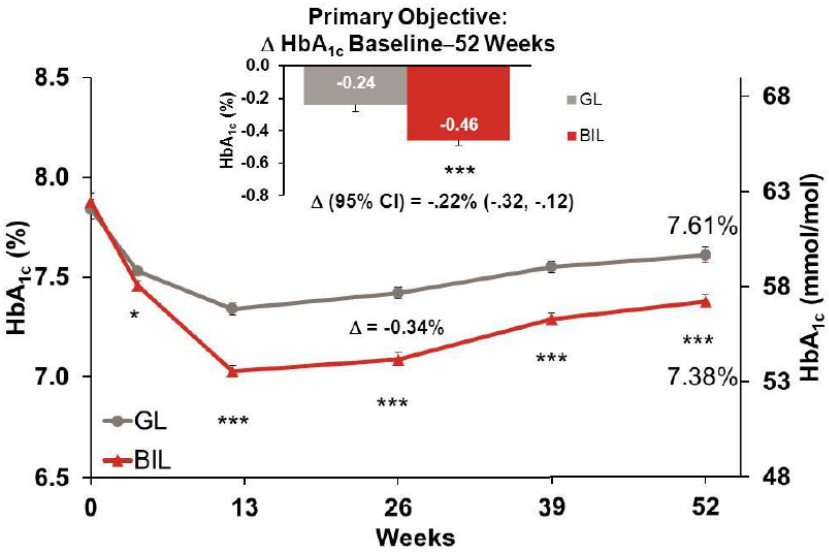
Study name	Population / design	Design and treatments	Status
IMAGINE 1 (NCT01481779)	• T1DM • Insulin pretreated	• Open-label, randomized; 26, 52, and 78 weeks • BIL vs insulin glargine • In combination with pre-prandial insulin lispro	Start: Jan 2012 LPV: Jun 2014
IMAGINE 2 (NCT01435616)	• T2DM • Insulin naïve	• Double-blind, randomized; 52 and 78 weeks • BIL vs insulin glargine • In combination with OAMs	Start: Oct 2011 LPV: Jan 2014
IMAGINE 3 (NCT01454284)	• T1DM • Insulin pretreated	• Double-blind, randomized; 26 and 52 weeks • BIL vs insulin glargine • In combination with pre-prandial insulin lispro	Start: Jan 2012 LPV: Feb 2014
IMAGINE 4 (NCT01468987)	• T2DM • Insulin pretreated	• Double-blind, randomized; 26 weeks • BIL vs insulin glargine • In combination with pre-prandial insulin lispro	Start: Dec 2011 LPV: Aug 2013
IMAGINE 5 (NCT01582451)	• T2DM • Insulin pretreated	• Open-label, randomized; 26 and 52 weeks • BIL vs insulin glargine • In combination with OAMs	Start: Apr 2012 LPV: Dec 2013
IMAGINE 6 (NCT01790438)	• T2DM • Insulin naïve	• Open-label, randomized; 26 weeks • BIL vs human insulin NPH	Start: Mar 2013 LPV: May 2014
IMAGINE 7 (NCT01792284)	• T1DM • Insulin pretreated	• Open-label, randomized; 12 weeks • BIL fixed dosing vs variable dosing • In combination with pre-prandial insulin lispro	Start: Feb 2013 LPV: Apr 2014

HbA_{1c}, glycosylated hemoglobin; LPV, last patient visit; NPH, neutral protamine Hagedorn; OAM, oral antidiabetic medication; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

http://www.clinicaltrials.gov, accessed 4/10/2014

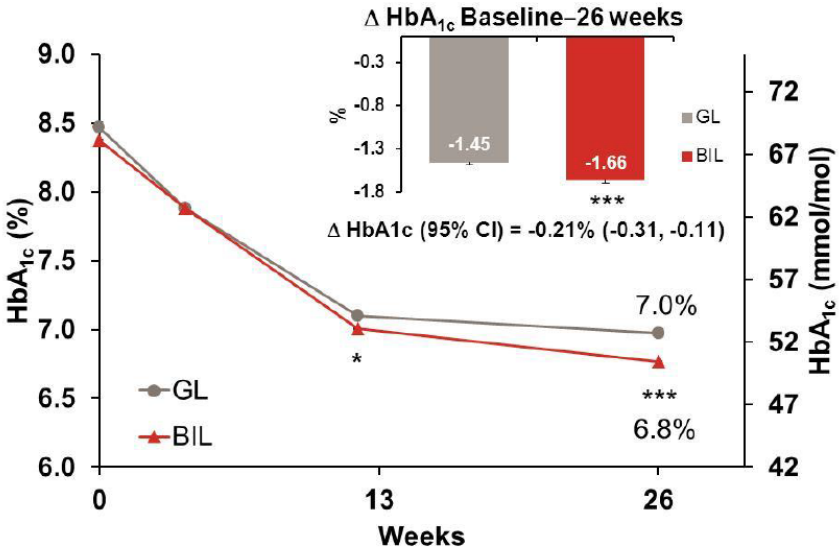
The BIL Phase 3 program

DM1: insulina basal + prandial (IMAGINE 3): -0.22%



LS mean ± SE; *p<.05, ***p<.001 for difference between treatments

DM2: insulina basal + prandial (IMAGINE 4): -0.20%



LS Mean ± SE; *p<.05, ***p<.001 for between-treatment differences

Basal insulin peglispro is superior to insulin glargine in reducing HbA1c in insulin-naïve patients with type 2 diabetes treated with oral antihyperglycaemic drugs: IMAGINE 2

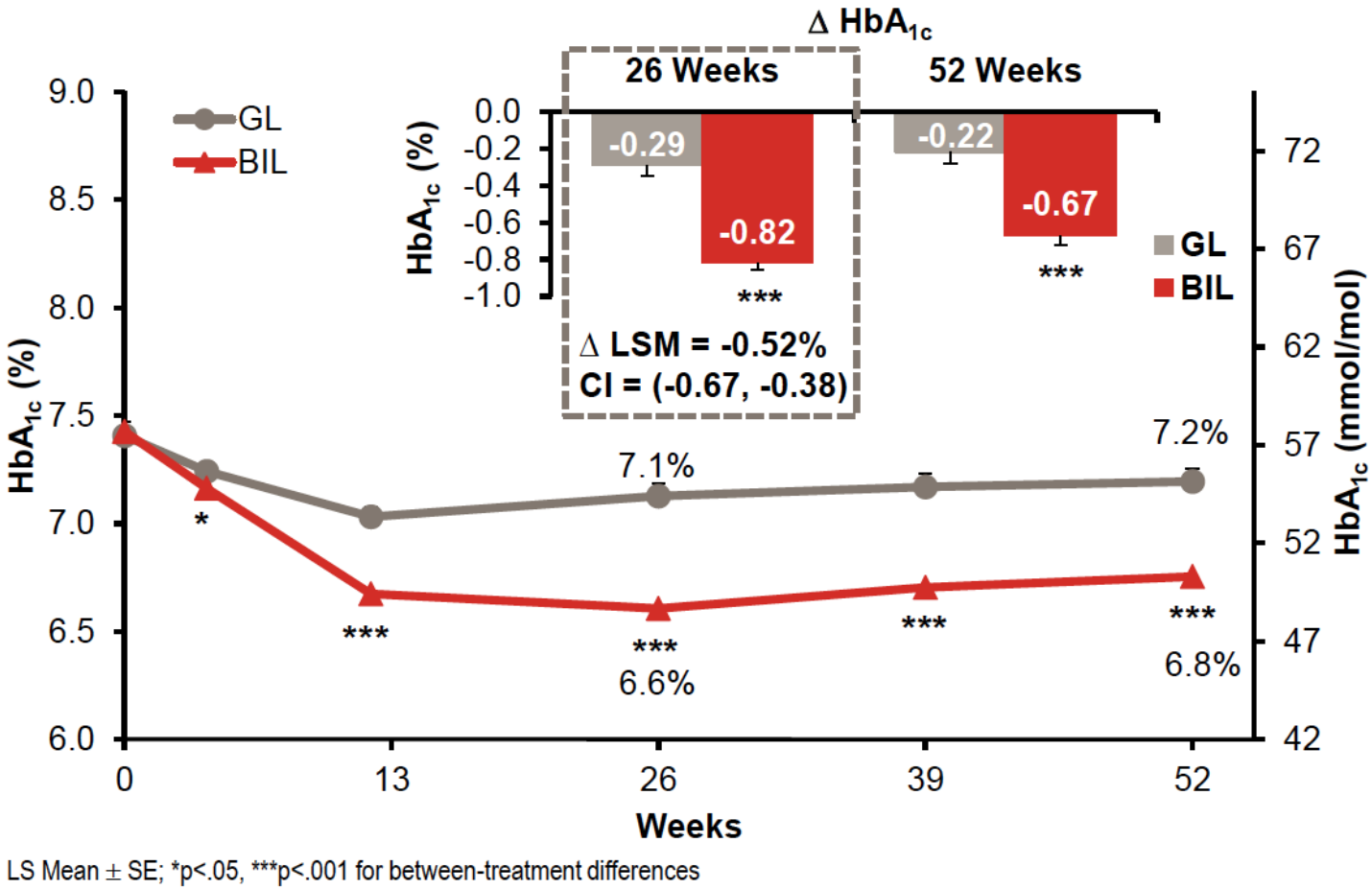
BIL-treated patients had statistically superior HbA1c change at week 52 compared to GL-treated patients (-1.6 vs -1.3%; Δ=-0.3% [95% CI: -.40, -.19]).

Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

Chang AM et al. 972-P. European Association for the Study of Diabetes 51st Annual Meeting; Stockholm, Sweden; September 14-18, 2015

The BIL Phase 3 program

DM2: insulina basal + ADOs (tto previo con insulina basal; IMAGINE 5)



LS Mean ± SE; *p<.05, ***p<.001 for between-treatment differences

Trescoli C et al. 971-P. European Association for the Study of Diabetes 51st Annual Meeting; Stockholm, Sweden; September 14-18, 2015

New Basal Insulin Formulations

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- **Estudios pivotales**
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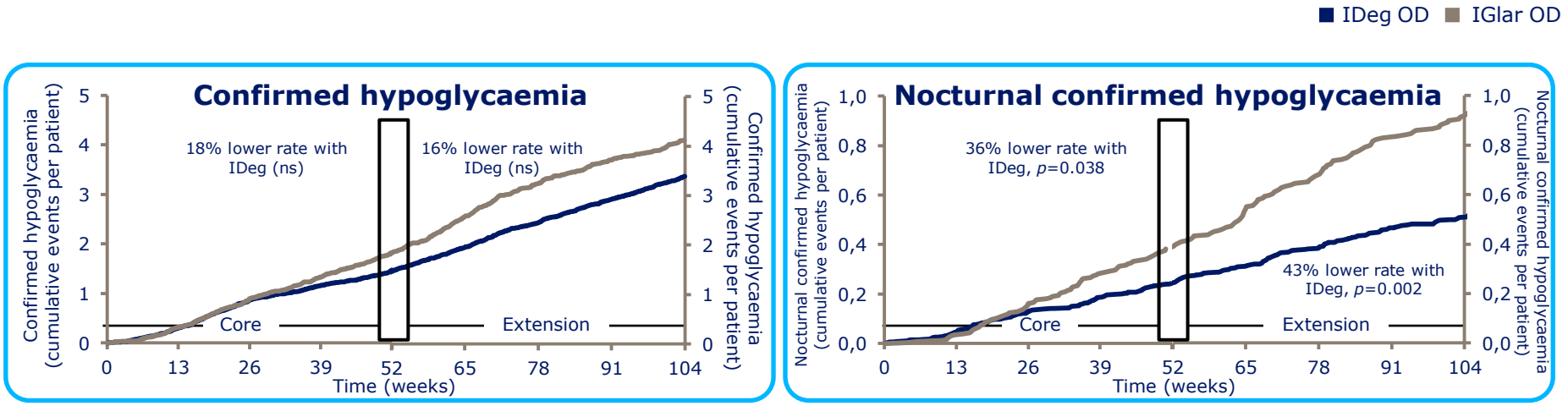
    - HbA1c
    - Glucemia basal
  - **Hipoglucemias**
  - Peso
  - Dosis de insulina
- Seguridad
  - Cardiovascular
  - No cardiovascular

Insulin-naïve T2D: results

BEGIN ONCE LONG – 2 years



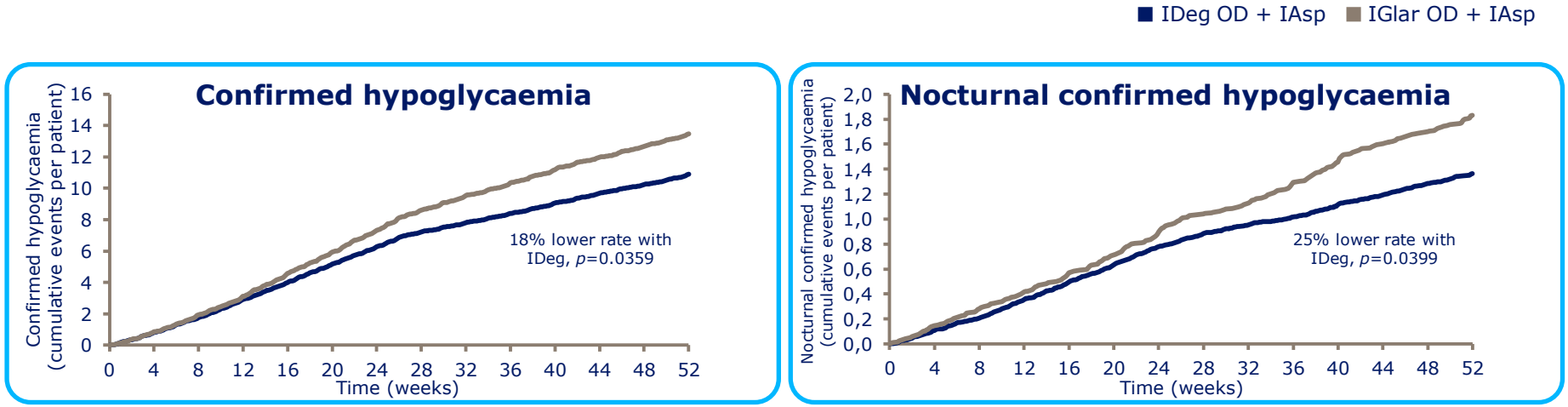
Nocturna -36 a -43%

Black box denotes both treatment arms switching to NPH for 1 week then resuming IDeg or IGlar to allow for antibody measurement

Zinman *et al. Diabetes Care* 2012;35:2464–71; Rodbard *et al. Diabet Med* 2013;30:1298–304

Basal–bolus in T2D: results

BEGIN BB T2D



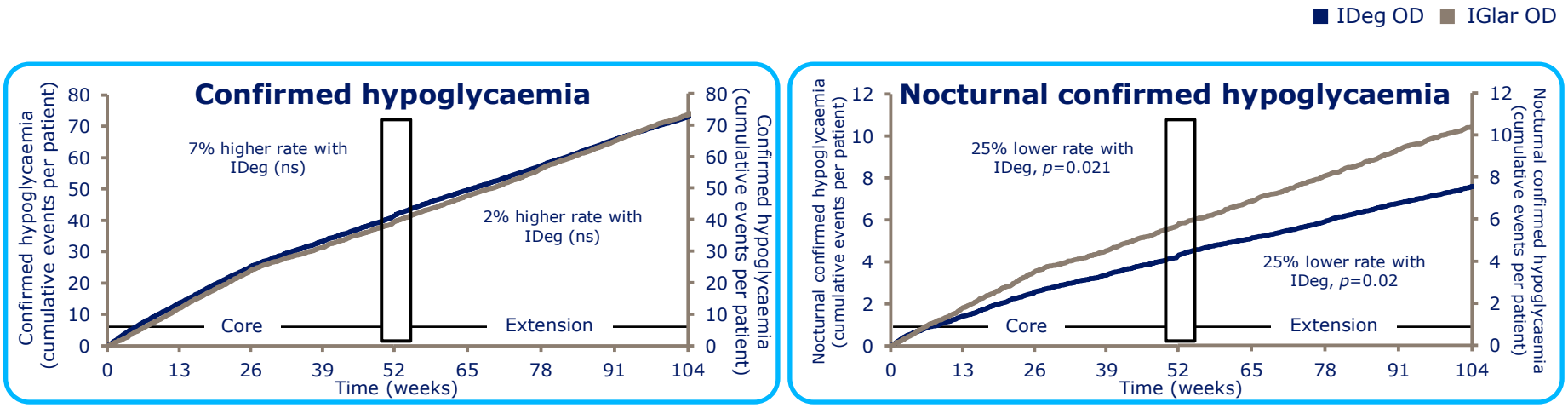
Confirmada -18%

Nocturna -25%

Garber *et al. Lancet* 2012;379:1498–507

Basal–bolus in T1D: results

BEGIN BB T1D – 2 years



Nocturna -25%

Black box denotes both treatment arms switching to NPH for 1 week then resuming IDeg or IGlar to allow for antibody measurement

Heller *et al. Lancet* 2012;379:1489–97; Bode *et al. Diabet Med* 2013;30:1293–7

Phase 3a summary: IDeg vs IGlar

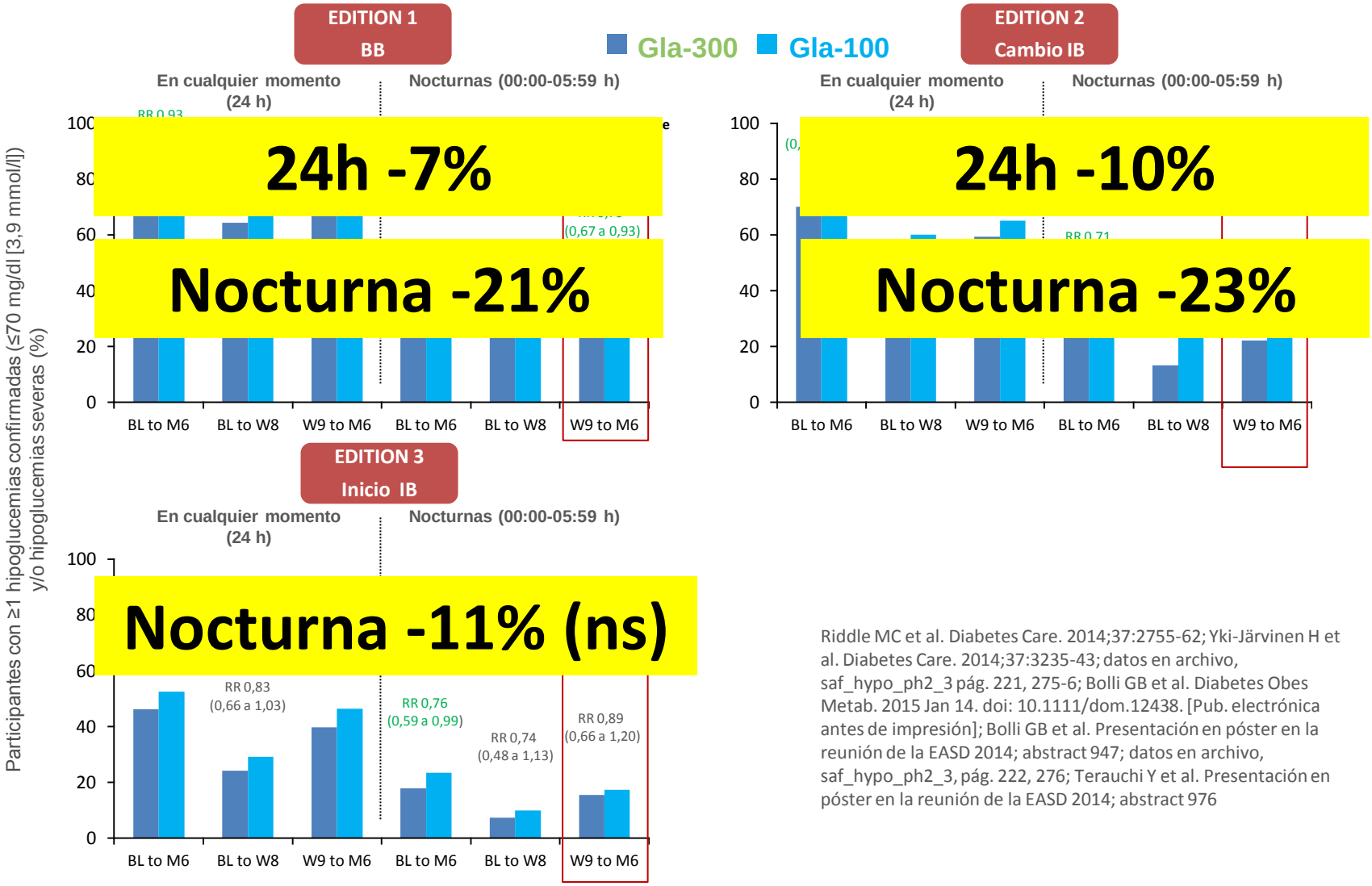
Trial	Population/ comparator	Duration (wks)	Hypoglycaemia	
			Total	Nocturnal
ONCE LONG (core and extn)	Insulin naïve, T2D	104	↓ 16%	↓ 43%
BB	Previously treated with insulin, T2D	52	↓ 18%	↓ 25%
T1 BB LONG (core and extn)	Type 1	104	↑ 2%	↓ 25%

extn, extension; non-inf., non-inferior; wks, weeks
* Data depict results for IDeg Flexible vs. IGlar

Insulin degludec significantly better

No significant difference

Incidencia de hipoglucemias confirmadas (≤70 mg/dl) o severas en DMT2

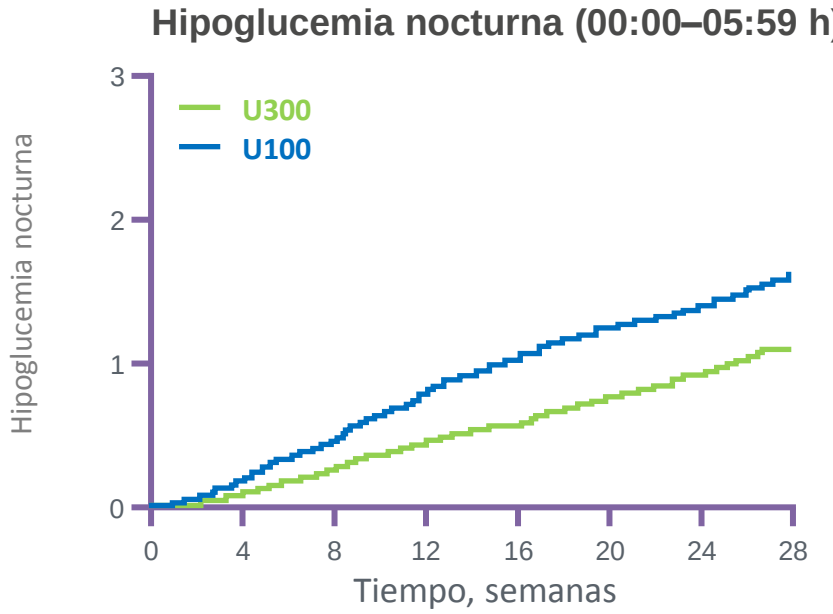


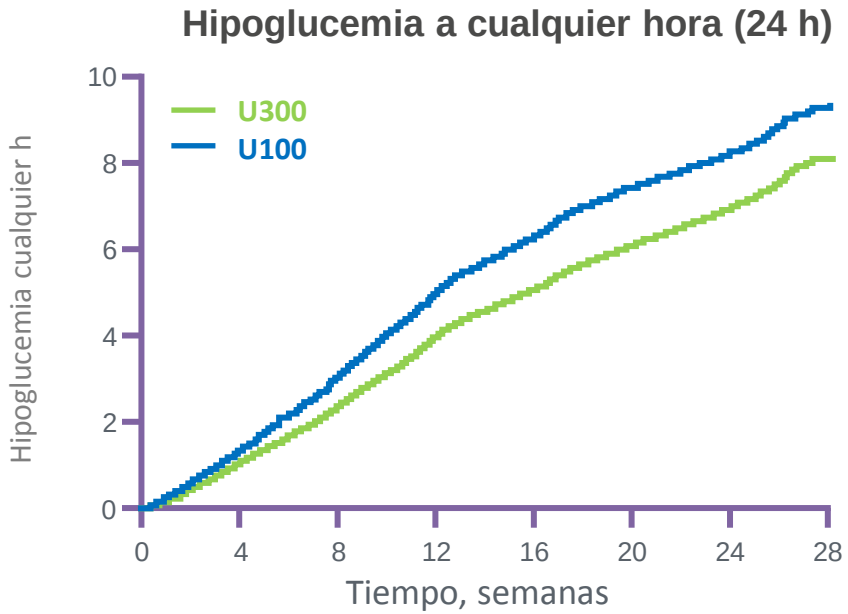
Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43; datos en archivo, saf_hypo_ph2_3 pág. 221, 275-6; Bolli GB et al. Diabetes Obes Metab. 2015 Jan 14. doi: 10.1111/dom.12438. [Pub. electrónica antes de impresión]; Bolli GB et al. Presentación en póster en la reunión de la EASD 2014; abstract 947; datos en archivo, saf_hypo_ph2_3, pág. 222, 276; Terauchi Y et al. Presentación en póster en la reunión de la EASD 2014; abstract 976

Población por IDTm en el principal criterio de valoración secundario; población de seguridad para otros datos; BL: basal; M6: mes 6; S8: semana 8; S9: semana 9; RR: riesgo relativo

Análisis agrupado EDITION 1, 2 y 3 en DMT2

Menos hipoglucemias confirmadas y/o severas con U300 vs Lantus® por la noche y durante todo el día (24 h)





	U300	U100	
Tasa por paciente y año	2.10	3.06	-31%
RR (95% CI) vs U100	0.69 (0.57 to 0.84)		
P value	0.0002		

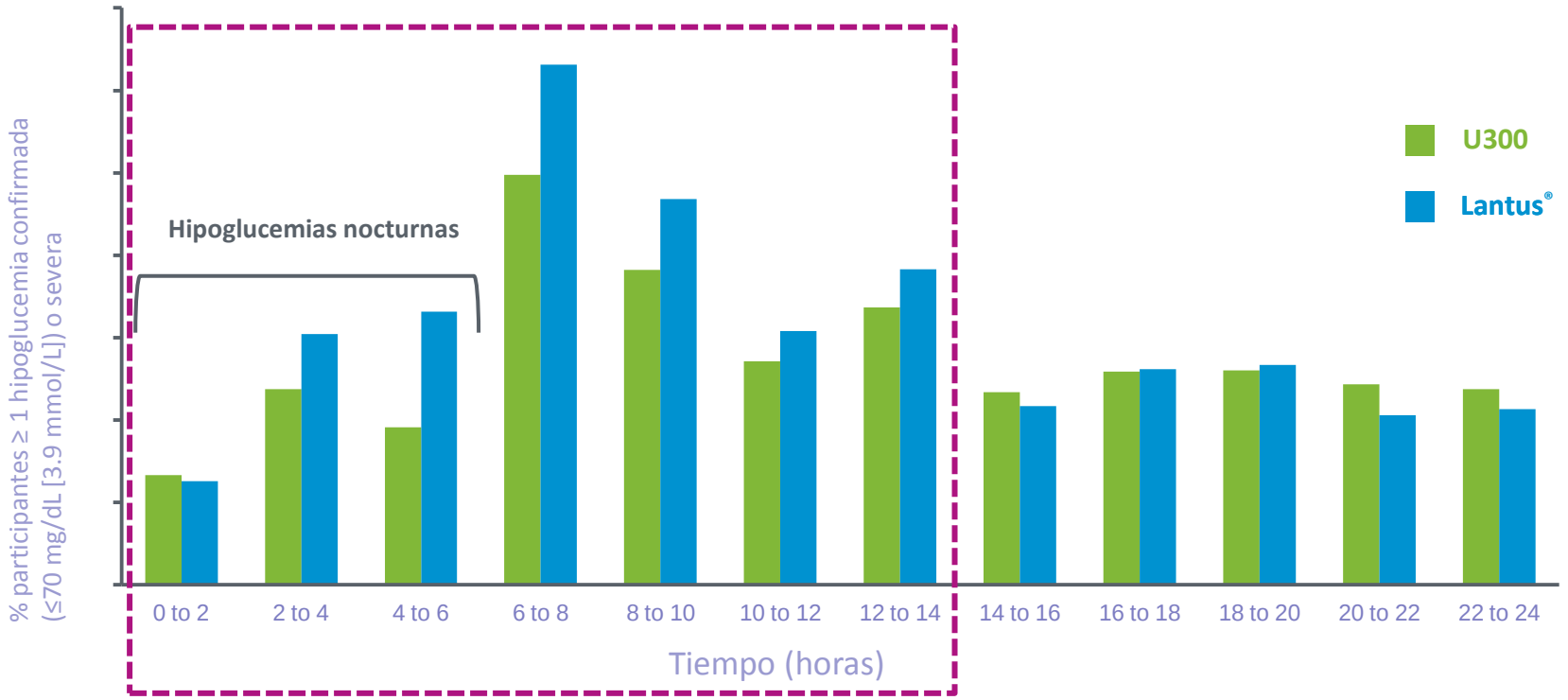
	U300	U100	
Tasa por paciente y año	15.22	17.73	-14%
RR (95% CI) vs U100	0.86 (0.77 to 0.97)		
P value	0.0116		

*eventos confirmados: basado en niveles de glucosa plasmática ≤3.9 mmol/L (≤70 mg/dL)

Ritzel R et al. New insulin glargine 300 U/mL: Glycemic control and hypoglycemia in a meta-analysis of Phase 3ª EDITION clinical trials in people with T2DM. Poster presentation on EASD 2014. Abstract 963 Available at http://www.easdvirtualmeeting.org/resources/18908 Accessed November 2014

Análisis agrupado EDITION 1, 2 y 3 en DMT2

Hipoglucemia confirmada y/o severa durante las 24 horas



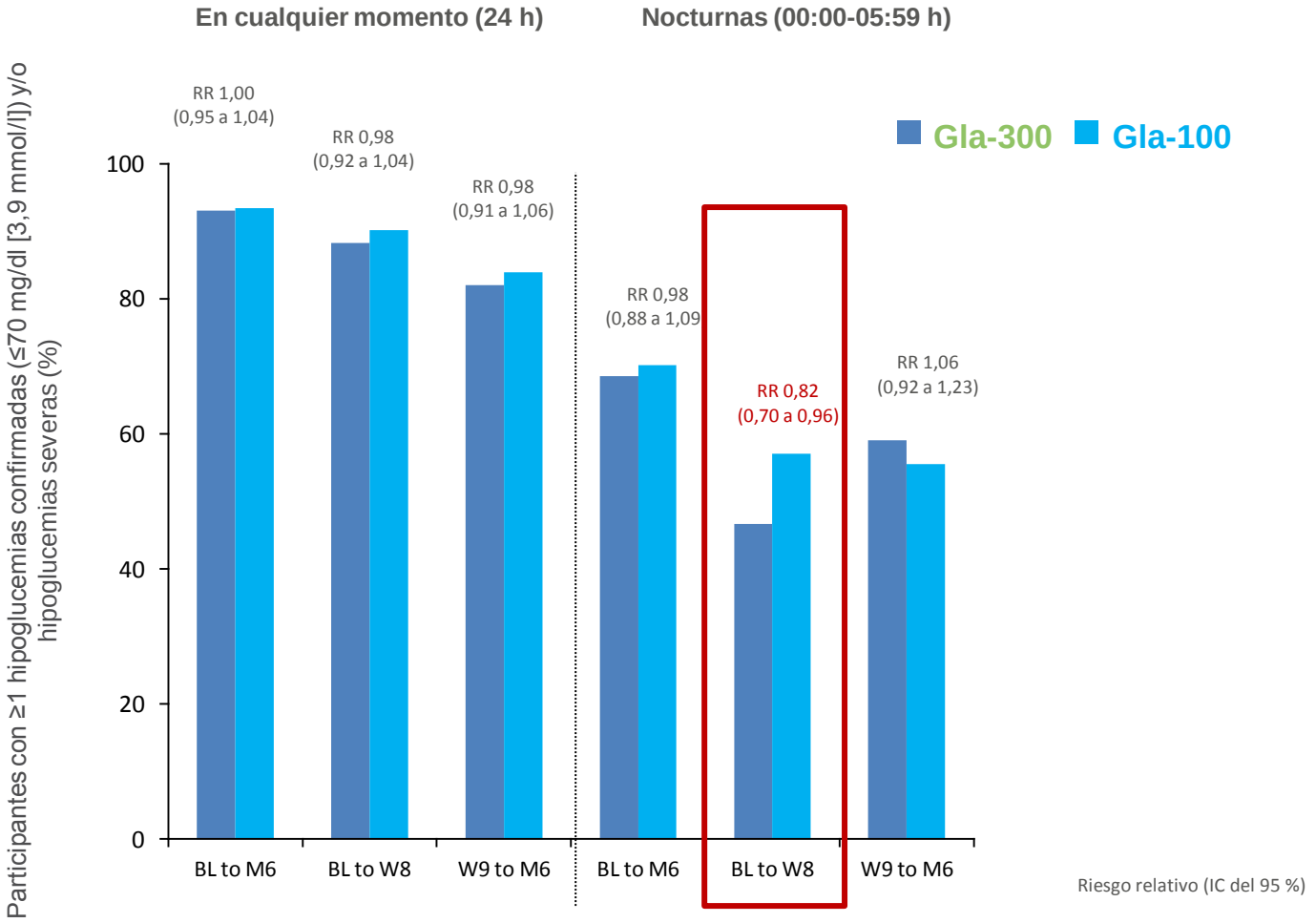
→Menos pacientes ≥ 1 hipoglucemia sintomática con Gla-300 vs Gla-100: 49,6% vs 56,4%; RR 0,88 [95% CI: 0,82 a 0,94] durante los 6 meses de estudio

→Hipoglucemia severa baja en ambos grupos (≥ 1 evento): 2,3% con Gla-300 vs 2,6% con Gla-100; 0,11 eventos/participante /año en ambos grupos.

Ritzel R et al. New insulin glargine 300 U/mL: Glycemic control and hypoglycemia in a meta-analysis of Phase 3ª EDITION clinical trials in people with T2DM. Poster presentation on EASD 2014. Abstract 963 Available at http://www.easdvirtualmeeting.org/resources/18908 Accessed November 2014

Incidencia de hipoglucemias confirmadas (≤70 mg/dl) o severas en DMT1

EDITION 4



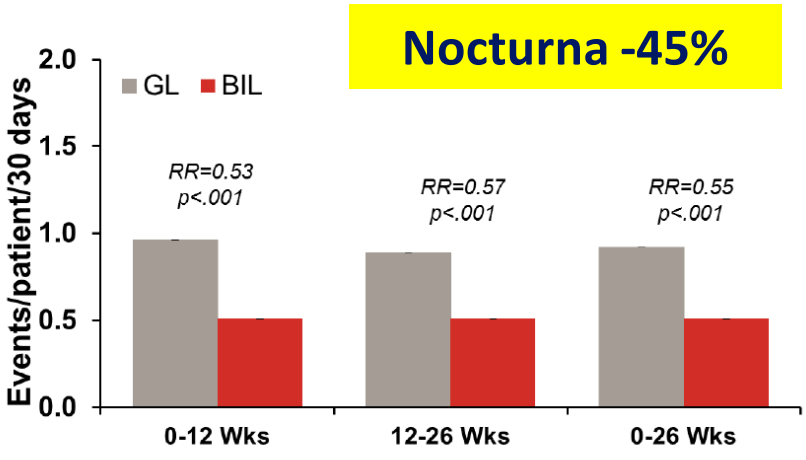
El estudio no se diseñó ni tuvo la capacidad para demostrar la diferencia en el riesgo de hipoglucemias entre Gla-300 y Gla-100 como criterio de valoración preespecificado

Datos en archivo, saf_hypo_ph2_3, pág. 219, 273; Home PD et al. Presentación en póster en la reunión de la ADA 2014; abstract 80-LB; datos en archivo, JP1-efc12449_15_3_1_ae_data, pág. 7, 9; Matsuhisa M et al. Presentación en póster en la reunión de la EASD 2014; abstract 975

T2D: PEGLISPRO vs Glargine

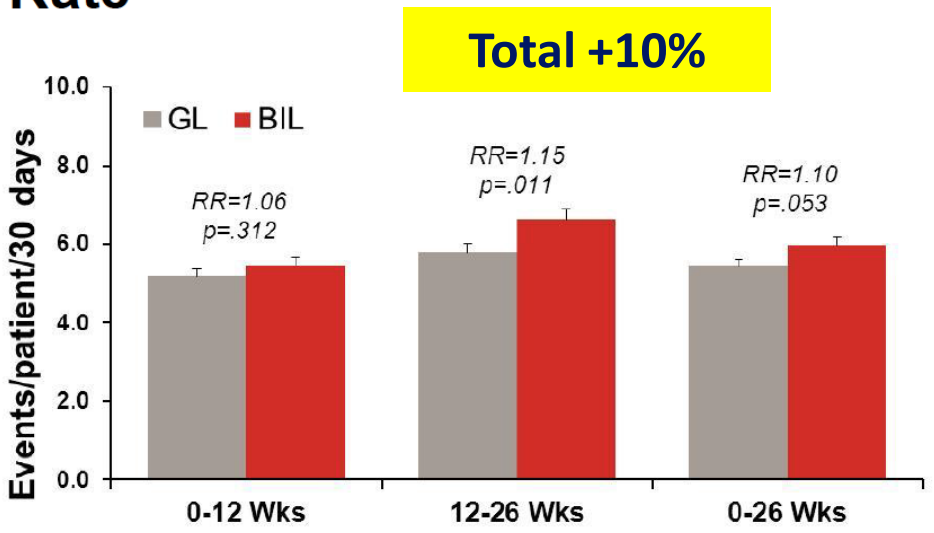
IMAGINE 4. DM2: insulina basal + prandial

Figure 6. Nocturnal Hypoglycaemia Rate



Group mean ± SE; RR=relative rate (BIL/GL)

Figure 7. Total Hypoglycaemia Rate



Group mean ± SE; RR=relative rate (BIL/GL)

Table 2. Severe Hypoglycaemia

Rate (events/100 patient years)†				Incidence, n (%)		
GL	BIL	RR	p-value	GL	BIL	p-value
4.8 ± 1.7	5.8 ± 1.4	1.21	.661	10 (1.5)	16 (2.3)	.149

†Aggregated rate ± SD; RR=relative rate BIL/GL; Overall study period

Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

T1D: PEGLISPRO vs Glargine

IMAGINE 3. DM1: insulina basal + prandial

Figure 5. Nocturnal Hypoglycaemia

Nocturna -47%

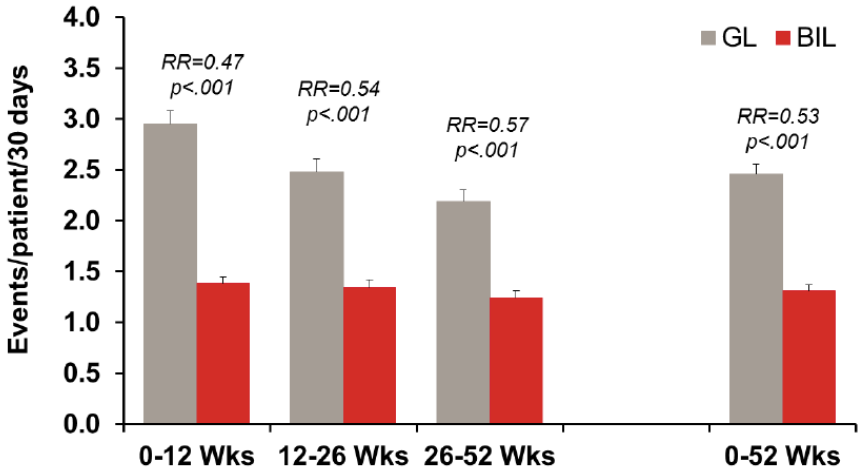


Figure 6. Total Hypoglycaemia

Total +11%

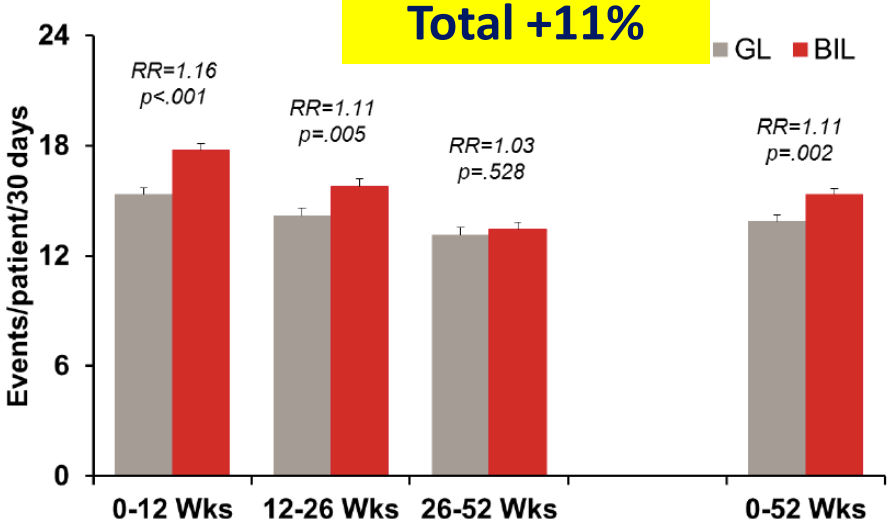
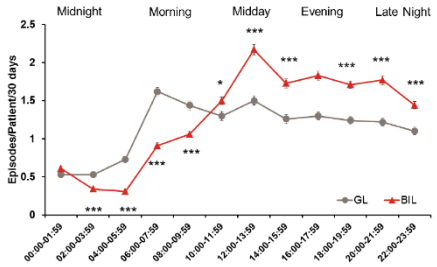


Table 2. Severe Hypoglycaemia

Events/100 patient years†				Incidence (n, %)		
GL N=449	BIL N=663	RR BIL/GL	p-value	GL N=449	BIL N=663	p-value
22.2 ± 3.3	19.1 ± 2.5	0.86	.445	58 (13)	74 (11)	.375

† Aggregated rate ± SE; RR=relative rate; Overall study period; Each event was validated by an investigator

Figure 7. Total Hypoglycaemia by 2-Hour Intervals (0–52 Weeks)



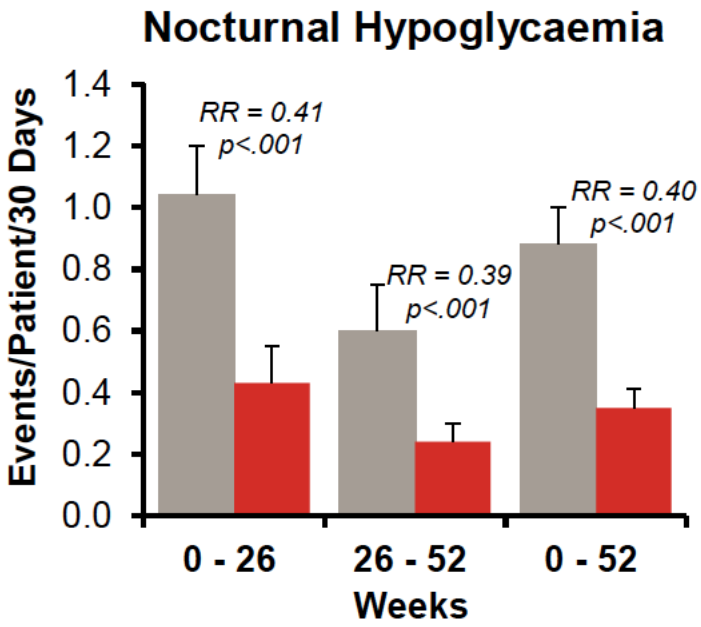
Group mean ± SE; *p<.05, ***p<.001 for difference between treatments

Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

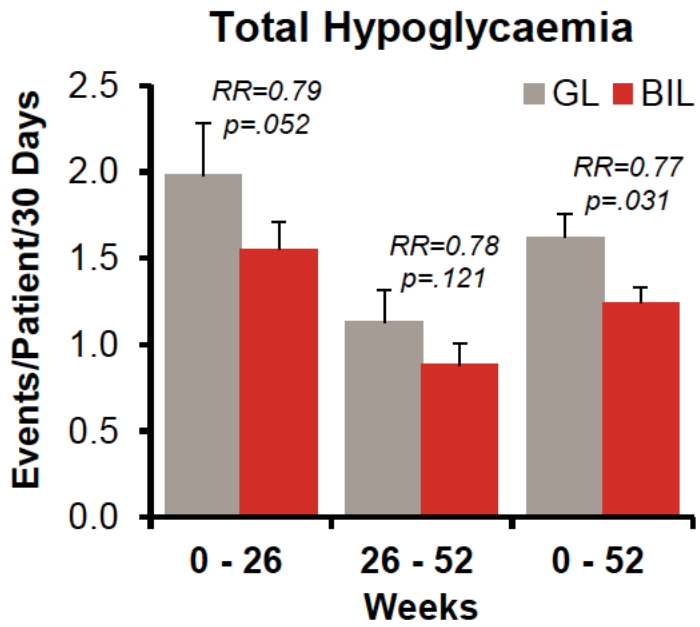
T1D: PEGLISPRO vs Glargine

IMAGINE 5. DM2: insulina basal + ADOs (tto previo con insulina basal)

Nocturna -60%



Total -23%



Group mean ± SE. Hypoglycaemia was defined as SMBG ≤70 mg/dL (≤3.9 mmol/L) and/or signs/symptoms of hypoglycaemia. Nocturnal hypoglycaemia was defined as hypoglycaemia occurring between bedtime and waking. RR=relative rate (BIL/GL)

Trescoli C et al. 971-P. European Association for the Study of Diabetes 51st Annual Meeting; Stockholm, Sweden; September 14-18, 2015

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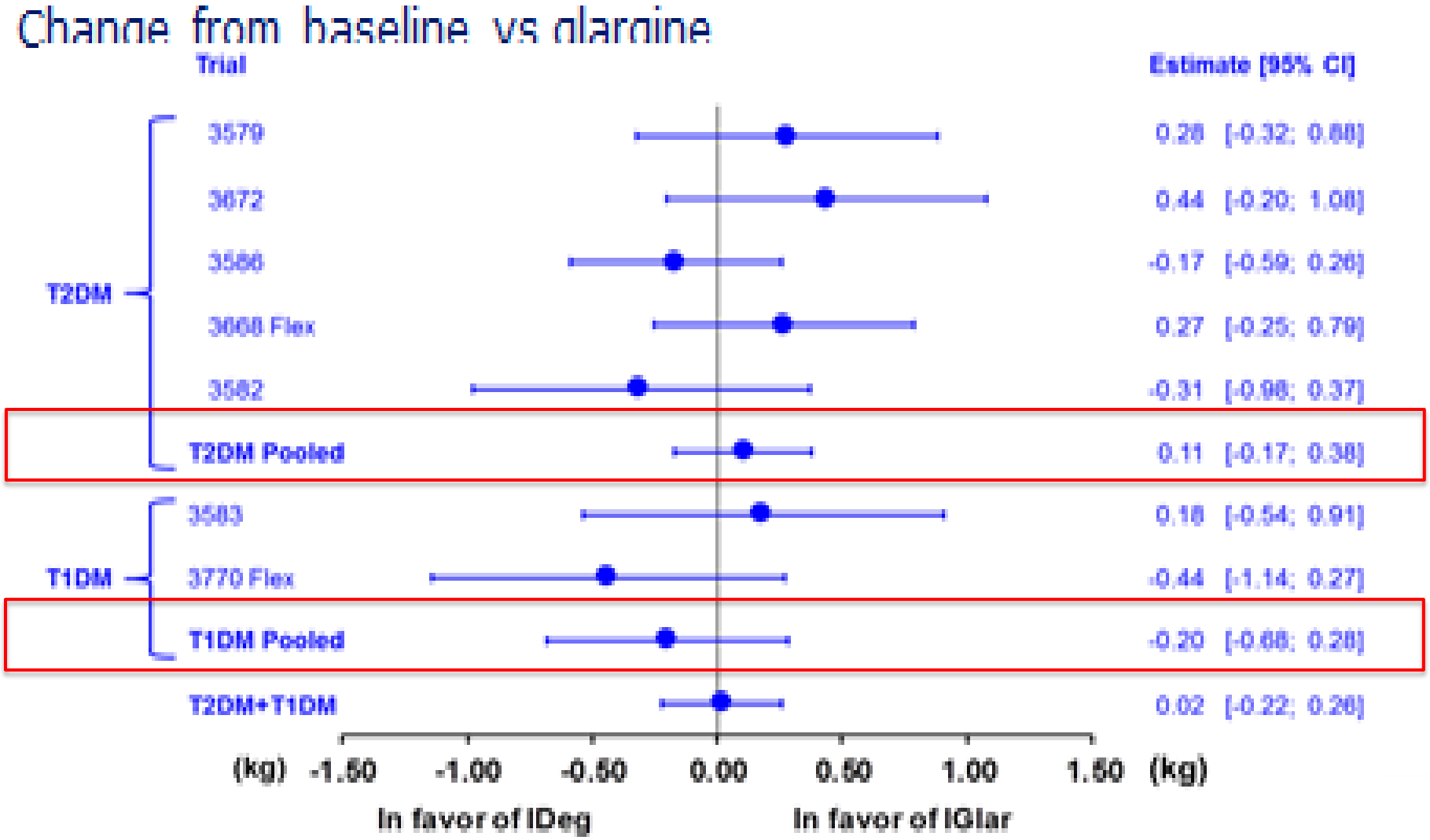
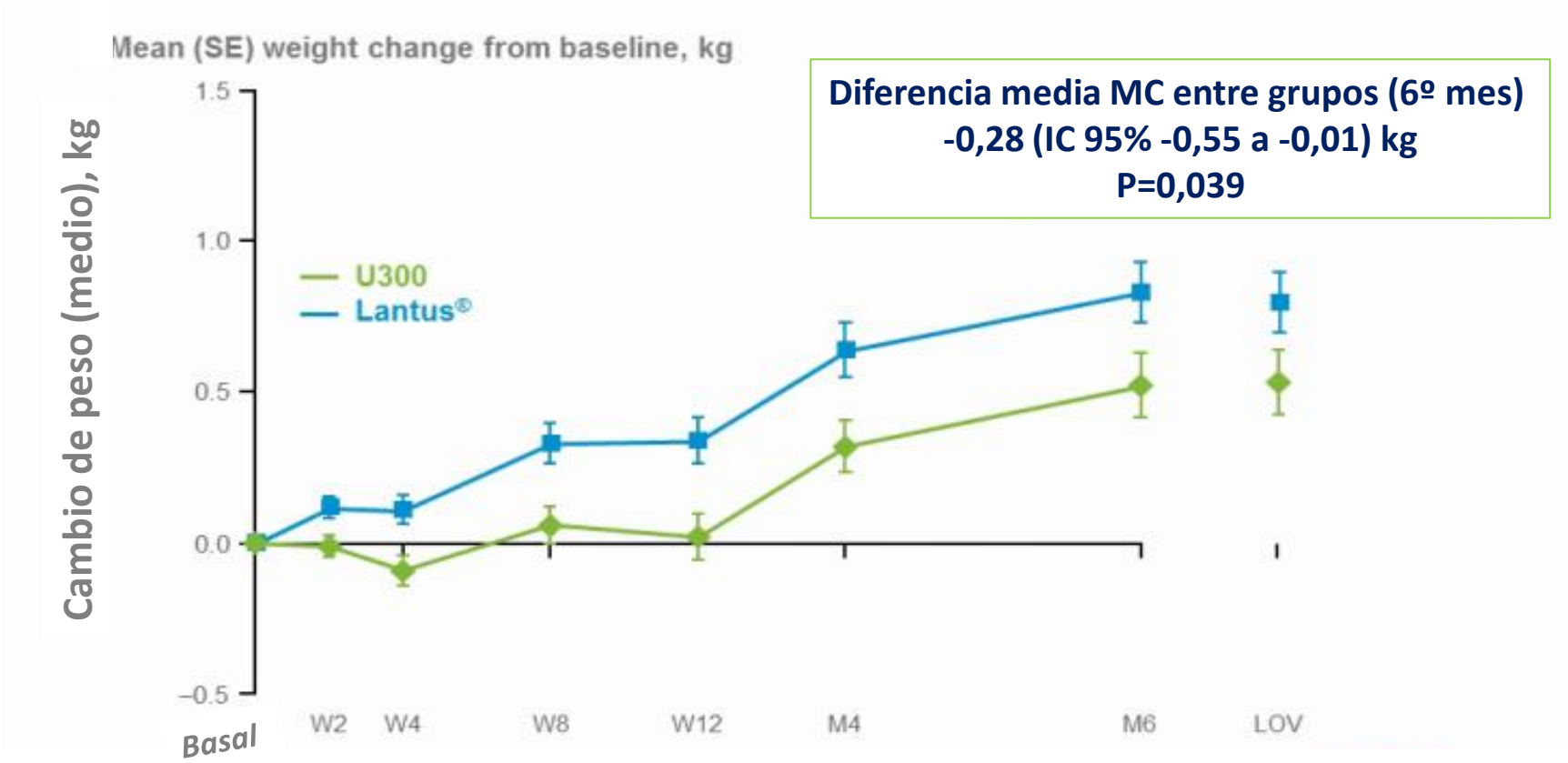
  - Hipoglucemias
  - **Peso**
  - Dosis de insulina
- Seguridad
  - Cardiovascular
  - No cardiovascular

Degludec: Weight neutral vs Glargine



Análisis agrupado EDITION 1, 2 y 3 en DMT2

Diferencia pequeña, pero significativa, en el aumento de peso con U300 vs Lantus



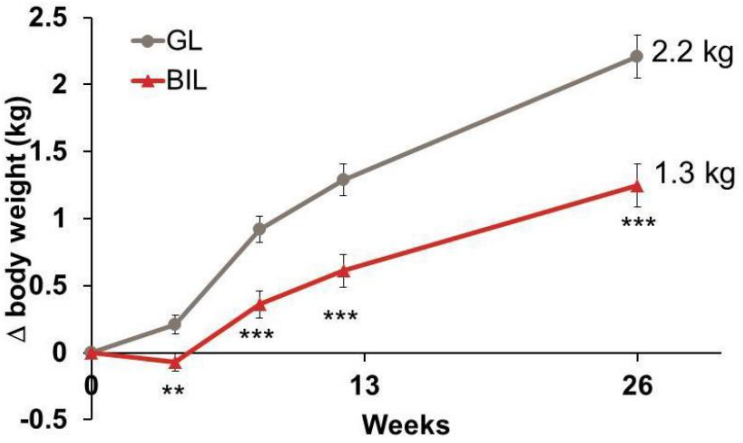
Diferencia media MC entre grupos (6º mes)
-0,28 (IC 95% -0,55 a -0,01) kg
P=0,039

W: semanas; M: meses

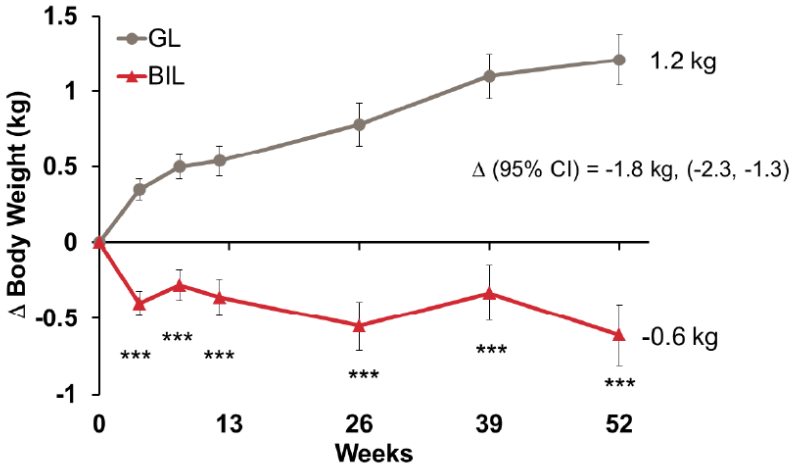
Ritzel R et al. New insulin glargine 300 U/mL: Glycemic control and hypoglycemia in a meta-analysis of Phase 3ª EDITION clinical trials in people with T2DM. Poster presentation on EASD 2014. Abstract 963 Available at http://www.easdvirtualmeeting.org/resources/18908 Accessed November 2014

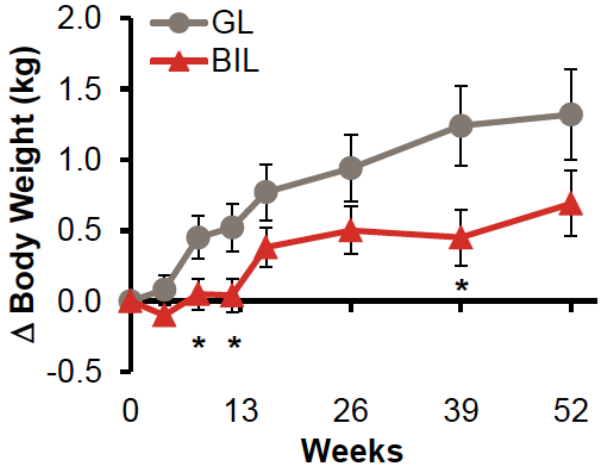
PEGLISPRO
Peso

DM2: basal y bolos



DM1: basal y bolos





DM2: basal

Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015
Trescoli C et al. 971-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015
Chang AM et al. 972-P. European Association for the Study of Diabetes 51st Annual Meeting; Stockholm, Sweden; September 14-18, 2015

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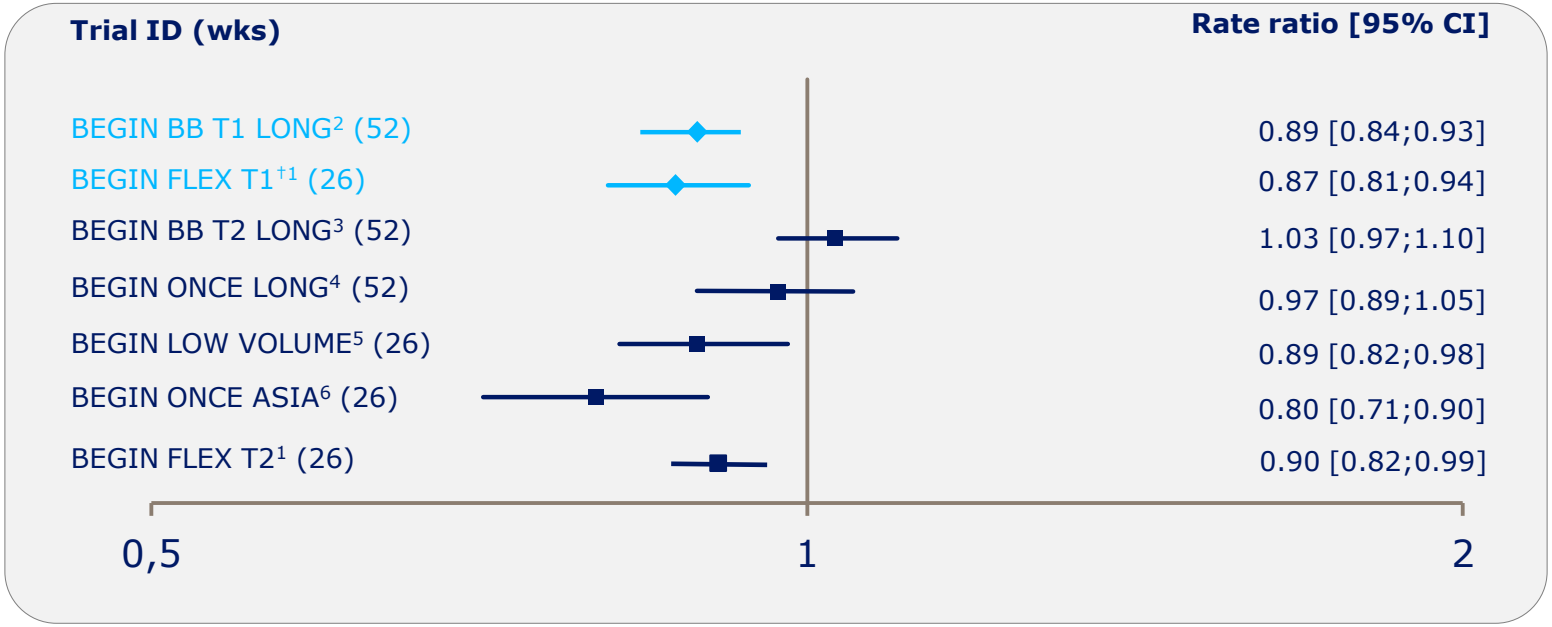
  - Peso
  - **Dosis de insulina**
- Seguridad
  - Cardiovascular
  - No cardiovascular

DEGLUDEC
Total daily dose overview by trial



For T1D patients, the total daily dose of IDeg was significantly **12%** lower than IGlar ($p<0.0001$)[1]

For insulin-naïve T2D patients, the total daily dose was **10%** lower with IDeg than IGlar ($p=0.0004$)[1]

†The ratios reported in Mathieu *et al.* 2013 (Table 2) deviate from those above as the publication analyses all IDeg patients (i.e. both the forced flex and standard arms)

References: 1. Data on file, DOF-MA-IDeg-24APR2013-001, Novo Nordisk A/S; 2. Heller *et al. Lancet* 2012;379:1489–97; 3. Garber *et al. Lancet* 2012;379:1498–507; 4. Zinman *et al. Diabetes Care* 2012;35:2464–71 (+ supplementary online data); 5. Gough *et al. Diabetes Care* 2013;36:2536–42; 6. Onishi *et al. J Diabetes Investig* 2013;4:605–12 (+ supplementary online information)

Glargina U 300
Dosis de insulina basal en el mes 6

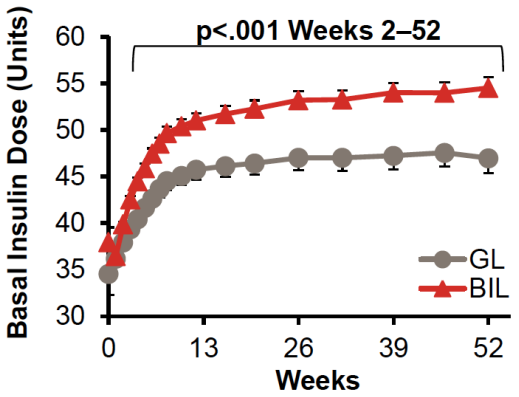
T2
T1

Dosis de insulina basal en el mes 6 (U/kg)				
	Estudios de DMT2			Estudios de DMT1
	EDITION 1 BB	EDITION 2 Cambio IB	EDITION 3 Inicio IB	EDITION 4
Gla-300	0,98	0,93	0,62	0,47
Gla-100	0,88	0,85	0,53	0,40
Diferencia relativa Gla-300 vs Gla-100, %	**+11,55**	**+10,44**	**+16,58**	**+17,5[1]**

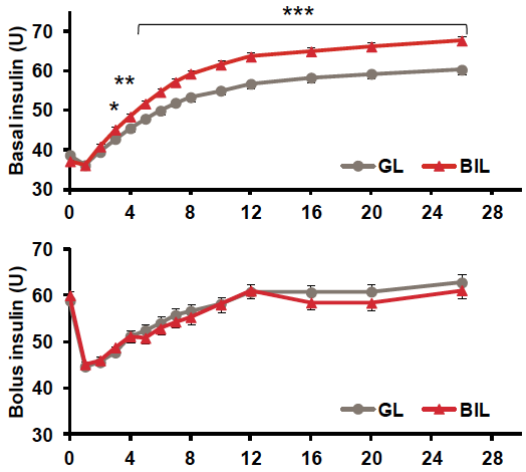
Datos en archivo, E19_Insulin dose_Absolute and Relative differences_M12_2014-09-03.doc, pág. 6, 12, 14, 22, 38, 44 [1]Ficha técnica en EE. UU., 27 feb 2015

PEGLISPRO
Dosis de insulina

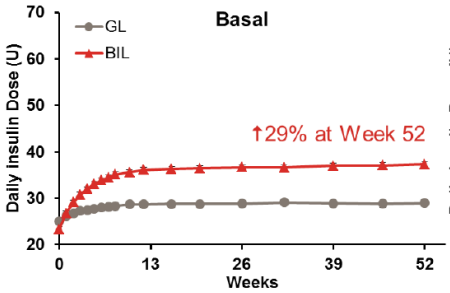
DM2: tto previo con insulina basal



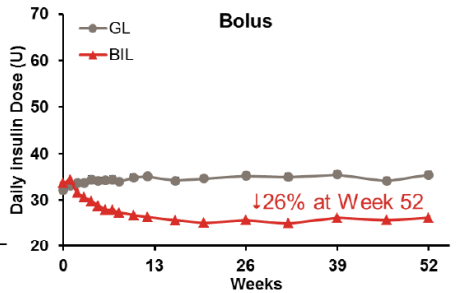
LS Mean ± SE



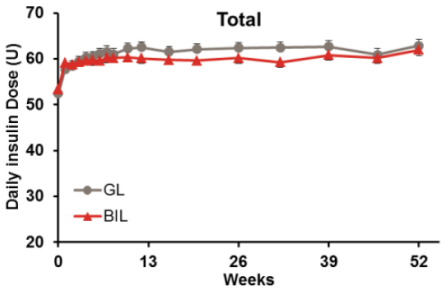
DM1: basal y bolos



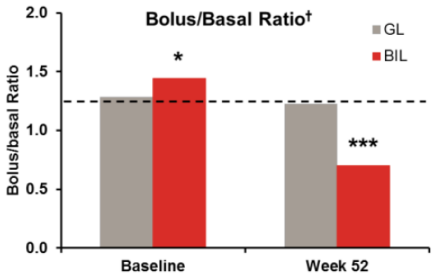
LS Mean ± SE; BIL dose was higher than GL dose from Weeks 2–52



LS Mean ± SE; Bolus dose was lower in BIL group from Weeks 1–52



LS Mean ± SE; Total insulin dose was similar throughout study



*p<.05, ***p<.001 for difference between treatments; †Ratio of LS mean insulin doses at the given time point

Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015
Trescoli C et al. 971-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

New Basal Insulin Formulations

- Introducción
- Mecanismo de acción, duración, variabilidad
- **Estudios pivotales**
  - Control glucémico
    - HbA1c
    - Glucemia basal
  - Hipoglucemias
  - Peso
  - Dosis de insulina
- **Seguridad**
  - **Cardiovascular**
  - **No cardiovascular**

DEGLUDEC
Seguridad cardiovascular

novo nordisk®

DEVOTE

Log-in to devotetrial.com

DEVOTE – degludec cardiovascular outcomes trial

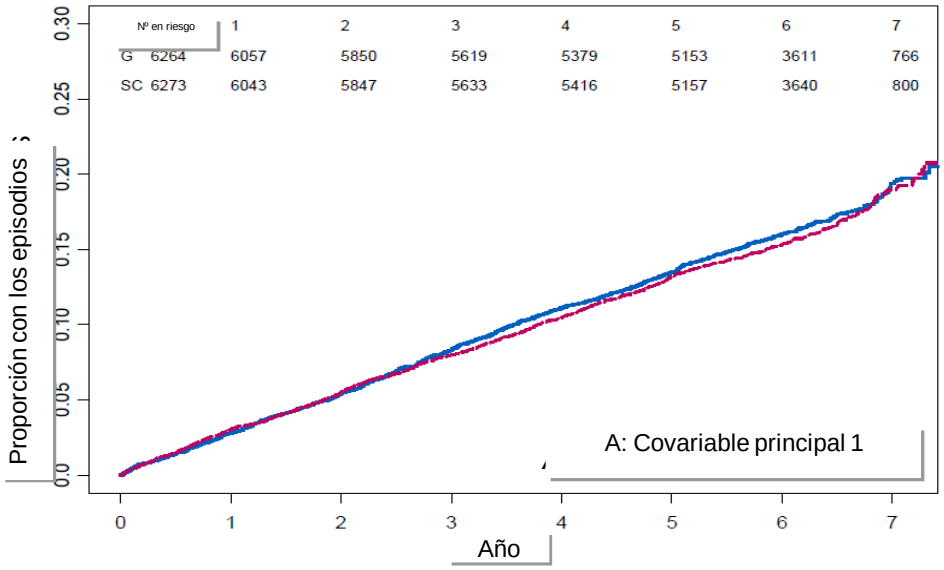
DEVOTE is a clinical trial comparing the cardiovascular safety of insulin degludec to that of insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events.

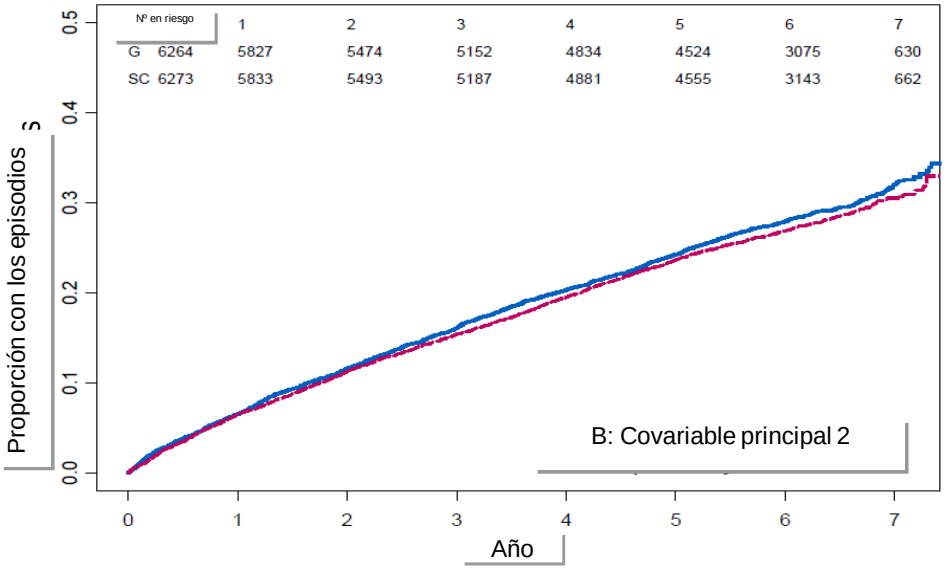
The trial is a randomised, double-blind, global trial which will include 7,500 patients. The trial started in October 2013 and continues for up to 5 years.

Trial ID:

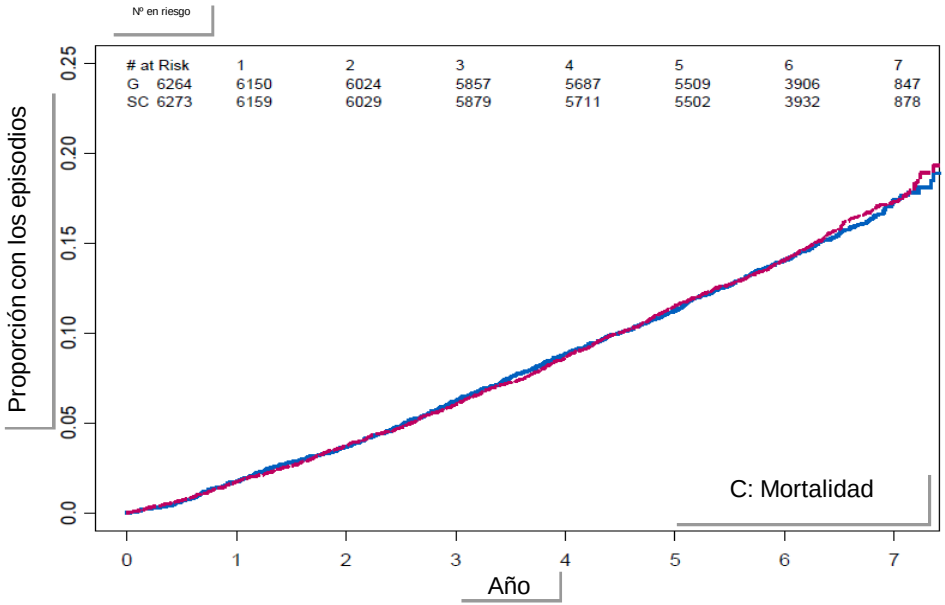
Novo Nordisk Trial ID: EX1250-4080
Clinical Trials.gov Registration: NCT01959529
EudraCT Number: 2013-002371-17
Other Identifier: U1111-1141-7614

GLARGINA U-300
Seguridad cardiovascular (ORIGIN)





La mortalidad es un criterio de valoración secundario del estudio

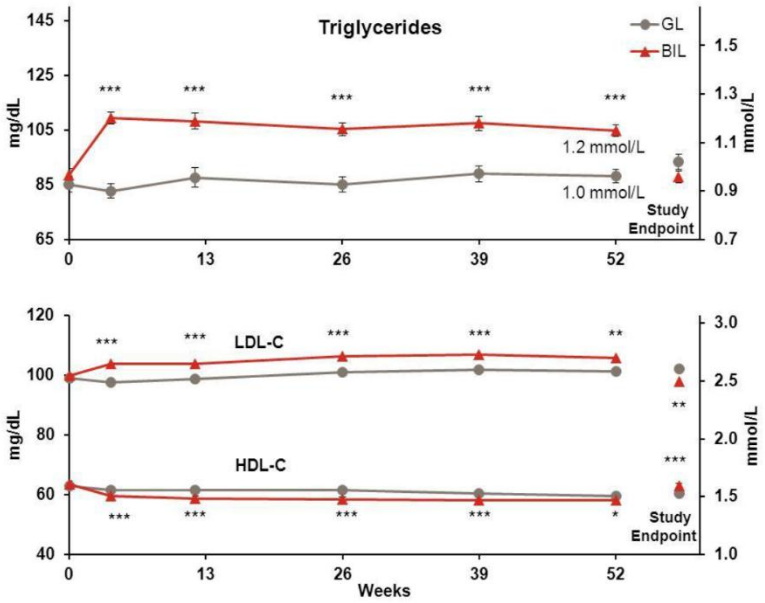


The ORIGIN trial Investigators. Basal insulin and Cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012 Jul 26;367(4):319-28

PEGLISPRO
Seguridad cardiovascular

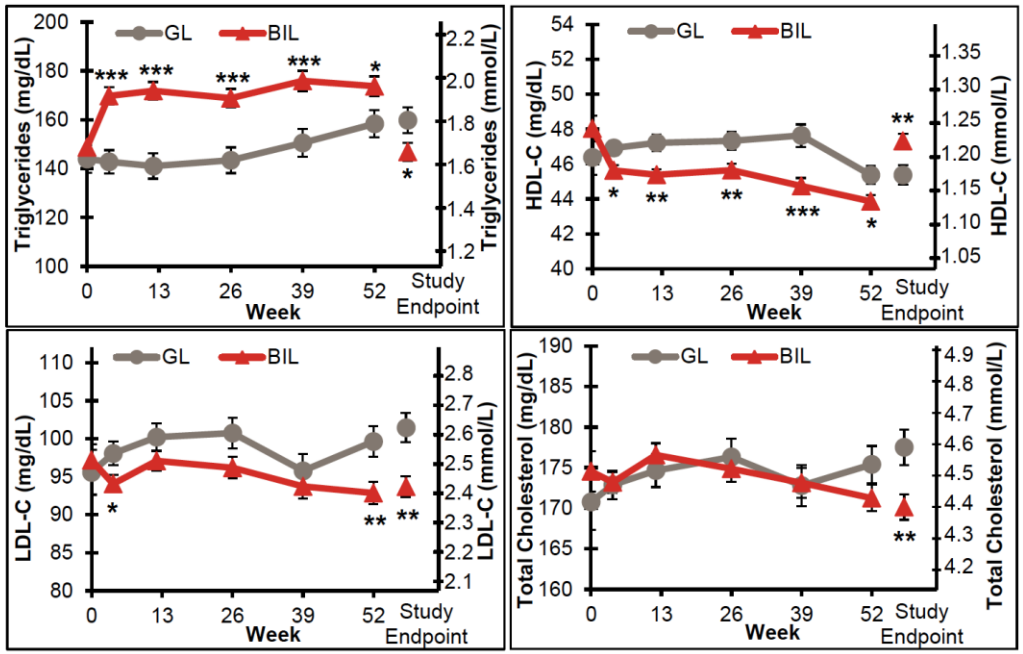
DM1

Figure 10. Blood Lipids



DM2

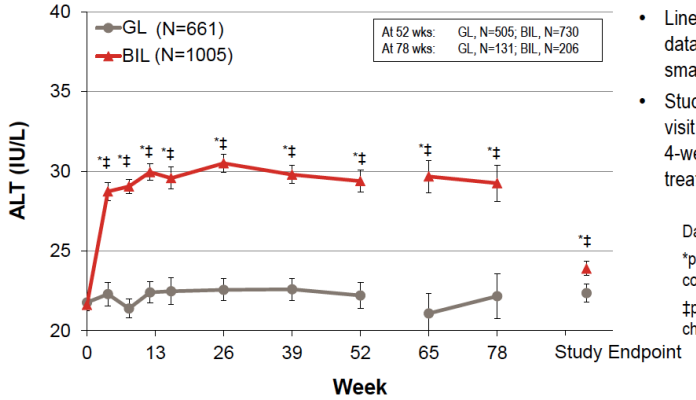
Figure 9. Lipid Profile



Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015
Trescoli C et al. 971-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

PEGLISPRO
Seguridad no cardiovascular

Figure 1. ALT Time Course in Patients with T1D

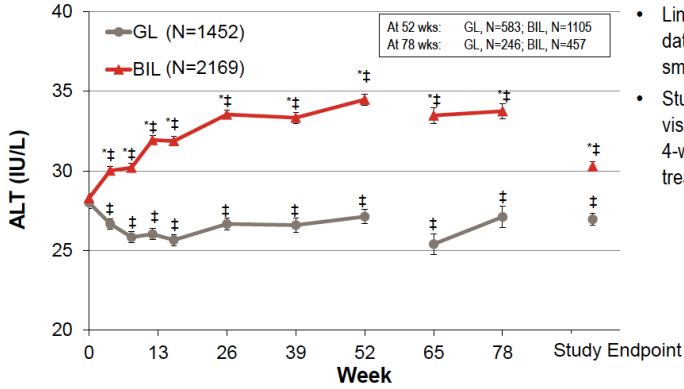


- Line graph is interrupted since data after 52 weeks is from a smaller cohort of patients.
- Study endpoint refers to last visit completed, including 4-week follow-up visit after treatment completion.

Data are LS mean ± SE
*p<.05 between treatment group comparison
‡p<.05 within treatment group change from baseline

♦ ALT increased with BIL treatment and decreased after discontinuation of BIL.

Figure 5. ALT Time Course in Patients with T2D



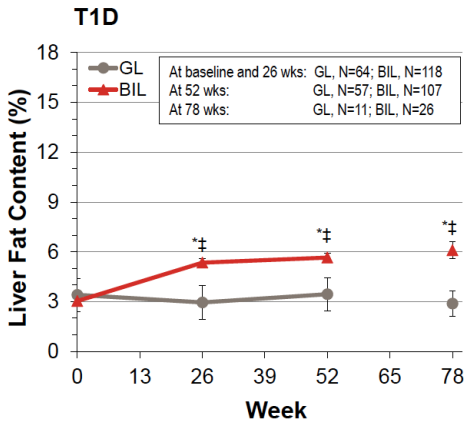
- Line graph is interrupted since data after 52 weeks is from a smaller cohort of patients.
- Study endpoint refers to last visit completed, including 4-week follow-up visit after treatment completion.

Data are LS mean ± SE
*p<.05 between treatment group comparison
‡p<.05 within treatment group change from baseline

♦ ALT increased with BIL treatment and decreased after discontinuation of BIL.

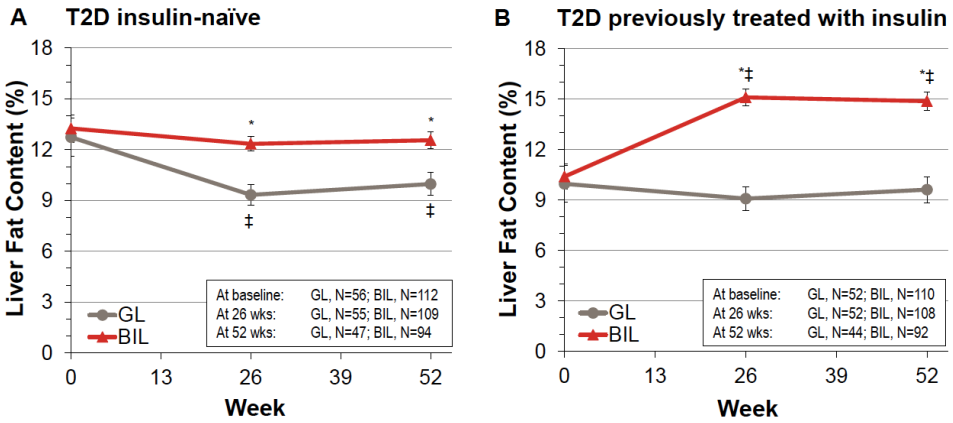
Figure 4. Liver Fat Content by MRI in T1D

- Line graph is interrupted since data after 52 weeks is from a smaller cohort of patients.
- MRIs were not performed after drug discontinuation.



Data are LS mean ± SE
*p<.05 between treatment group comparison
‡p<.05 within treatment group change from baseline

Figure 8. Liver Fat Content by MRI in T2D



Mark L. Hartman1 et al. Liver Enzyme and Liver Fat Content (LFC) Results from Basal Insulin Peglispro (BIL) Clinical Trials in Type 1 (T1D) and Type 2 Diabetes (T2D). 973-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

PEGLISPRO
Seguridad no cardiovascular

Injection site reactions of special interest	GL (N=449) n (%)	BIL (N=663) n (%)	p-value
Patients with ≥1 TEAE	1 (0.2)	88 (13.3)	<.001
Lipohypertrophy	1 (0.2)	51 (7.7)	<.001
Injection site hypertrophy	0 (0.0)	13 (2.0)	.001
Injection site swelling	0 (0.0)	11 (1.7)	.004
Lipodystrophy acquired	0 (0.0)	7 (1.1)	.046

†The injection site was inspected at each visit thus providing a prospective evaluation of the injection site.

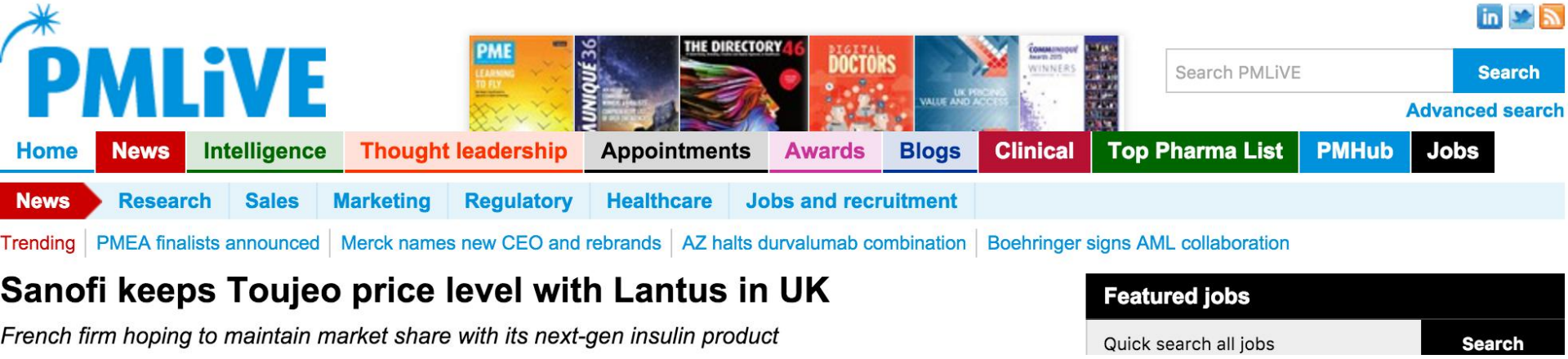
Lunt H et al. 967-P. American Diabetes Association's 75th Scientific Sessions; Boston, MA; June 5 - 9, 2015

New Basal Insulin Formulations
PRECIO

Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin – from the UK health care cost perspective

	Product	Price per pack*	Units per pack	Price per unit
Insulin	Degludec (in FlexTouch® pen, Novo Nordisk Ltd, Crawley, UK)	£72.00	1500	£0.0480
	Lantus® (in Solostar® pen, Sanofi, Guildford, UK)	£41.50	1500	£0.0277
Needles†	NovoFine® 8 mm 30G (Novo Nordisk Ltd)	£9.24	100	£0.0924
	ClickFine® 8 mm (Ypsomed Ltd, Selby, UK)	£9.11	100	£0.0911
SMBG tests‡	Test strip (OneTouch® Ultra®, Lifescan, High Wycombe, UK)	£15.00	50	£0.30
	Lancet (OneTouch® Ultra®, Lifescan)	£3.49	100	£0.0349
	Unit cost, SMBG test			£0.3349

Diabetes, Obesity and Metabolism 16: 366–375, 2014



RESUMEN
Nuevas insulinas basales vs Glargina U-100

	COMPARATIVA FRENTE A GLARGINA U-100										
	DURACIÓN > 24 H	VARIABILIDAD	HbA1c	GB	HIPO TOTAL	HIPO NOCTURNA	PESO	DOSIS INSULINA	SEGURIDAD CV	SEGURIDAD NO CV	PRECIO
DEGLUDEC									¿?		
GLARGINA U-300											
PEGLISPRO									¿?		¿?

Mejor que G-100

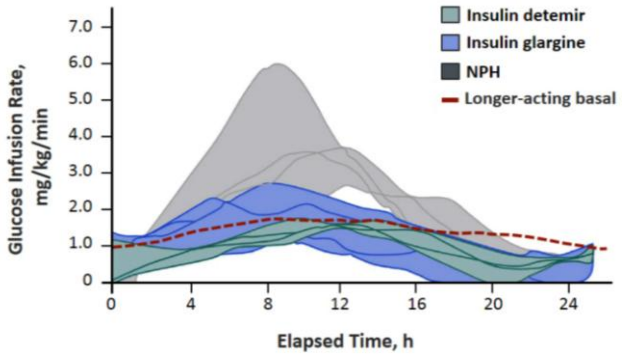
Igual que G-100

Peor que G-100

Characteristics of New Basal Insulin Analogs

Benefits over Glargine

- Longer duration of action
- Less variability
- Less weight gain
- Less (nocturnal) hypoglycemia
- Better glycaemic control?



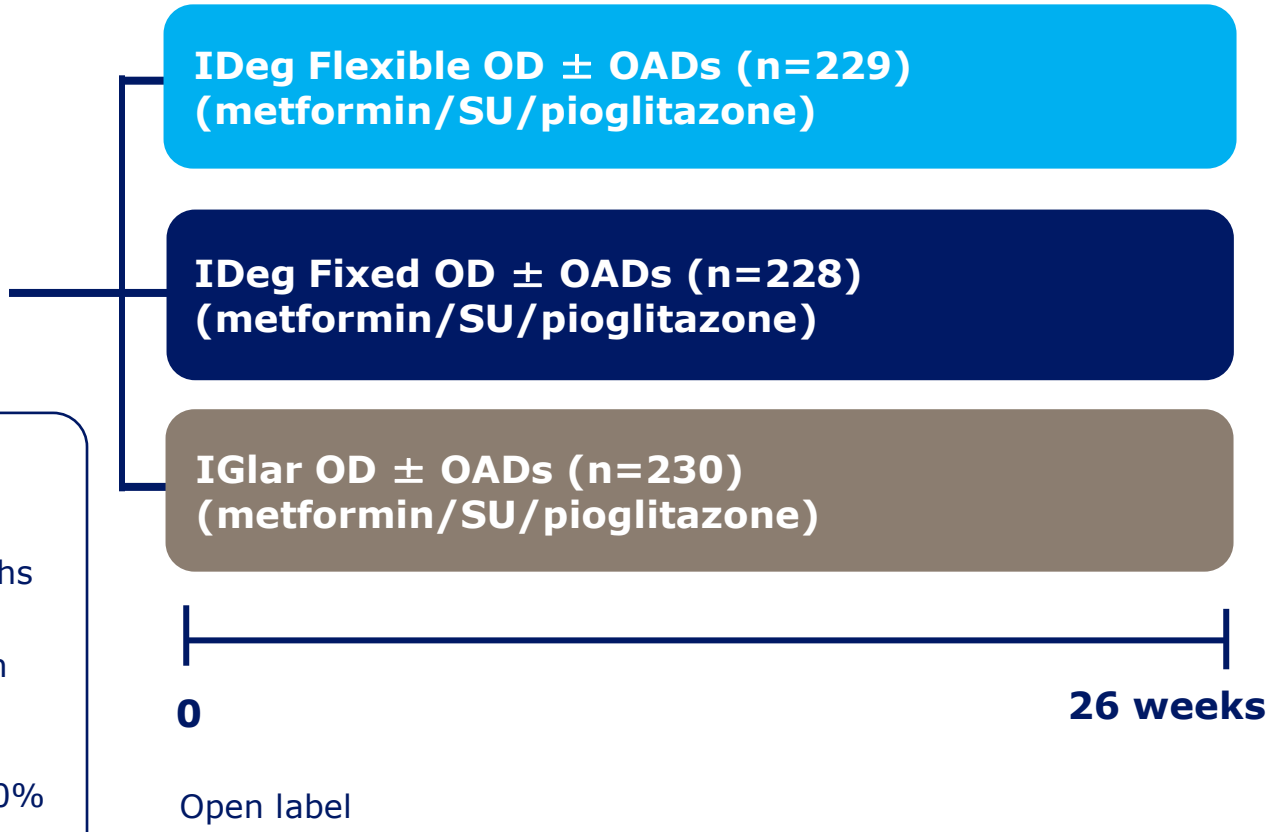
PD = pharmacodynamic; PK = pharmacokinetic.
Heise T. et al. *Diabetes*. 2004:53:1614-1620.[10]

Simon ACR. *Diabetes Technol Ther.* 2011;13(suppl 1):S103-108. Grunberger G. *Diab Obes Metab*. 2013;15(suppl 1):1-5.

MUCHAS GRACIAS

Flexible vs Fixed dosing in T2D: study design

BEGIN FLEX T2D



Inclusion criteria

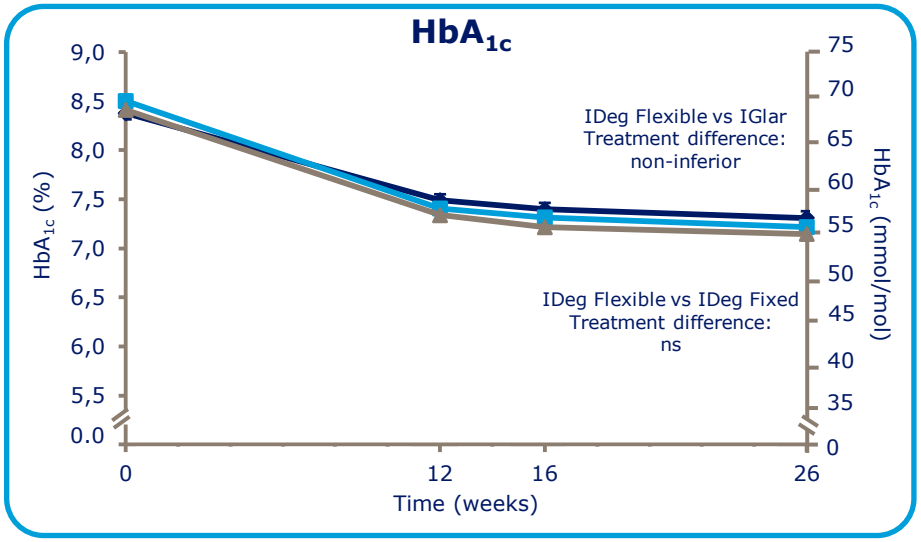
- Type 2 diabetes ≥6 months
- Previously treated with OADs and/or basal insulin
- HbA_{1c}:
  OADs only 7–11%
  Basal insulin ± OADs 7–10%
- BMI ≤40 kg/m^2
- Age ≥18 years

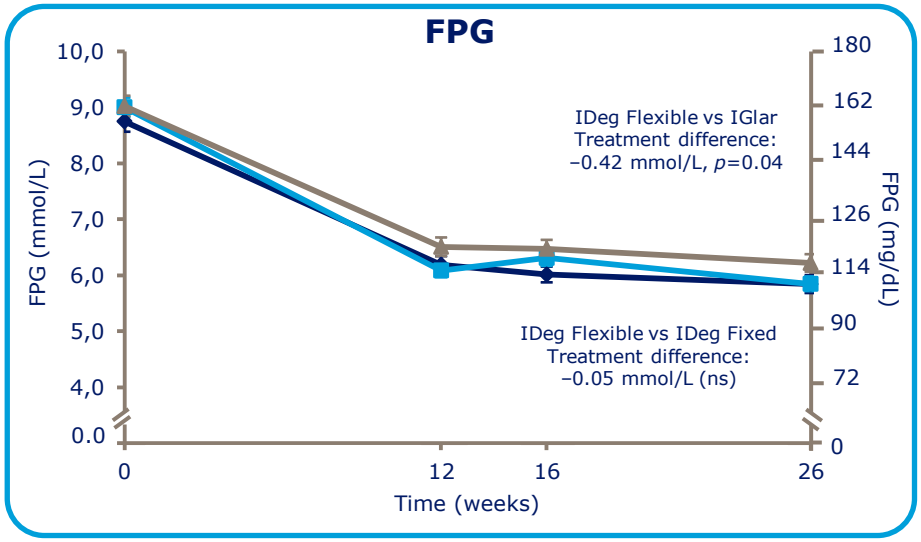
Meneghini *et al. Diabetes Care* 2013;36:858–64

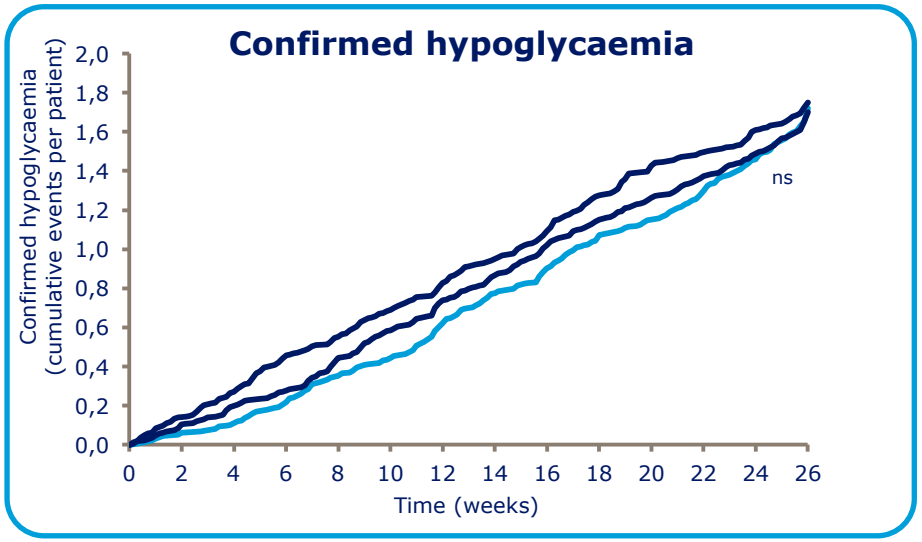
Flexible vs Fixed dosing in T2D: results

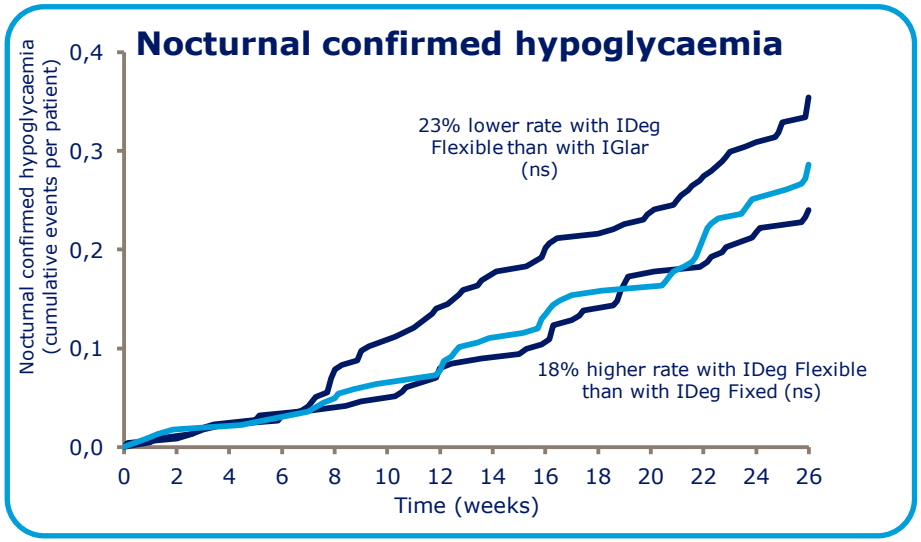
BEGIN FLEX T2D

IDeg Flexible OD IDeg Fixed OD IGlar OD





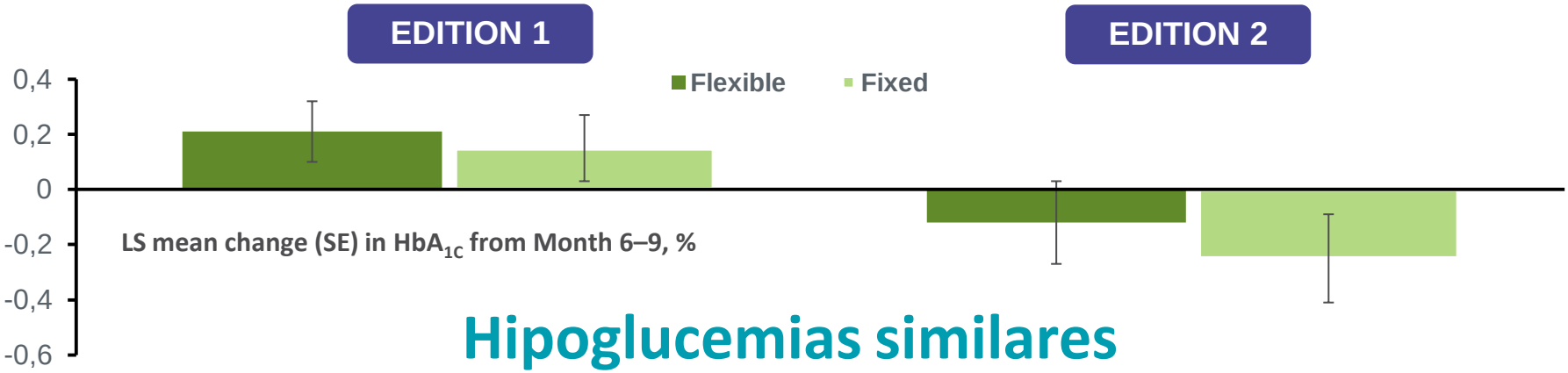




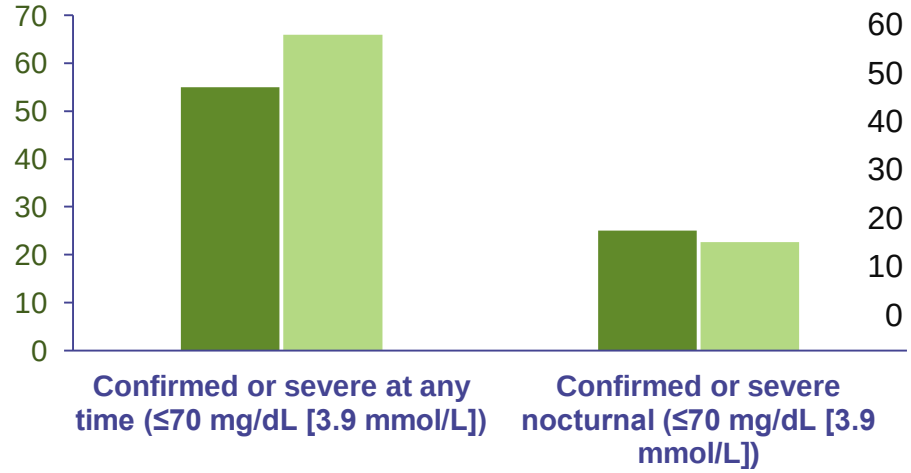
Meneghini *et al. Diabetes Care* 2013;36:858–64

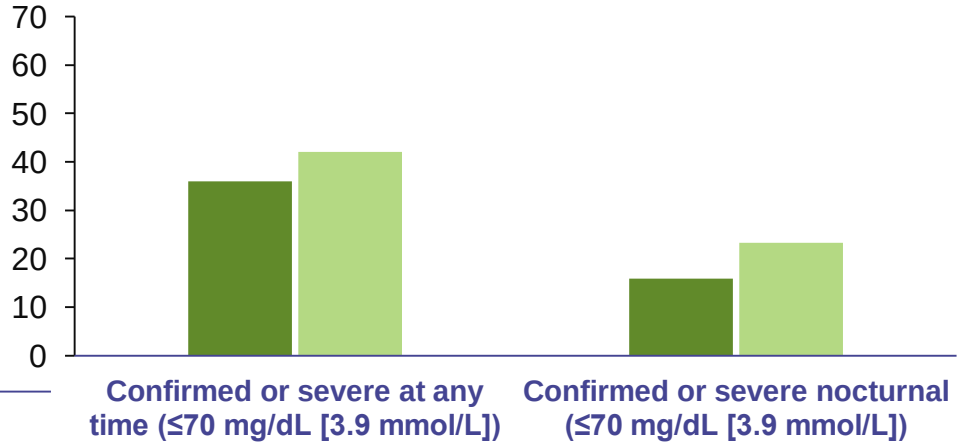
Dosificación flexible vs fija: EDITION 1 & 2 sub-estudios

Control glucémico similar con intervalos fijos de administración (24 h) vs intervalos flexibles (24 ± 3 h)



Hipoglucemias similares

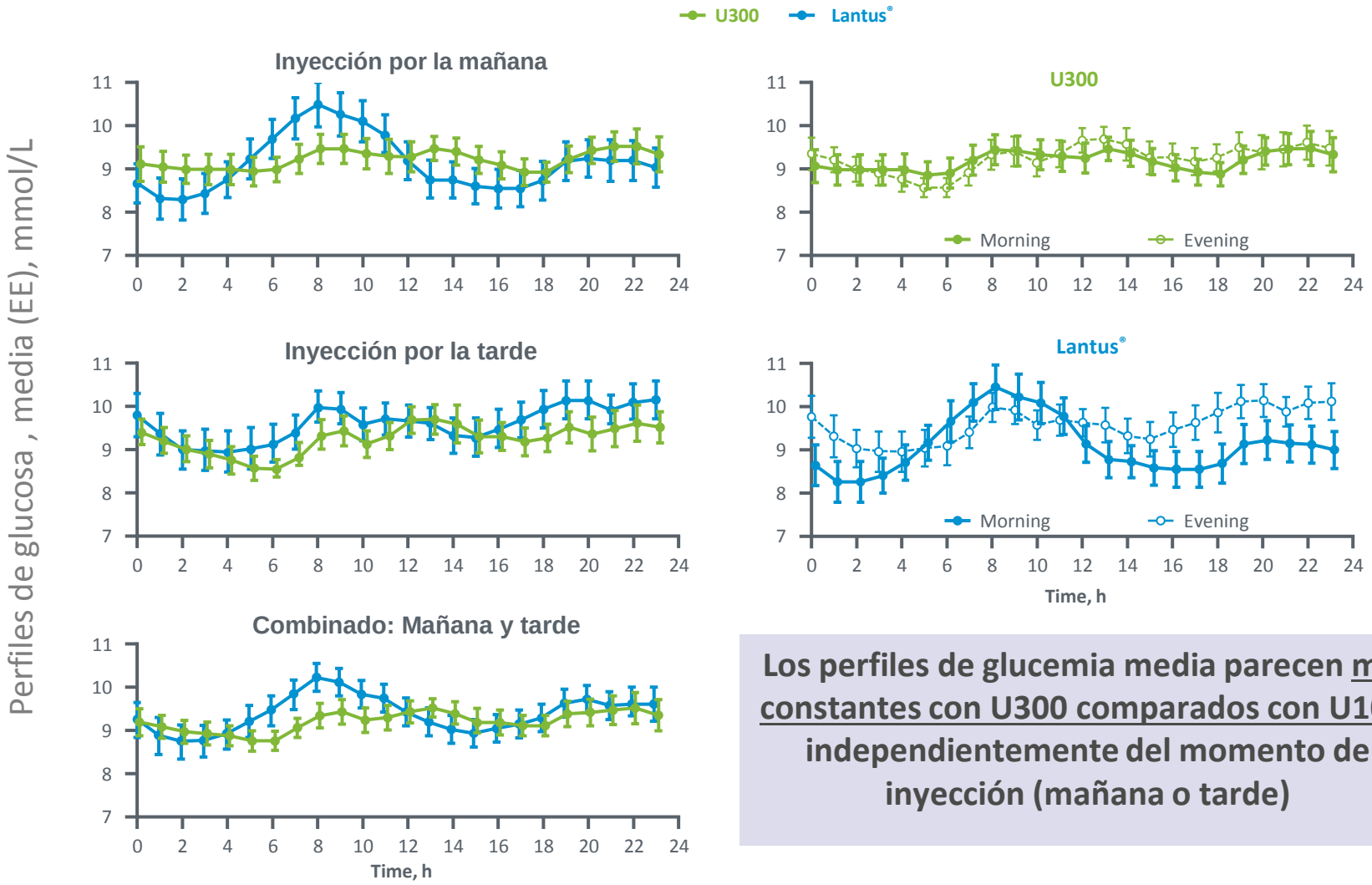




Jeandidier N et al. Poster presentation at EASD 2014; Abstract 961 Available at: http://www.easdvirtualmeeting.org/resources/18792 Accessed September 2014

Estudio PDY12777: monitorización continua glucosa DM1

Perfil de glucosa más constante con U300 vs U100



Los perfiles de glucemia media parecen <u>más constantes con U300 comparados con U100</u>, independientemente del momento de inyección (mañana o tarde)

Average 24-h glucose profiles during the last 2 weeks of each treatment period (CGM population; pooled data period A + B)
Bergenstal RM et al. Poster presentation at EASD 2014; Abstract 949 Available at: http://www.easdvirtualmeeting.org/resources/18574 Accessed September 2014