



# XXXII Congreso Nacional de la SEMI

XIV Congreso de la Sociedad Canaria de Medicina Interna  
26-28 Octubre 2011



## Agonistas del Receptor de GLP-1 en el tratamiento de la diabetes mellitus tipo 2

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**Costa Meloneras**

Palacio de Congresos Expomeloneras  
Maspalomas, San Bartolomé de Tirajana  
Gran Canaria, Las Palmas

# Conflictos de interés

- Comités de asesoramiento internacional: Lilly, Novartis
- Comités de asesoramiento nacional: Lilly, Novartis, Novo-Nordisk, Sanofi-Aventis
- Conferencias: Lilly, Novo-Nordisk

# Opciones Terapéuticas en la Diabetes Tipo 2 hasta el 2012



**Inhibidores de DPP-4**  
**Agonistas del R de GLP-1**

**Detemir**

**Aspart**

**Glargina**

**Glinidas**

**Glitazonas**

**Lispro**

**Metformina**

**Insulina Humana**

**Sulfonilureas**

**Insulina animal**

1922

1950's

1982-5

1995

1996

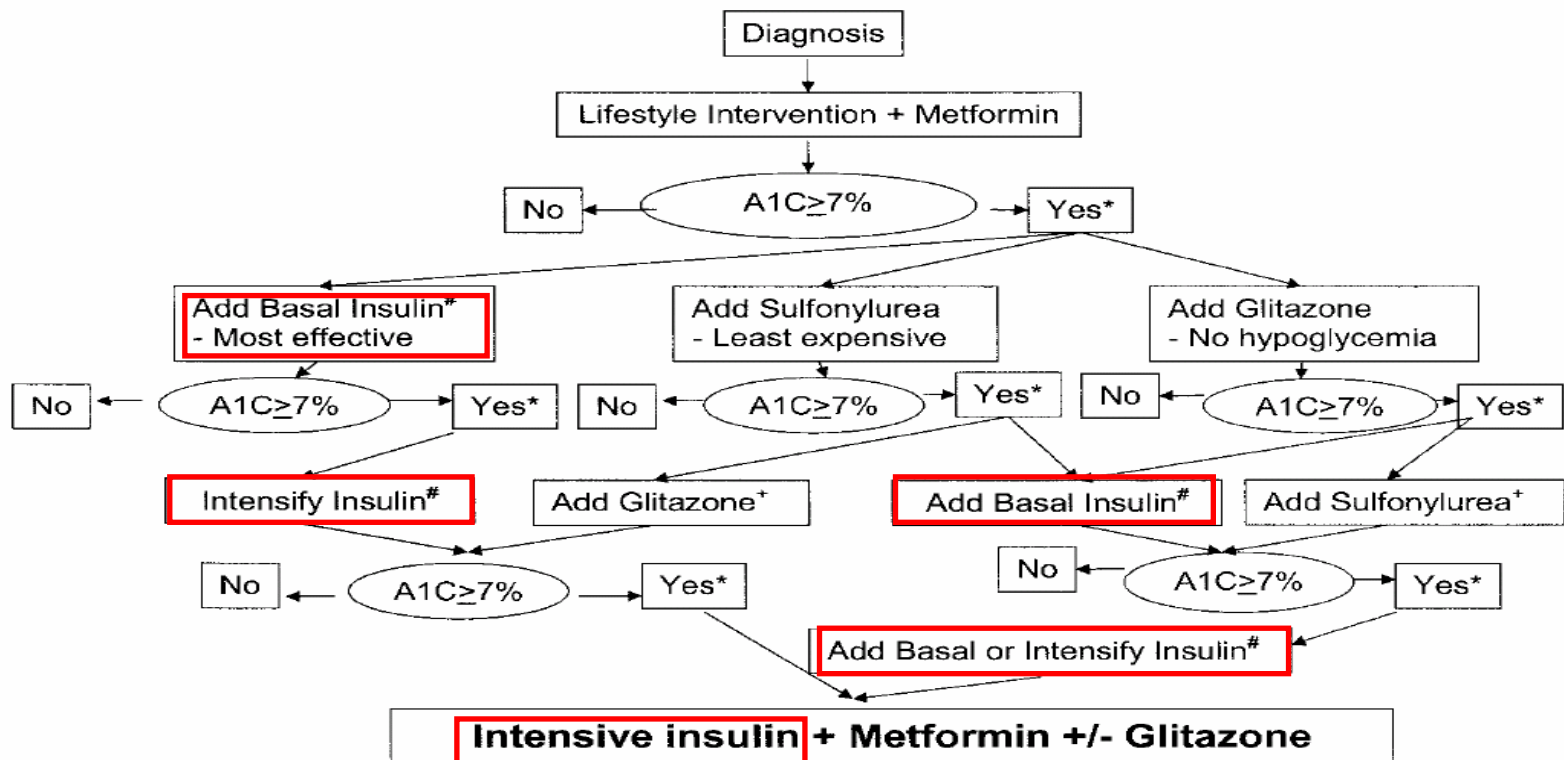
2001

2003 →

# Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

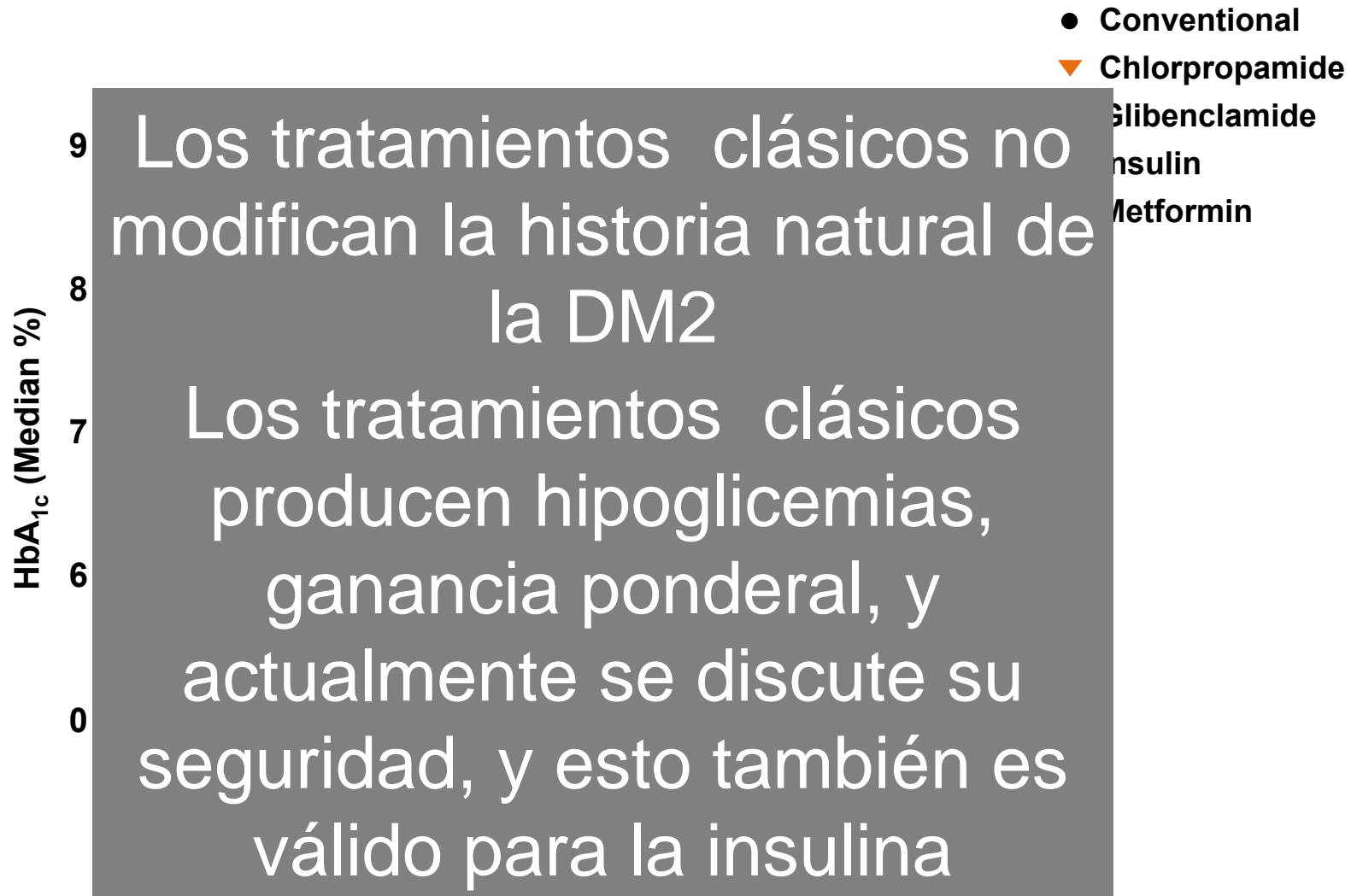
A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes 2006

*Management of hyperglycemia in type 2 diabetes*

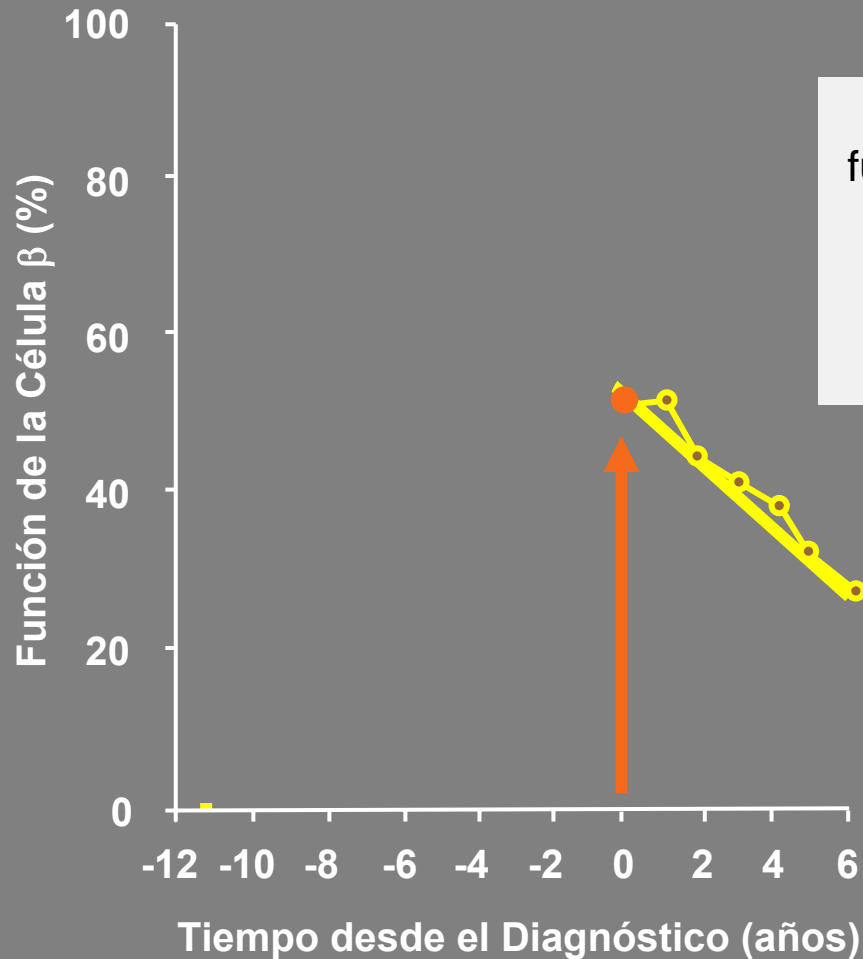


# La DM2 es una enfermedad progresiva: UKPDS 6-Year Data

(y tampoco la terapia insulínica)



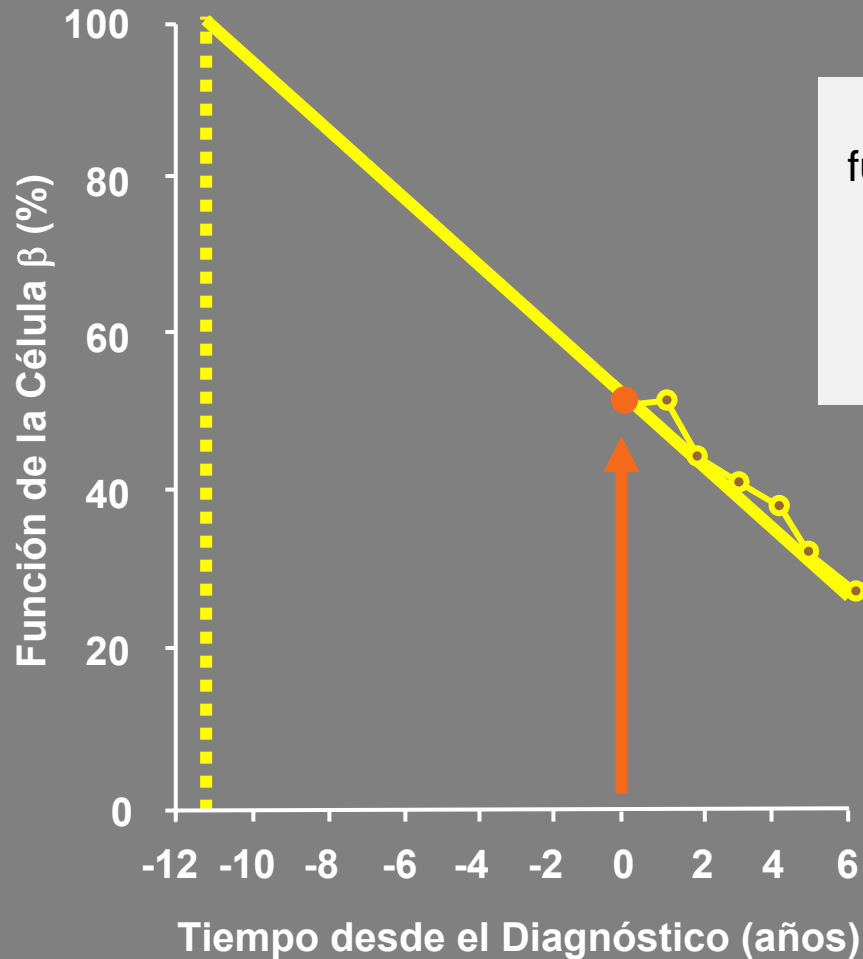
# La función de la célula $\beta$ disminuye a lo largo del tiempo en pacientes con Diabetes Tipo 2



Es posible que la función de la célula  $\beta$  ya haya disminuido en un 50% en el momento del diagnóstico

La función de la célula  $\beta$  disminuye progresivamente con el tiempo aproximadamente un 6% por año

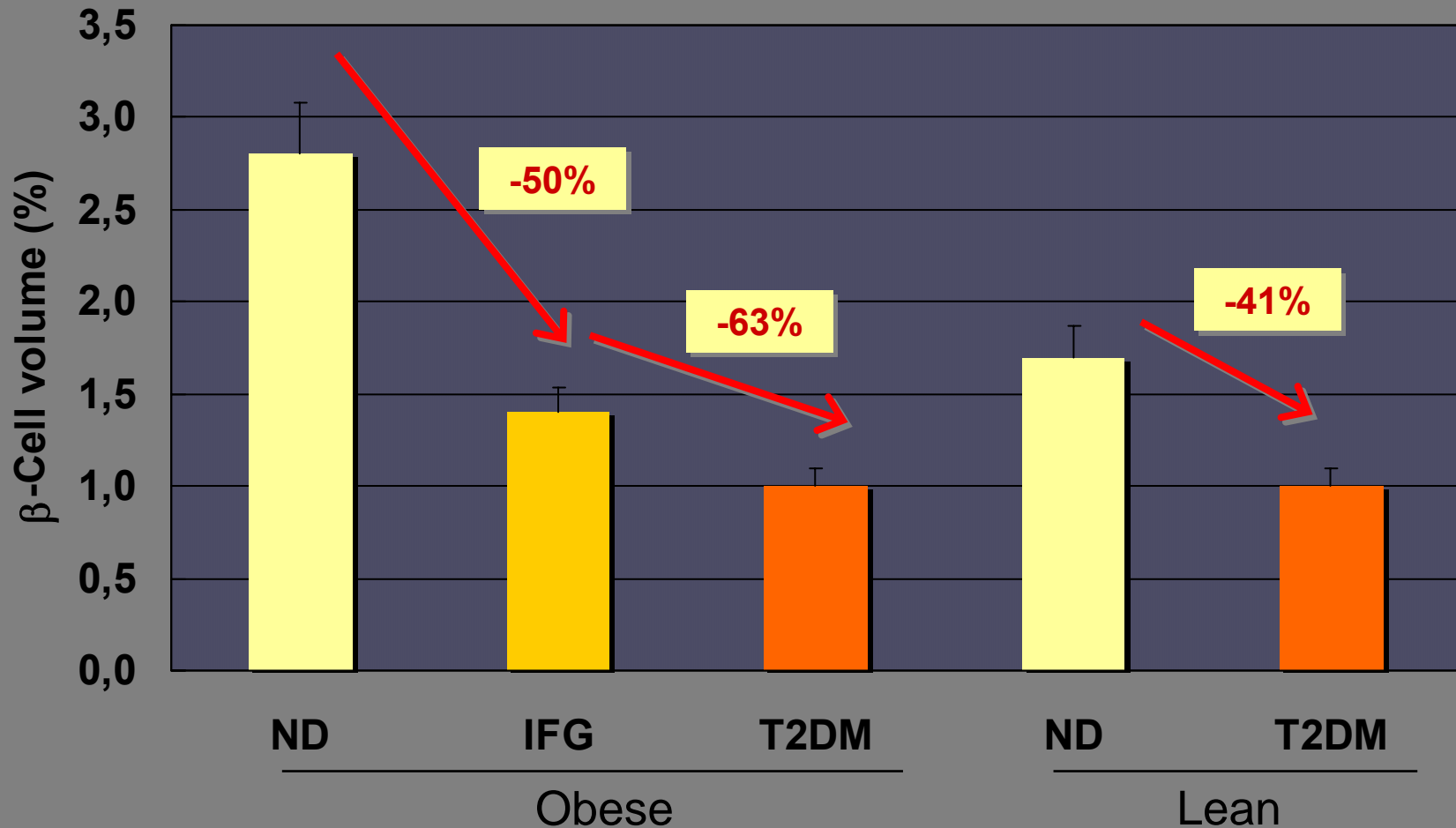
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# $\beta$ cell mass in T2 DM



ND=non-diabetic; IFG=impaired fasting glucose; T2DM=Type 2 diabetes mellitus

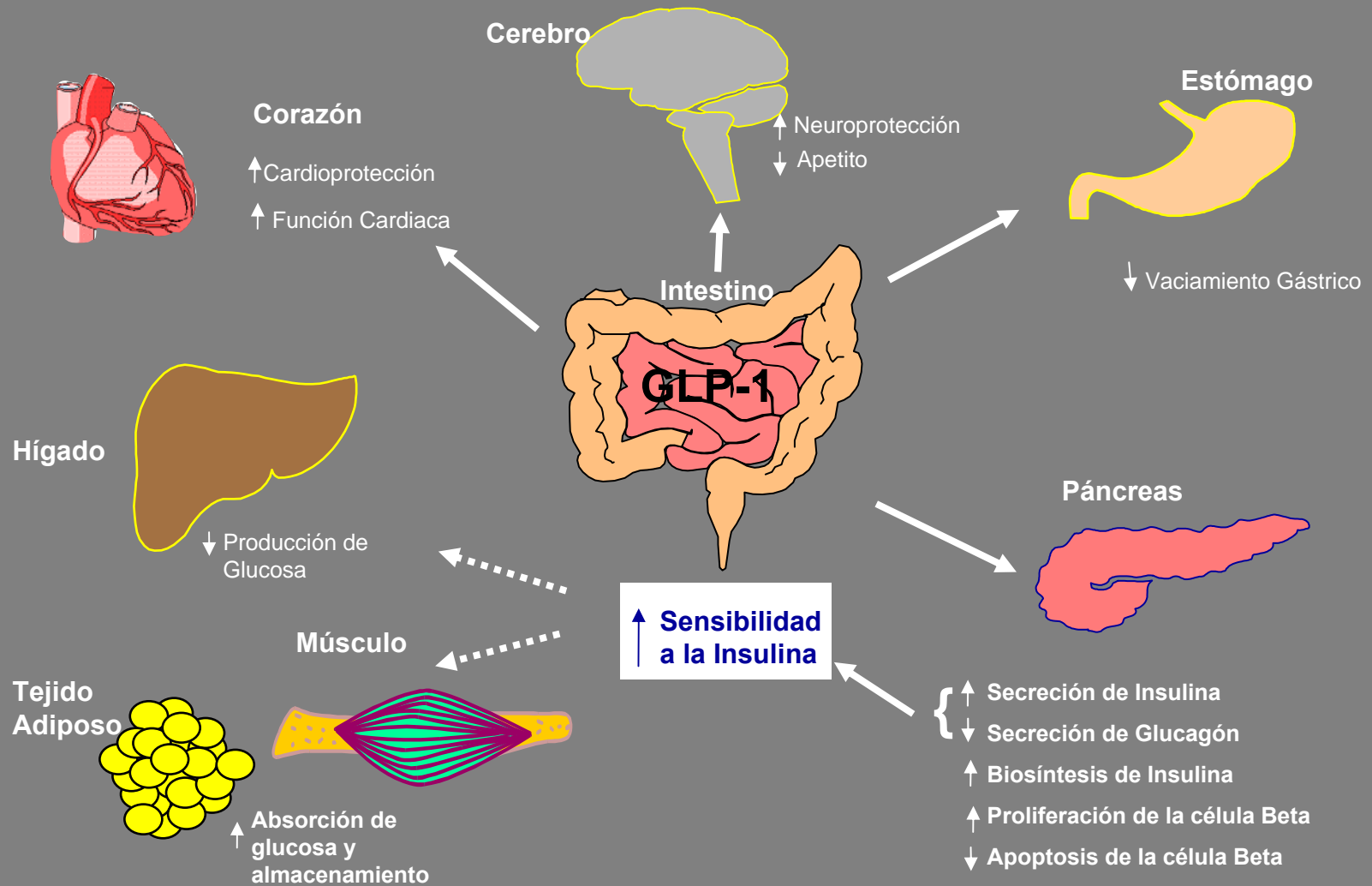
Butler AE et al. *Diabetes*. 2003;52:102-110.



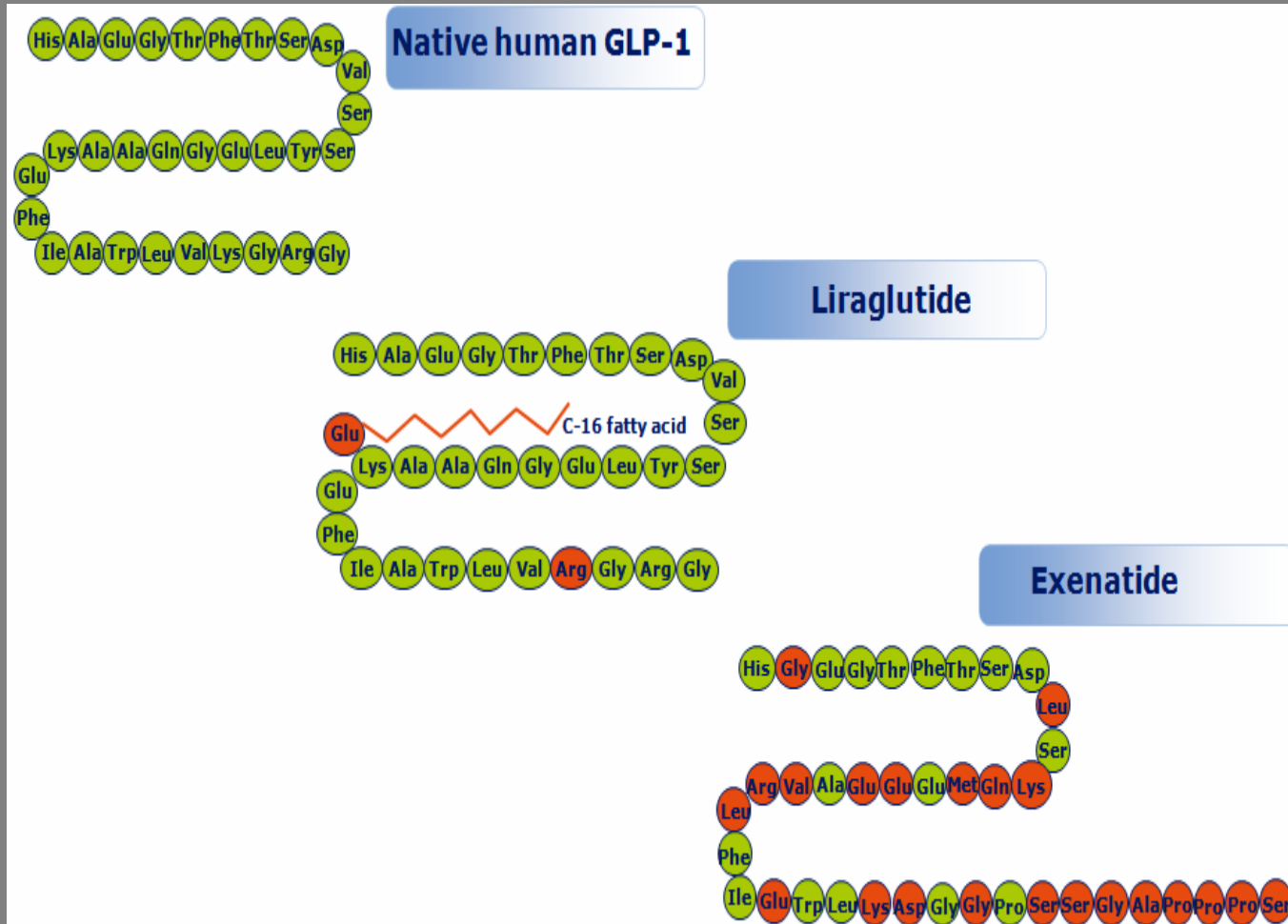
# The ideal antidiabetic drug

- Longer durability of glucose control/efficacy
- Agents that delay/prevent loss of  $\beta$ -cell function
- Agents that increase  $\beta$ -cell mass and function
- Therapies that provide superior control of postprandial glucose
- Agents that do not cause increased weight gain, and/or increase cardiovascular risk in any manner
- Agents that improve metabolic syndrome risk factors
- Agents that directly affect the progression of diabetic complications

# Acciones clásicas y nuevas de la molécula de supervivencia GLP-1



# Structure of native GLP-1 and two GLP-1 R agonists

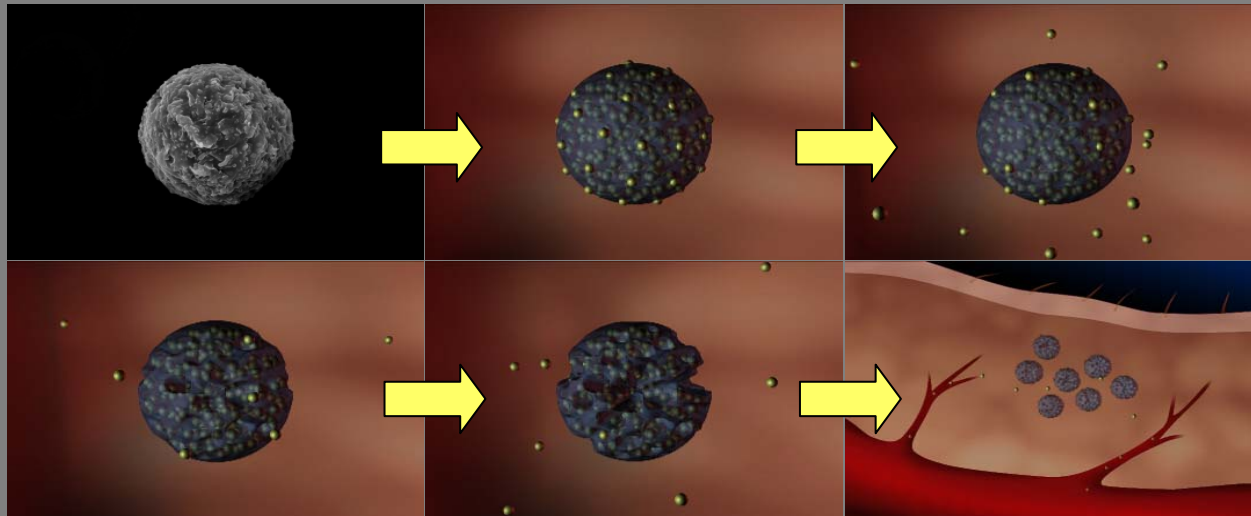


# Agonistas del Receptor GLP-1 de acción prolongada

Compuesto	Formulación	Laboratorio
Exenatina (Byetta®)*	2/día	Lilly/Amylin
Liraglutida	1/día	Novo Nordisk
Exenatina LAR	1/semana	Lilly/Amylin
Taspoglutida (R1583)	1/semana	Roche/Ipsen
Syncria (albiglutida)	1/semana	GlaxoSmithKline
Lixisenatida (AVE0010)	1/día	Sanofi-Aventis
PC_DACTM: exendina 4	1/3 semana	ConjuChem
CJC-1134	1/semana	ConjuChem
NN9535 (semaglutide)	1/semana	Novo Nordisk
NN9924	oral	Novo Nordisk
LY2428757		Lilly
LY2199265		Lilly

# Exenatide LAR: Microsphere Delivery System for Continuous Therapeutic Levels

- ◆ Exenatide is incorporated into PLG microspheres<sup>1</sup>
  - PLG is a medical biodegradable polymer (degraded to CO<sub>2</sub> and water)<sup>2</sup>
  - Via hydration, exenatide at or near the surface dissolves and diffuses away (initial release)<sup>3</sup>
  - PLG degrades, creating pores for exenatide diffusion and release from microspheres (sustained release)<sup>4</sup>
  - Allows gradual drug delivery at a controlled rate<sup>2</sup>

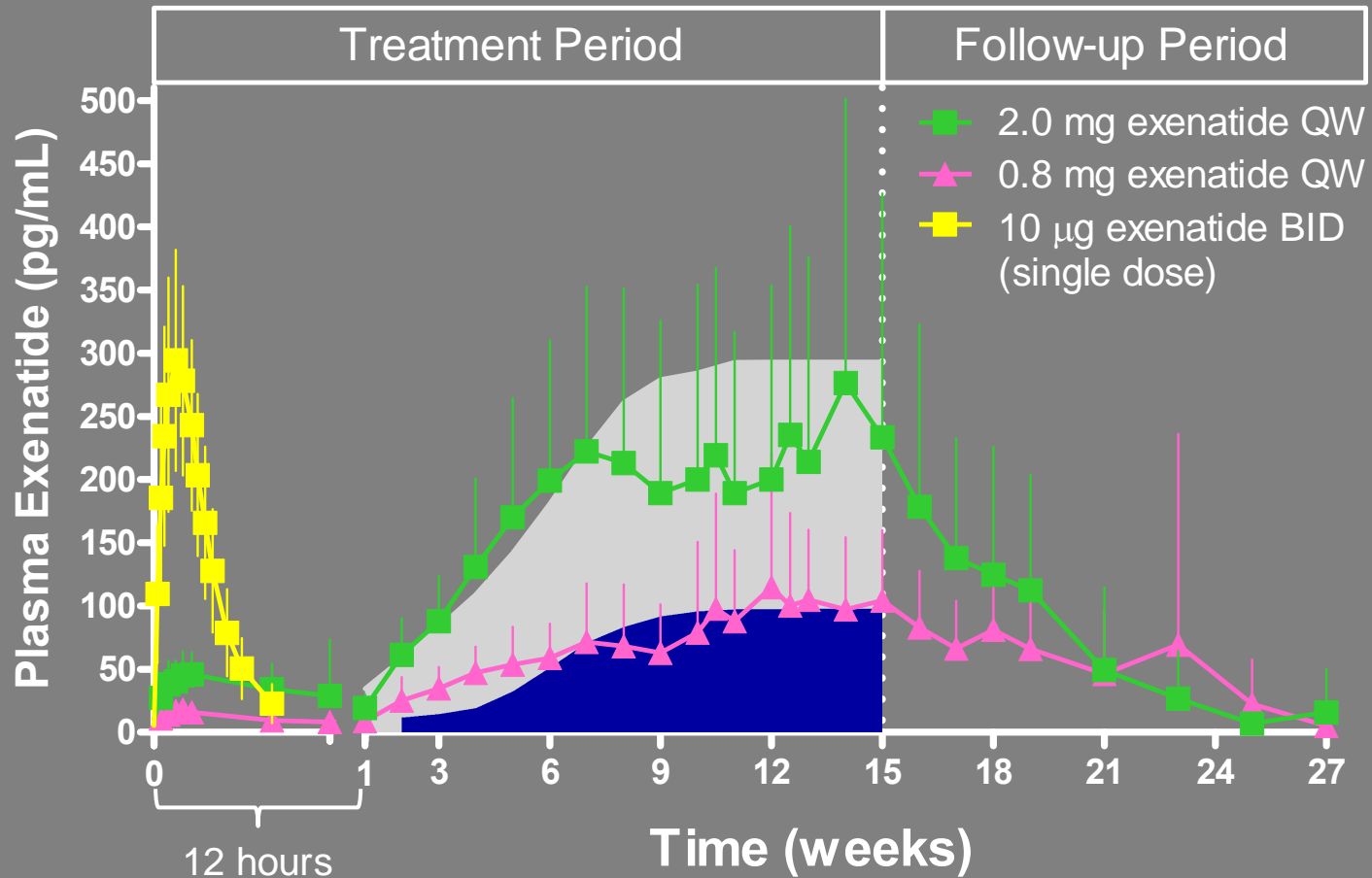


PLG indicates poly(D,L-lactide-co-glycolide).

1. Malone J et al. Expert Opin Investig Drugs. 2009;18:359-367. 2. Tracy MA et al. Biomaterials. 1999;20:1057-1062.

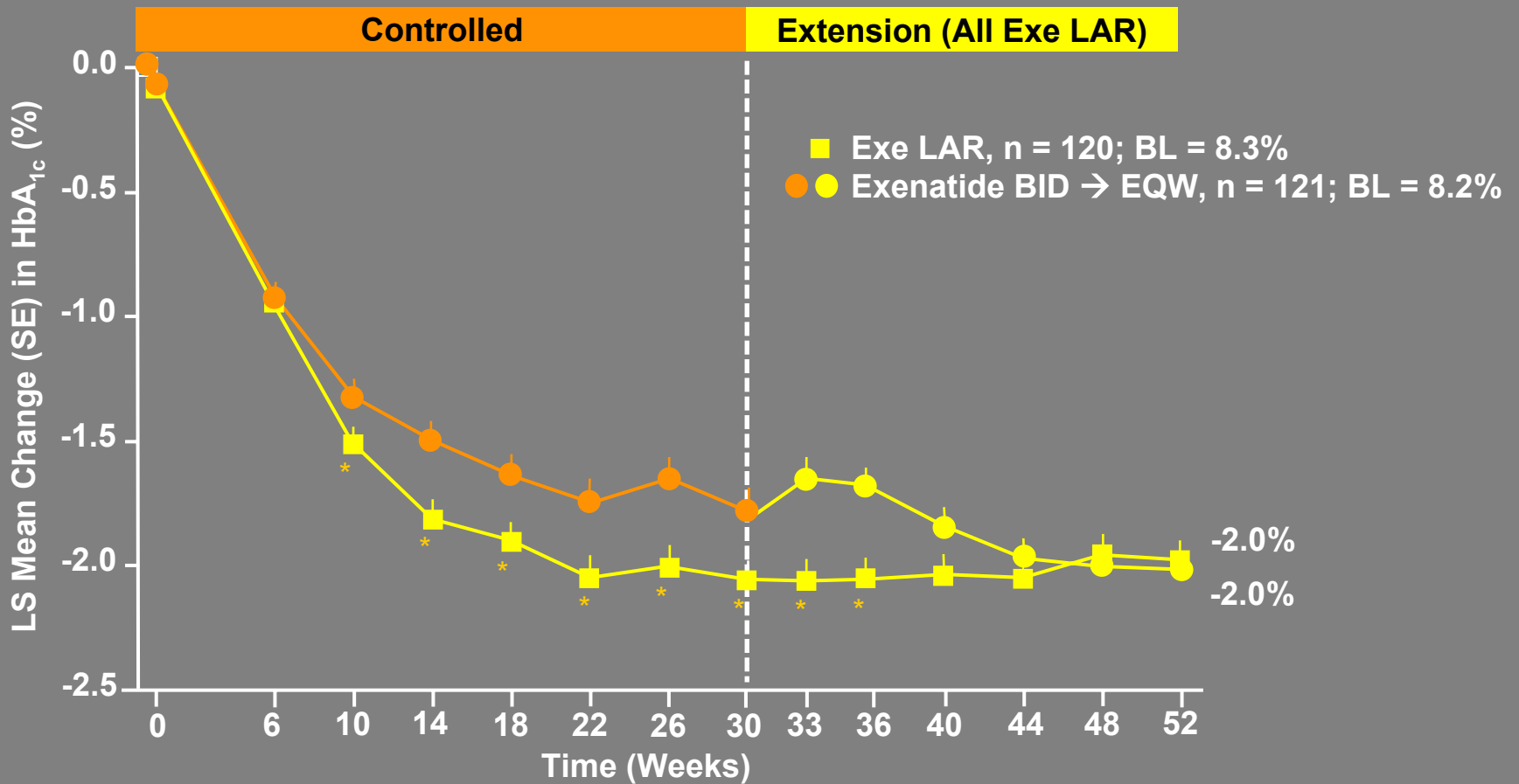
3. Langer R, Folkman J. Nature. 1976;263:797-800. 4. Bawa R. et al. J. Controlled Release. 1985;1:259-267.

# Plasma Exenatide LAR reaches Steady-State Concentrations Within 6-7 Weeks



- Data are mean  $\pm$  SD

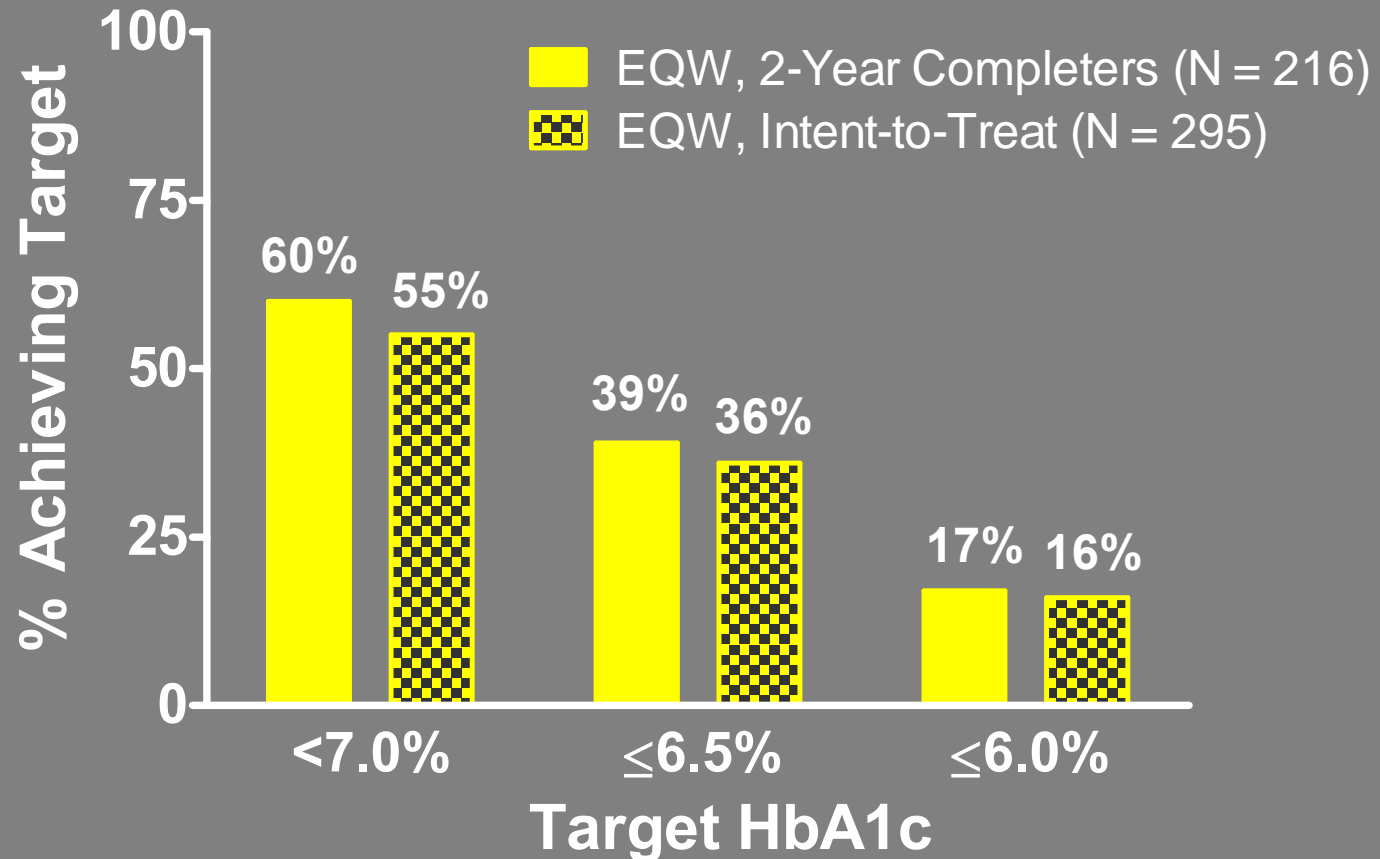
# HbA<sub>1c</sub> Changes Over 52 Weeks of Exenatide LAR treatment



• \*p<.05

Buse et al. *Diabetes Care* 2010;33(6):1255-61.

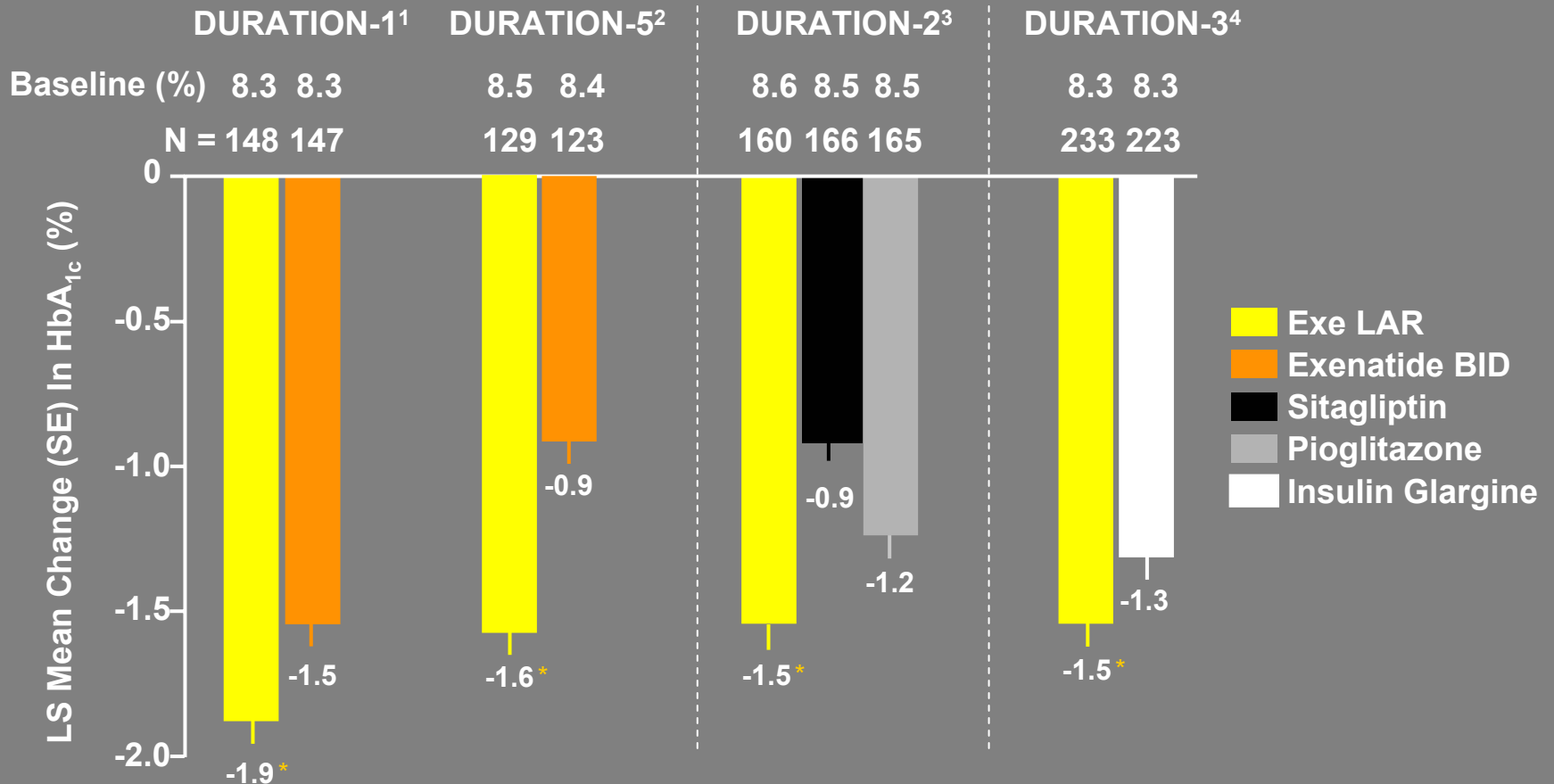
# Exenatide LAR: Subjects Achieving HbA<sub>1c</sub> Target Goals After 2 Years



- EQW: exenatide once a week (Exenatide LAR)



# Changes in HbA<sub>1c</sub> vs. Comparators



• \*p<.05 vs. comparator, intent-to-treat population

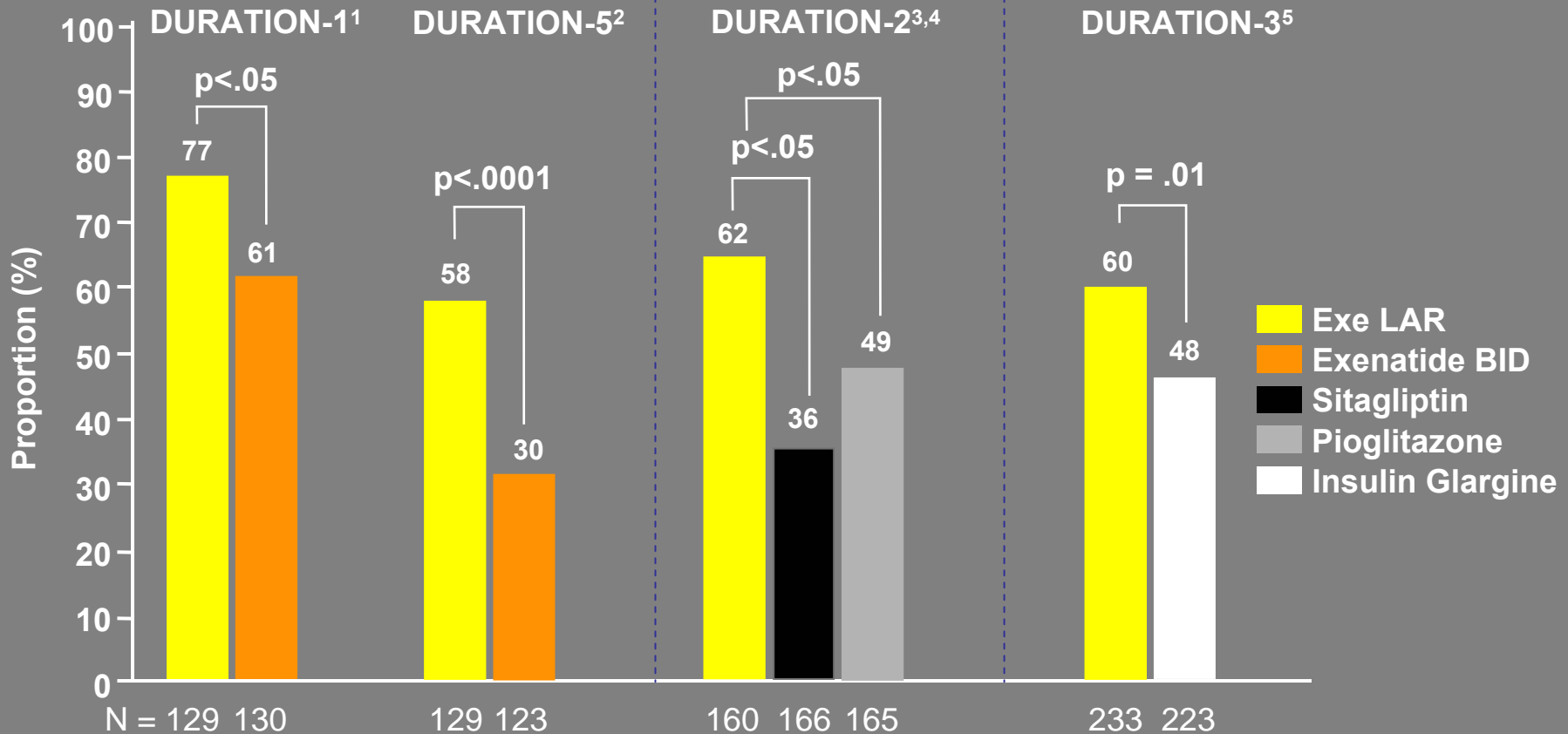
1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):2010-81.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

# Proportion of Subjects Achieving HbA<sub>1c</sub> Target of ≤7% (or <7%) vs. Comparators



- DURATION-1: evaluable population; DURATION-5, -2, and -3: intent-to-treat population; DURATION-5 and -3: target of <7%

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

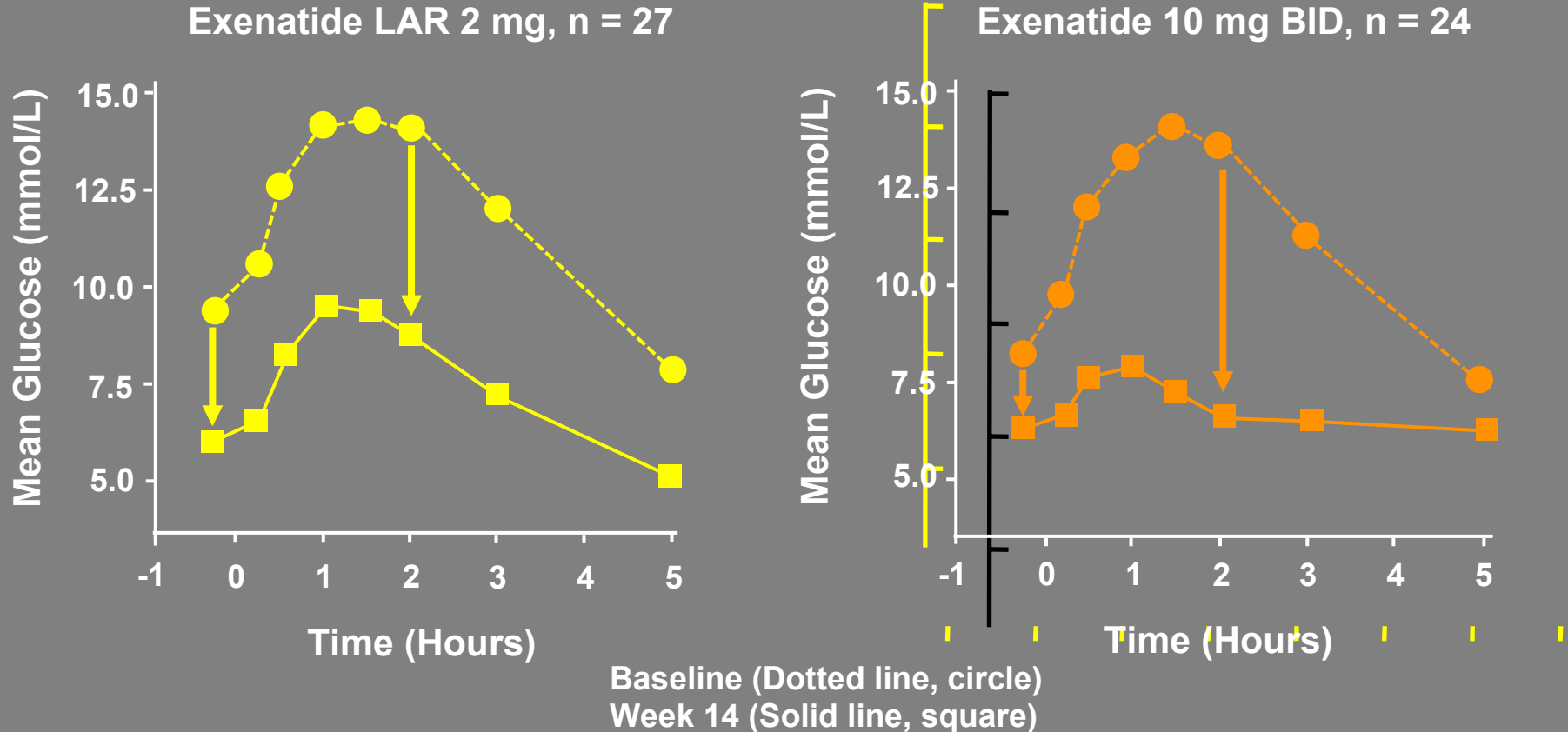
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):2010-81.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Data on file, Amylin Pharmaceuticals, Inc.

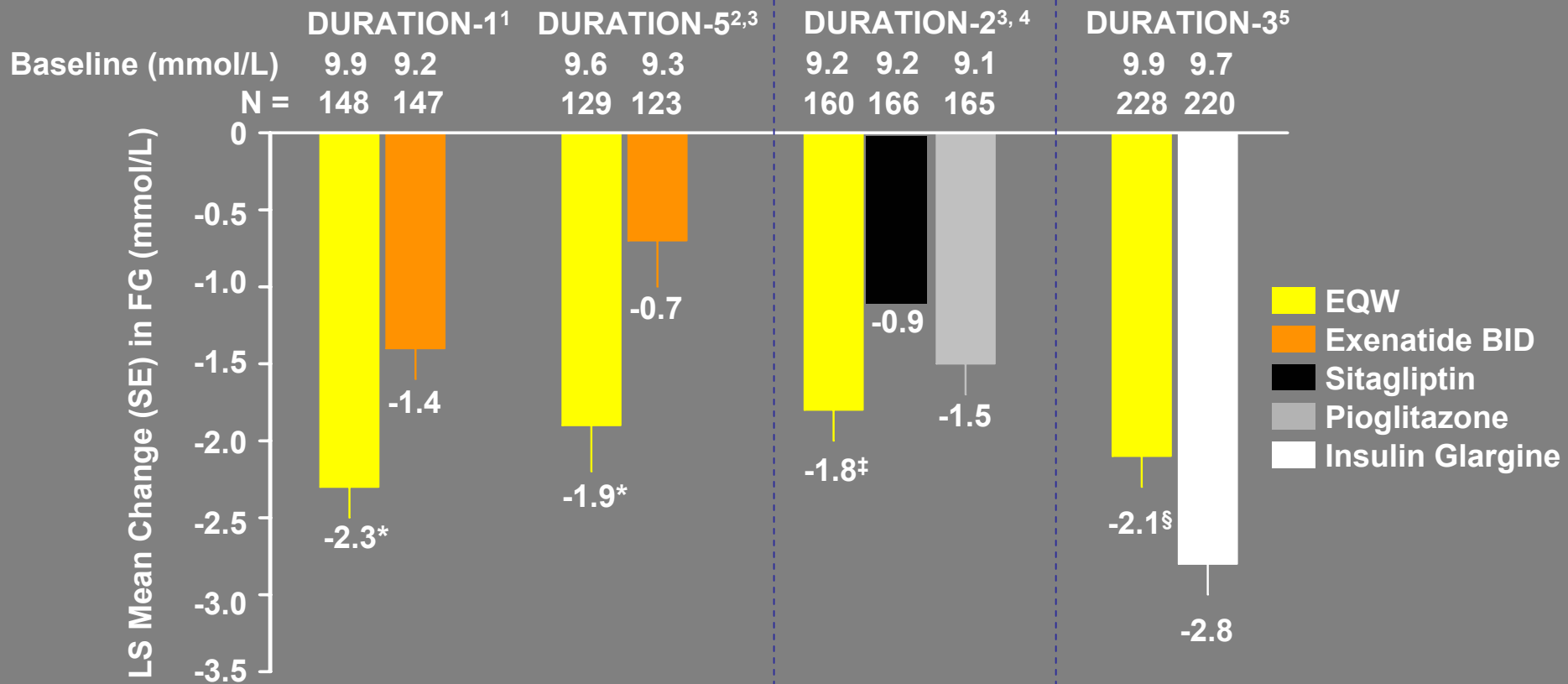
5. Diamant et al. *Lancet* 2010;375(9733):2234-43.

# Postprandial Glucose Changes: Exenatide LAR vs Exenatide twice a day



- $p = .0124$ , Exenatide LAR vs. exenatide twice a day

# Changes in Fasting Glucose vs. Comparators



- \*p<.001 vs. exenatide BID, <sup>‡</sup>p=.004 vs. sitagliptin, <sup>§</sup>p=.001 vs. insulin glargine
- Intent-to-treat population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

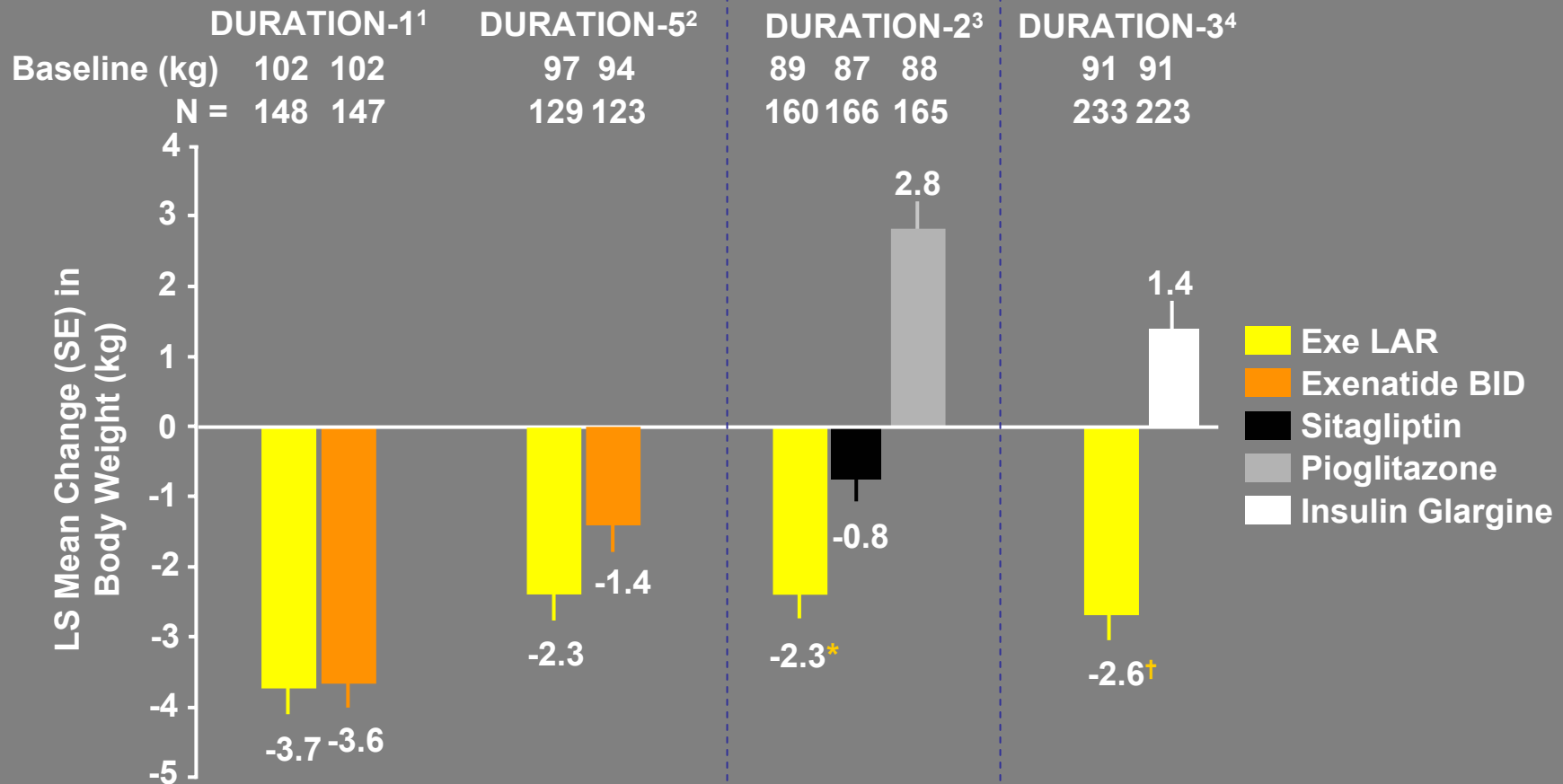
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Data on file, Amylin Pharmaceuticals, Inc.

4. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

5. Diamant et al. *Lancet* 2010;375(9733):2234-43.

# Changes in Body Weight vs. Comparators



- \*p<.001 vs. sitagliptin and p<.0001 vs. pioglitazone †p<.05 vs. insulin glargine, intent-to-treat population

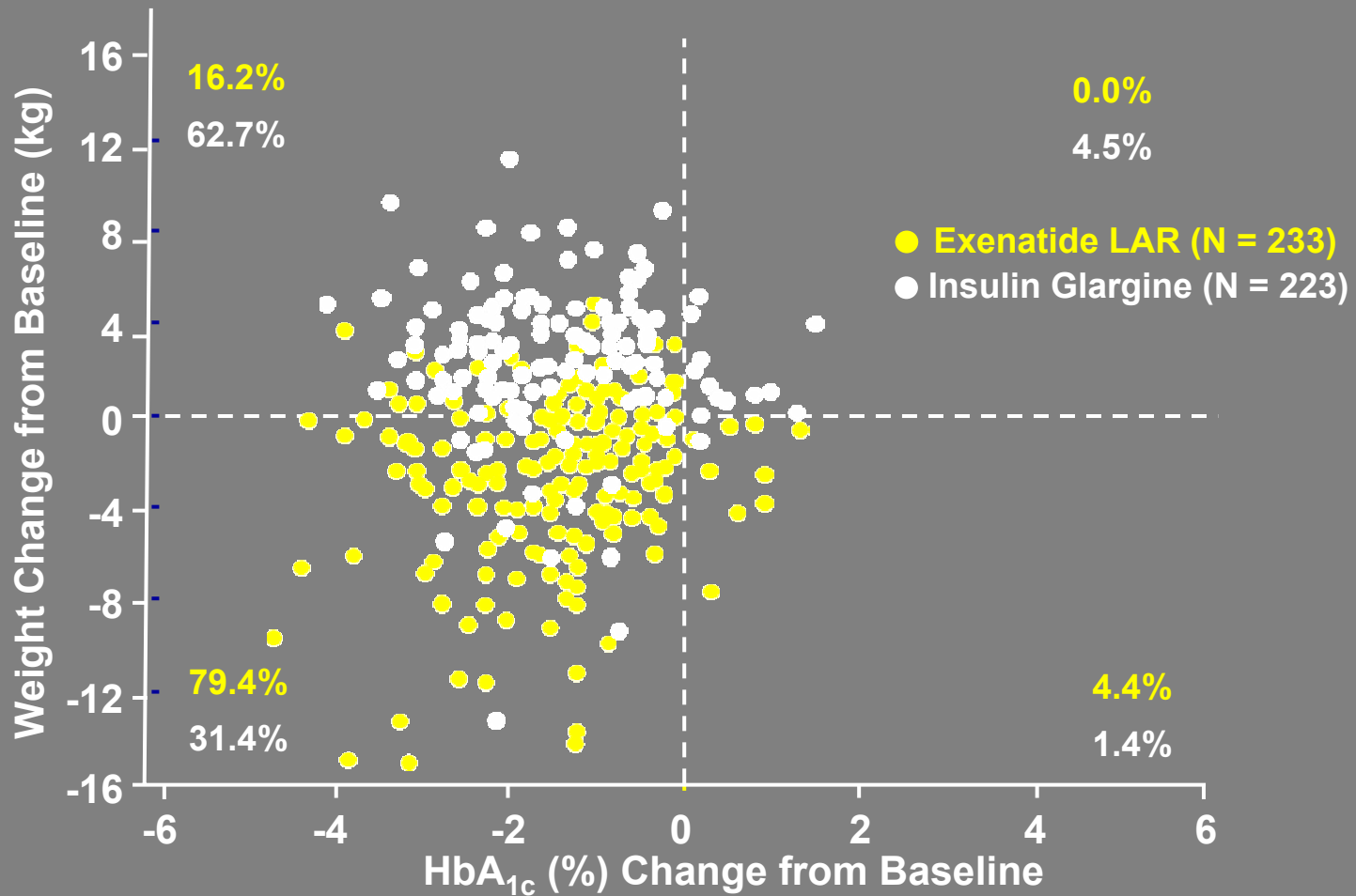
1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

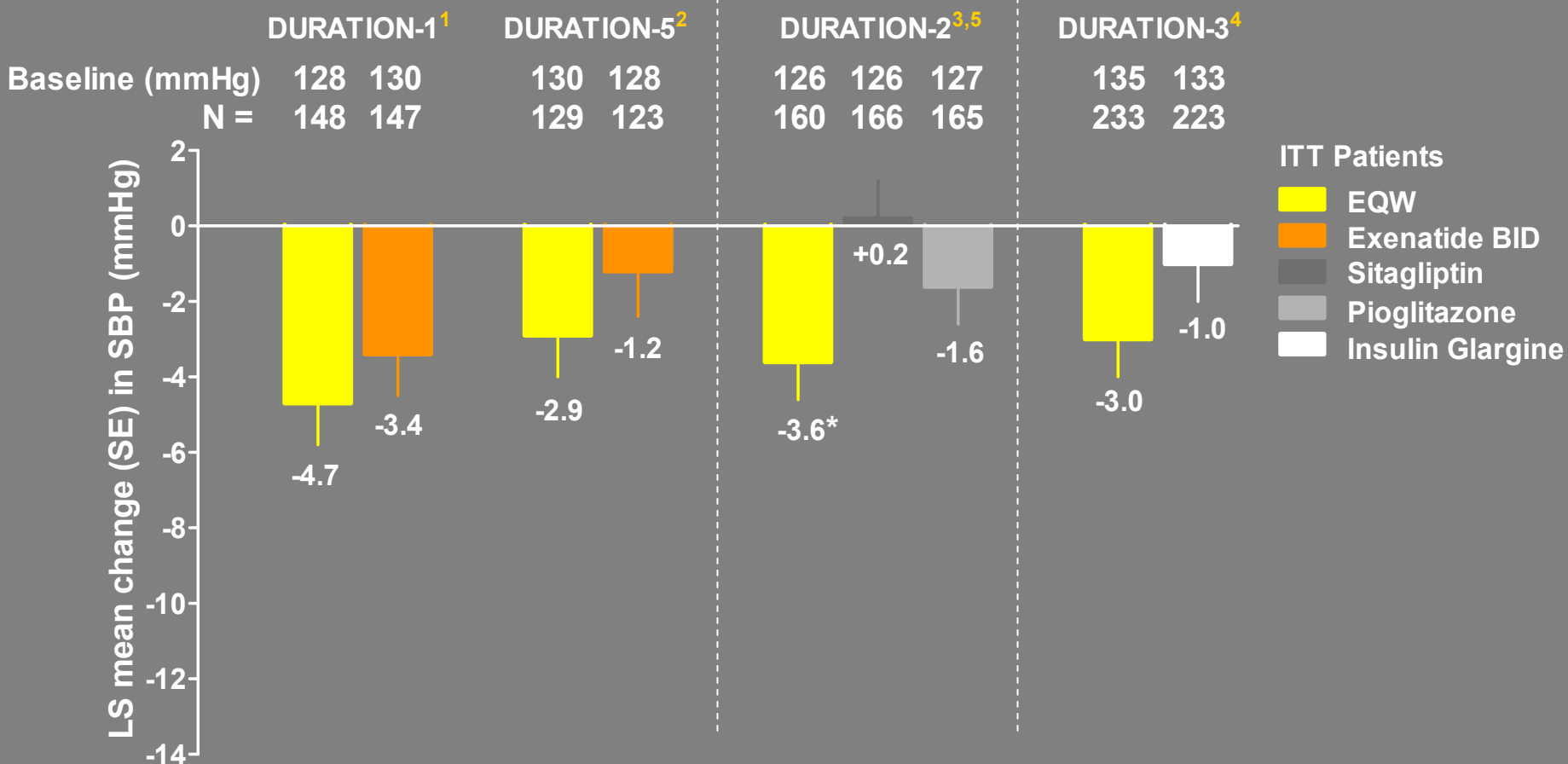
4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

# Changes in HbA1c and Body Weight: Exenatide LAR vs insulin glargine



- Intent-to-treat population

# Changes in Systolic Blood Pressure vs. Comparators



• \*p = .010 vs. sitagliptin, intent-to-treat (ITT) population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

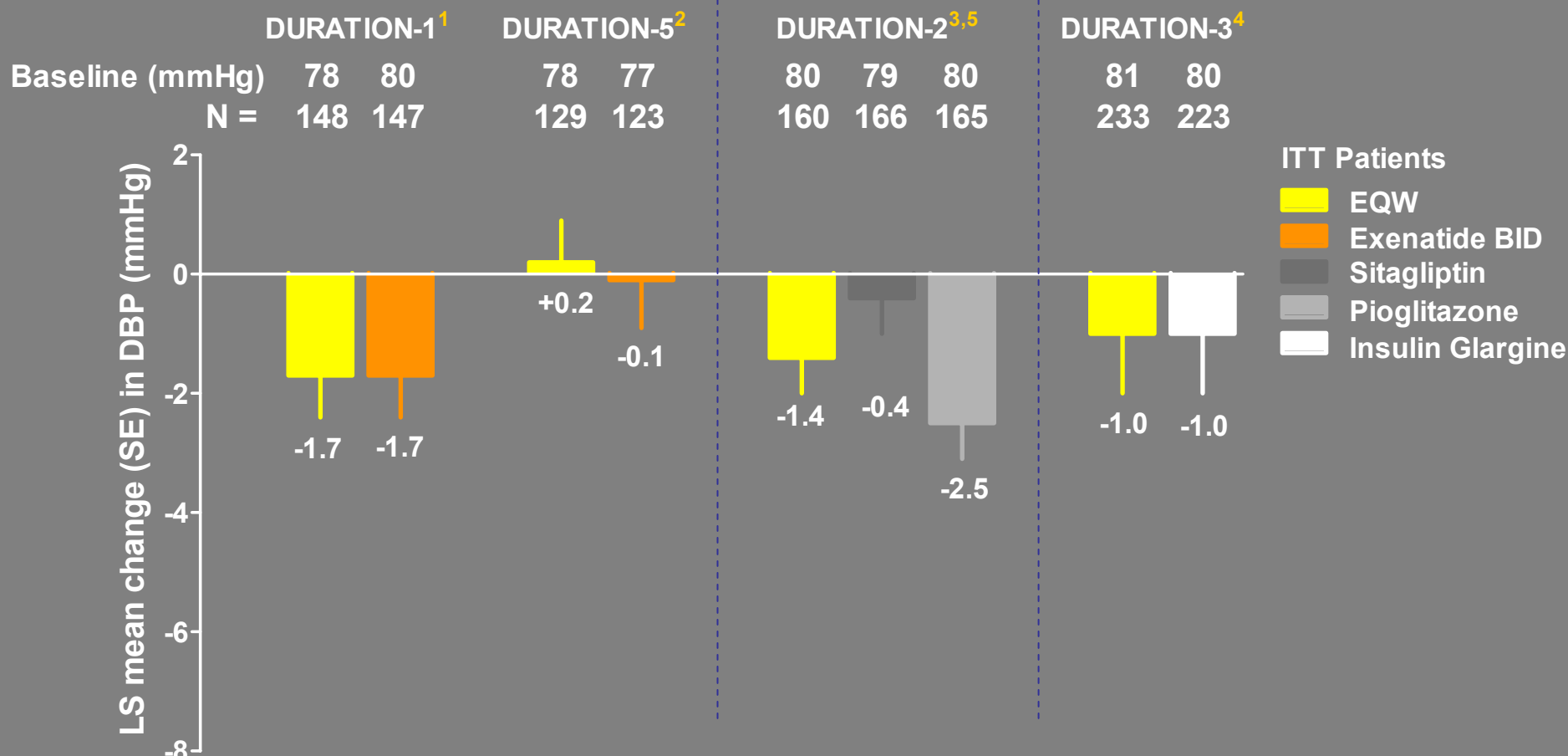
2. Blevins et al *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

5. Data on file, Amylin Pharmaceuticals, Inc.

# Changes in Diastolic Blood Pressure vs. Comparators

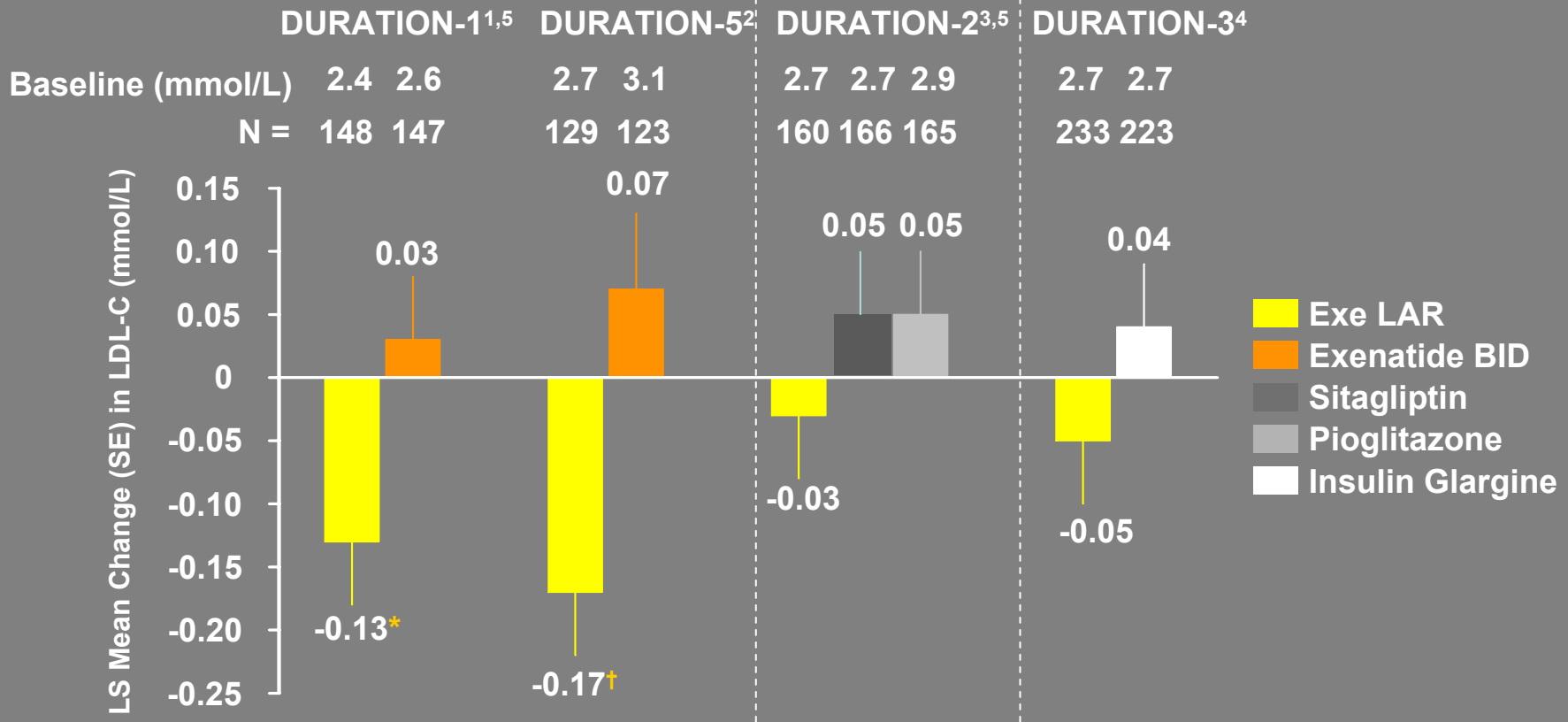


- No statistically significant between-group differences in diastolic blood pressure reduction were observed.
- Intent-to-treat (ITT) population
- EQW: exenatide once a week (LAR), BID: twice a day

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.  
 2. Blevins et al *J Clin Endocrinol Metab* 2011;96(5):1301-10.  
 3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.  
 4. Diamant et al. *Lancet* 2010;375(9733):2234-43.  
 5. Data on file, Amylin Pharmaceuticals, Inc.



# Changes in LDL-C: Exenatide LAR vs Comparators



- \*p=.02 vs. exenatide BID, †p<.01 vs. exenatide BID, intent-to-treat population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

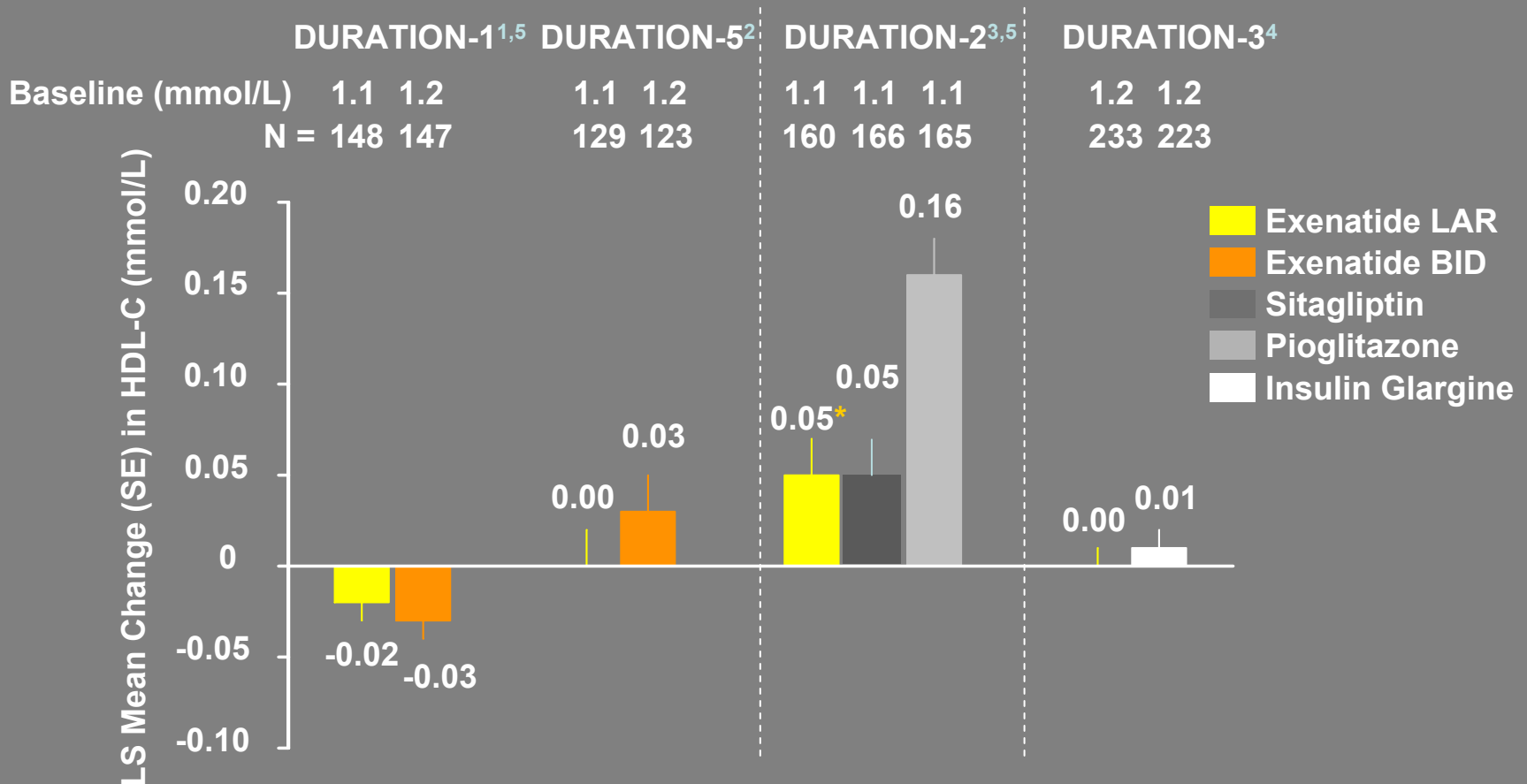
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

5. Data on file, Amylin Pharmaceuticals, Inc.

# Changes in HDL-C: Exenatide LAR vs Comparators



- \*p<.001 EQW vs. pioglitazone, intent-to-treat population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

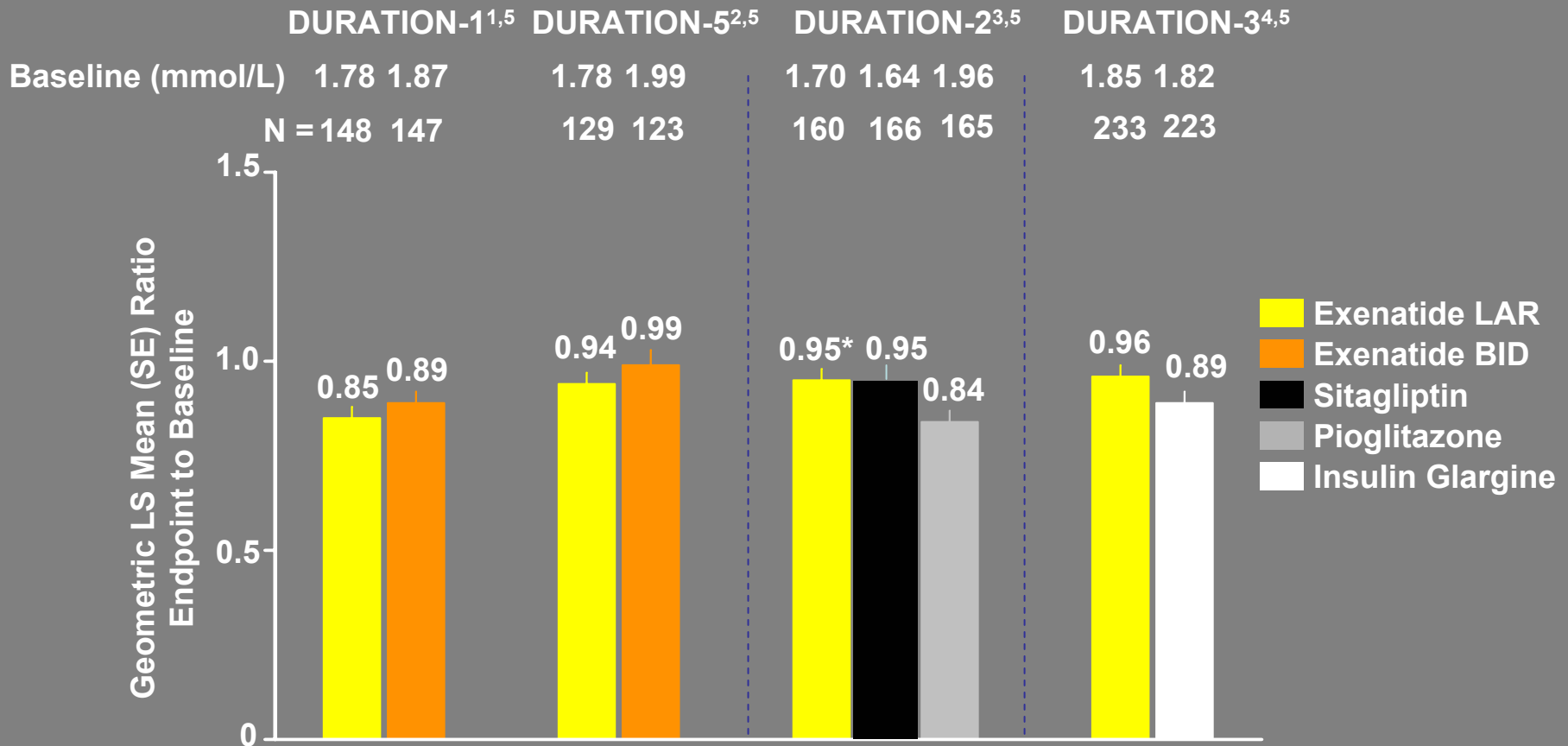
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

5. Data on file, Amylin Pharmaceuticals, Inc.

# Changes in Triglycerides: Exenatide LAR vs. Comparators



• \*p=.006 EQW vs. pioglitazone, intent-to-treat population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

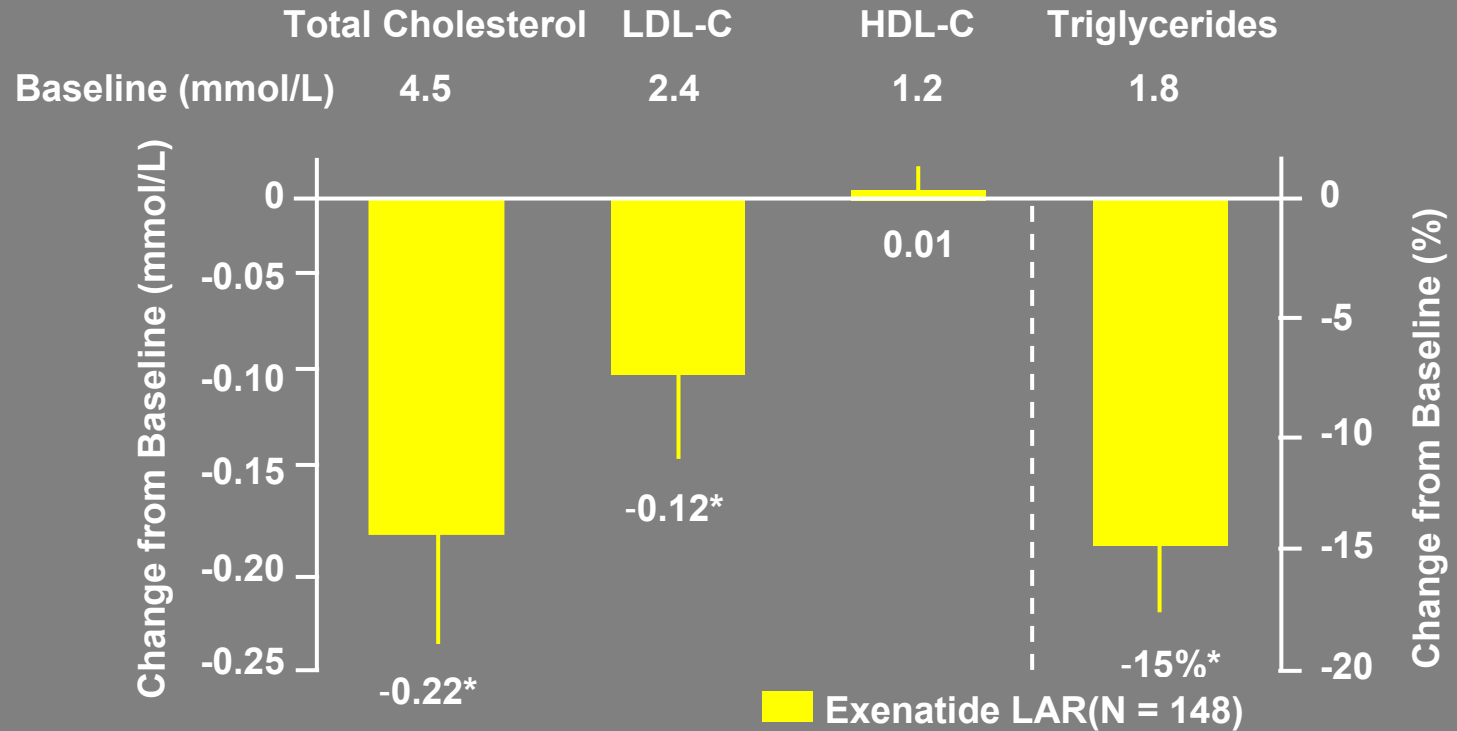
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375 (9733):2234-43.

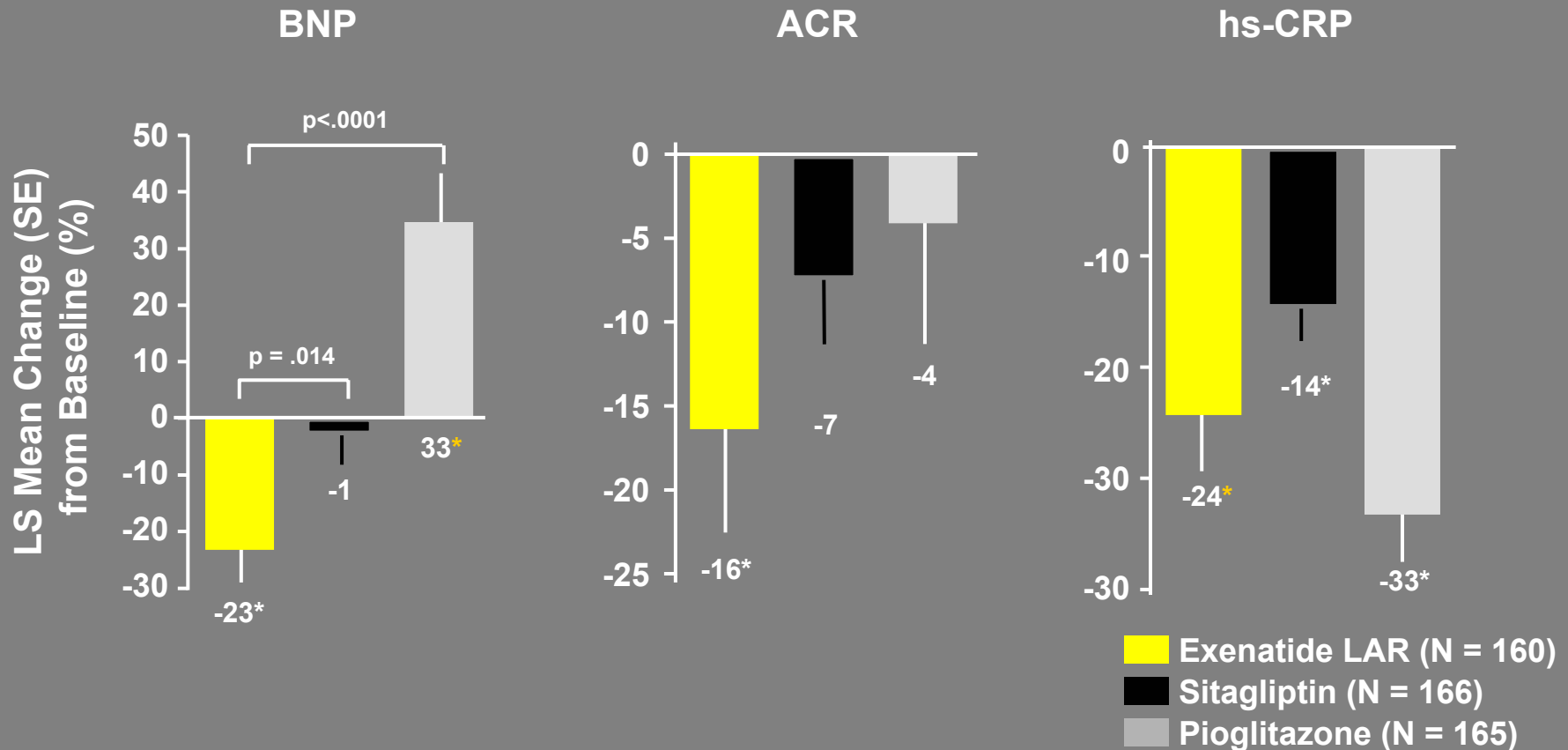
5. Data on file, Amylin Pharmaceuticals, Inc.

# Fasting Lipid Profile Changes After 2 Years of Exenatide LAR treatment



- \*p<.05 vs. baseline, completer sample

# Changes in Cardiovascular Risk Biomarkers under exenatide LAR



- \*p<.05 vs. baseline, intent-to-treat population
- BNP: B-type natriuretic peptide, ACR: albumin-to-creatinine ratio, hs-CRP: high-sensitivity C-reactive protein

Bergental et al. *Lancet* 2010;376(9739):431-9.

# Exenatide LAR: Adverse Events ≥5%

	ExeLAR <sup>1-5</sup> N=670 n (%)	ExeBID <sup>1,2,5</sup> N=268 n (%)	SITA <sup>3,5</sup> N=166 n (%)	PIO <sup>3,5</sup> N=165 n (%)	Insulin Glargine <sup>4,5</sup> N=223 n (%)
Nausea	126 (18.8)	93 (34.7)	16 (9.6)	8 (4.8)	4 (1.8)
Diarrhea	83 (12.4)	24 (9.0)	16 (9.6)	12 (7.3)	8 (3.6)
Headache	55 (8.2)	17 (6.3)	15 (9.0)	7 (4.2)	20 (9.0)
Nasopharyngitis	51 (7.6)	9 (3.4)	4 (2.4)	5 (3.0)	40 (17.9)
Vomiting	51 (7.6)	38 (14.2)	4 (2.4)	5 (3.0)	3 (1.3)
Injection site pruritus	43 (6.4)	3 (1.1)	-	-	1 (0.4)

- Intent-to-treat population, SITA: sitagliptin, PIO: pioglitazone

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

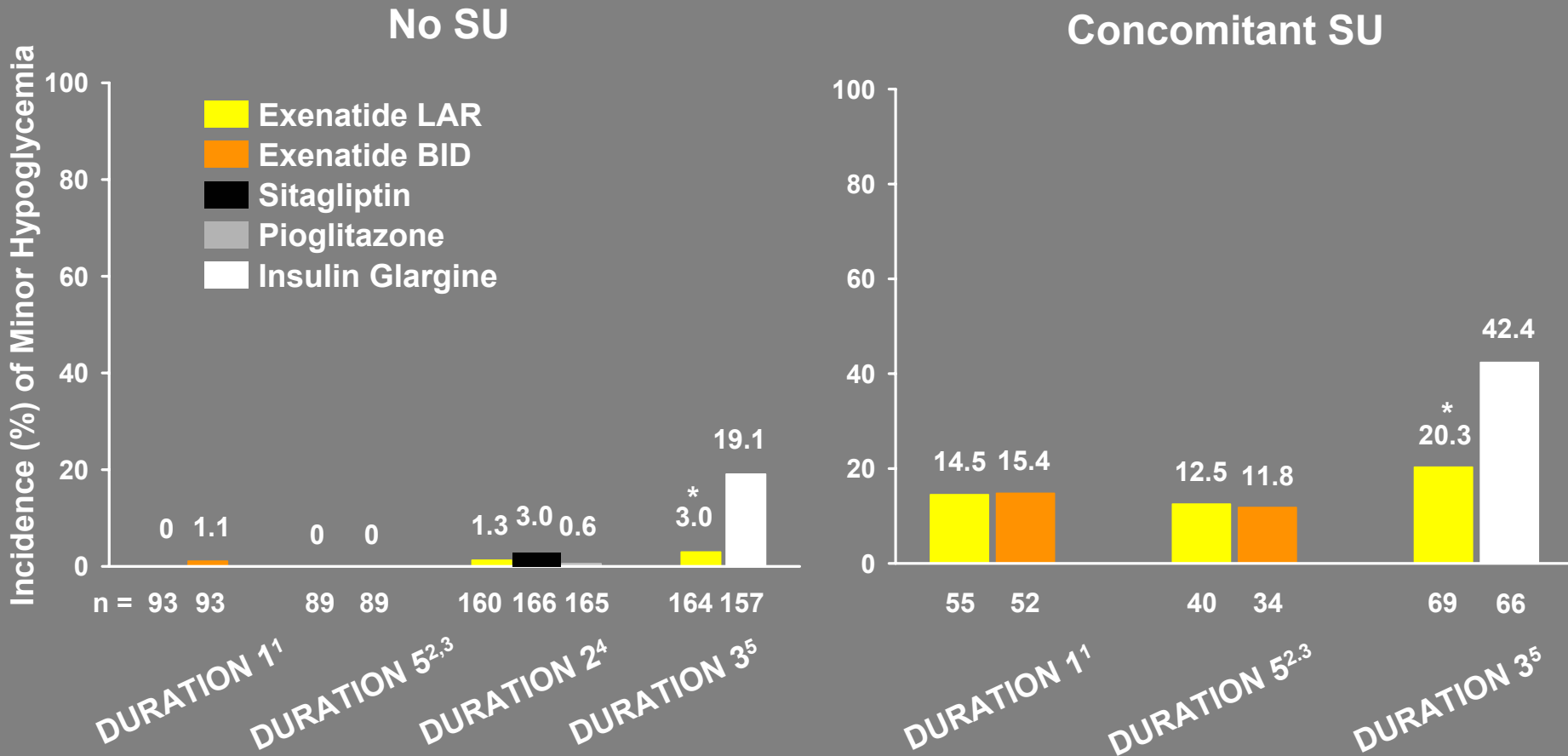
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

4. Diamant et al. *Lancet* 2010;375(9733):2234-43.

5. Data on file, Amylin Pharmaceuticals, Inc.

# Incidence of Hypoglycemia by SU use



• \*p<.05 Exenatide LAR vs. insulin glargine, intent-to-treat population

1. Drucker et al. *Lancet* 2008;372(9645):1240-50.

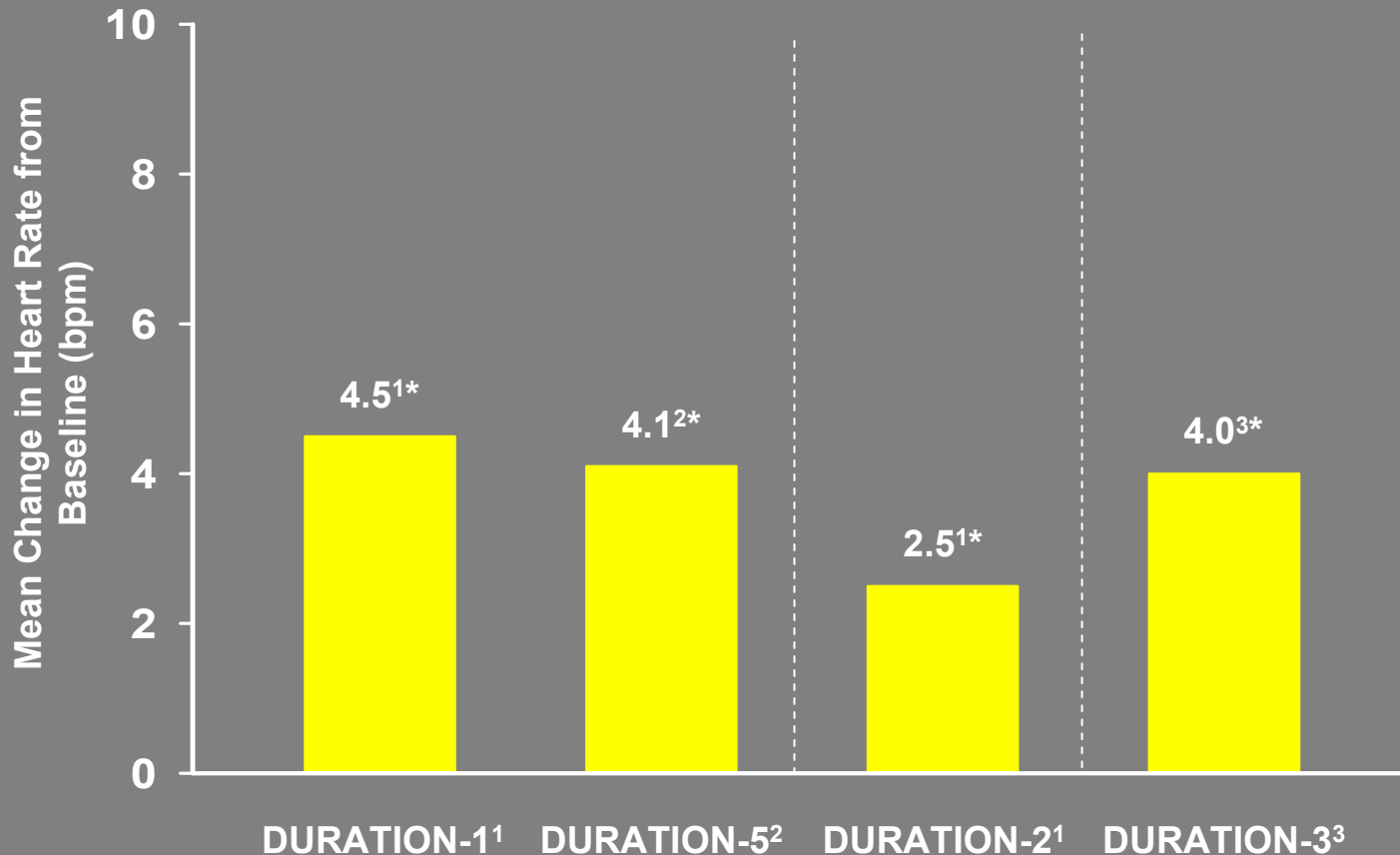
2. Blevins et al. *J Clin Endocrinol Metab* 2011;96(5):1301-10.

3. Data on file, Amylin Pharmaceuticals, Inc.

4. Bergenstal et al. *Lancet* 2010;376(9739):431-9.

5. Diamant et al. *Lancet* 2010;375(9733):2234-43.

# Exenatide LAR: Changes in Heart Rate













- \*p<.05 vs. baseline
- bpm: beats per minute

1. Data on file, Amylin Pharmaceuticals, Inc.
2. Blevins et al. *J Clin Endocrin Metab* 2011;96(5):1301-10
3. Diamant et al. *Lancet* 2010;375(9733):2234-43.



# Are GLP-1 R agonists the ideal antidiabetic drugs ?

- Longer durability of glucose control/efficacy 
- Agents that delay/prevent loss of  $\beta$ -cell function  
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## Gracias por vuestra atención



**Costa Meloneras**

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Maspalomas, San Bartolomé de Tirajana  
Gran Canaria, Las Palmas