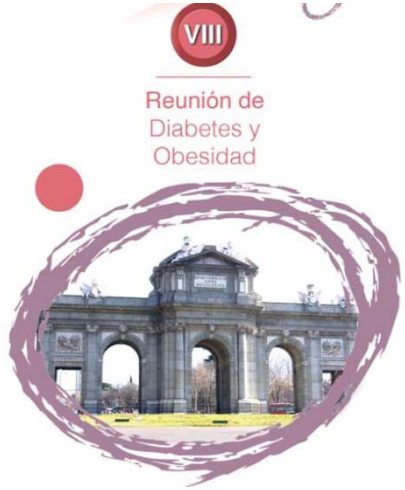
VIII REUNIÓN DIABETES Y OBESIDAD

MESA 2: NOVEDADES TERAPÉUTICAS EN DIABETES



Insulin Degludec

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Madrid, 1 de Febrero 2014

Conflicto de intereses

- FJ. Ampudia-Blasco ha recibido honorarios como ponente y/o asesor de Lilly, Novo Nordisk y sanofi-aventis.

- Además, el Dr. Ampudia-Blasco ha participado en ensayos clínicos financiados total o parcialmente por Lilly, Novo Nordisk y sanofi-aventis.

- El Dr. Ampudia-Blasco declara no ser empleado ni tener acciones de ninguna de las compañías mencionadas previamente.

‘Peaks and Troughs’ in Daily Glucose Profiles

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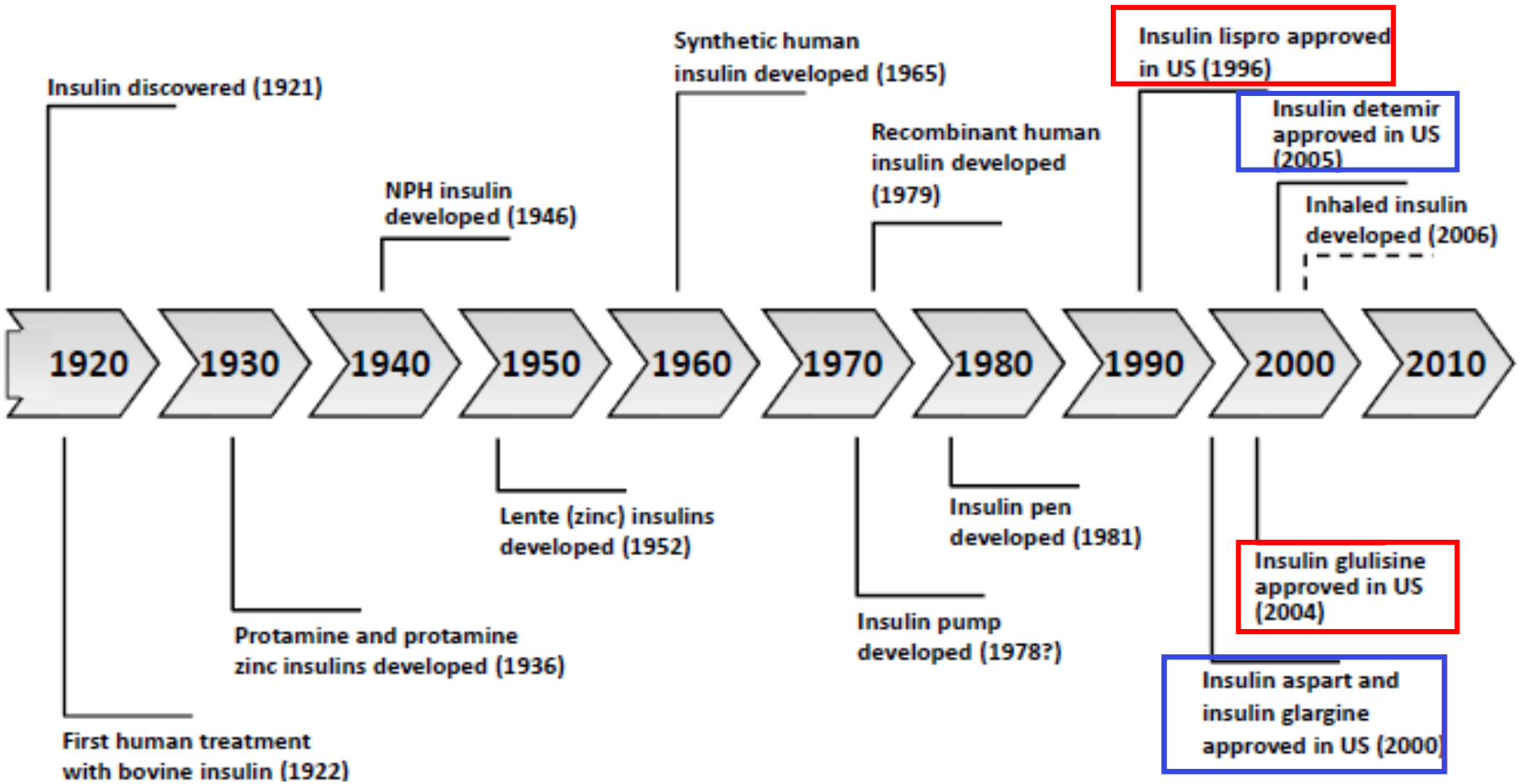
Milestones in Insulin Development



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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.

The question is:

Do we need new basal insulins?

Will the next generation of basal insulins offer clinical advantages?

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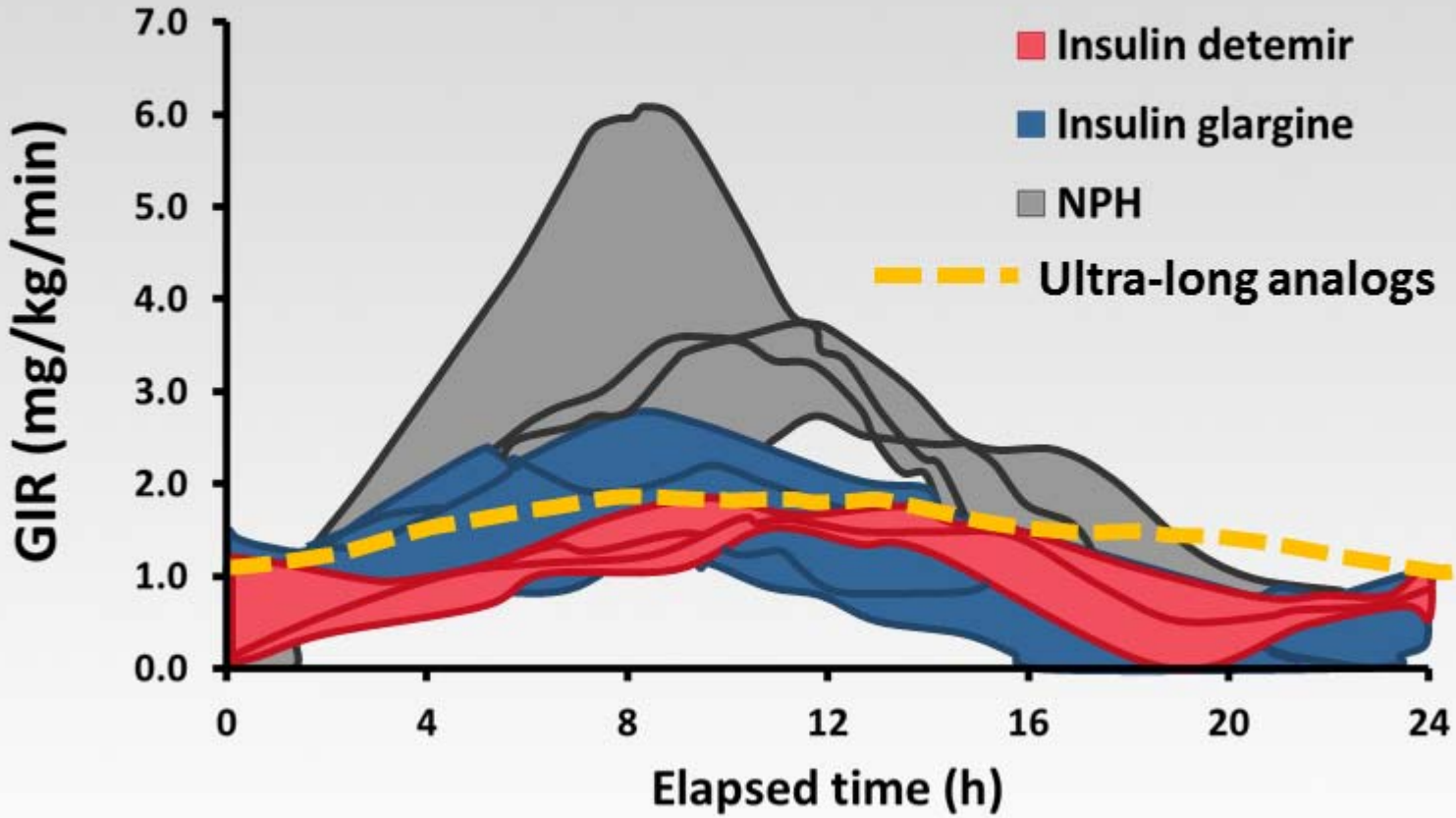
Agenda

- Limitations of existing basal insulins
- Degludec - next generation of basal insulins:
  - Phase III development program
  - Flexibility studies
  - Future combinations

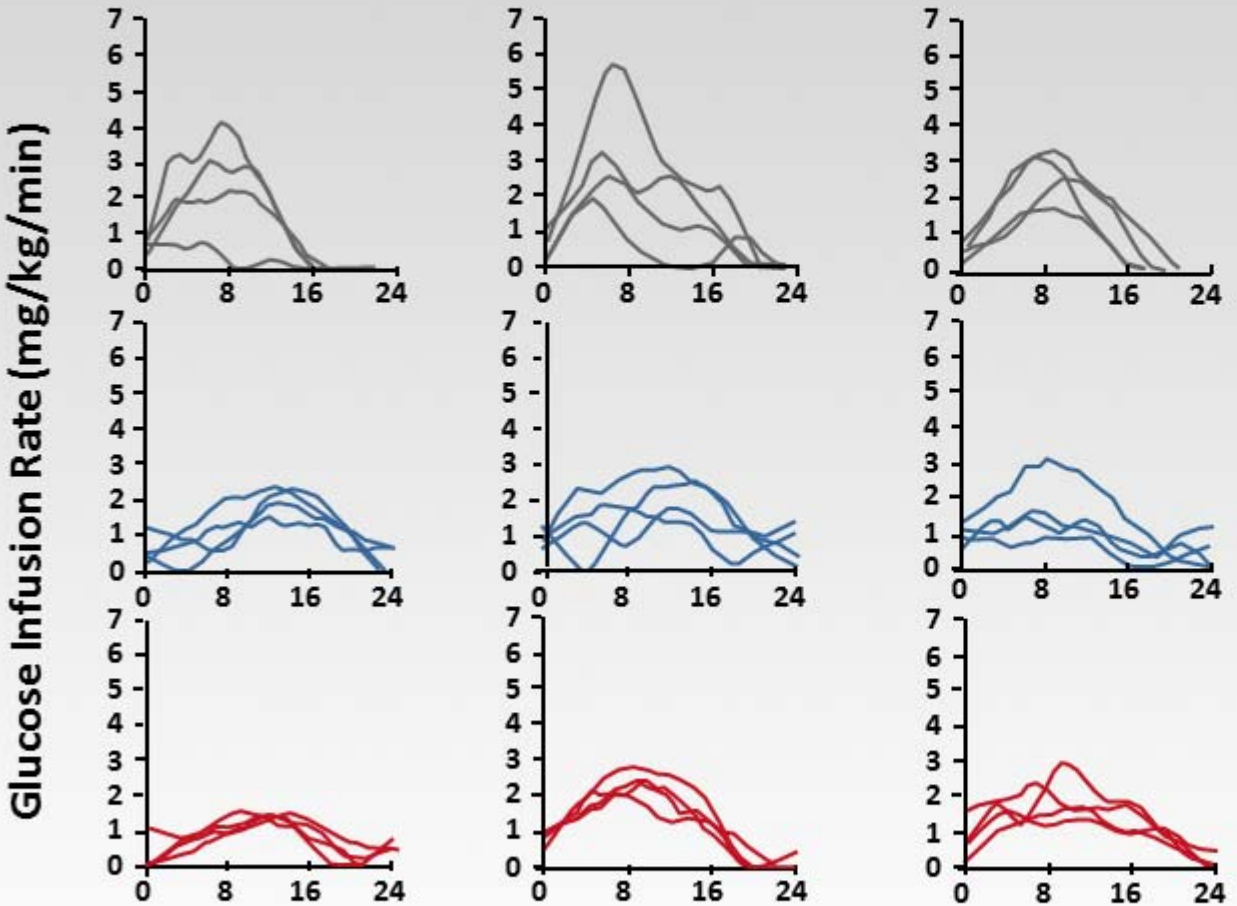
Biologic Activity over 24 Hours: More Consistent for Basal Insulin Analogs

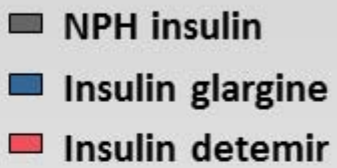


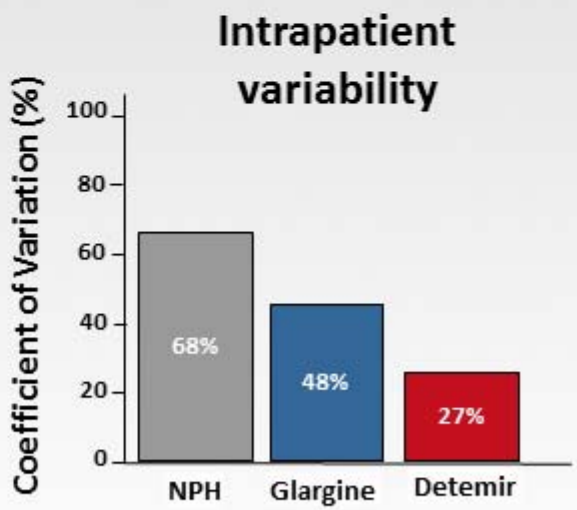
GIR = glucose infusion rate

Adapted from Heise T, et al. *Diabetes.* 2004;53(6):1614-1620.

Profiles of Current Basal Insulins:
Too Short, Still Peaked, and Variable







From Heise T, et al. *Diabetes.* 2004;53(6):1614-1620.

Revisiting the ideal basal insulin: Key characteristics

Longer duration of action	→	Control fasting blood glucose with one injection per day in all individuals
Flat time–action profile	→	Lower risk of hypoglycaemia
Less day-to-day variability	→	Potential for titration to lower FPG target without hypoglycaemia

Agenda

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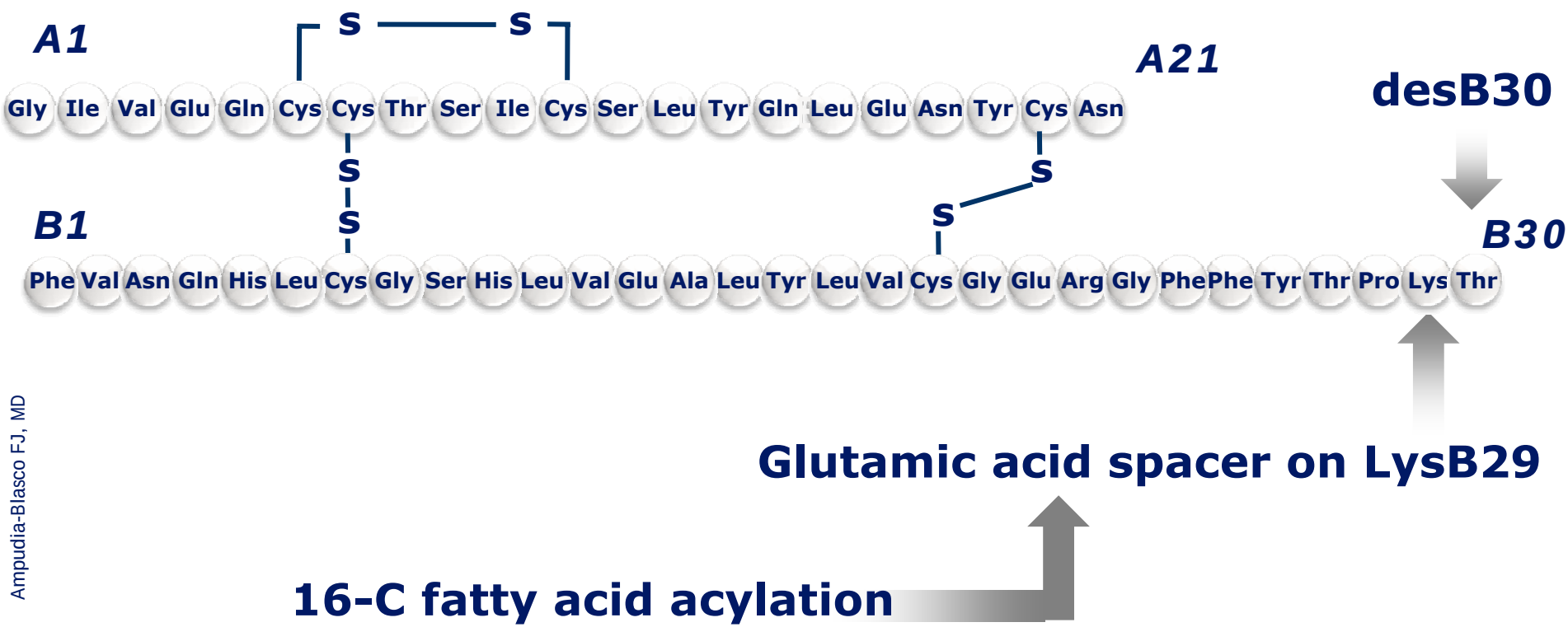
Insulin degludec: estructure



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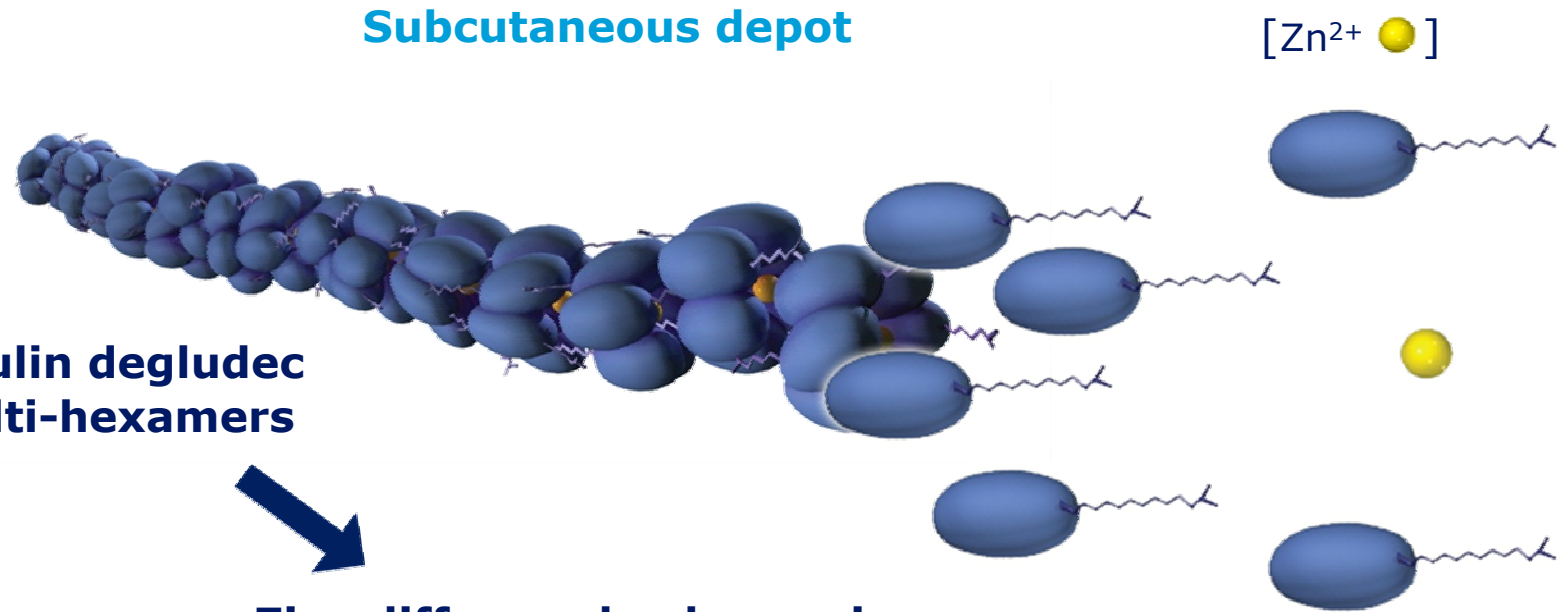
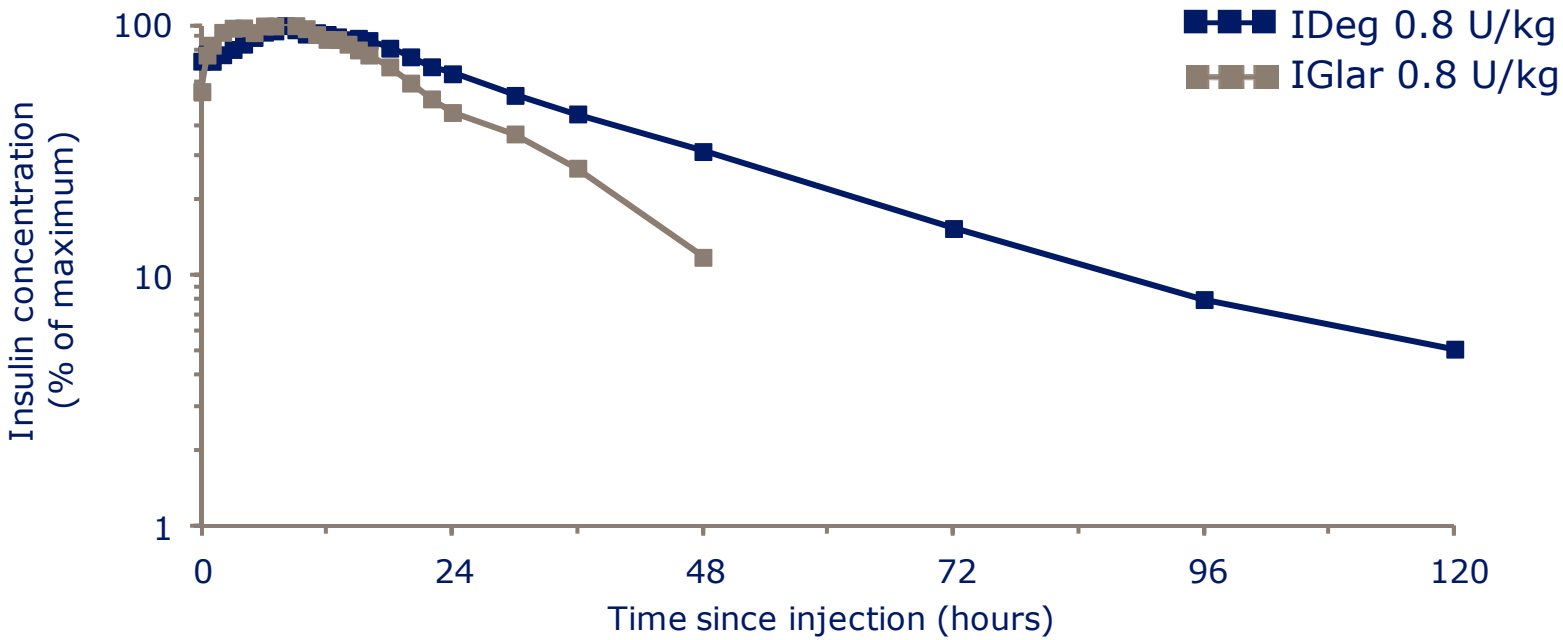
Meneghini *et al. Expert Rev. Endocrinol. Metab.* 2012; 7:9–14

Insulin degludec: slow release following injection



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

PK profile and half-life of insulin degludec and insulin glargine in Type 1



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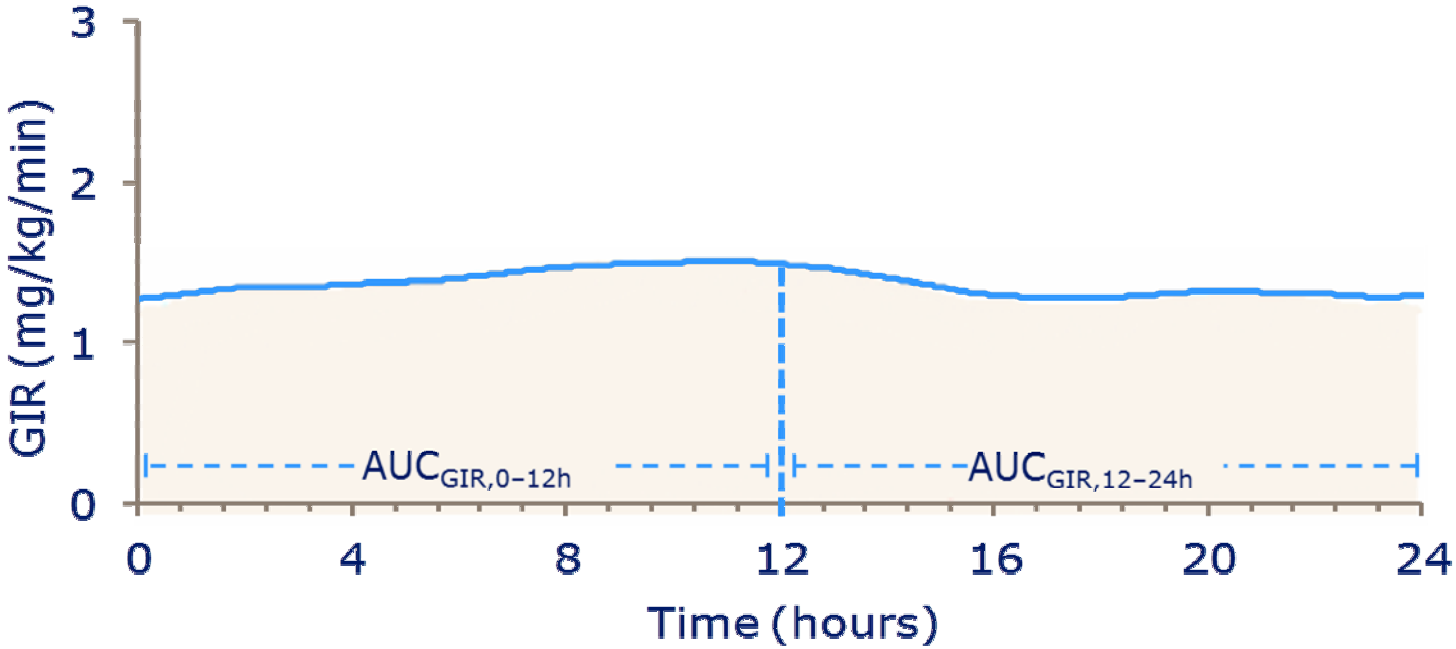
	IDeg			IGlar		
	0.4 U/kg	**0.6 U/kg**	**0.8 U/kg**	**0.4 U/kg**	**0.6 U/kg**	**0.8 U/kg**
Half-life (hours)	25.9	27.0	23.9	11.8	14.0	11.9
Mean half-life	**25.4**			**12.5**		

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

Insulin degludec in T2DM at steady state

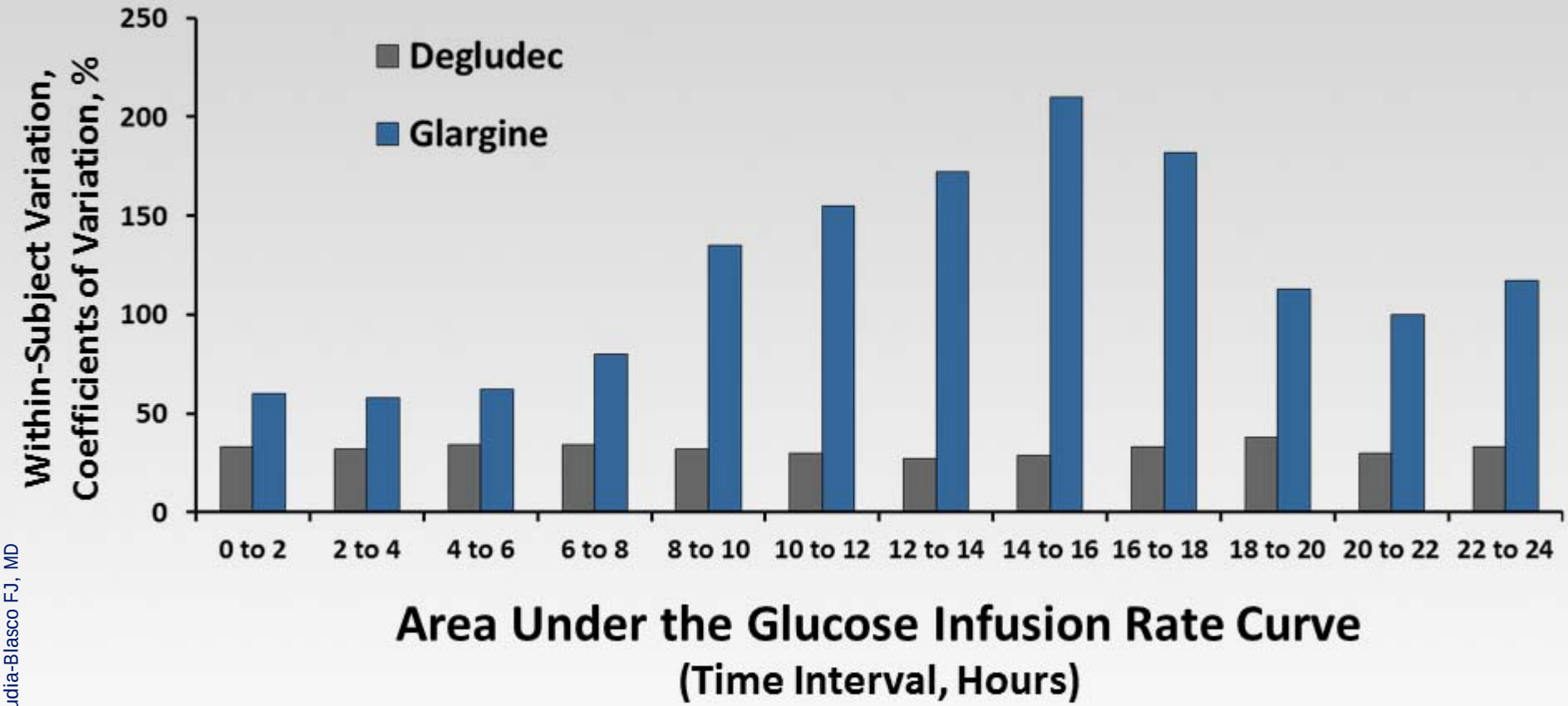


	0.4 U/kg (n=22)	0.6 U/kg (n=37)	0.8 U/kg (n=21)
$AUC_{GIR,0-12h}/AUC_{GIR,T}$ (%)	48.9	53.0	50.4

AUC: area under the curve
$AUC_{GIR,T}$, total area under the GIR curve over a 24-hour dosing interval at steady state

Nosek *et al.* IDF 2011:P-1452; *Diabetologia* 2011;54 (Suppl. 1):S429 (1055-P); *Diabetes* 2011;60 (Suppl. 1A):LB14

Pharmacodynamic Variability of Degludec



Ampudia-Blasco FJ, MD

Heise *et al. Diabetes Obes Metab. 2012*:14;859-64

Agenda

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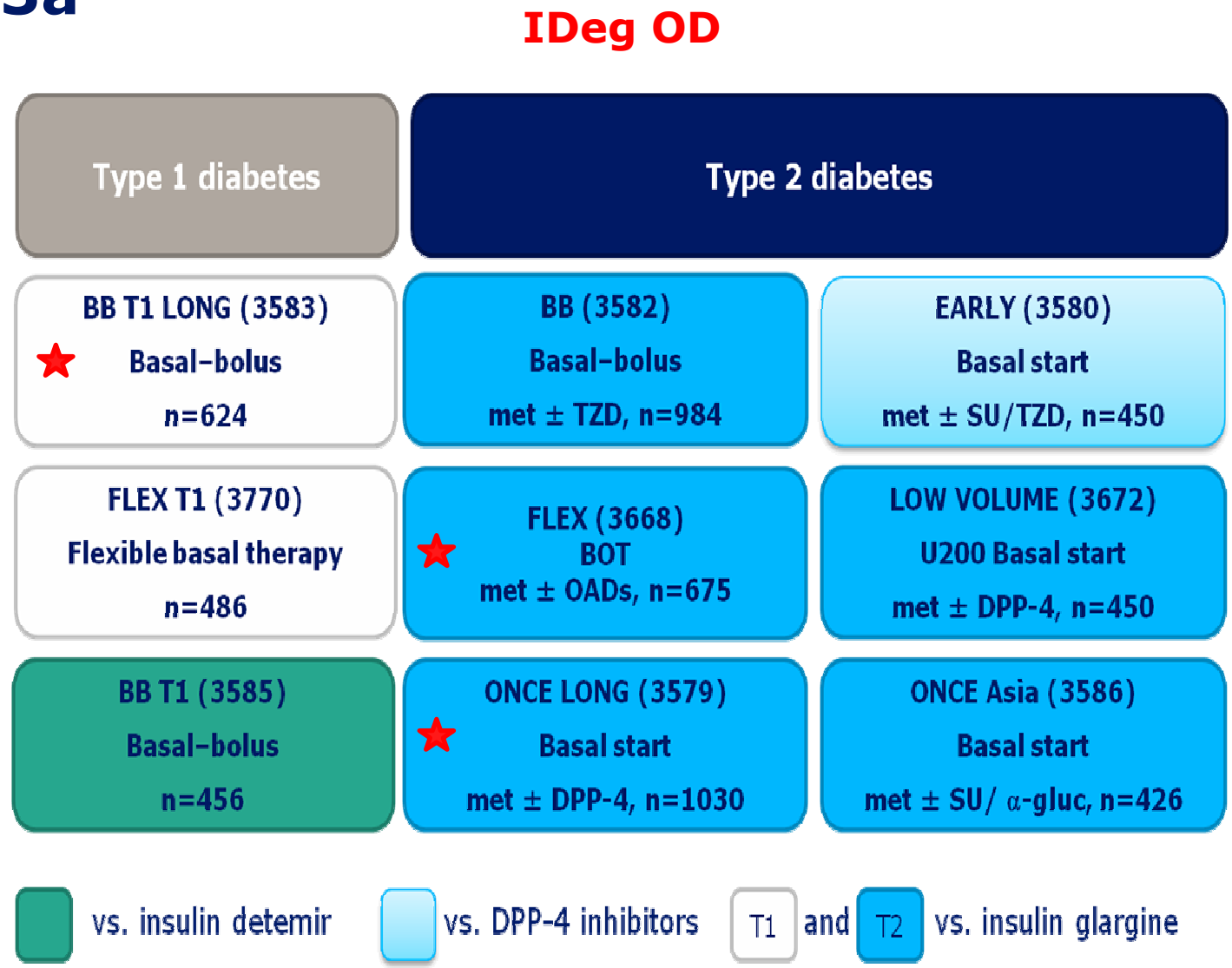
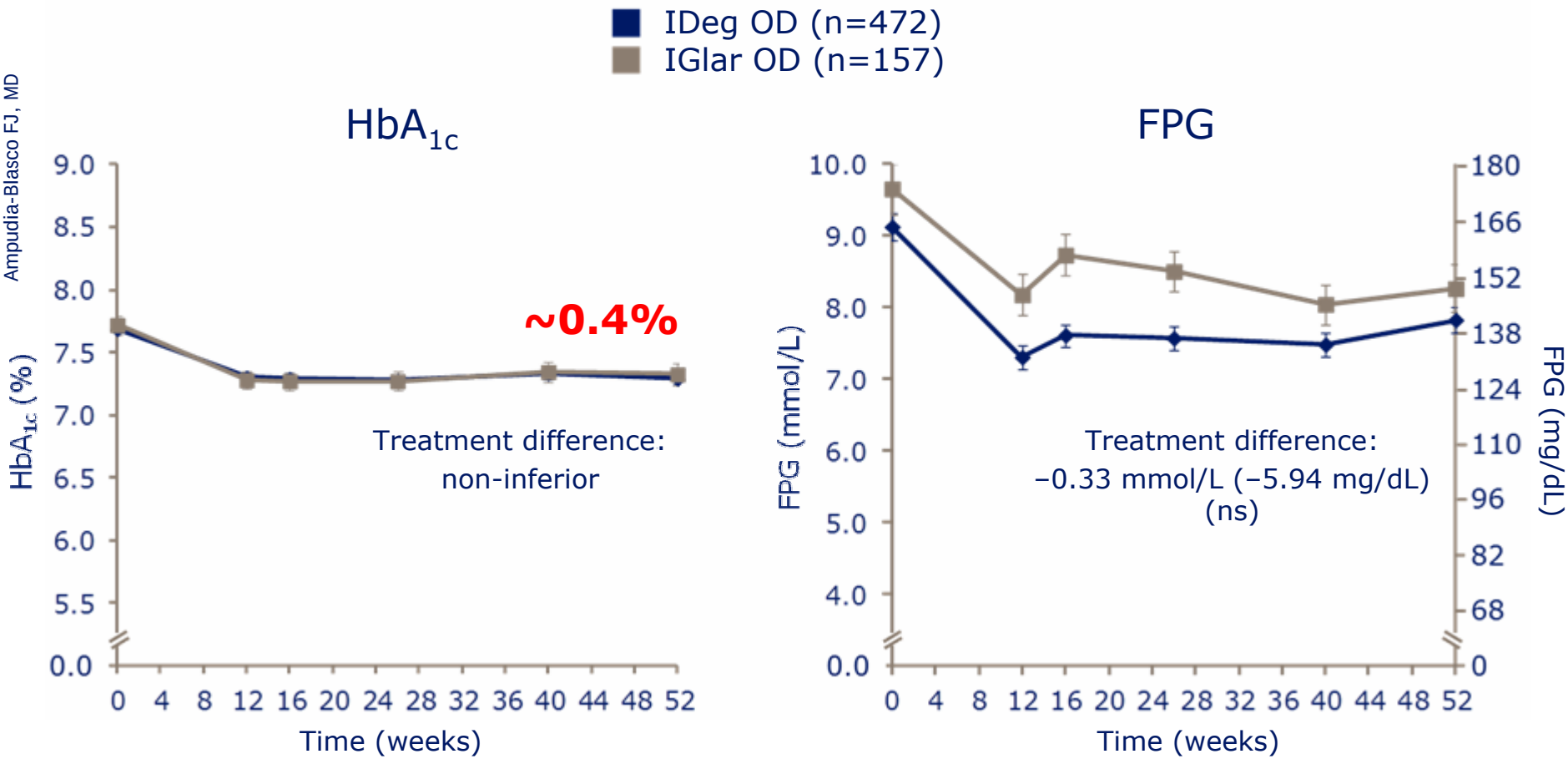
Degludec once-daily phase 3a



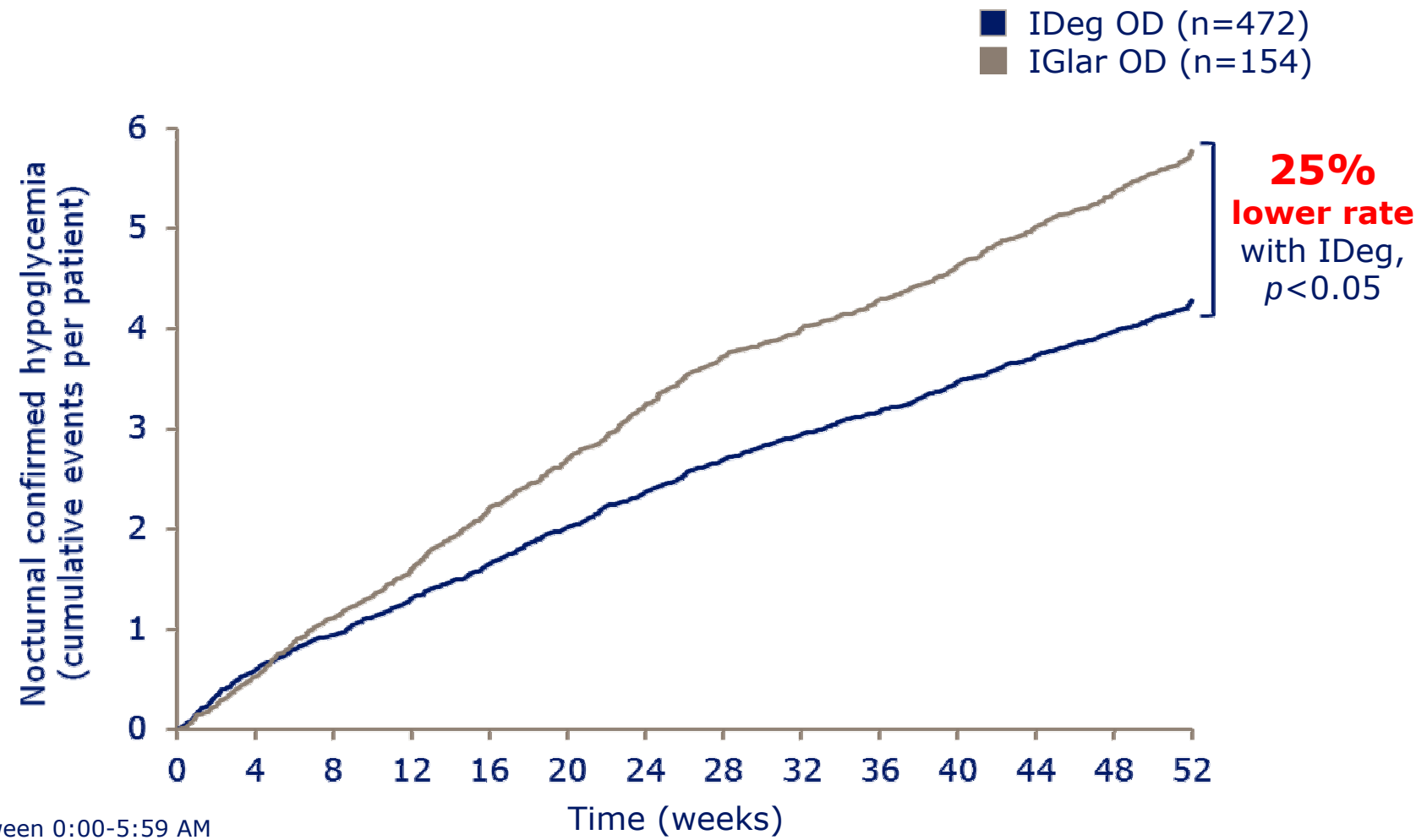
BEGIN® BB T1 LONG – HbA_{1c} and FPG over time



Mean±SEM; FAS; LOCF
Comparisons: estimates adjusted for multiple covariates

Heller *et al. Lancet* 2012;379:1489–97

BEGIN® BB T1 LONG
Nocturnal confirmed hypoglycemia*

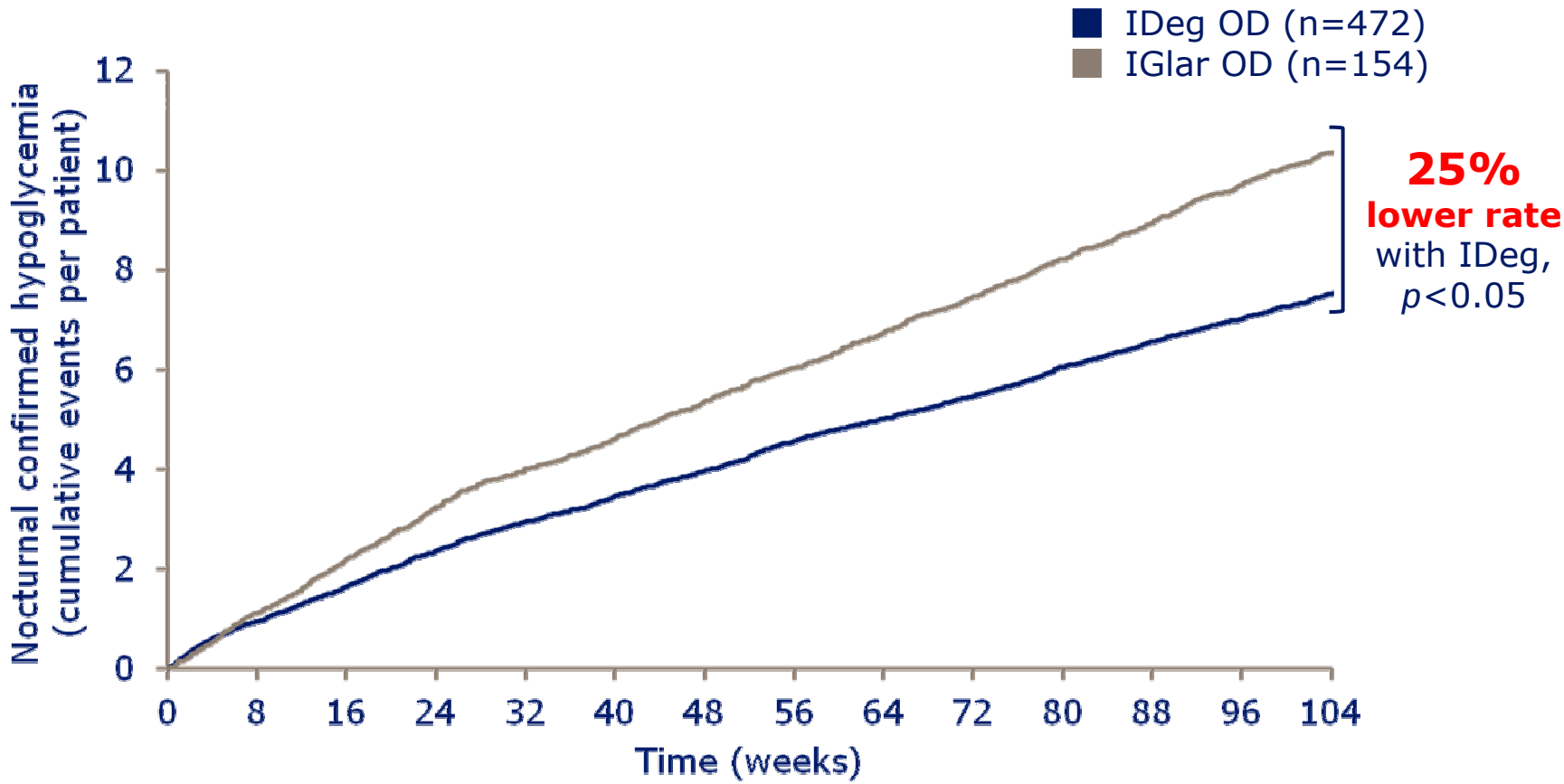


* Between 0:00-5:59 AM

SAS
Comparisons: estimates adjusted for multiple covariates

Heller *et al. Lancet* 2012;379:1489-97

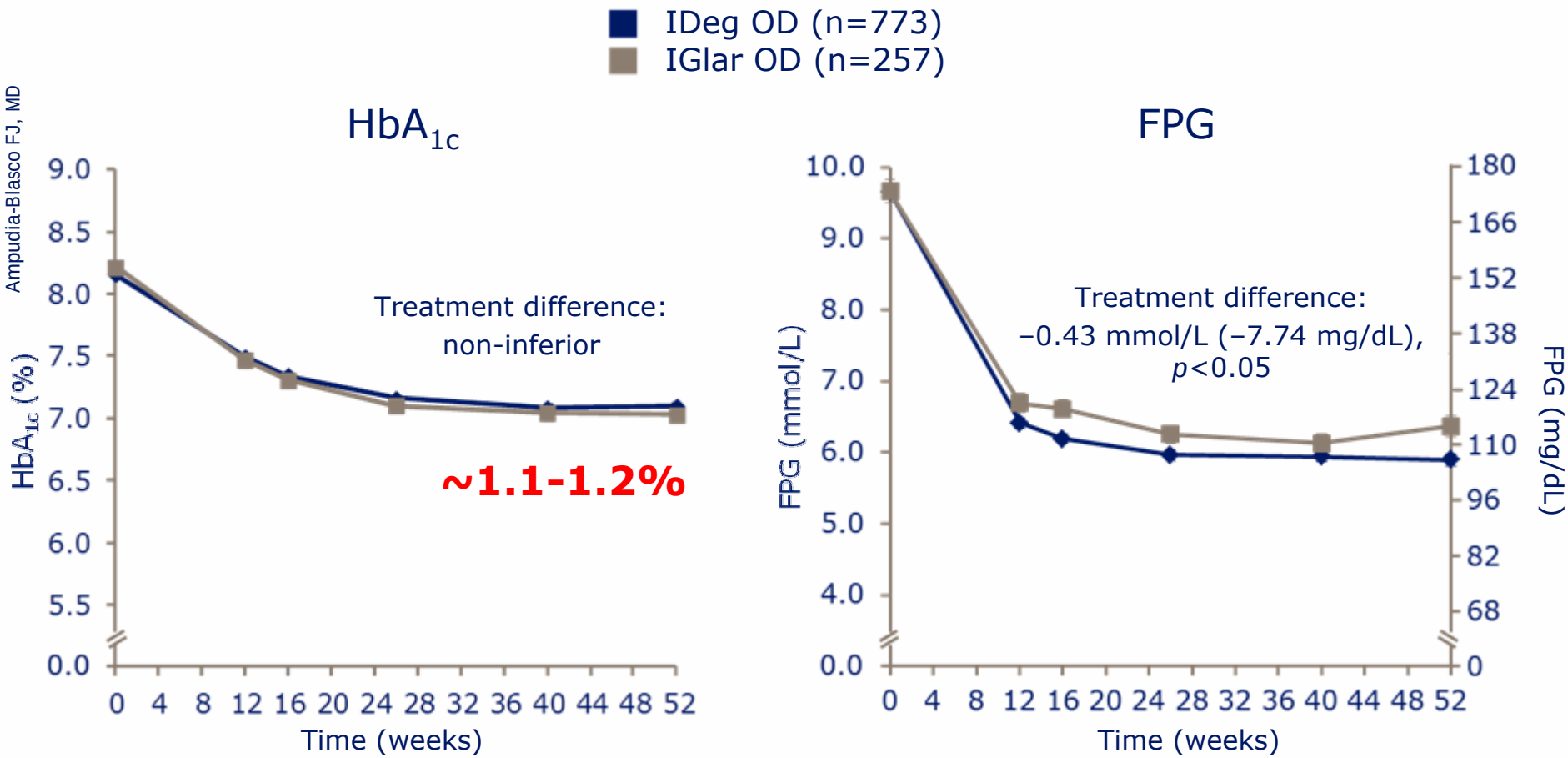
BB T1 extension: nocturnal confirmed hypoglycemia



SAS
Comparisons: Estimates adjusted for multiple covariates
NN1250-3644; IDeg basal–bolus in T1DM extension

Bode *et al. Diabet Med.* 2013; 30:1293-7

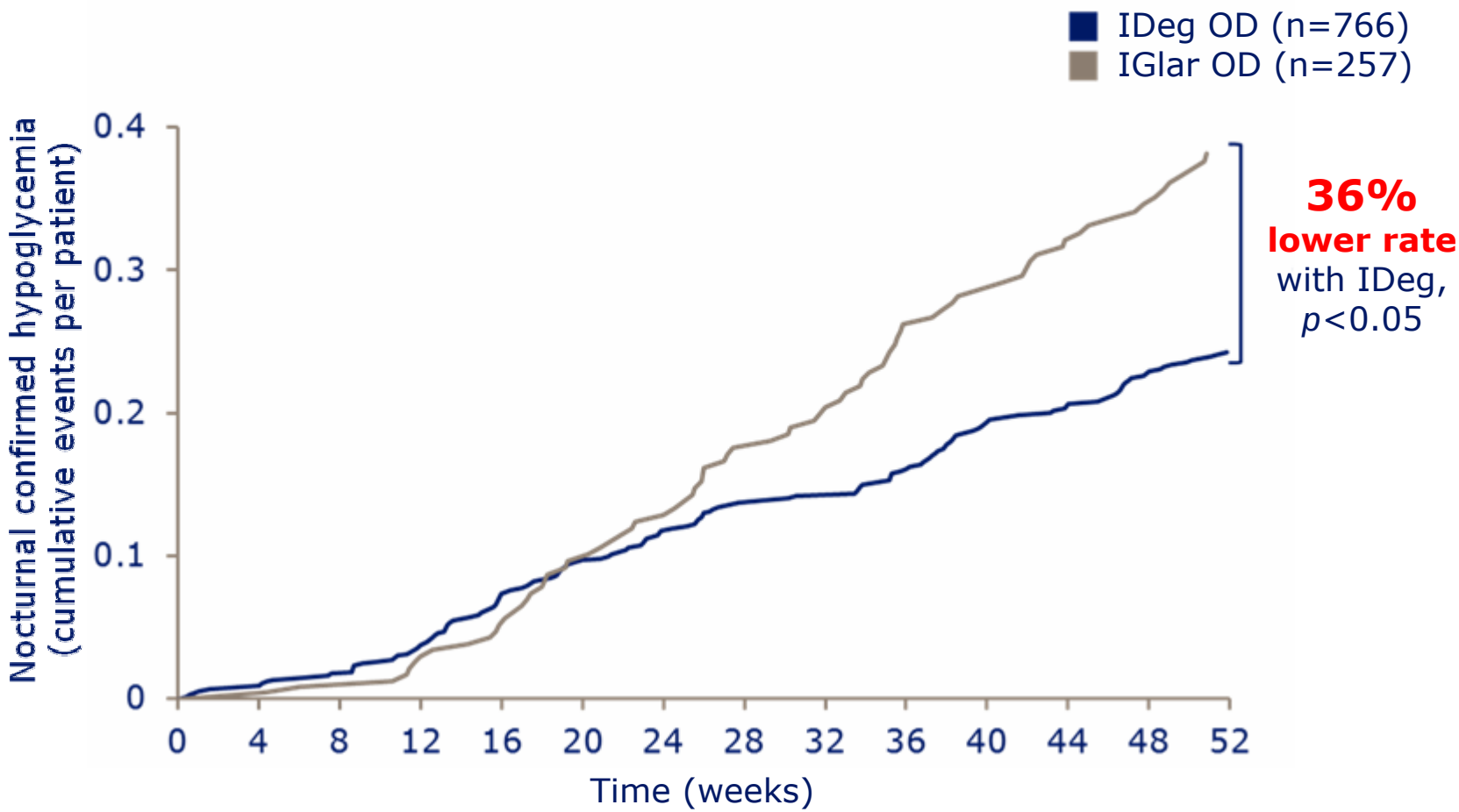
BEGIN® ONCE LONG – HbA_{1c} and FPG over time



Mean±SEM; FAS, full analysis set; LOCF, last observation carried forward
Comparisons: estimates adjusted for multiple covariates

Zinman *et al. Diabetes Care.* 2012;35:2464-71

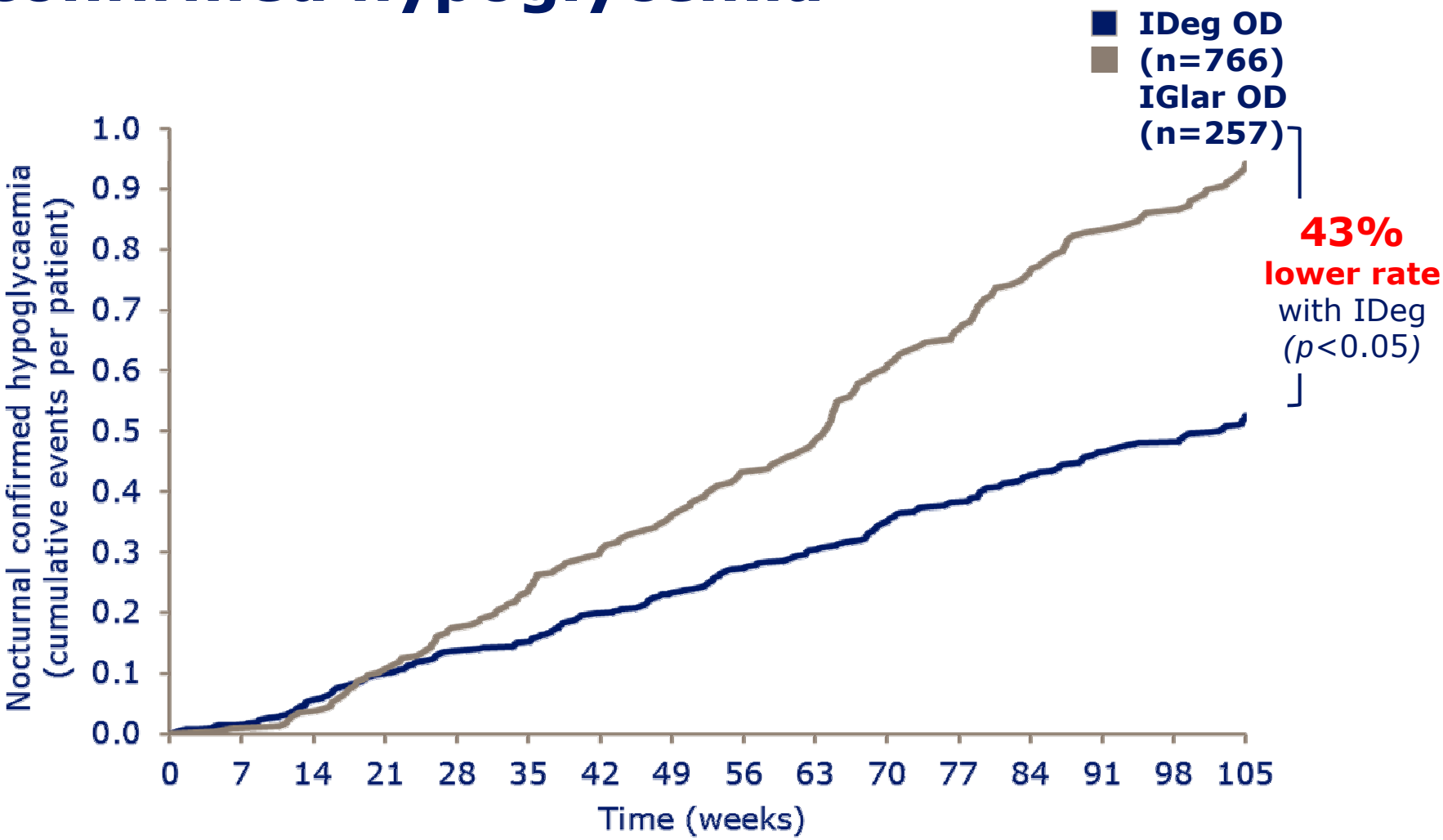
BEGIN® ONCE LONG – nocturnal confirmed hypoglycemia



SAS
Comparisons: estimates adjusted for multiple covariates

Zinman *et al. Diabetes Care.* 2012;35:2464-71

ONCE LONG extension: nocturnal confirmed hypoglycemia



SAS:Safety analysis set
Comparisons: Estimates adjusted for multiple covariates
NN1250-3643; IDeg OD vs IGlar OD in T2DM extension

Rodbard *et al. Diabet Med.* 2013; 30:1298-304.

Agenda

- Limitations of existing basal insulins
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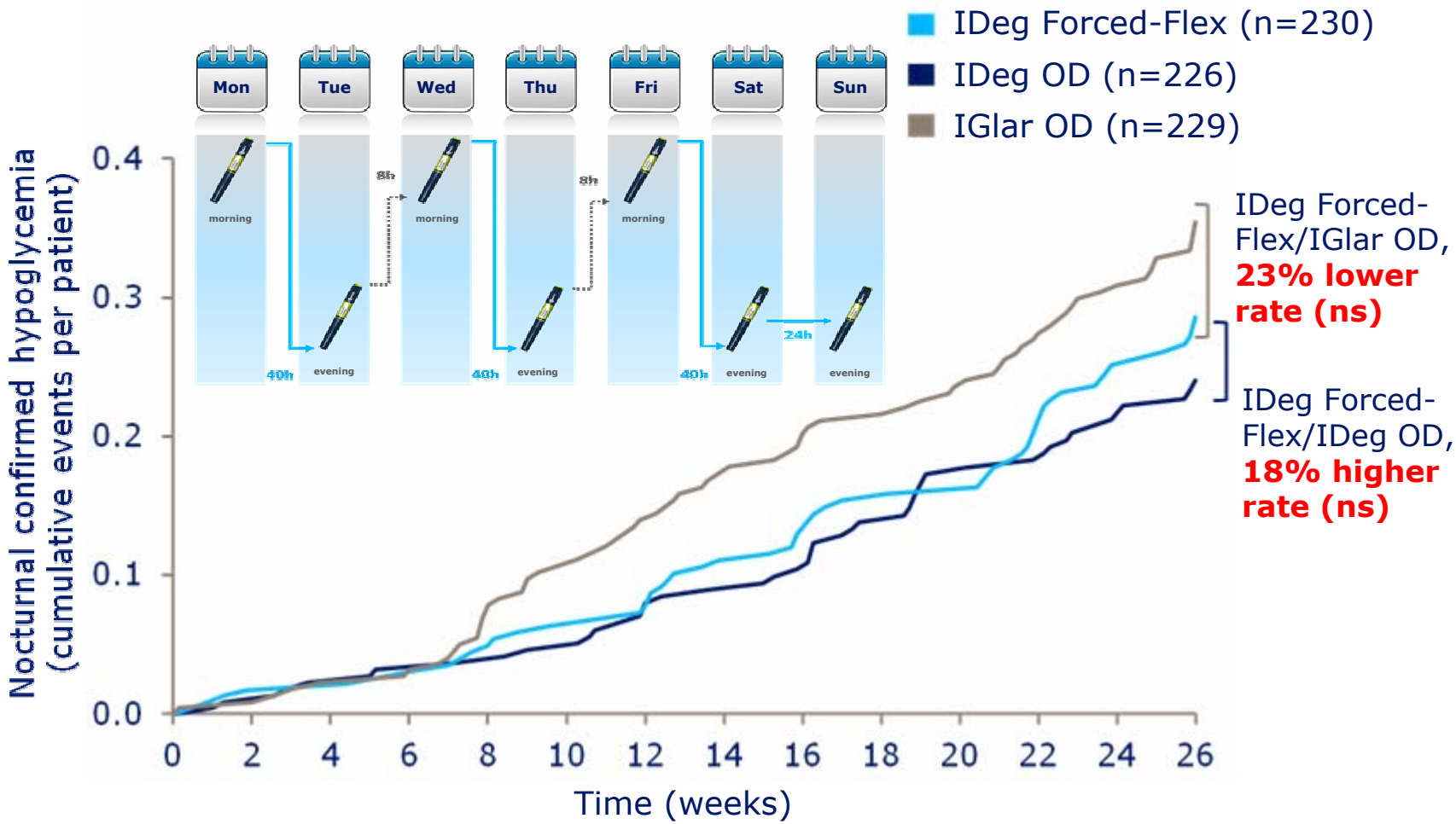
BEGIN® Flex – nocturnal confirmed hypoglycemia



SAS
Comparisons: estimates adjusted for multiple covariates

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

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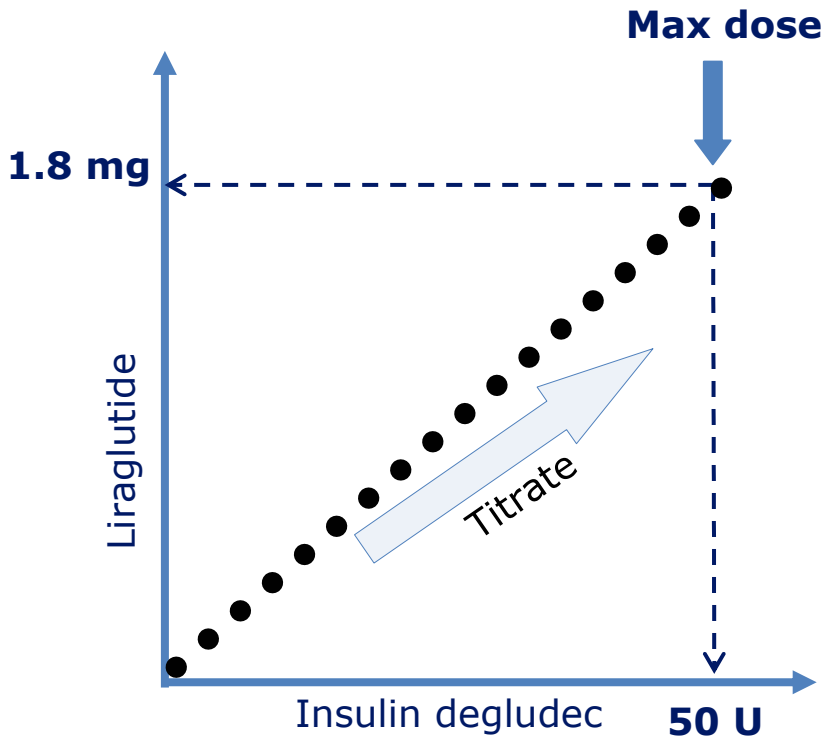
IDegLira – combination in a single daily injection

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

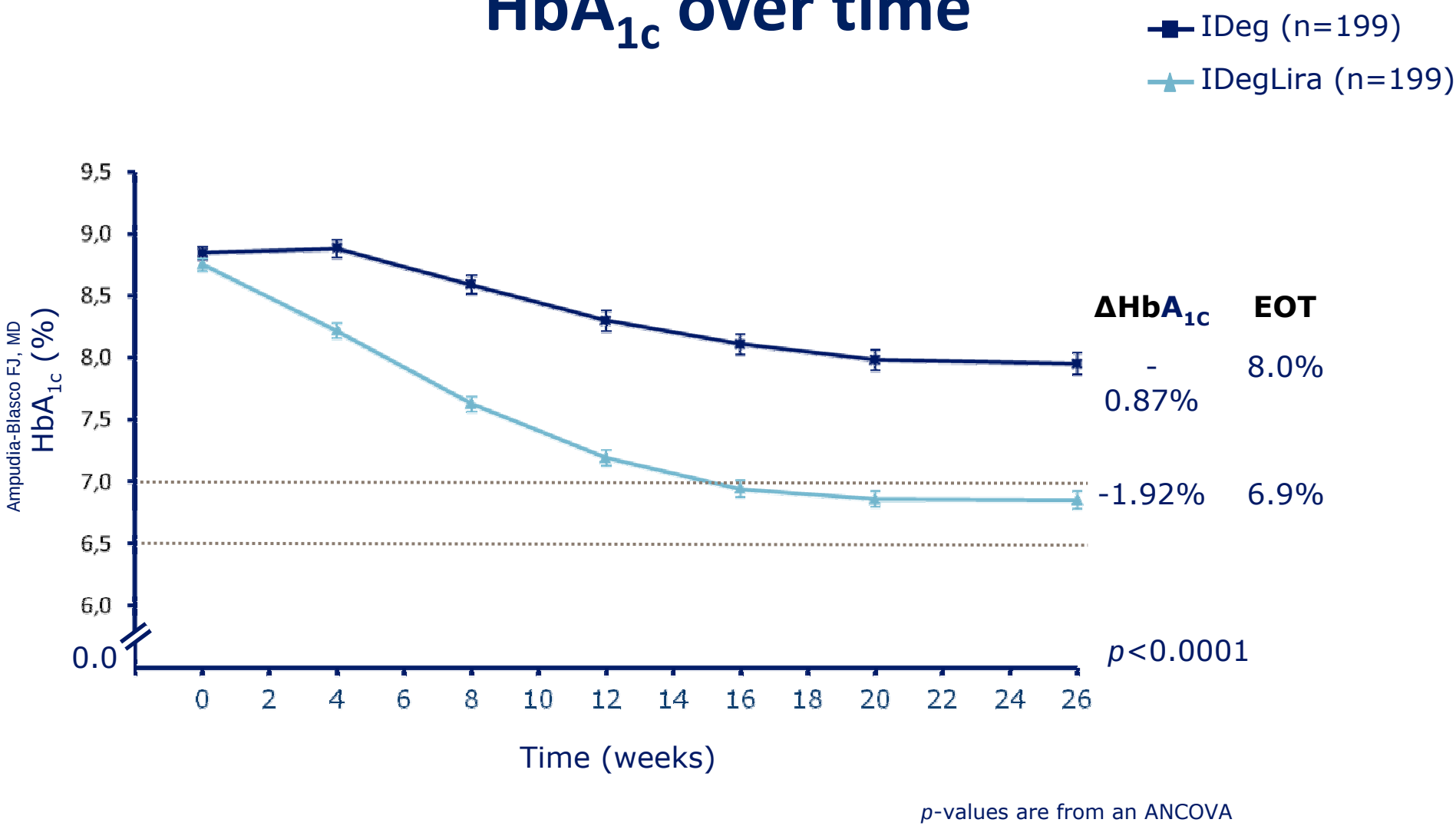


Insulin titration to achieve glycemic control

50 dose steps

50 U IDeg + 1.8 mg liraglutide

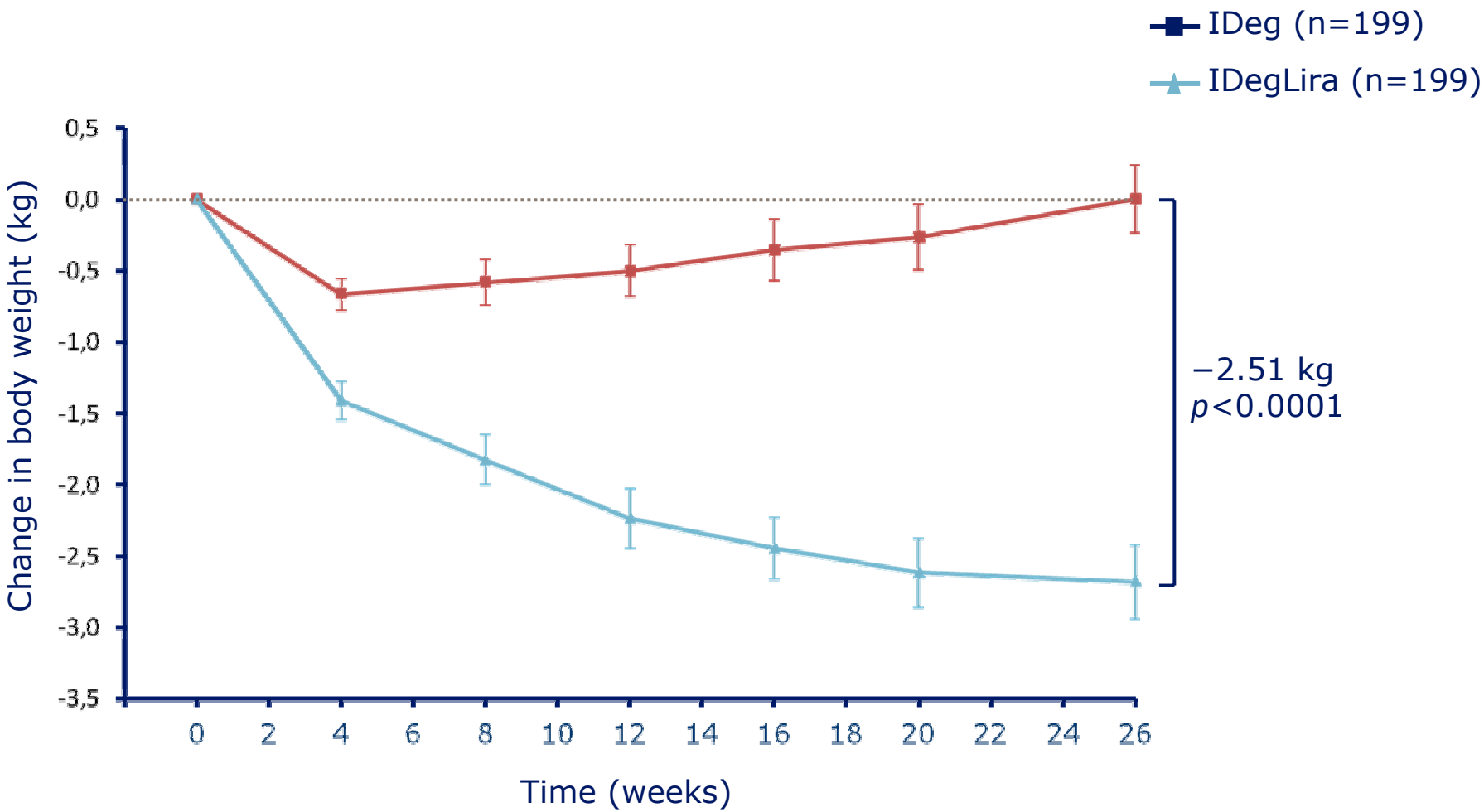
HbA_{1c} over time



p-values are from an ANCOVA

Mean values with error bars (standard error mean) based on FAS and LOCF imputed data;
AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association,
EASD, European Association for the Study of Diabetes; EOT, end of trial
--- ADA/EASD HbA_{1c} target <7.0%; AACE HbA_{1c} target ≤6.5%

Change in body weight over time



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Mean values with error bars (standard error mean) based on FAS and LOCF imputed data
Estimated treatment differences an *p*-values are from an ANCOVA analysis

Why do we Need Better Basal Insulins?

- Aunque glargina y detemir representan una mejora importante frente a NPH, muchos pacientes con diabetes no consiguen alcanzar los objetivos glucémicos.
- Idealmente, una insulina basal debe tener un perfil farmacocinético plano y sin picos, con una tasa estable y fiable de absorción y un perfil de acción más allá de las 24 h.
- Degludec representa una nueva generación análogos de insulina de acción prolongada. Degludec reduce aún más el riesgo de hipoglucemia (nocturna), aunque esta reducción sea de pequeña magnitud en comparación con glargina.
- Por su larga duración, degludec puede resultar beneficiosa además en aquellos pacientes que requieran una mayor flexibilidad en el momento de administración.

Be not afraid of going slowly, be afraid only of standing still

Chinese Proverb