DPP-4 inhibitor

The new class drug for Diabetes

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Cause of Death in Korea

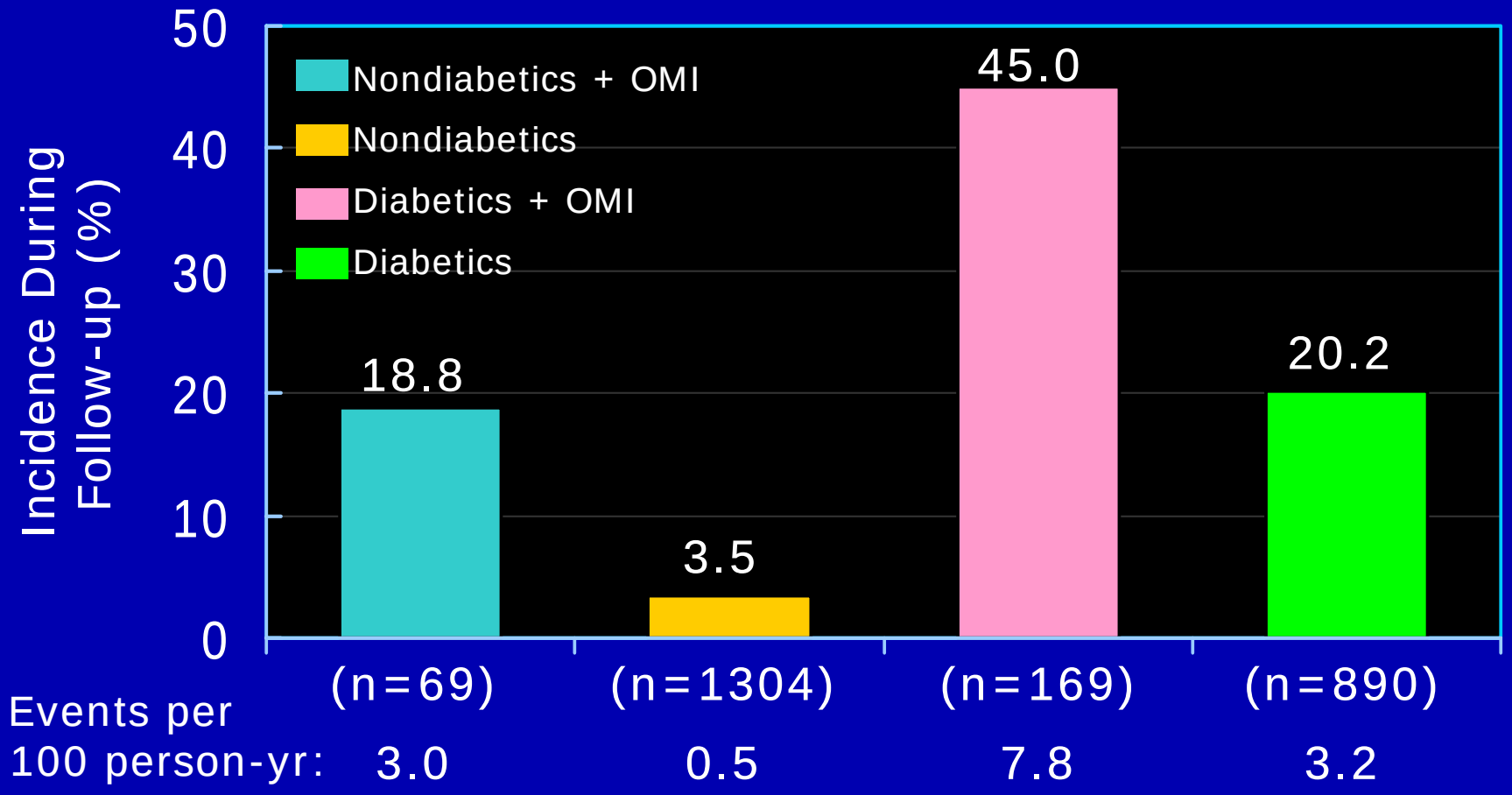
1st ; Neoplasm

2nd ; Cardiovascular Disease

3rd ; Cerebrovascular Disease

Diabetes

Incidence of Fatal or Nonfatal MI During a 7-Year Follow-up in Relation to History of MI in Non-diabetic vs Diabetic Subjects: *East-West Study*



Haffner SM et al. *N Engl J Med* 1998;339:229-234.

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Stepwise Selection of Risk Factors* in 2693 White Patients with Type 2 Diabetes with Dependent Variable as Time to First Event: *UKPDS*

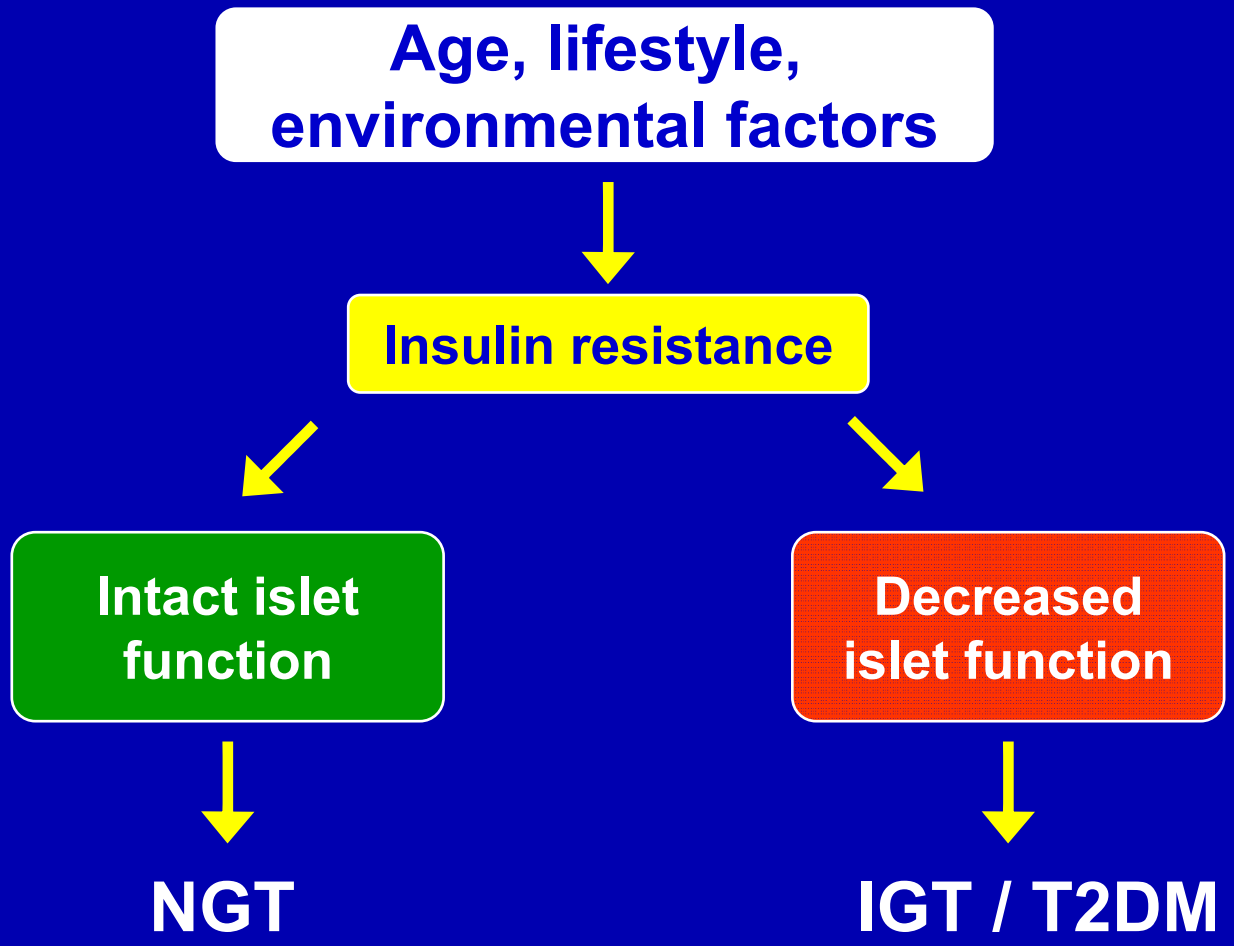
Coronary Artery Disease (n=280)

Position in Model	Variable	P Value
First	Low-Density Lipoprotein Cholesterol	<0.0001
Second	High-Density Lipoprotein Cholesterol	0.0001
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

*Adjusted for age and sex.

Turner RC et al. *BMJ* 1998;316:823-828.

Abnormal Pancreatic Islet Function Determines the Development of IGT and T2DM in the Setting of Insulin Resistance



T2DM = type 2 diabetes mellitus; NGT = normal glucose tolerance; IGT = impaired glucose tolerance

Adapted from Ahren B, Pacini G. *Diabetes Obes Metab*. 2005;7(1):2–8.

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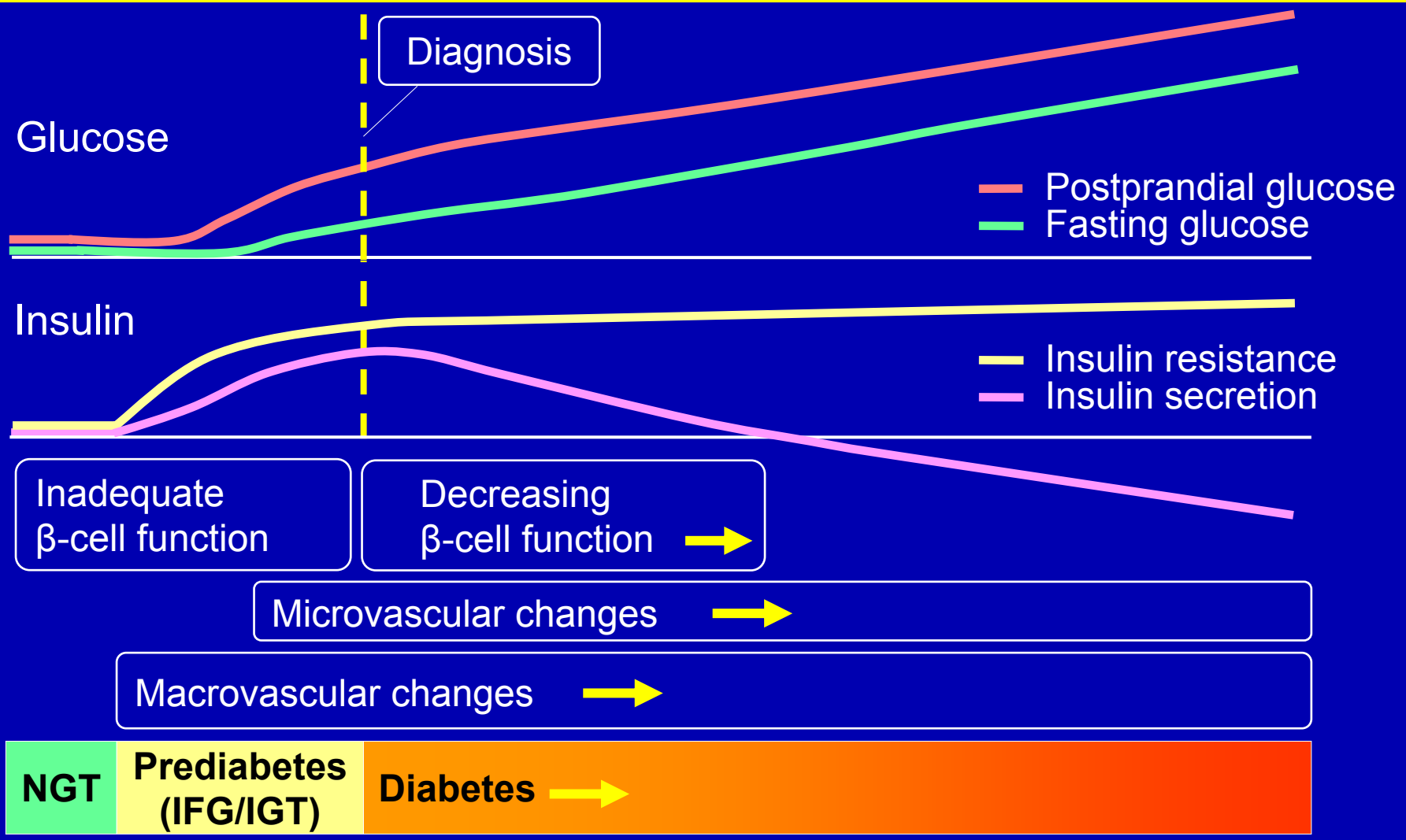
L1

Deterioration of Islet Function Drives Disease Progression



NGT = normal glucose tolerance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Adapted from *Type 2 Diabetes BASICS*. International Diabetes Center; 2000.

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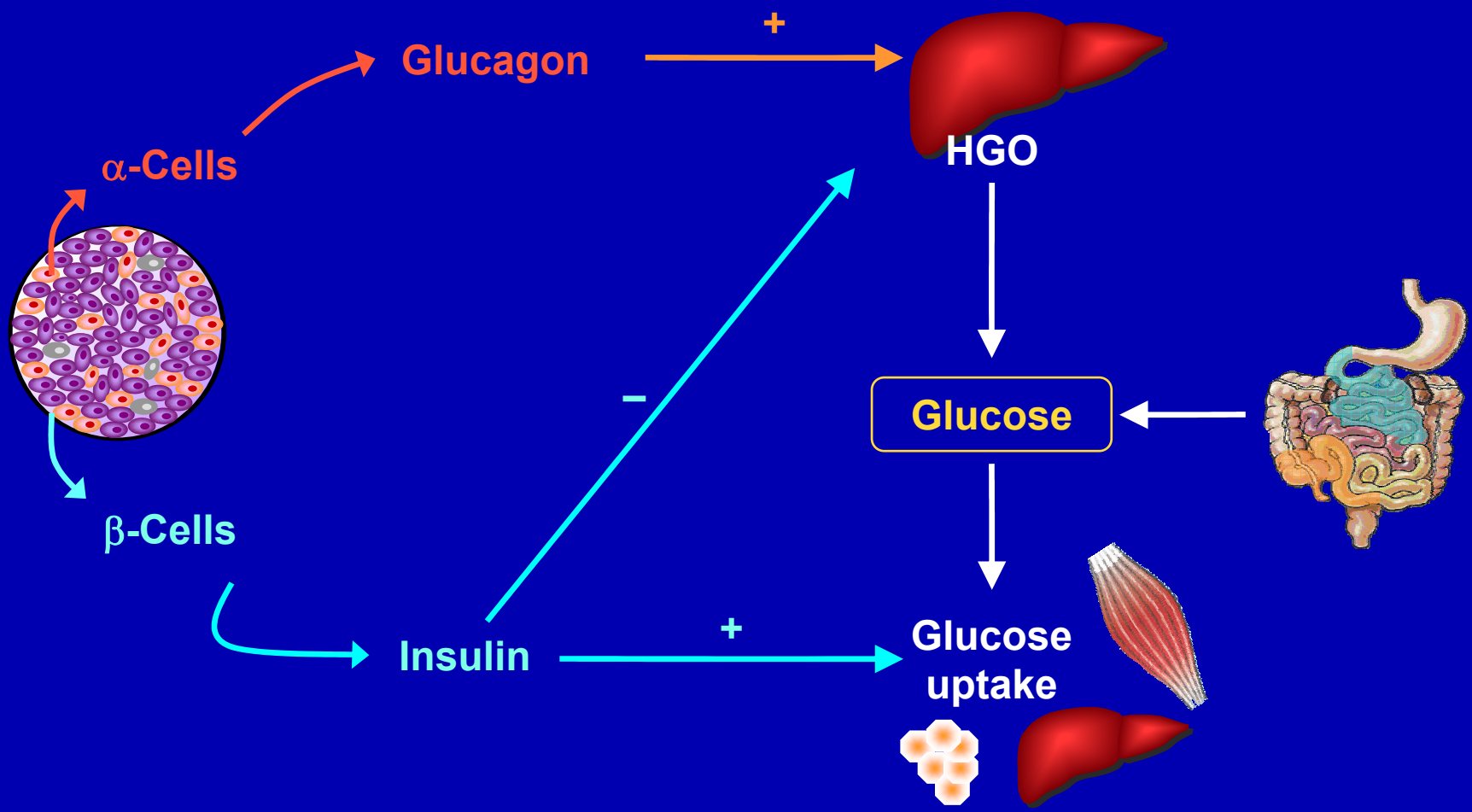
L1 Animation builds to be added during formatting
LatiD600IT, 2006-04-05

Pancreatic Islet Hormones are Critical for Normal Glucose Tolerance



HGO= Hepatic Glucose Output
Adapted from Unger RH. *Metabolism.* 1974;23:581.

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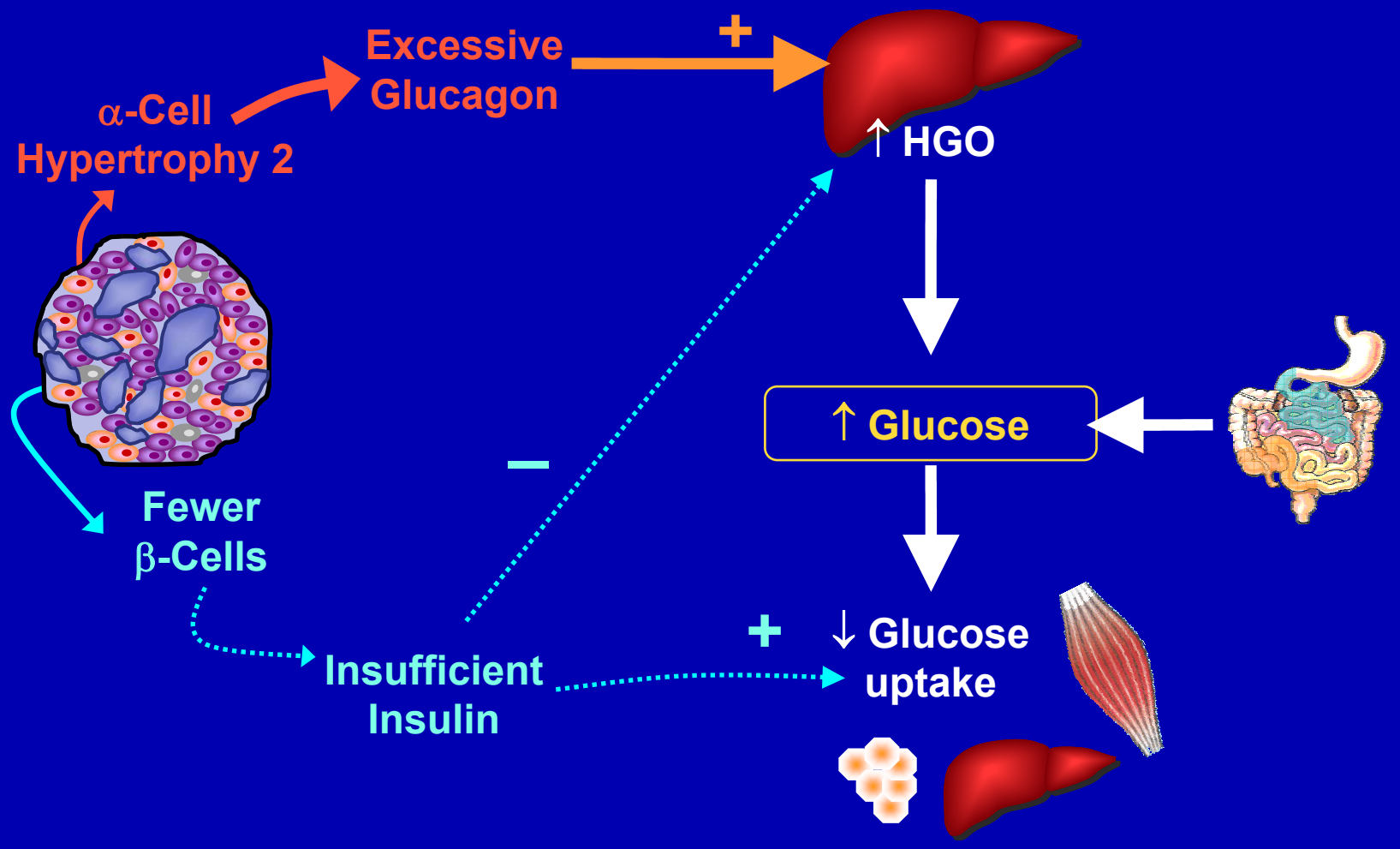
Pancreatic Islet Dysfunction leads to Hyperglycemia in T2DM



HGO= Hepatic Glucose Output

Adapted from Ohneda A, et al. *J Clin Endocrinol Metab.* 1978;46:504–510; and Gomis R, et al. *Diabetes Res Clin Pract*. 1989;6:191–198.

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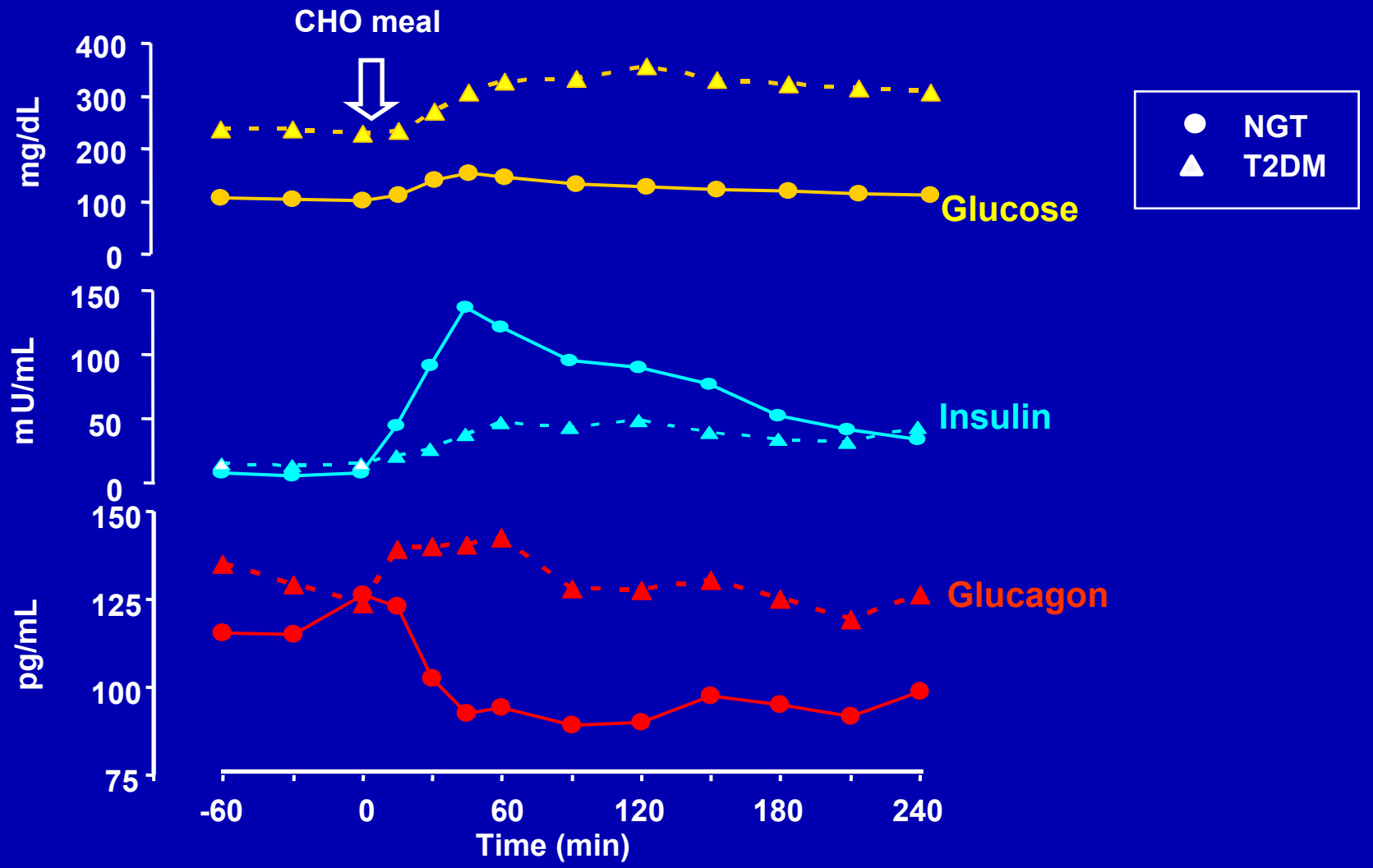
Insufficient Insulin and Elevated Glucagon in T2DM (↓ Insulin/Glucagon Ratio)



T2DM = Type 2 Diabetes Mellitus; NGT = Normal Glucose Tolerance; CHO = Carbohydrate
Adapted from Muller WA, et al. *N Engl J Med*. 1970;283:109–115.

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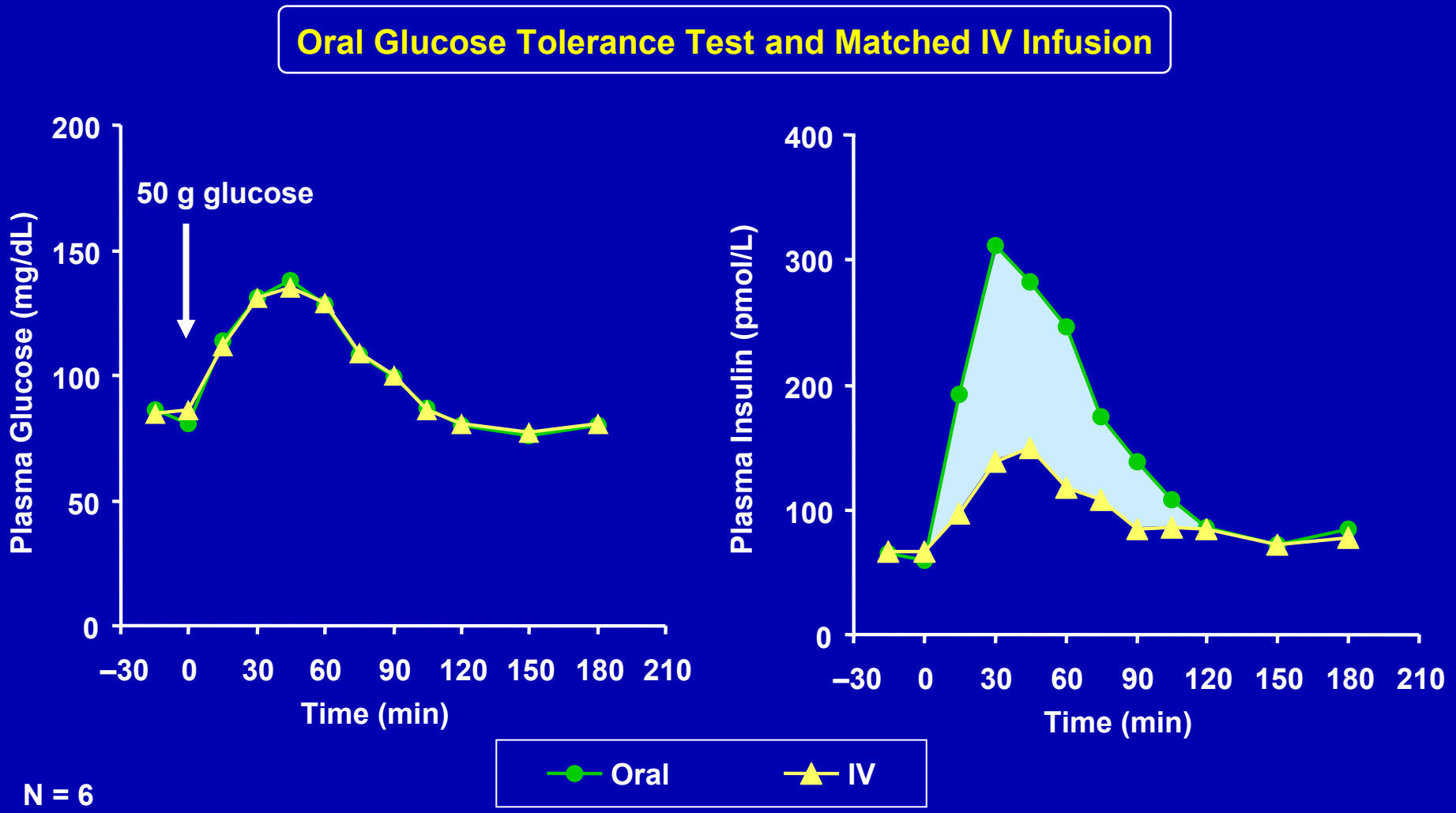
Proof of a Gastrointestinal 'Incretin Effect': Different Responses to Oral vs IV Glucose



IV = intravenous

Adapted from Nauck MA, *et al*. *J Clin Endocrinol Metab*. 1986;63:492–498.

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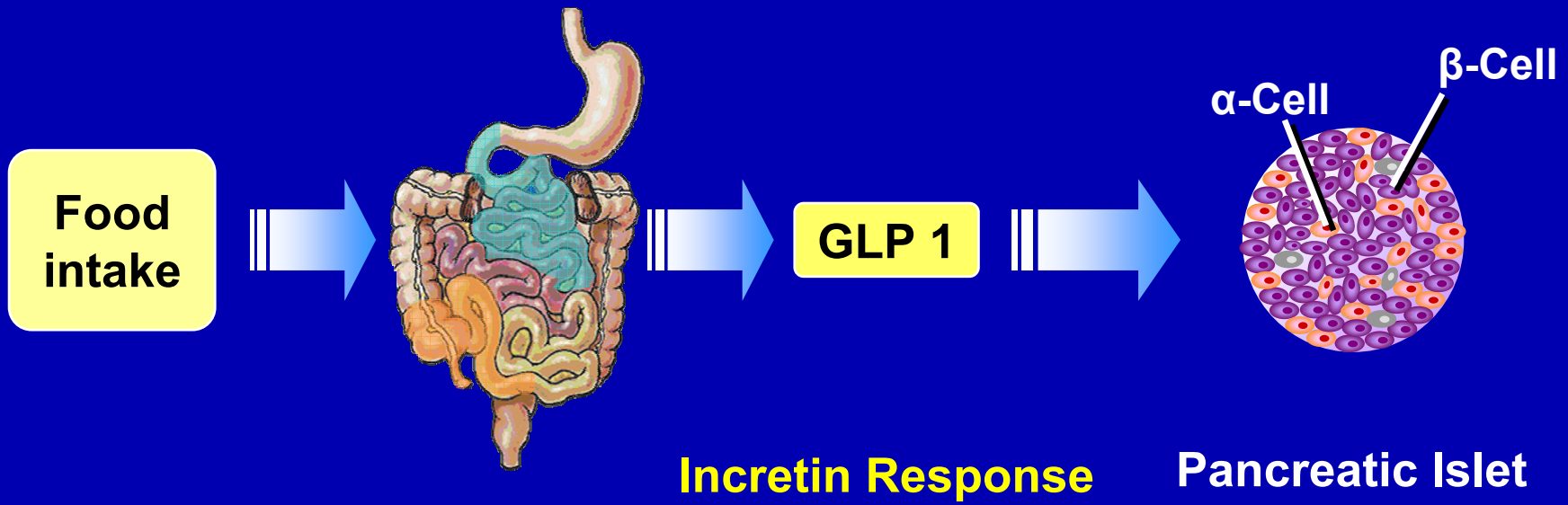
Pancreatic Islet Cells Are Targets for Incretin Hormones



GLP-1 = glucagon-like peptide-1

Adapted from Drucker D. *Diabetes Care.* 2003;26:2929–2940. Wang Q, et al. *Diabetologia.* 2004;47:478–487.

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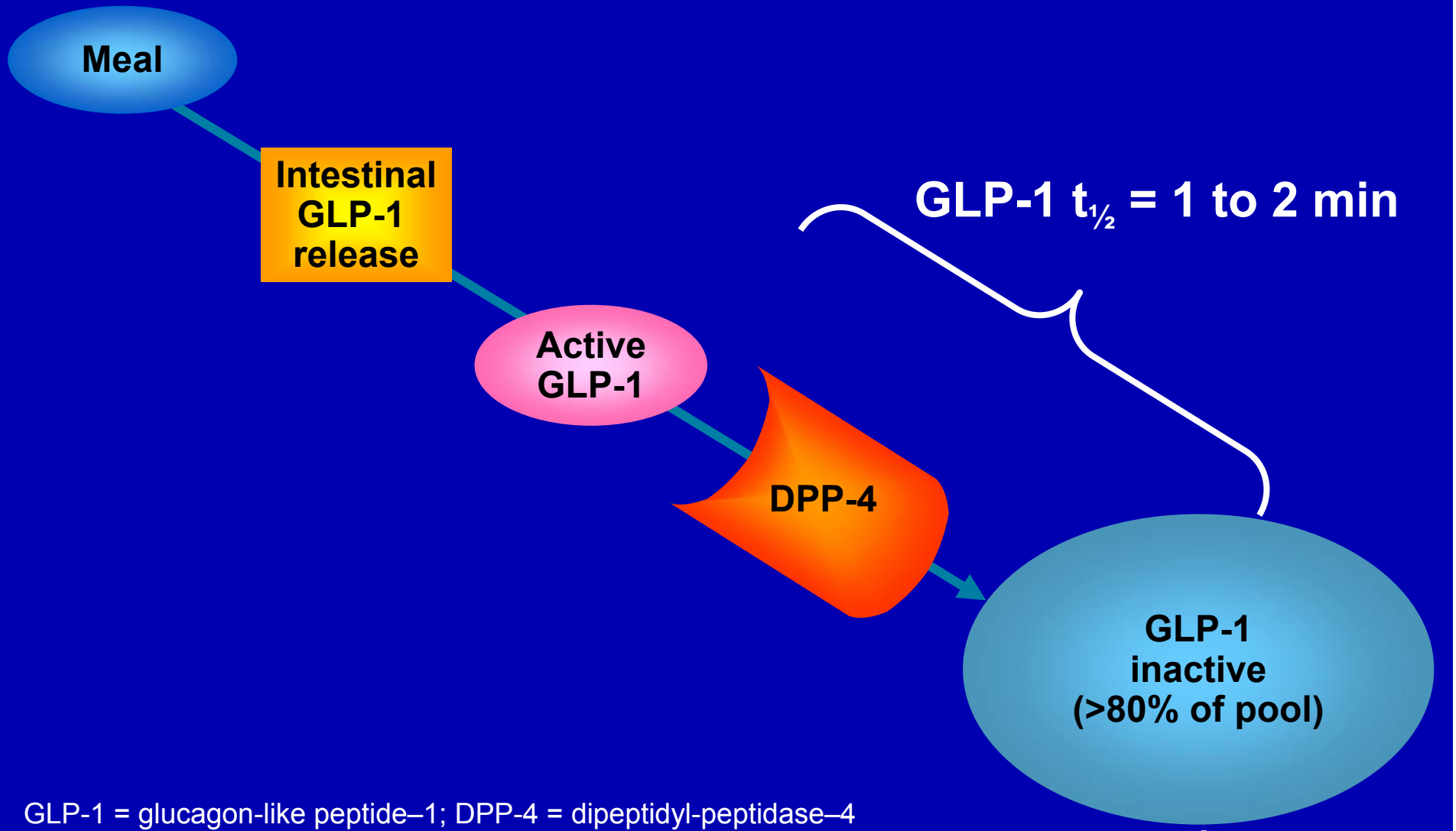
GLP-1 Secretion and Inactivation



GLP-1 = glucagon-like peptide–1; DPP-4 = dipeptidyl-peptidase–4

Adapted from Deacon CF, *et al. Diabetes*. 1995;44:1126-1131.

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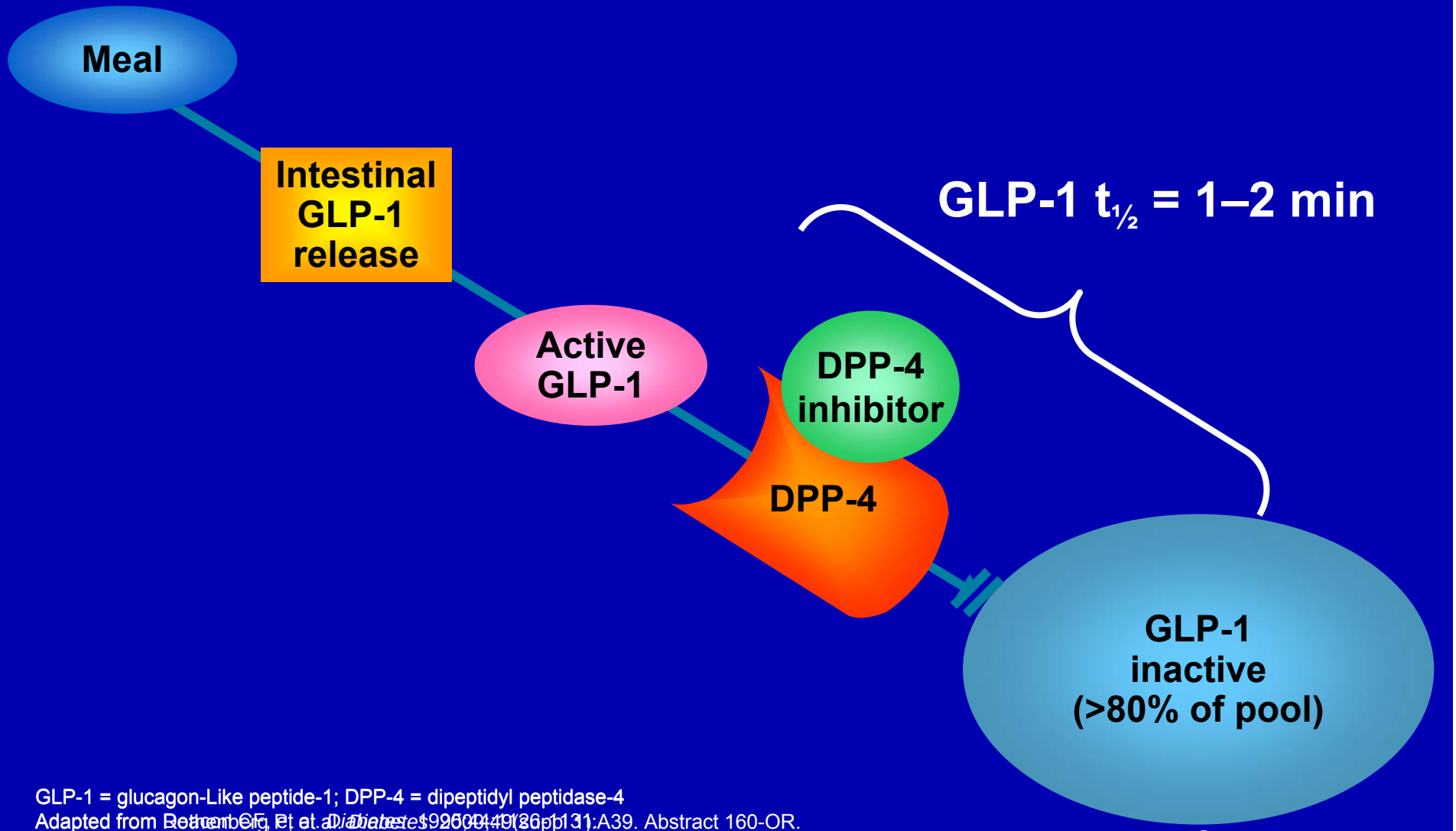
What Is DPP-4?

- A serine protease widely distributed throughout the body
- Cleaves N-terminal amino acids of a number of biologically active peptides, including the glucostatic incretins GLP-1 and GIP, for inactivation
- DPP-4 effects on GLP-1 and GIP proven to play a key role in incretin activity and glucose homeostasis
  - Inactivates GLP-1 >50% in ~1–2 min
  - Inactivates GIP >50% in ~7 min

DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; t½ = half-life

Adapted from Ahrén B. *Curr Enzyme Inhib*. 2005;1:65–73.

Inhibition of DPP-4 Increases Active GLP-1



GLP-1 = glucagon-Like peptide-1; DPP-4 = dipeptidyl peptidase-4

Adapted from Rothenberg P, et al. *Diabetes* 1996;45(Suppl 1):A39. Abstract 160-OR.

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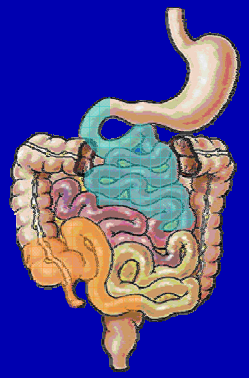
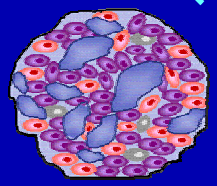
Blocking DPP-4 Can Improve Incretin Activity and Correct the Insulin : Glucagon Ratio in T2DM



T2DM

Incretin Response Diminished

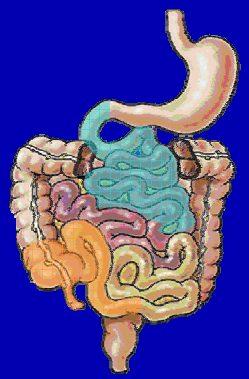
↓ Insulin



Further impaired islet function

↑ Glucagon

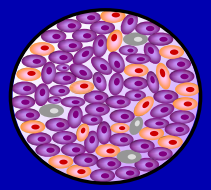
HYPERGLYCEMIA



DPP-4 Inhibitor

Incretin Activity Prolonged

↑ Insulin



Improved islet function

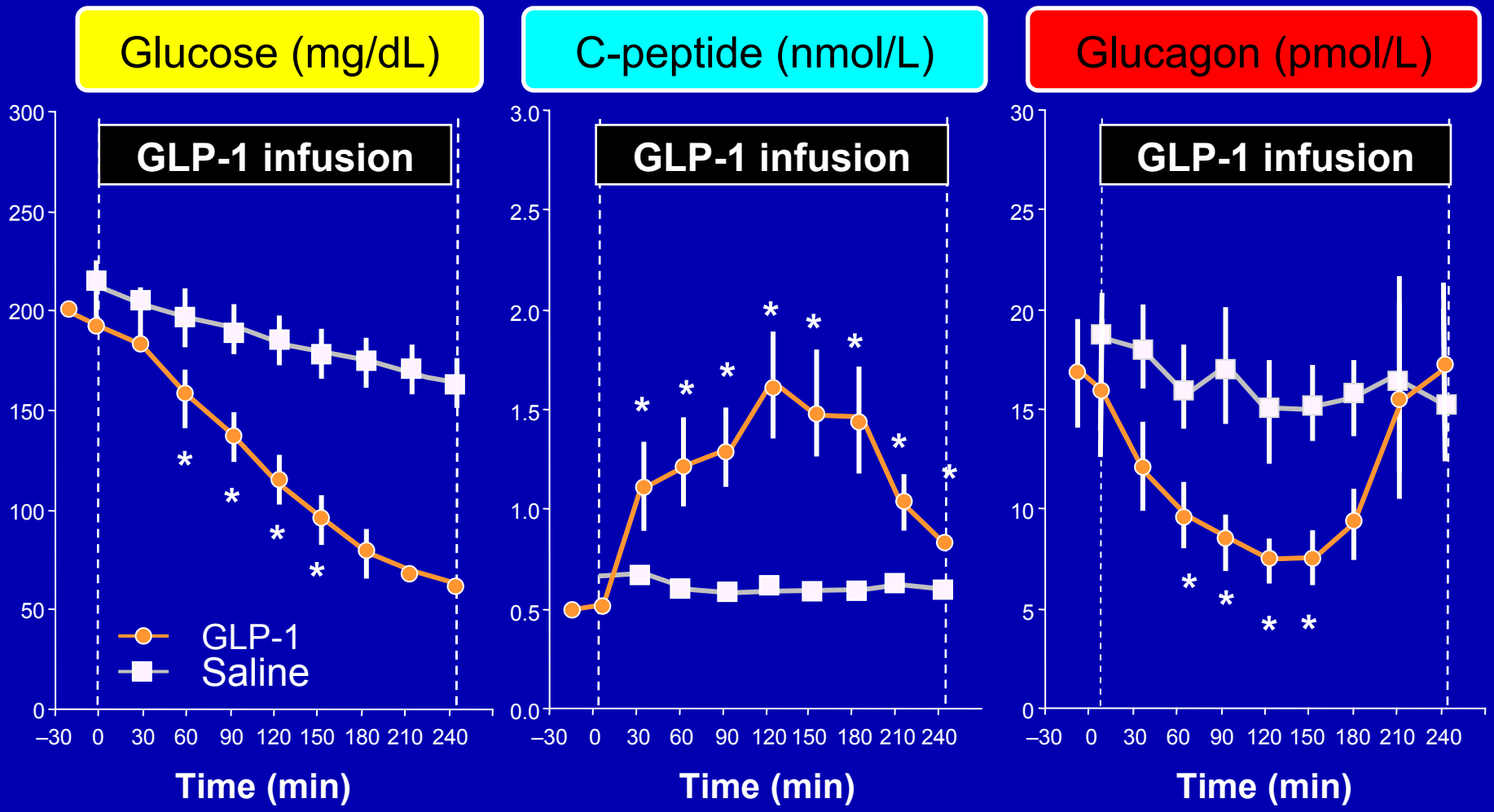
↓ Glucagon

IMPROVED GLYCEMIC CONTROL

DPP-4 = dipeptidyl peptidase-4; T2DM = type 2 diabetes mellitus

Adapted from Unger RH. *Metabolism.* 1974;23:581–593. Ahrén B. *Curr Enzyme Inhib.* 2005;1:65–73.

GLP-1 Restores Islet Glucose Sensing in Patients with T2DM



*$P < .05$

GLP-1 = glucagon-like peptide–1; T2DM= type 2 diabetes mellitus

Adapted from Nauck MA, *et al*. *Diabetologia.* 1993;36:741–744.

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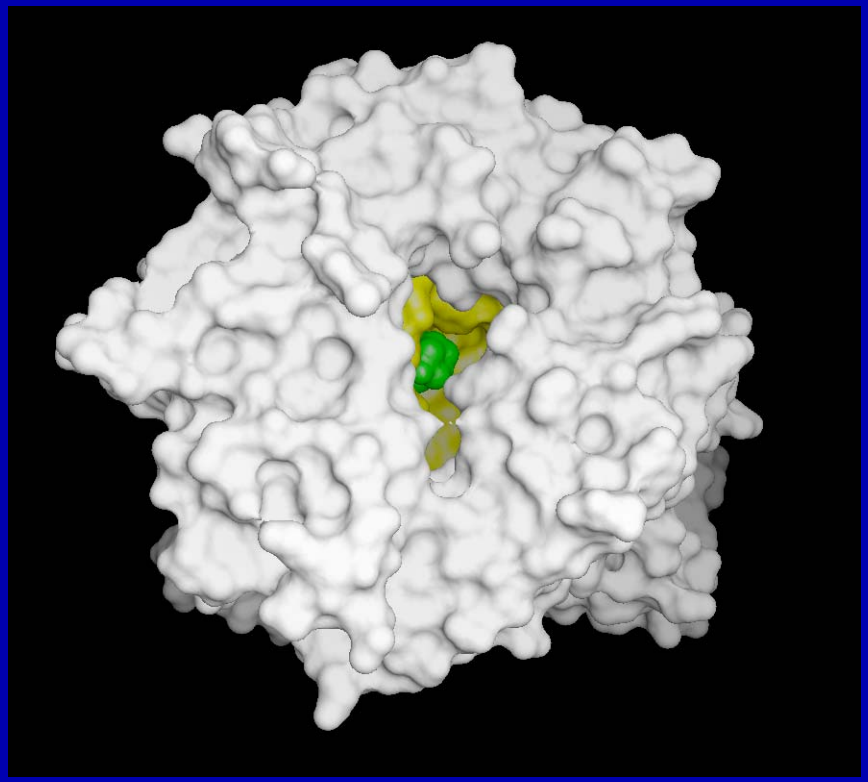
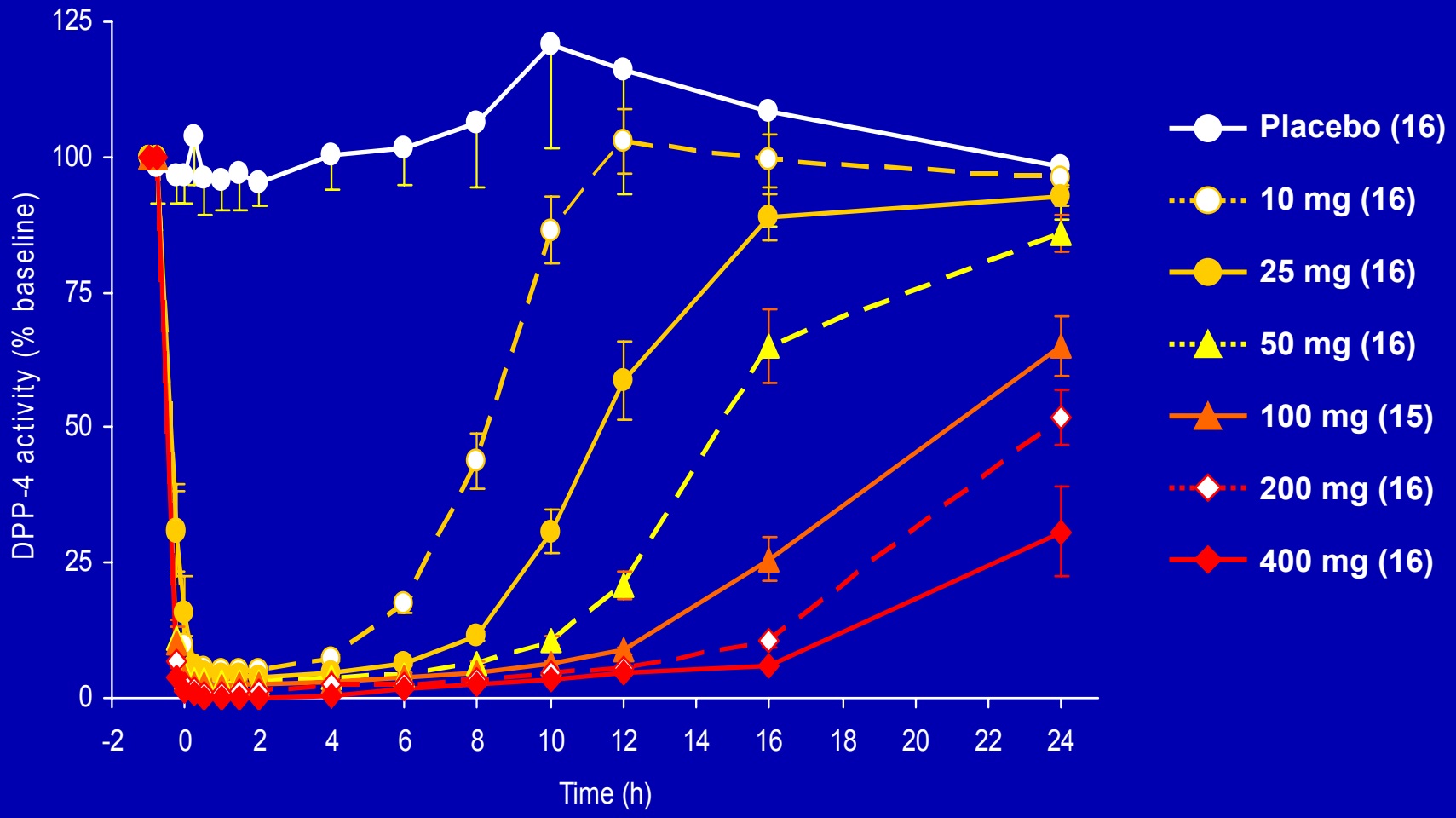
Vildagliptin (LAF237) Glycylpyrrolidine



- Highly selective DPP-4 inhibitor
- Has a high affinity for the human enzyme
- Reversible inhibition

X-ray crystallographic structure of LAF237 (green) bound to the active site (yellow) of human DPP-4

Plasma DPP-4 Activity after Single Oral Doses of Vildagliptin (10 to 400 mg) in Patients with T2DM



Data on file, Study LAF2215, Novartis

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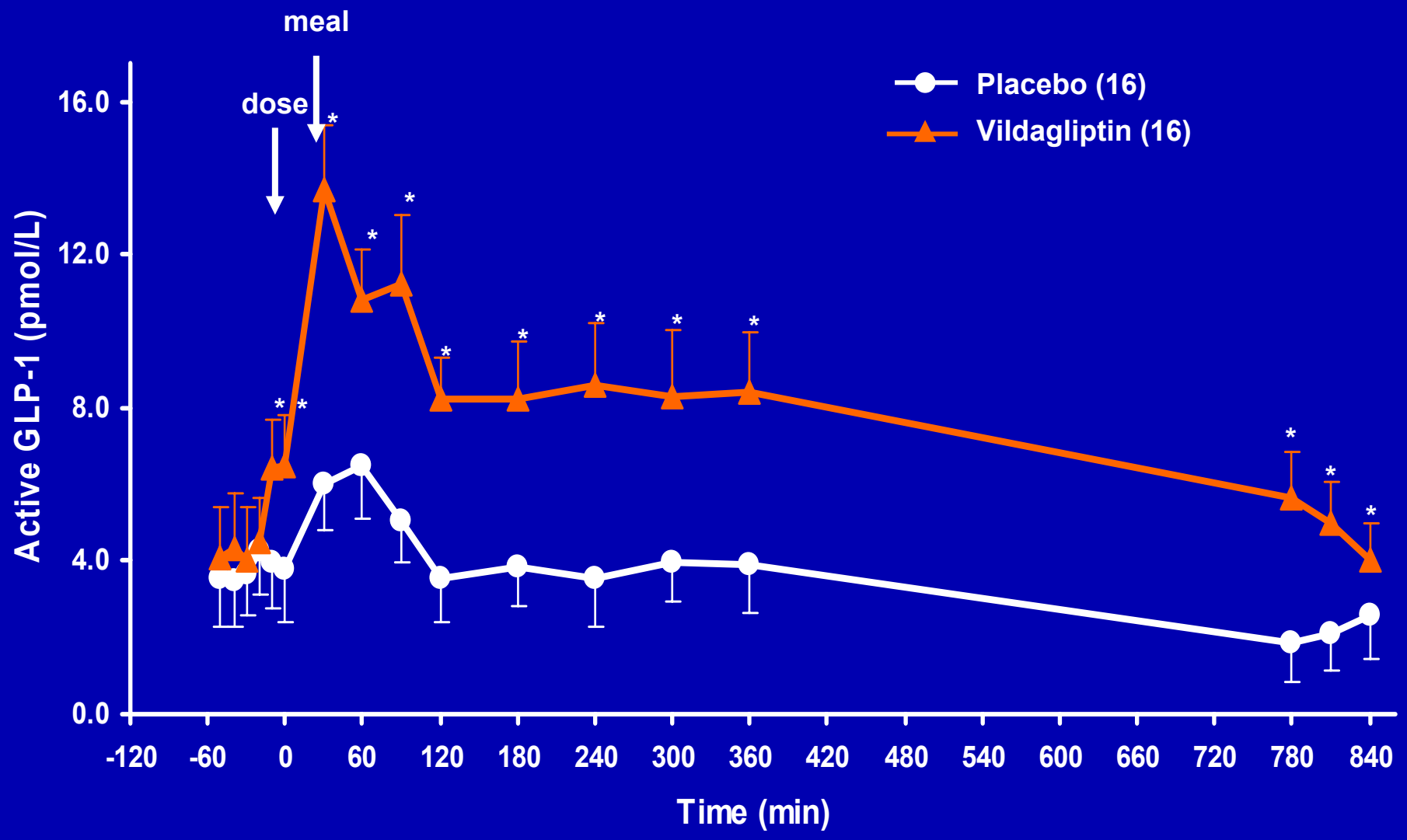
Plasma Levels of Intact (Active) GLP-1 after a Single Oral Dose of Vildagliptin (100 mg) or Placebo in Patients with T2DM



Study LAF2346, data on file

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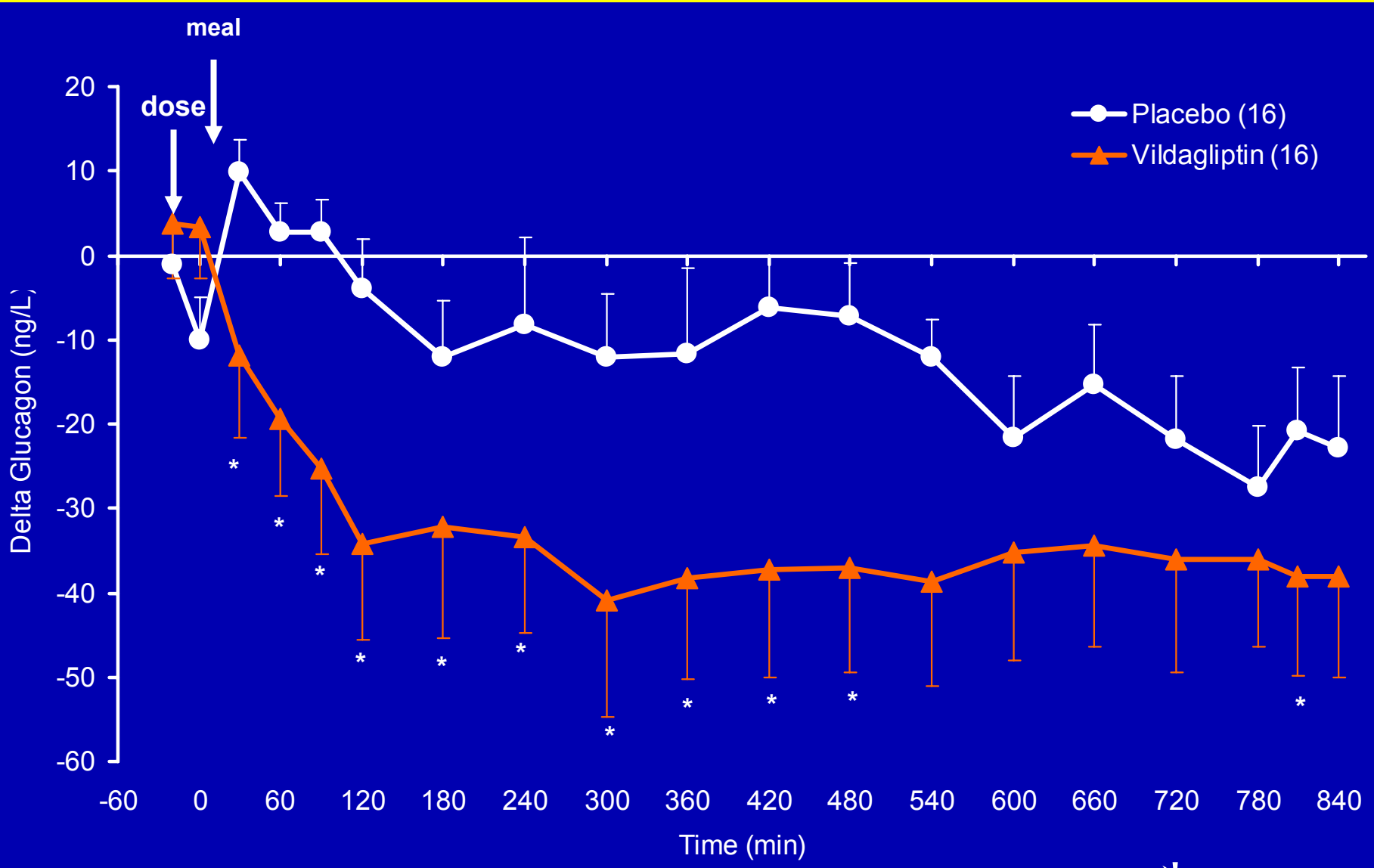
Change from Baseline (pre-meal) in Plasma Glucagon after Single Oral Dose of Vildagliptin (100 mg) or Placebo



Study LAF2346, data on file

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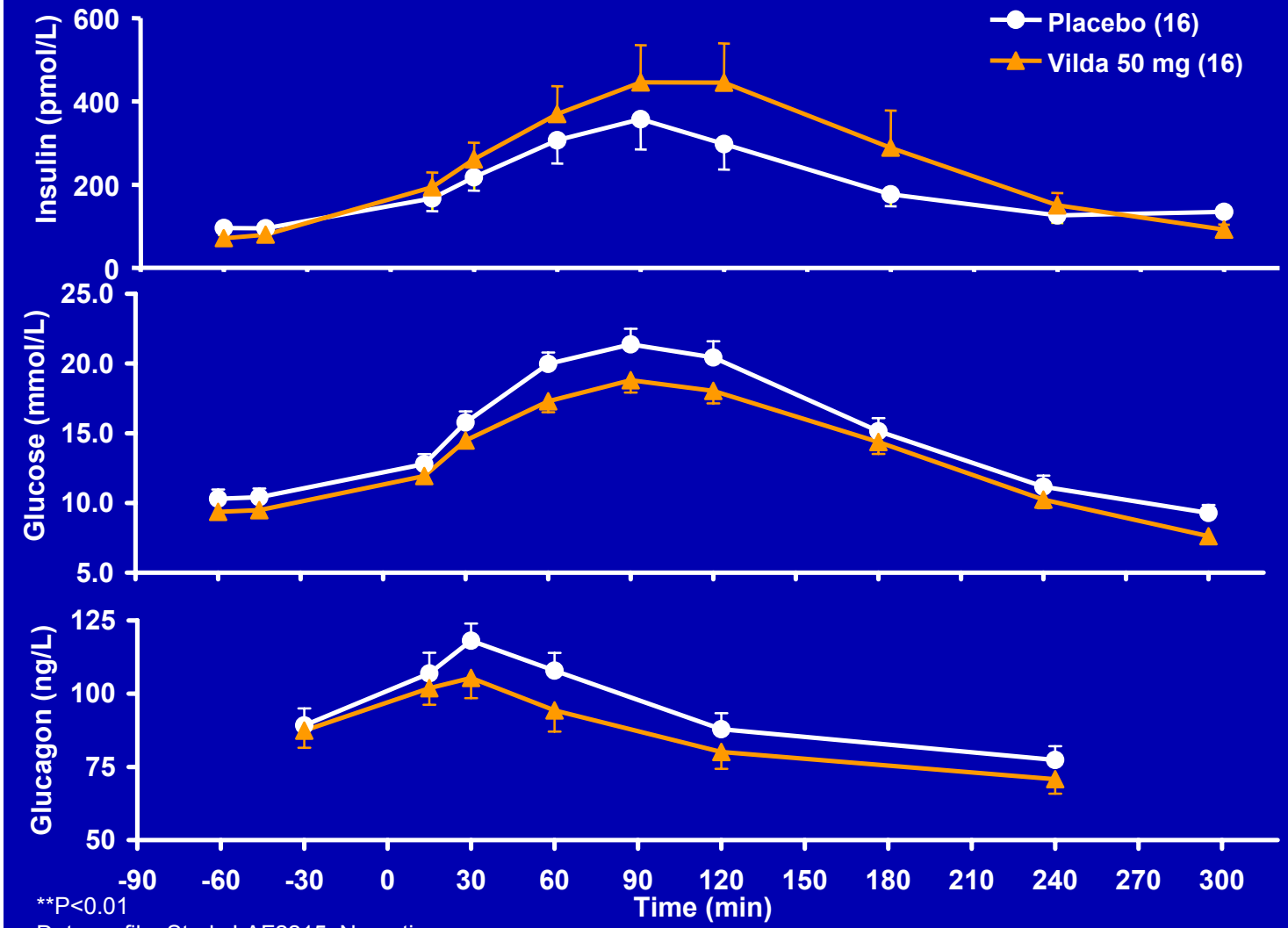
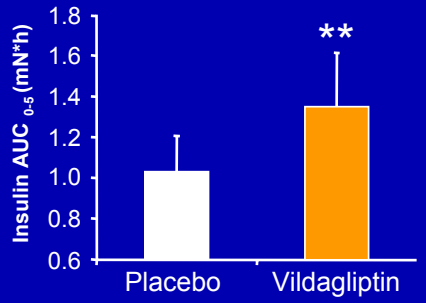
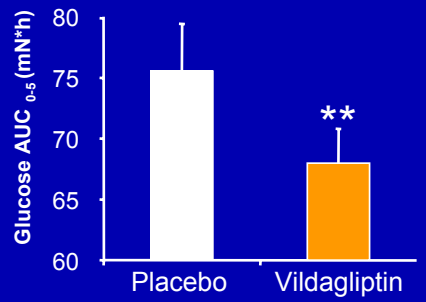
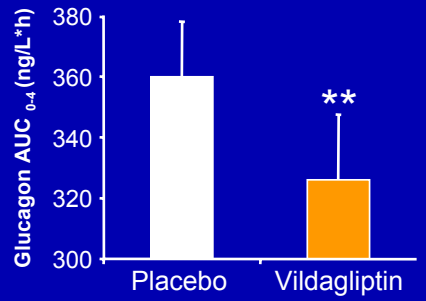
Vildagliptin increases Insulin, and decreases Glucagon concentrations Resulting in lower Glucose levels in Patients with T2DM

OGTT 30 min after single oral dose of Vildagliptin (50 mg)









**P<0.01

Data on file, Study LAF2215, Novartis

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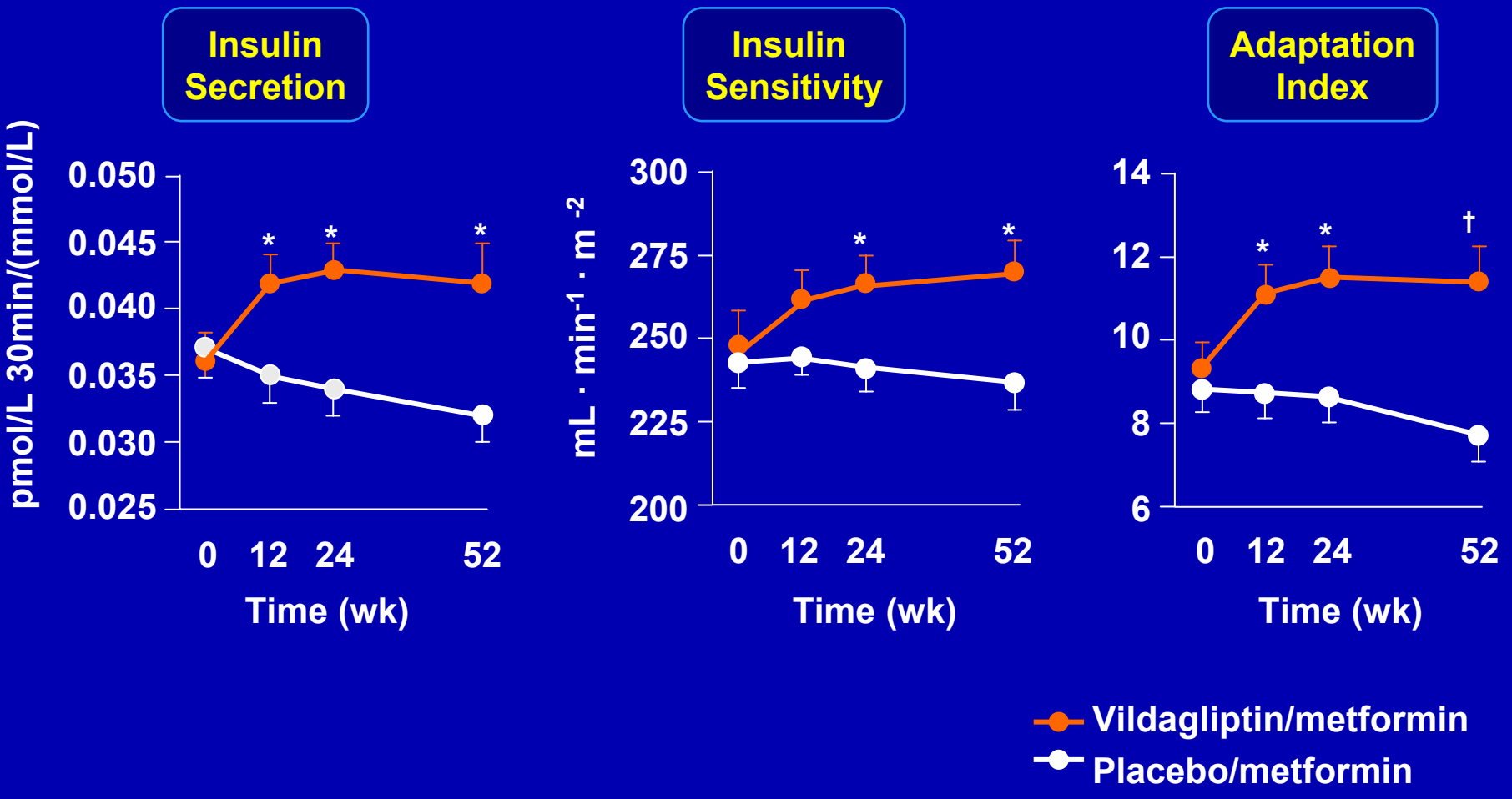
Meal-related β-Cell Function and Insulin Sensitivity after Vildagliptin vs. Placebo in Patients with T2DM

Patients on Stable Metformin Therapy



*P<0.05 vs. placebo; †P<0.01 vs. placebo

Adapted from Ahren B, et al. *Diabetes Care*. 2005;28:1936-1940

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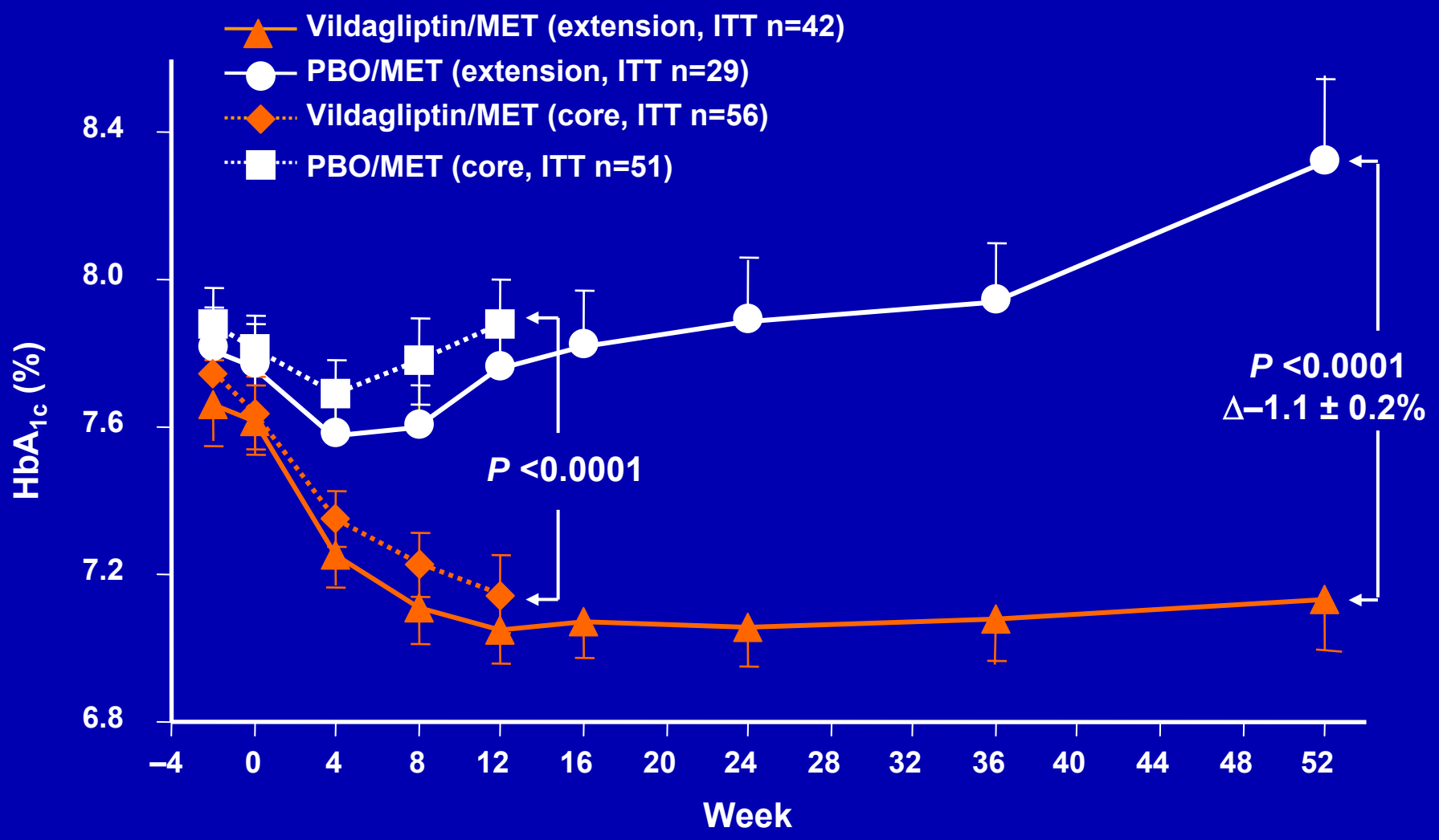
Vildagliptin Therapy Significantly Lowers HbA_{1c} over the course of 1 Year



Met=Metformin; PBO=Placebo; ITT=Intent-To-Treat

Adapted from Ahrén B, et al. *Diabetes Care*. 2004; 27(12):2874–2880

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New Approaches to Harnessing Incretins for Improved Glucose Control

Two Approaches to Prolonging Incretin Activity

DPP-4 Inhibitors	Incretin Mimetics
• Significant HbA_{1c} reduction	• Significant HbA_{1c} reduction
• Weight neutral	• Weight loss
• Oral administration	• Injection
• Almost no GI side effects	• Higher rate of GI side effects
• Very low rate of hypoglycemia	• Higher rate of hypoglycemia*
• Multiple targets (GLP-1, GIP)	• Single target (GLP-1)
• Drug overdose not toxic	• Drug overdose problematic

DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}
*When administered with sulfonylureas
Adapted from Ahrén B. *Curr Enzyme Inhib*. 2005;1:65–73. Drucker D. *Diabetes Care*. 2003;26:2929–2940.

Summary: Potential of DPP-4 Inhibition in the Treatment of T2DM

- DPP-4 is a ubiquitous enzyme that rapidly inactivates more than 50% of the glucostatic incretins GLP-1 and GIP
- Two approaches to prolonging incretin activity are:
  - DPP-4 inhibitors (oral agents): inhibit the degradation of active incretins
  - Incretin mimetics (injectable agents): degradation-resistant GLP-1 analogues
- Inhibiting DPP-4 results in:
  - Improved islet cell function through increased levels of intact incretin hormones (GLP-1, GIP)
  - Improved glycemic control

DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus

Summary

Vildagliptin inhibits DPP-4 resulting in

↑ Fasting and post prandial GLP-1 and GIP levels

Enhanced islet function

- ↑ sensitivity of glucagon secretion to glucose
- ↑ sensitivity of insulin secretion to glucose
- ↑ 1st phase insulin secretion
- ↑ capacity to secrete insulin

↓ Post prandial triglycerides

↓ Insulin resistance

No effect on gastric emptying

Vildagliptin in Monotherapy

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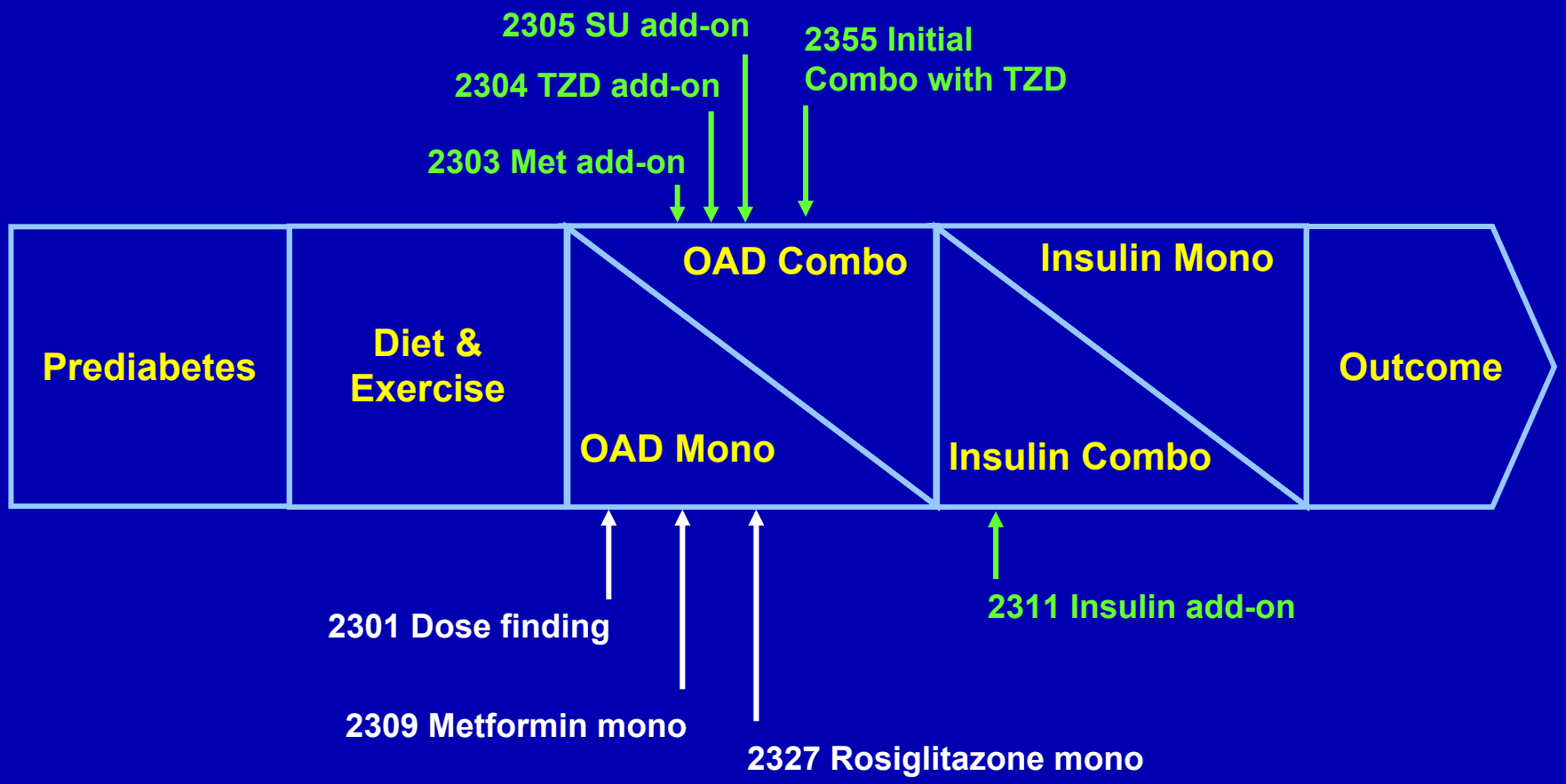
Overview of Phase III Studies



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Demographics: Key Monotherapy Studies

	N	Gender (%)		Age (y)	Race/Ethnicity (%)			
		F	M	Mean	Wh	His	As	Bl
Placebo-controlled monotherapy study								
Study 2301								
Vilda 50 mg qd	104	58.7	41.3	55.3	73.1	13.5	2.0	9.6
Vilda 50 mg bid	90	53.3	46.7	52.8	73.3	13.3	1.1	10.0
Vilda 100 mg qd	92	46.7	53.3	53.6	76.1	15.2	4.4	4.3
PBO	94	52.1	47.9	52.2	69.1	11.7	5.3	12.8
Active-controlled monotherapy studies								
Study 2309								
Vilda 50 mg bid	526	47.1	52.9	52.8	67.9	19.8	2.1	8.0
Met 1000 mg bid	254	42.5	57.5	53.6	69.7	21.7	2.4	5.1
Study 2327								
Vilda 50 mg bid	459	42.5	57.5	54.5	79.5	11.1	2.4	5.9
Rosi 8 mg qd	238	42.4	57.6	54.2	79.8	12.2	1.6	4.6

F = female, M = Male; Wh = white/Caucasian, His = Hispanic/Latino, As = Indian/non-Indian Asians, Bl = black/African origin

Primary efficacy ITT patients

Data on file, Novartis

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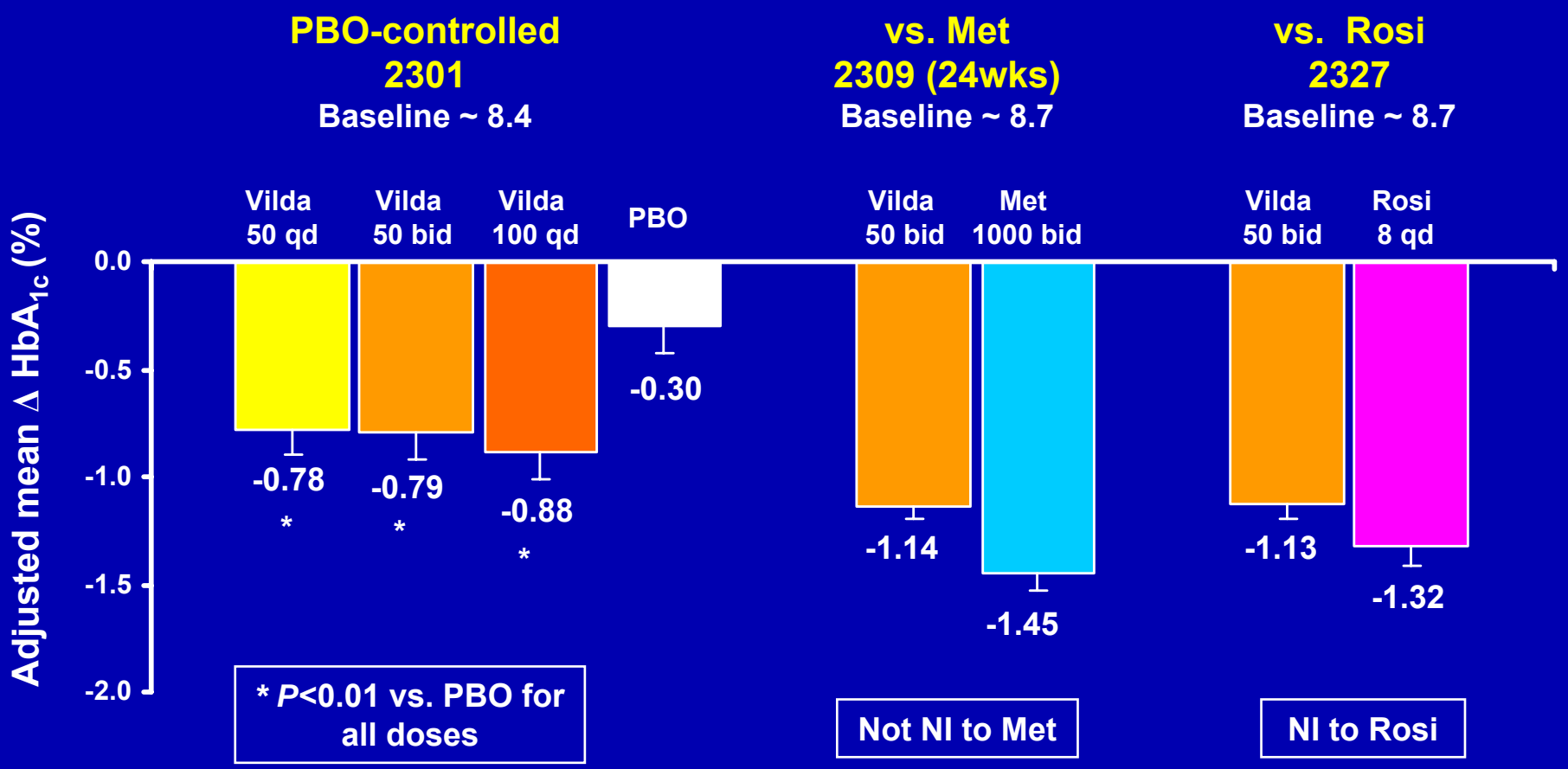
Disease Features at Baseline: Key Monotherapy Studies

	N	BMI (kg/m^2)	HbA_{1c} (%)	FPG (mmol/L)	Duration (y)
		Mean	Mean	Mean	Mean
Placebo-controlled monotherapy study					
Study 2301					
Vilda 50 mg qd	104	32.9	8.2	9.8	2.1
Vilda 50 mg bid	90	33.3	8.6	10.1	2.1
Vilda 100 mg qd	92	32.4	8.4	9.9	2.4
PBO	94	32.6	8.4	9.9	1.6
Active-controlled monotherapy studies					
Study 2309					
Vilda 50 mg bid	526	32.4	8.7	10.5	2.4
Met 1000 mg bid	254	32.5	8.7	10.5	2.2
Study 2327					
Vilda 50 mg bid	459	32.2	8.7	10.3	2.3
Rosi 8 mg qd	238	32.9	8.7	10.3	2.7

Primary efficacy ITT patients

Data on file, Novartis

Monotherapy: HbA_{1c} Reduction



ITT=intention to treat; NI=non-inferiority
Primary efficacy ITT population
Data on file, Novartis

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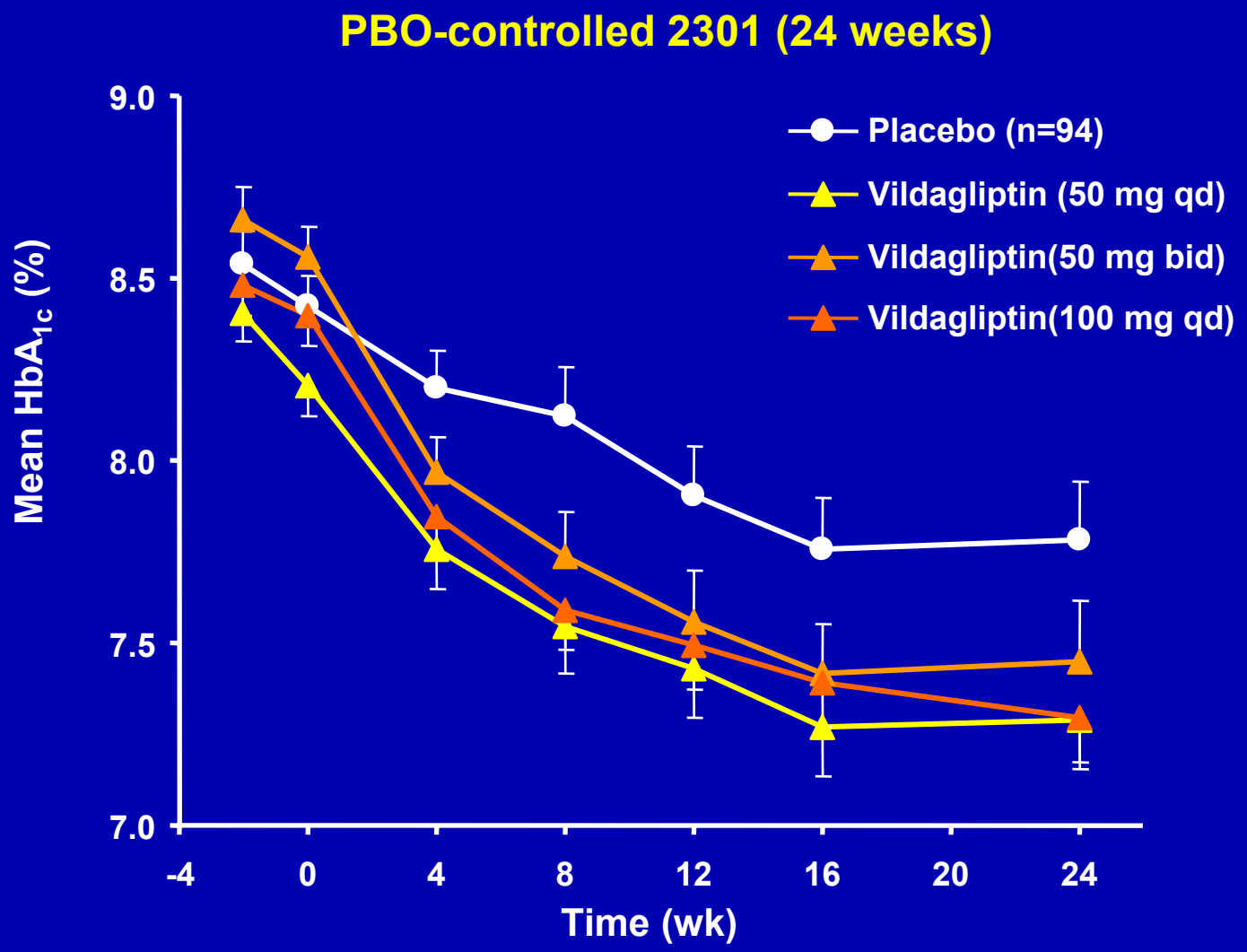
Monotherapy: Time Course of HbA_{1c} Reduction



Data on file, Novartis

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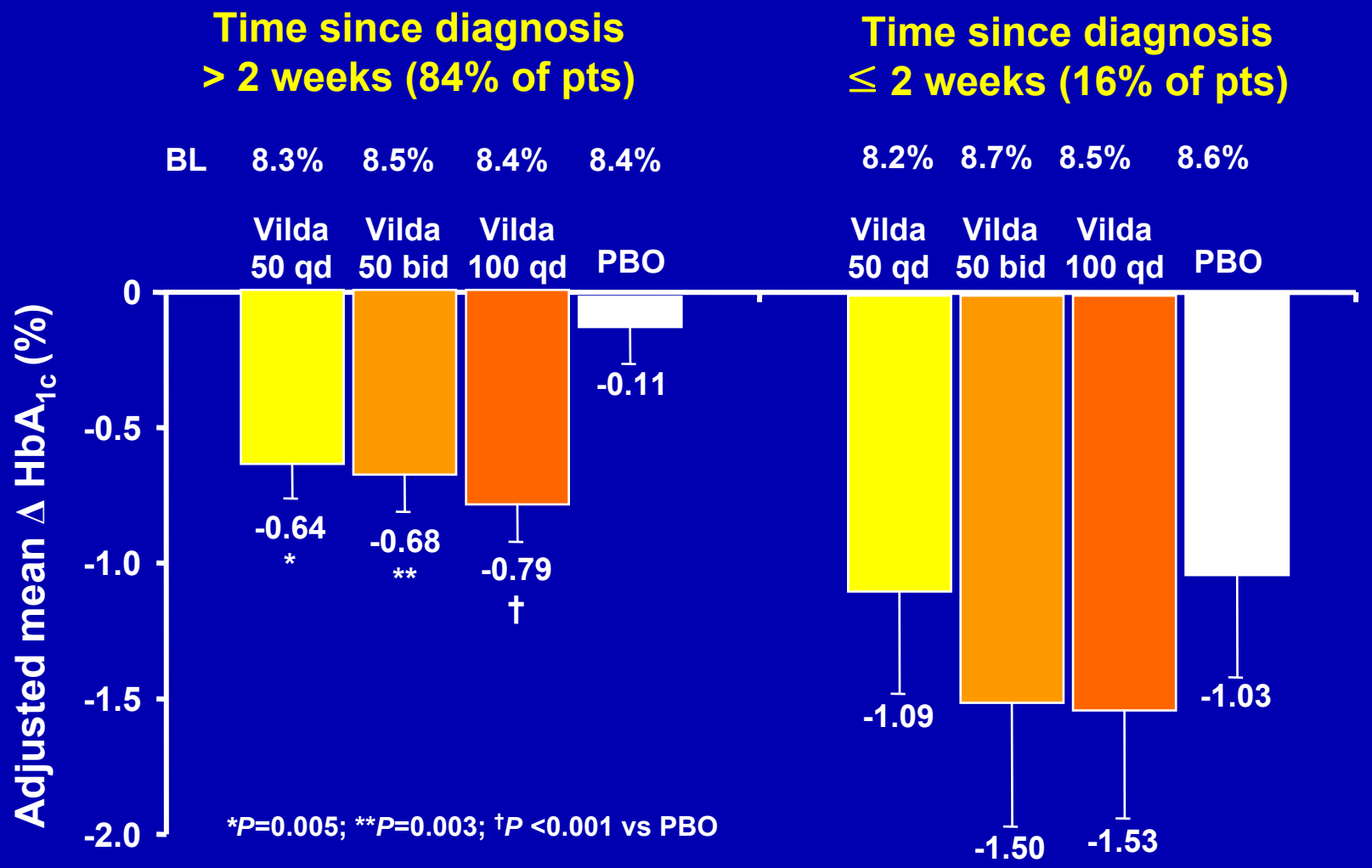
Study 2301: Efficacy of Monotherapy in Stable vs. Newly Diagnosed Patients



Vilda=vildagliptin; PBO=Placebo
Primary ITT population
Data on file, Novartis

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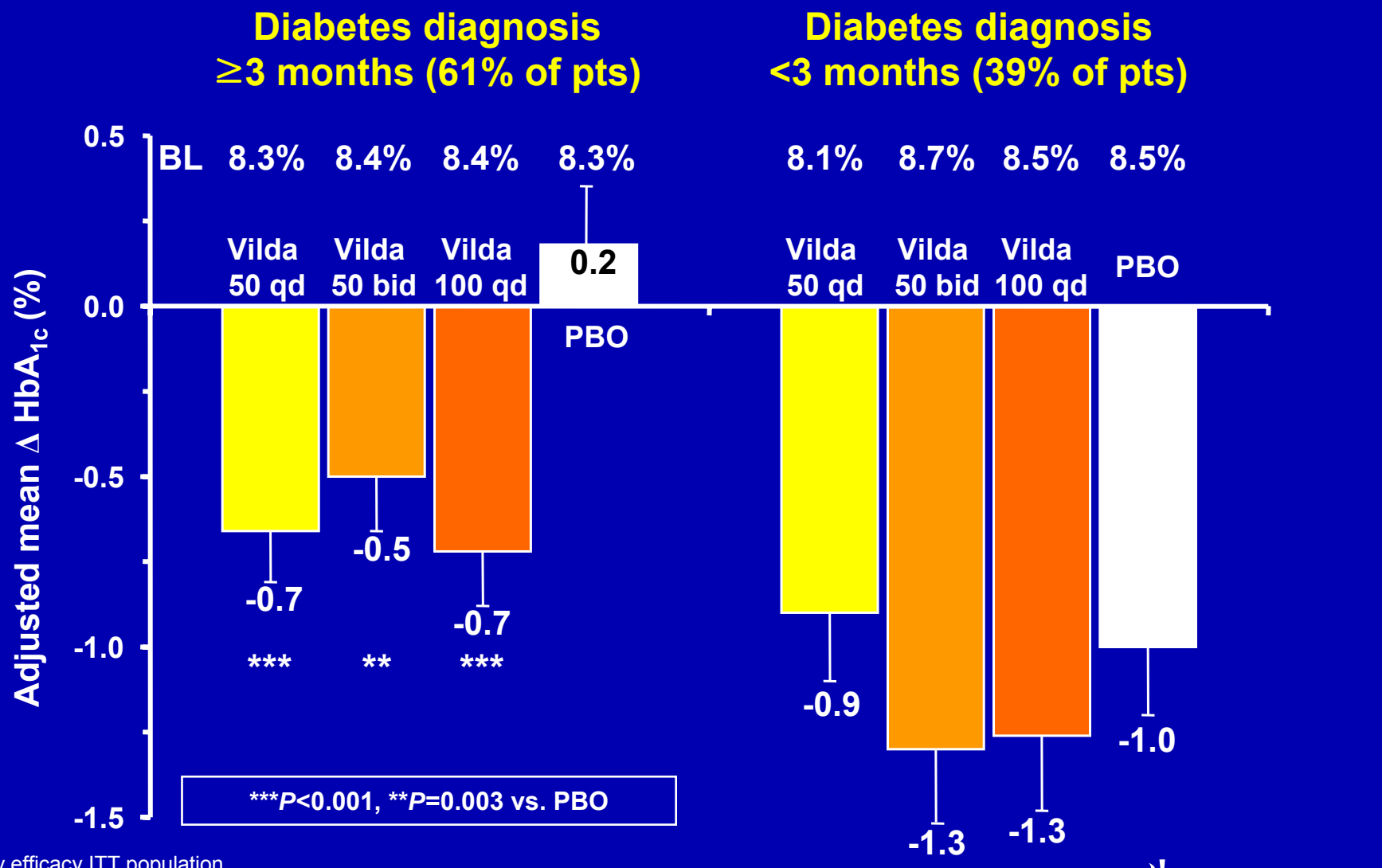
Study 2301: Efficacy of Monotherapy in Stable vs. Newly Diagnosed Patients



Primary efficacy ITT population
Data on file, Novartis

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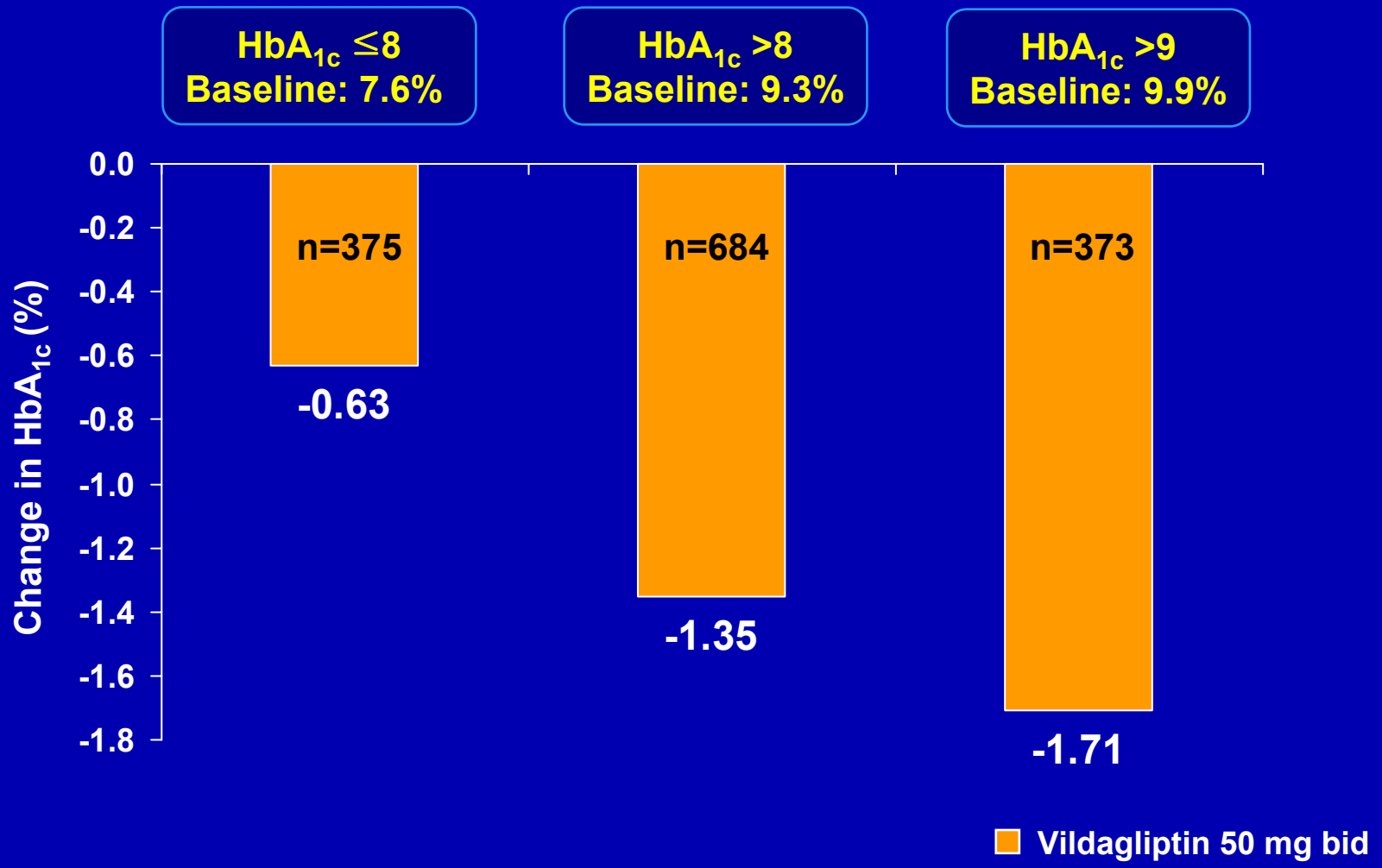
Efficacy by BL HbA_{1c} Subgroups: Pooled Monotherapy Data (Vildagliptin 100 mg/day)



Pooled analysis from LAF237A2301, 2309, 2327
primary efficacy ITT population
Data on file, Novartis Pharmaceuticals

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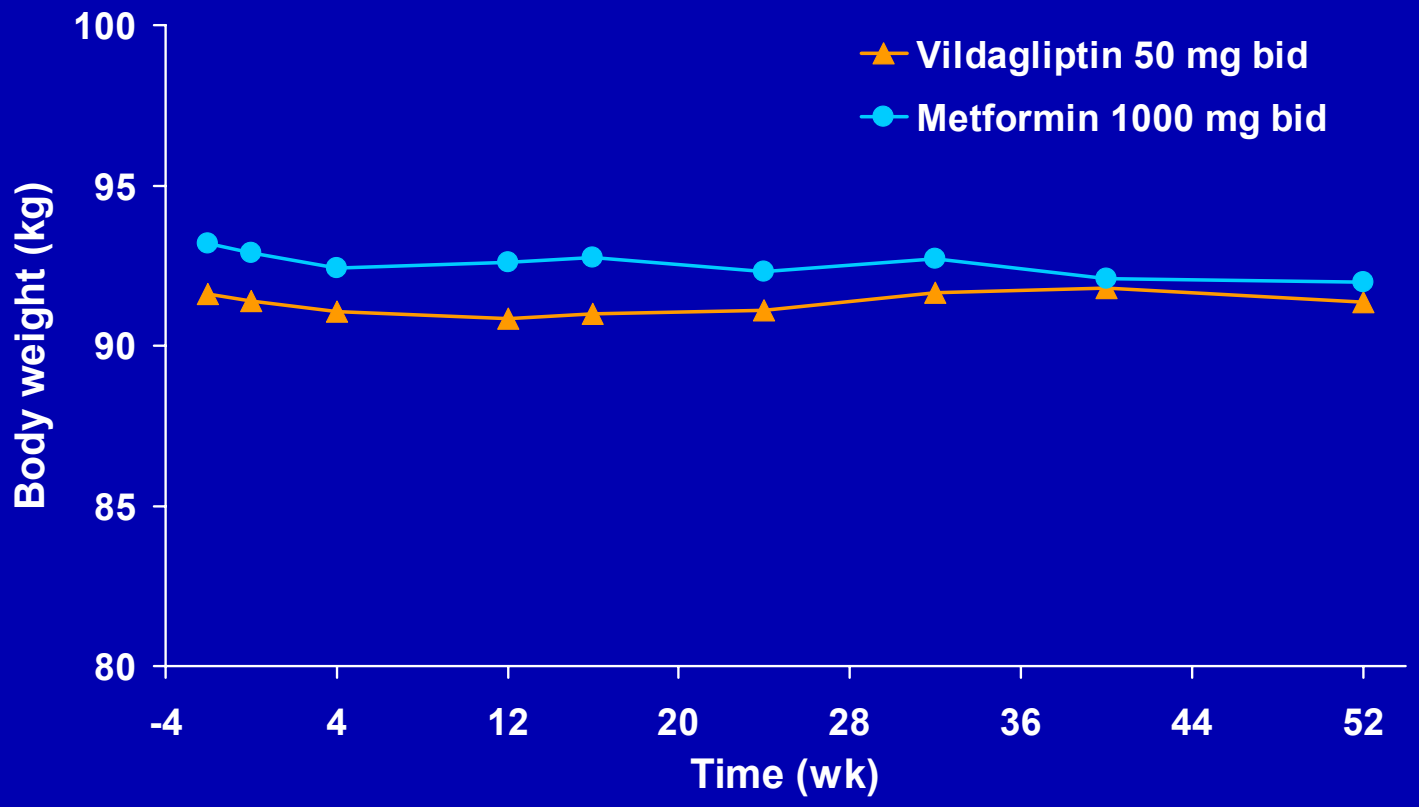
No Weight Gain Associated with Vildagliptin Monotherapy over 52 weeks

Vildagliptin vs. Metformin (52 weeks)



Vilda=Vildagliptin; Met=Metformin
ITT population
Data on file, Novartis Pharmaceuticals, LAF237A2309

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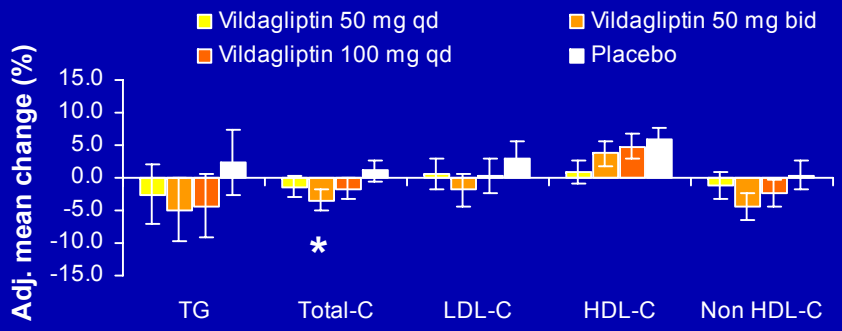
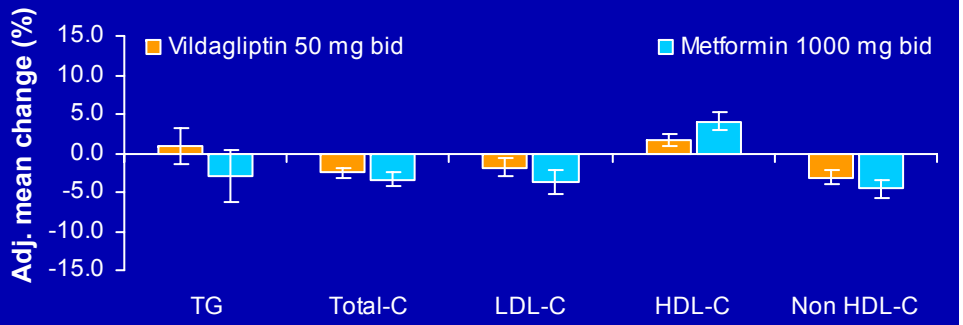
Monotherapy: Fasting Lipids

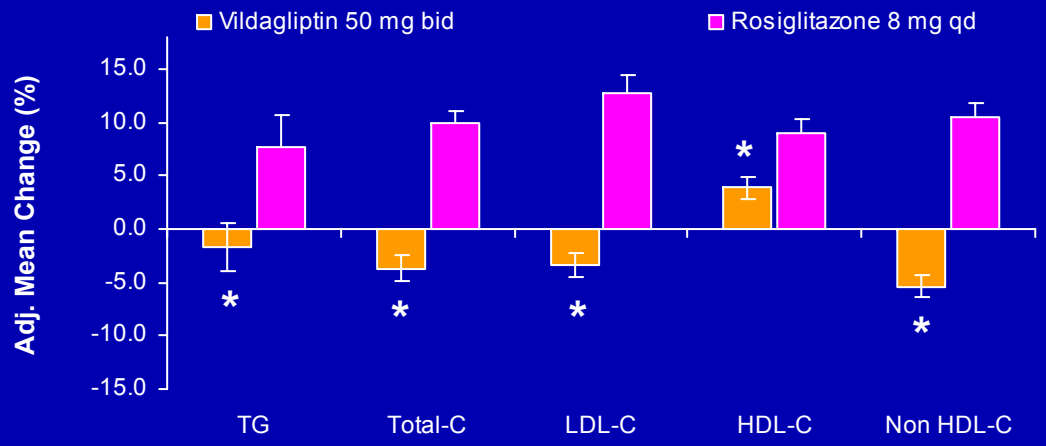
vs. Placebo 2301



vs. Metformin 2309 (Wk 24)



vs. Rosiglitazone 2327



Data on file, Novartis

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Favorable Safety and Tolerability of Vildagliptin in *Monotherapy*

- **Overall incidence of AEs comparable to Placebo**
  - No relationship to dose in the frequency of AEs
  - Severity of AEs comparable in all vildagliptin dose groups
  - No relationship between duration of exposure and onset of AEs
  - Discontinuation rate due to AEs less than Placebo
- **No increased risk of hypoglycemia at any dose**
- **Superior GI tolerability vs metformin (diarrhea: 6% vs 26%)**
- **No increased rates of notable changes** in labs, vital signs, and clinically relevant prolongations of ECG conduction intervals during chronic use or at C_{max} compared with placebo

Vildagliptin Safety in *Monotherapy*: AEs ≥ 5% Incidence in Any Group

Preferred term, %	Vilda 50 mg qd (N=323)	Vilda 50 mg bid* (N=1292)	Vilda 100 mg qd (N=238)	Met up to 1 g bid (N=252)	Rosi 8 mg qd (N=267)	Pio 30 mg qd (N=55)	PBO (N=255)
Any	56.3	63.5	64.3	75.4	64.0	45.5	60.0
Nasopharyngitis	6.2	7.7	7.6	9.5	7.5	1.8	7.1
Headache	4.6	7.1	7.1	7.1	5.2	5.5	5.9
Dizziness	4.6	5.7	6.3	6.0	4.1	3.6	4.3
Upper respiratory tract infection	1.2	4.8	3.8	6.0	3.0	1.8	2.7
Diarrhea	0.9	3.5	0.8	26.2	2.6	3.6	3.1
Nausea	1.5	3.2	1.7	10.3	0.7	1.8	3.9
Abdominal pain	0.3	1.4	0.0	7.1	0.7	3.6	1.2

AE=adverse event; Vilda=vildagliptin; Met=metformin; Rosi=rosiglitazone; Pio=pioglitazone; PBO=placebo
*Preferred terms are sorted by descending order of incidence in the vildagliptin 50 mg bid group.
Note: A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Data on file, Novartis.

Vildagliptin Monotherapy: Lower Incidence Rate of Edema vs Rosiglitazone

Preferred Term	Vilda N=515 (%)	Rosi N=267(%)
Any AE	316 (61.4)	171 (64.0)
Peripheral Edema	11 (2.1)	11 (4.1)
Headache	26 (5)	14 (5.2)
Diarrhea	7 (1.4)	7 (2.6)
Nausea	18 (3.5)	2 (0.7)
Vomiting	11 (2.1)	0 (0)
Hypertension	11 (2.1)	5 (1.9)
Paraesthesia	10 (2)	10 (3.7)
Upper respiratory infections	23 (4.5)	8 (3)
Myalgia	6(1.2)	3 (1.1)
ECG abnormalities	51 (9.9)	32 (12)

Vildagliptin Hypoglycemic Events in *Monotherapy*

	Vilda 50 mg qd (N=323)	Vilda 50 mg bid* (N=1292)	Vilda 100 mg qd (N=238)	Met up to 1 g bid (N=252)	Rosi 8 mg qd (N=267)	Pio 30 mg qd (N=55)	PBO (N=255)
% of Pts with > 1 hypoglycemic event	0.6	0.3	0.8	0.4	0.4	0	0
% of Pts who disc. due to hypo	0	0	0	0	0	0	0
Total no of hypos	2/323	4/1292	3/238	1/252	1/267	0/55	0/255
Severity							
Grade 1	2	4	3	1	1	0	0
Grade 2	0	0	0	0	0	0	0
Suspected Grade 2	0	0	0	0	0	0	0

Hypoglycemic events are defined as:
Grade 1: Symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L; **Grade 2**: Symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is <3.1 mmol/L, **Suspected Grade 2:** Symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no plasma glucose measurement is available
Data on file, Novartis

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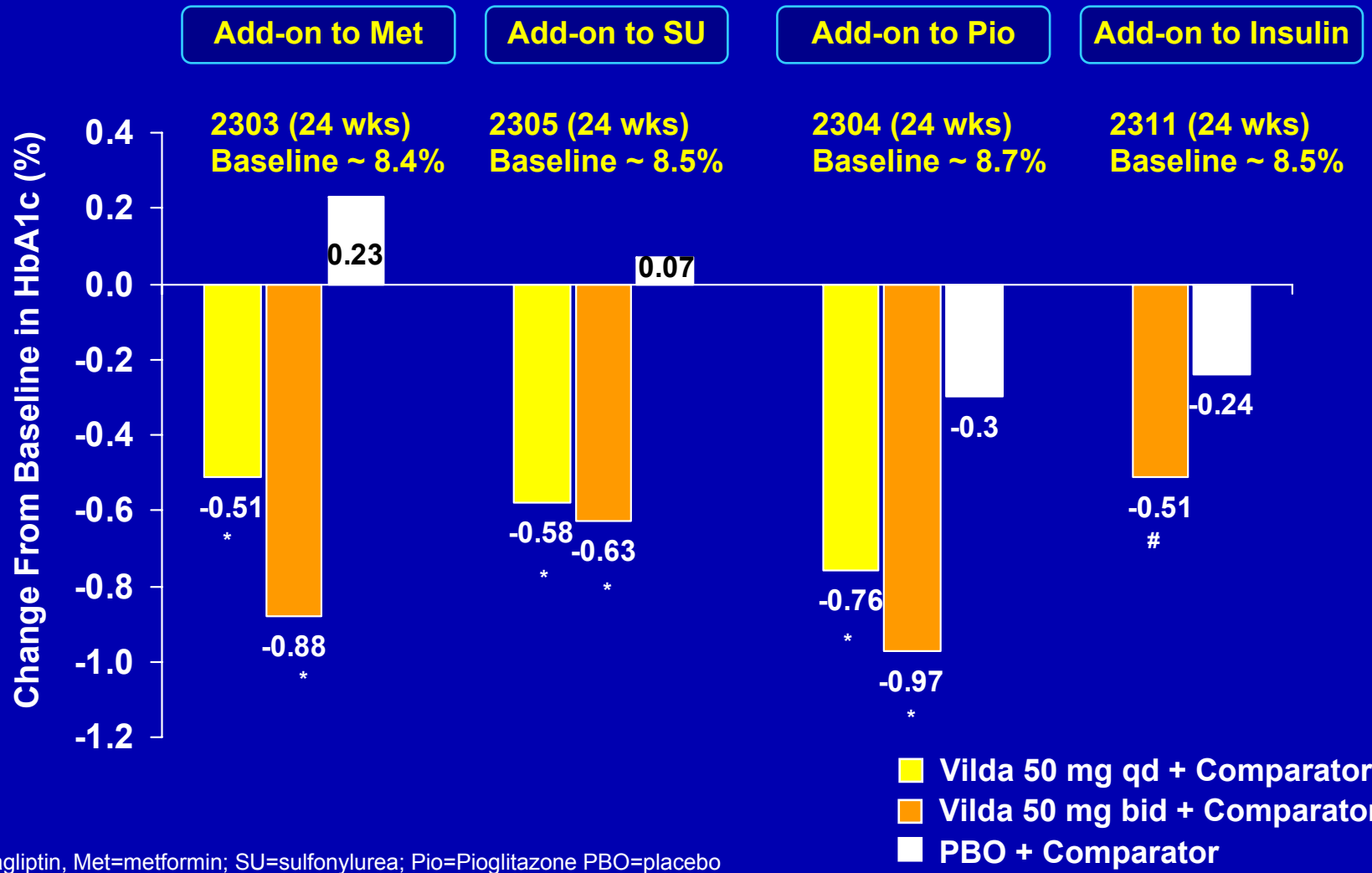
General Summary: Vildagliptin in Monotherapy

- Produces significant reductions in HbA1c levels (up to 1.8% in monotherapy)
- Sustains meaningful HbA1c reductions out to 1 year
- Has neutral effect on body weight
- Convenience of use: Simple oral dosing, no need for titration, very low potential for drug-drug interaction
- Superior GI tolerability vs metformin
- Overall incidence of AEs comparable to placebo
- No increased risk of hypoglycemia at any dose
- Potential for disease modification based on islet-cell effects and animal data

Vildagliptin in Combotherapy

Vildagliptin Shows Consistent and Clinically Relevant Reductions of HbA1c in Add-on Combination Therapy



Vilda-vildagliptin, Met=metformin; SU=sulfonylurea; Pio=Pioglitazone PBO=placebo
Primary efficacy ITT population
* P<0.001, # P=0.022 (vs PBO)
Data on file, Novartis Pharmaceuticals

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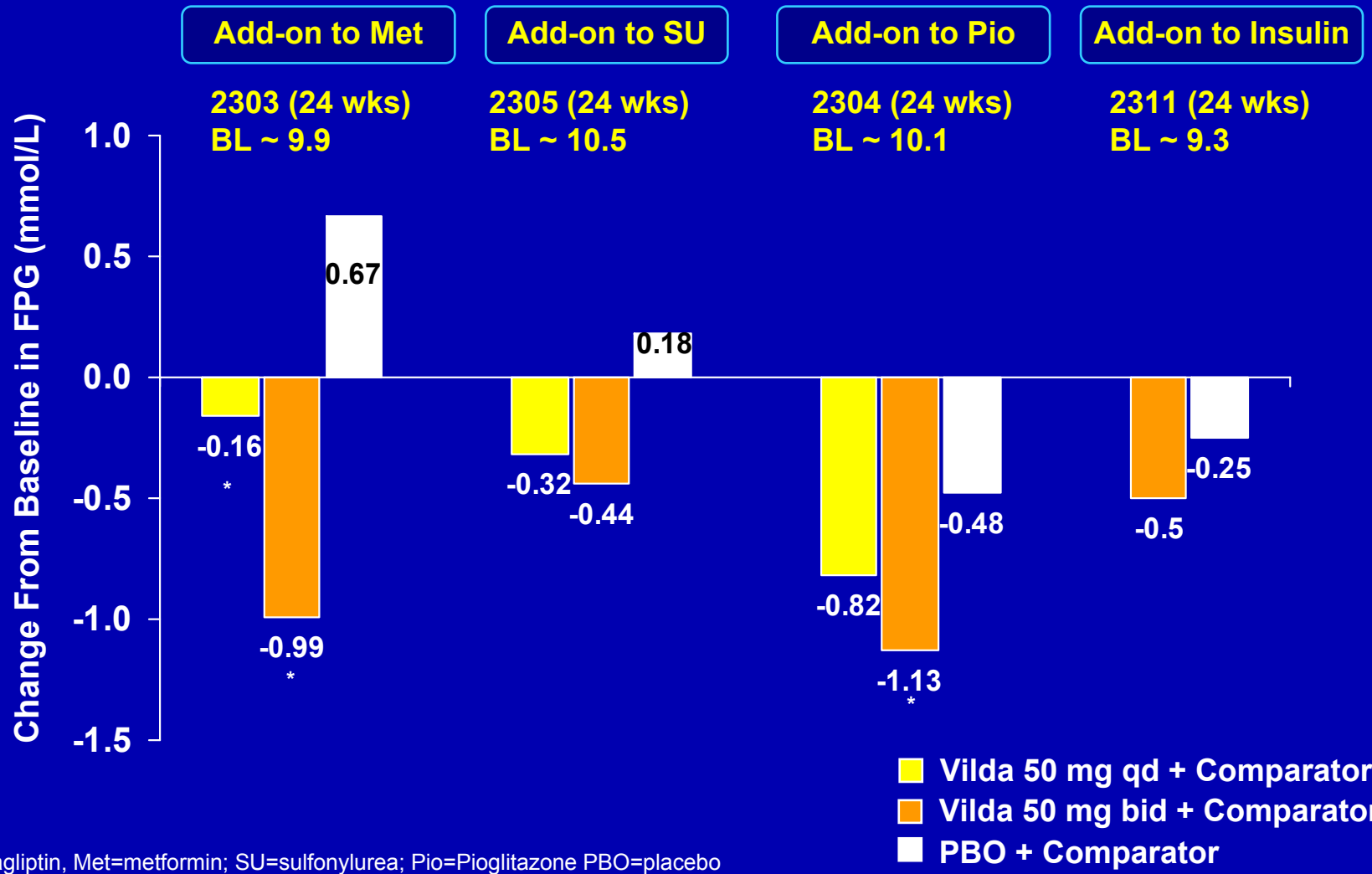
FPG Reductions in Add-on Combination Therapy



Vilda-vildagliptin, Met=metformin; SU=sulfonylurea; Pio=Pioglitazone PBO=placebo
Primary efficacy ITT population
* P<0.05, vs PBO+Comparator
Data on file, Novartis Pharmaceuticals

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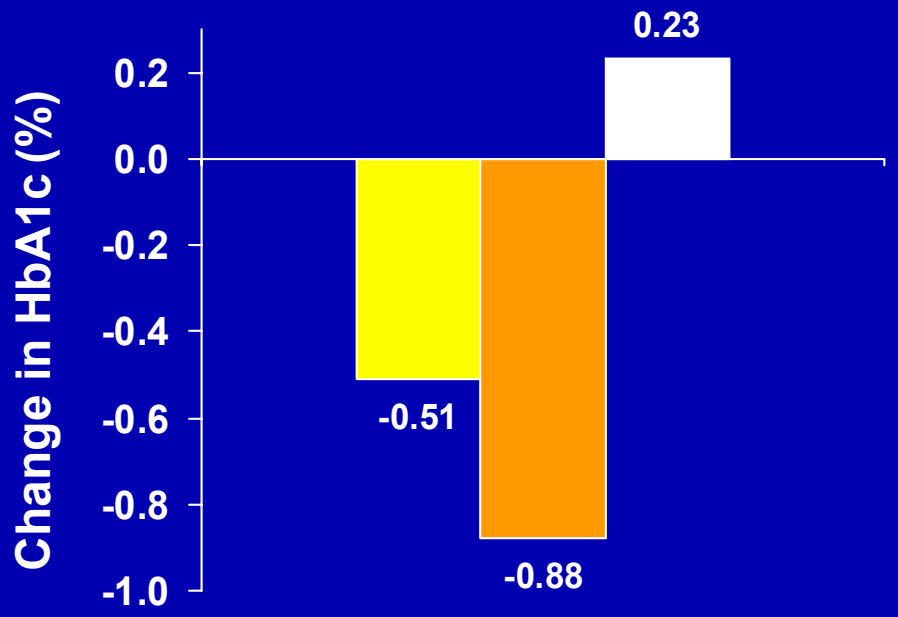
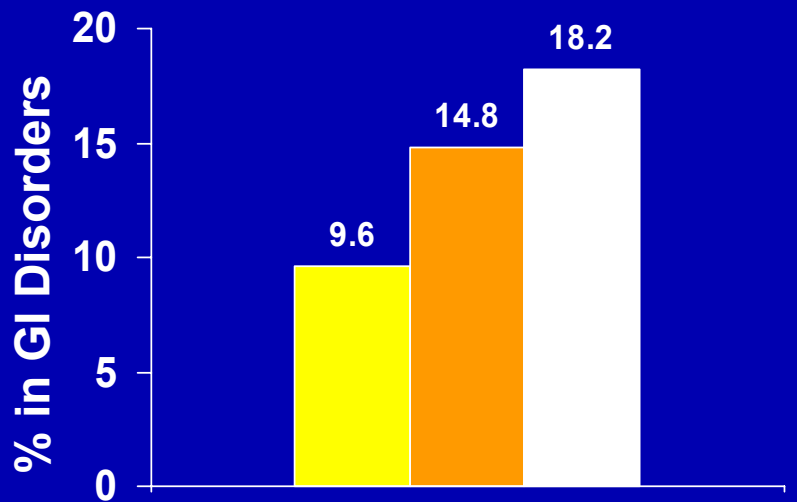
Add-on to Metformin: Improved Glycemic Control With Fewer GI Side Effects

HbA_{1c} Reduction From Baseline



% GI Disorders



Vilda 50 mg qd + Met (n=143)
Vilda 50 mg bid + Met (n=143)
PBO + Met (n=130)

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Add-on to SU: Hypoglycemic Events

Event	Vilda 50 mg qd + Glim (n=170)	Vilda 50 mg bid + Glim (n=169)	PBO + Glim (n=176)
% Pts with >1 hypo	1.2	3.6	0.6
% Pts who D/C due to hypo	0	0	0
Total no. of hypo	3	11	1
Severity			
Grade 1 (n)	3	11*	0
Suspected Grade 2 (n)	0	0	1

Vilda=vildagliptin; PBO=placebo; D/C=discontinued
Safety population, * 6 events occurred in the same patient
Data on file, Novartis Pharmaceuticals, LAF237A2305

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Add-On to Pioglitazone: Hypoglycemic Events

Event	Vilda 50mg qd + Pio 45mg N=146	Vilda 50mg bid + Pio 45mg N=158	Placebo + Pio 45mg N=158
% Pts with >1 hypo	0	0.6	1.9
% Pts who D/C due to hypo	0	0	0
Total no. of hypo	0	2	3
Severity			
Grade 1 (n)	0	2	3

Vilda=vildagliptin; PBO=placebo; D/C=discontinued; Pio=pioglitazone; Pts=patients; Hypo=hypoglycemic event
Safety population
Data on file, Novartis Pharmaceuticals, LAF237A2304

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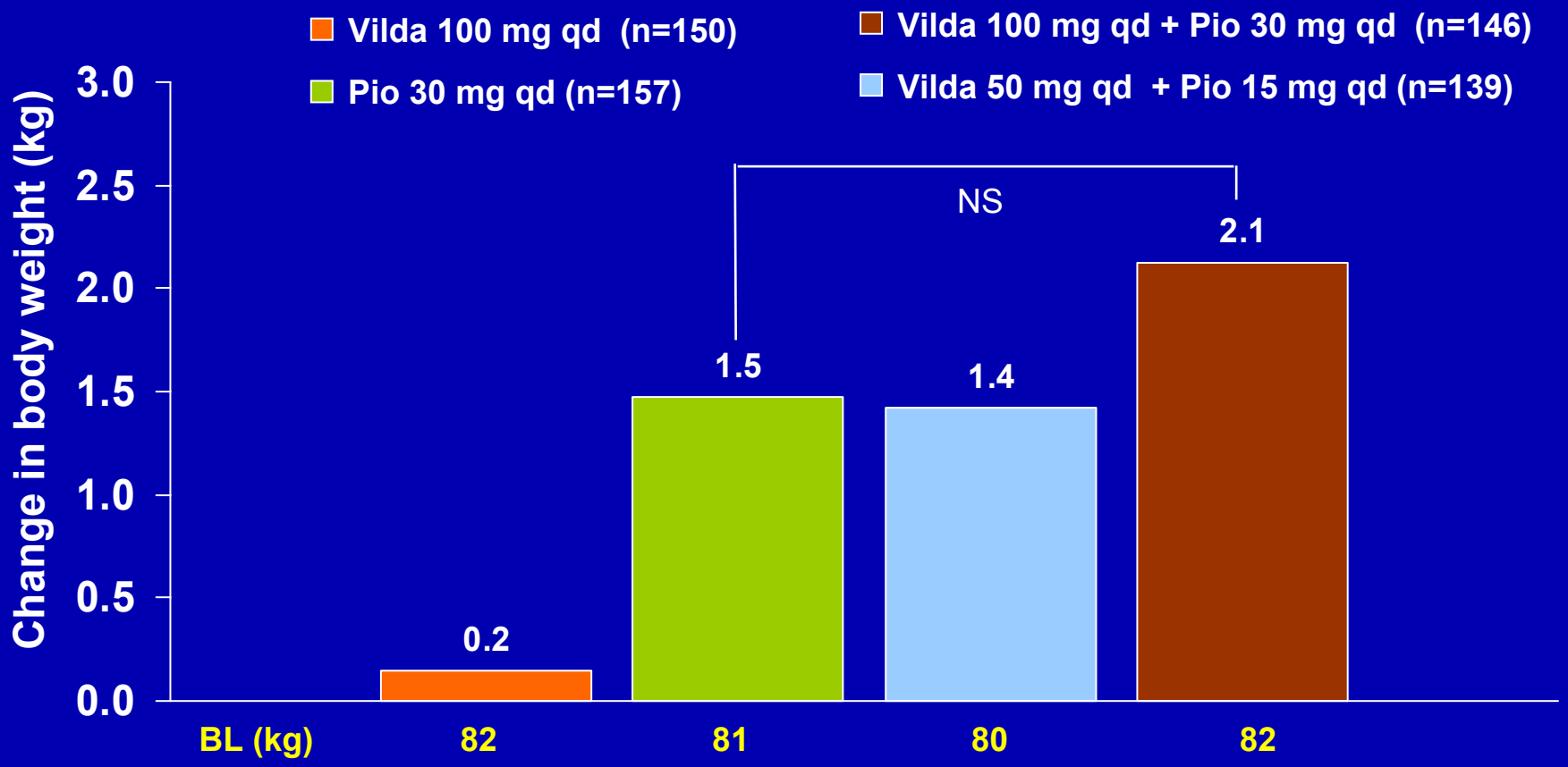
No Additional Weight Gain in Initial Combination with Pioglitazone

Mean body weight change from baseline



Vilda=vildagliptin; Pio=pioglitazone
ITT population (intention-to-treat)
NS: Weight change not statistically significant vs Pio 30 mg
Data on file, Novartis Pharmaceuticals, LAF237A2355

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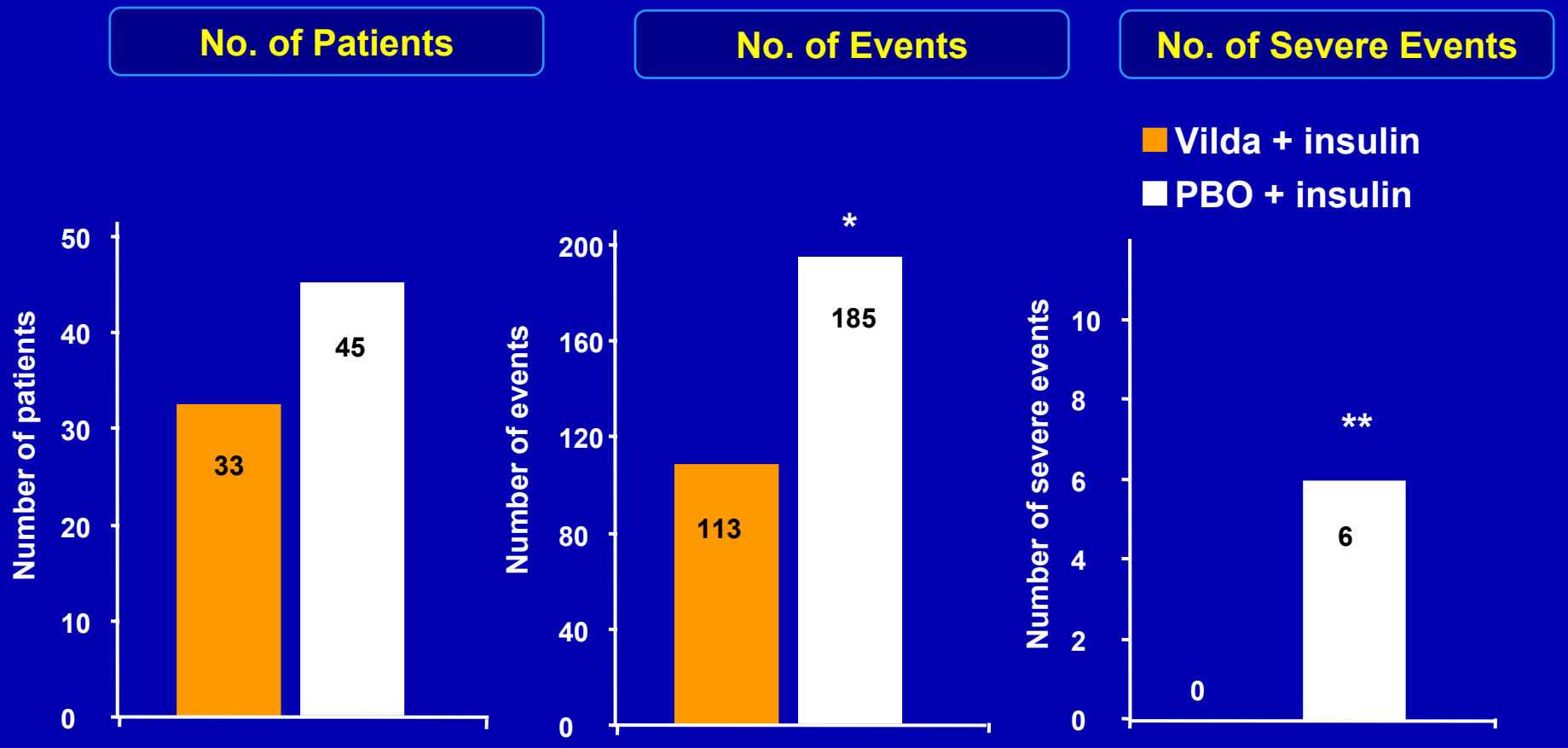
Add-on to Insulin: Less Hypoglycemic Events



*P<.001; **P<.05 between groups

- Incidence of hypoglycemia: fewer events (113 vs 185, P <0.01) and fewer patients affected (22.9% vs 29.6%)
- Severe, grade 2 events : none with vildagliptin add-on to insulin vs 6 events with PBO add-on to insulin (P < 0.01)

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Conclusion

The inhibition of DPP-4 enhances GLP-1 activities ;

elevating insulin levels

suppressing glucagon levels

A DPP-4 inhibitor, Vildagliptin, normalizes hyperglycemic conditions without inducing AE and hypoglycemia.

Combination of Vildagliptin with other anti-diabetic agents shows synergistic effects to further normalize hyperglycemia with high safety and efficacy.

Abbreviations

- CNS = central nervous system
- DPP-4 = dipeptidyl peptidase-4
- GI = gastrointestinal
- GIP = glucose-dependent insulinotropic peptide
- GLP-1 = glucagon-like peptide-1
- HbA_{1c} = hemoglobin A_{1c}
- IV = intravenous
- m/z = mass:charge ratio
- OGTT = oral glucose tolerance test
- qd = once daily
- $t_{1/2}$ = half-life
- T2DM = type 2 diabetes mellitus