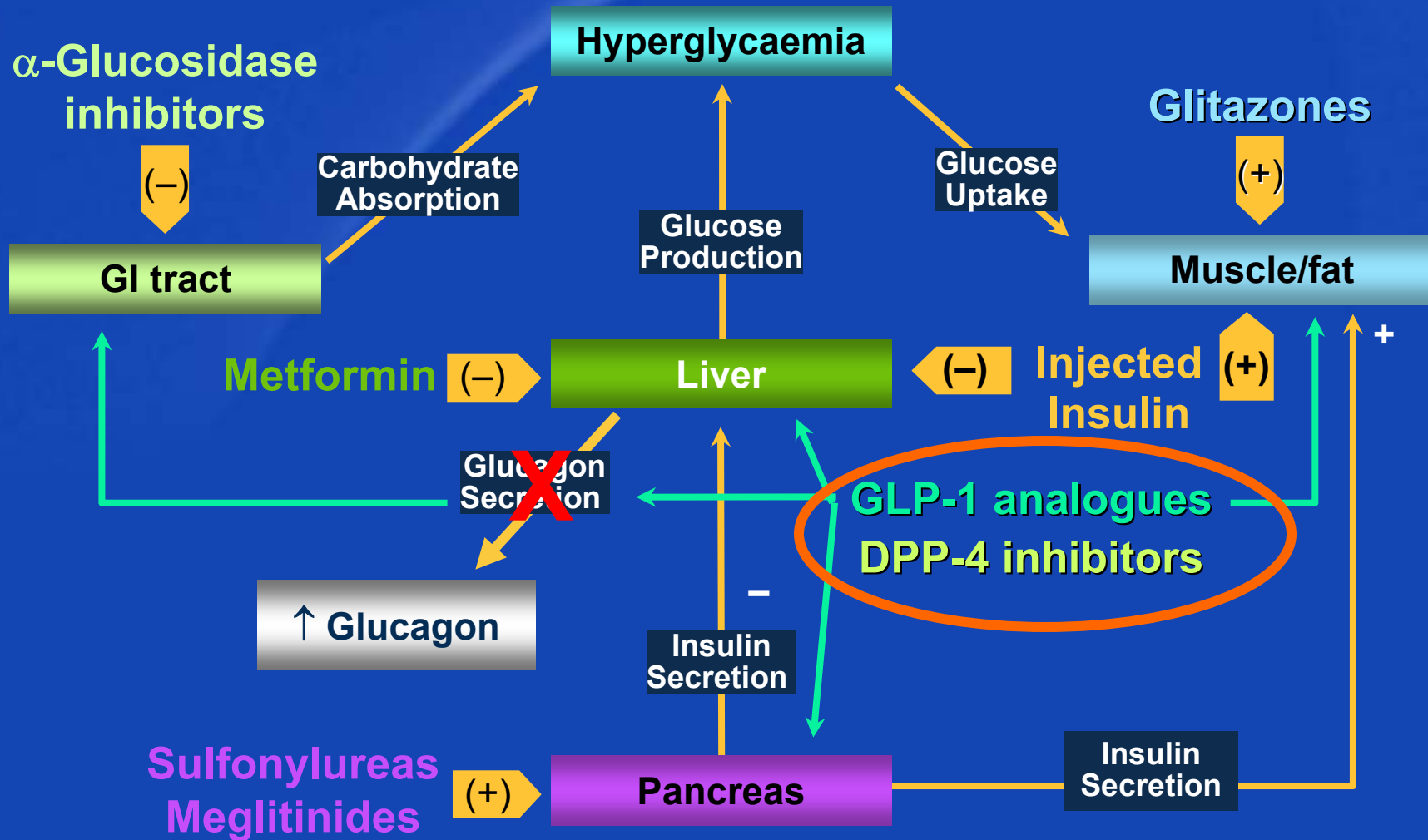




An update on DPP-4 inhibitors in the management of Type 2 diabetes: potential roles in monotherapy and combination therapy

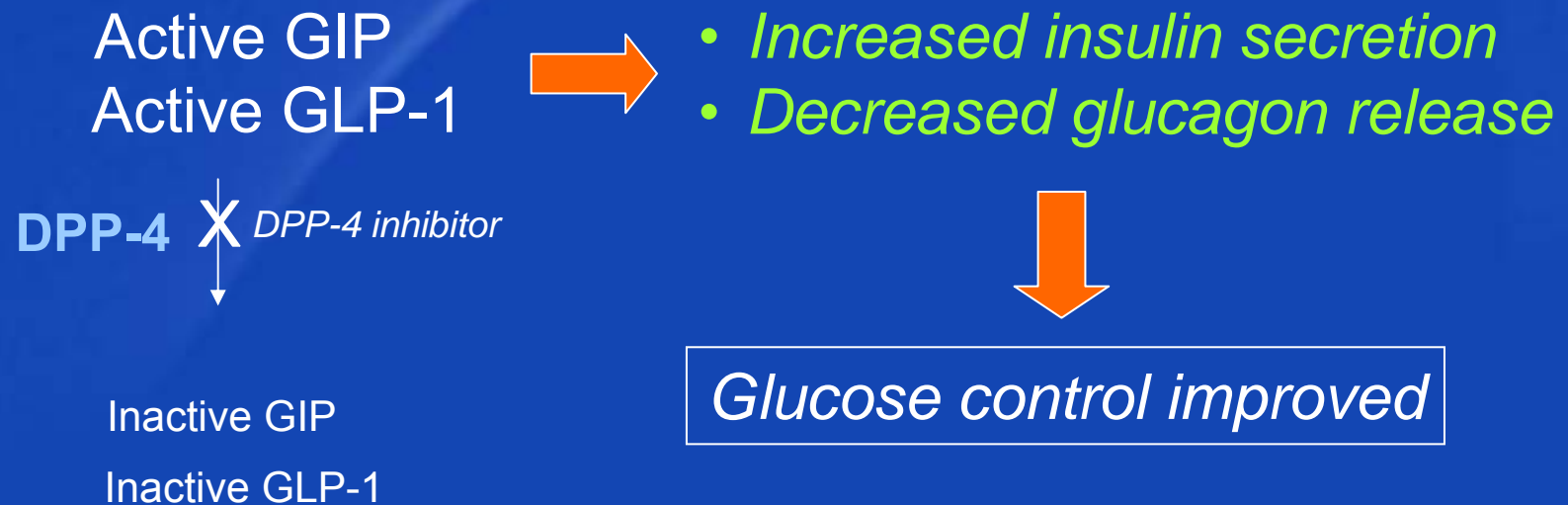
**Harvey L. Katzeff
Merck Research Laboratories
Rahway, New Jersey, USA**

Combining antihyperglycaemic agents: major sites of action



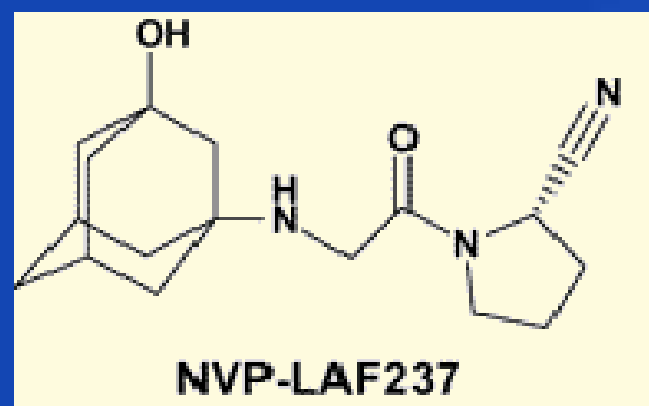
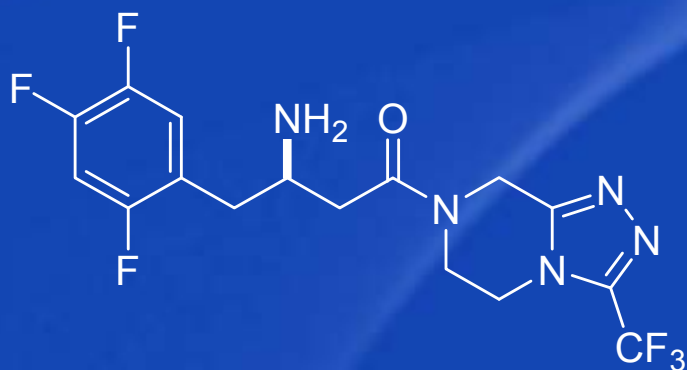
DDP-4=dipeptidyl-peptidase-4; GLP-1=glucagon-like peptide-1

Inhibition of DPP-4 increases active incretin levels, enhancing downstream incretin actions



GIP=glucose-dependent insulintropic peptide

Sitagliptin and vildagliptin overview



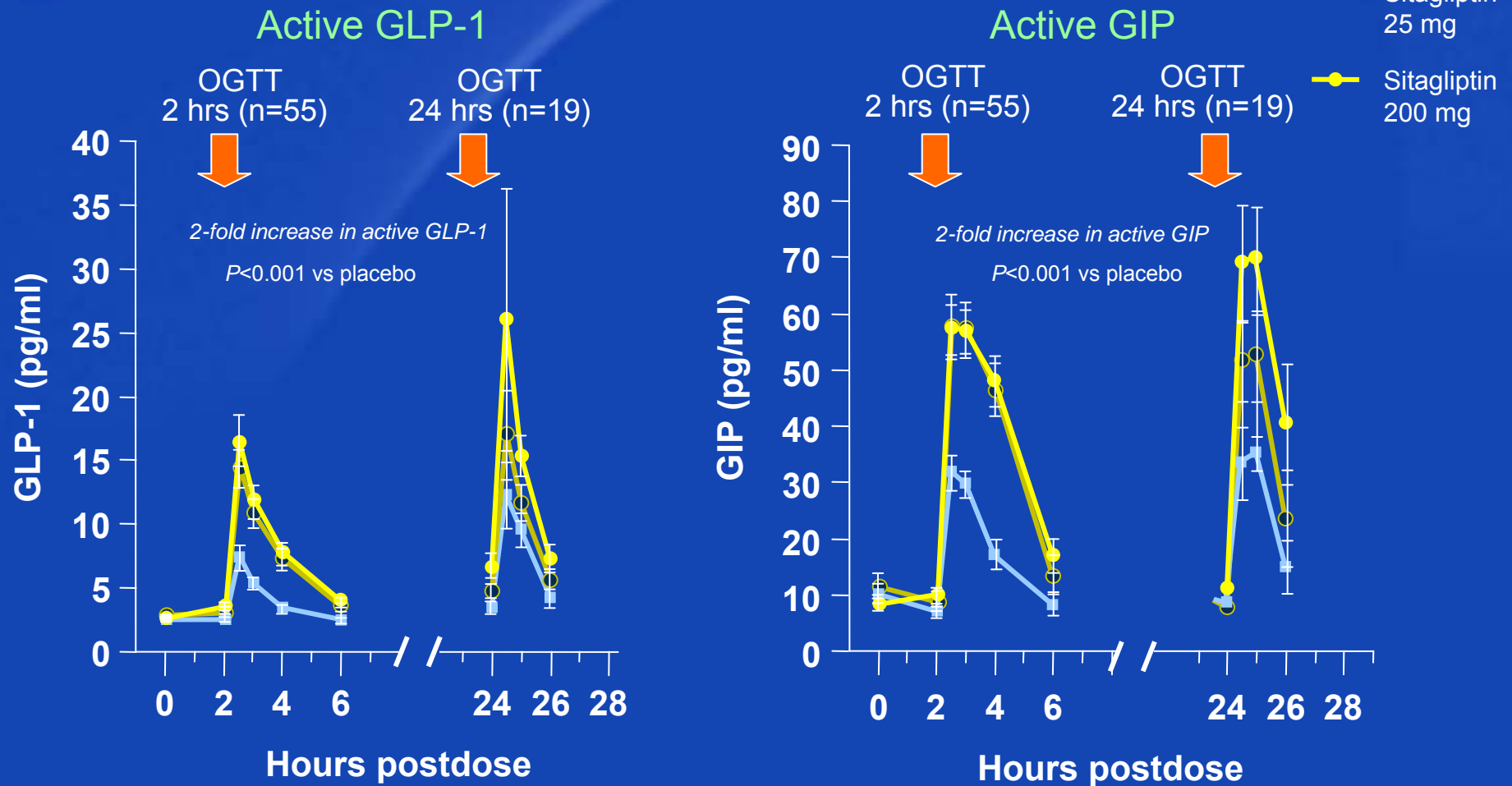
- DPP-4 inhibitors for the treatment of patients with Type 2 diabetes: sitagliptin has recently been FDA approved, and vildagliptin is currently under FDA review
- Provide potent and highly selective inhibition of the DPP-4 enzyme
- No CYP or drug-drug interaction
- 30%–85% excretion via the urine

Selectivity of oral DPP-4 enzyme inhibitors

Enzyme	Sitagliptin IC ₅₀ (nM)	Vildagliptin IC ₅₀ (nM)
DPP-4	18	120
DPP-8	48,000	9000
DPP-9	>100,000	–
DPP-2, DPP-7	>100,000	>100,000
FAP	>100,000	–
PEP	>100,000	–
APP	>100,000	–

A single dose of sitagliptin increased active GLP-1 and GIP over 24 hours

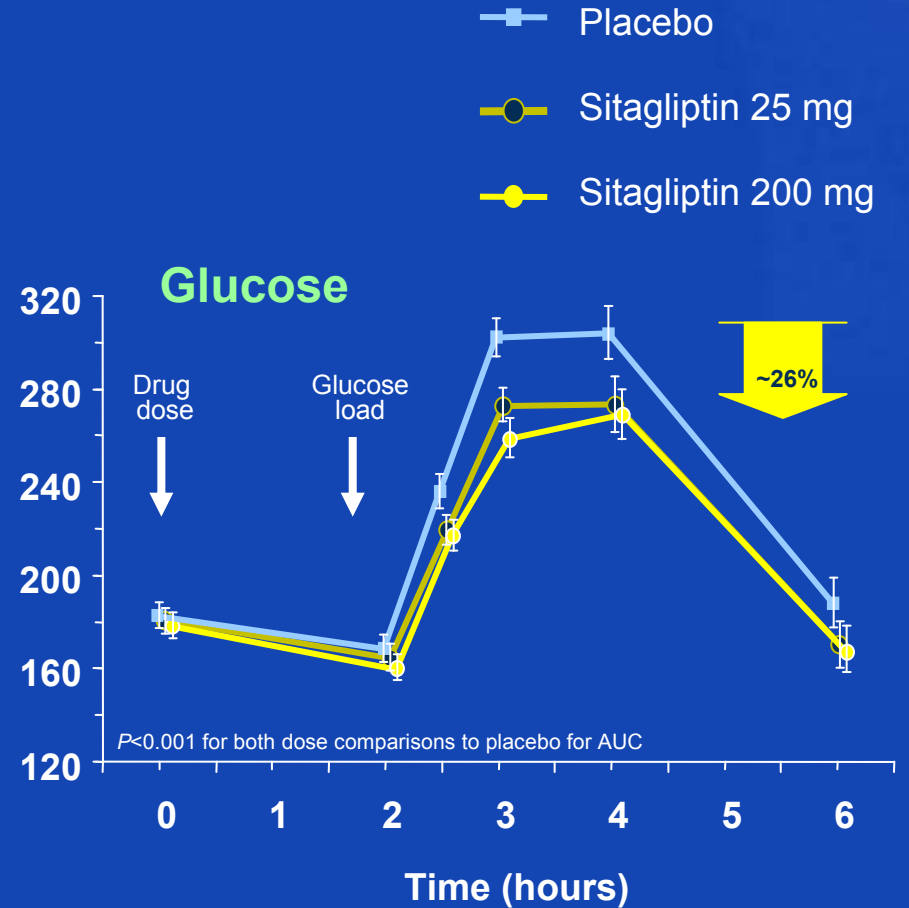
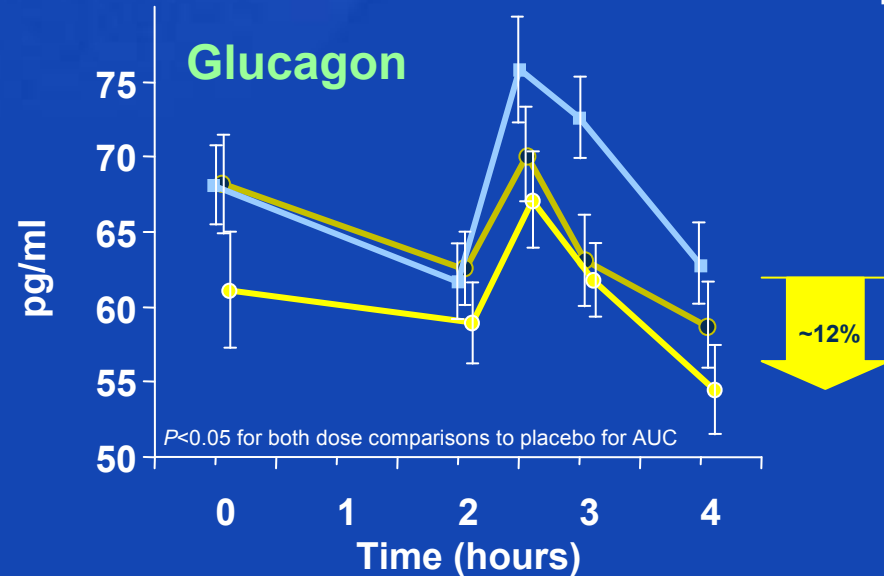
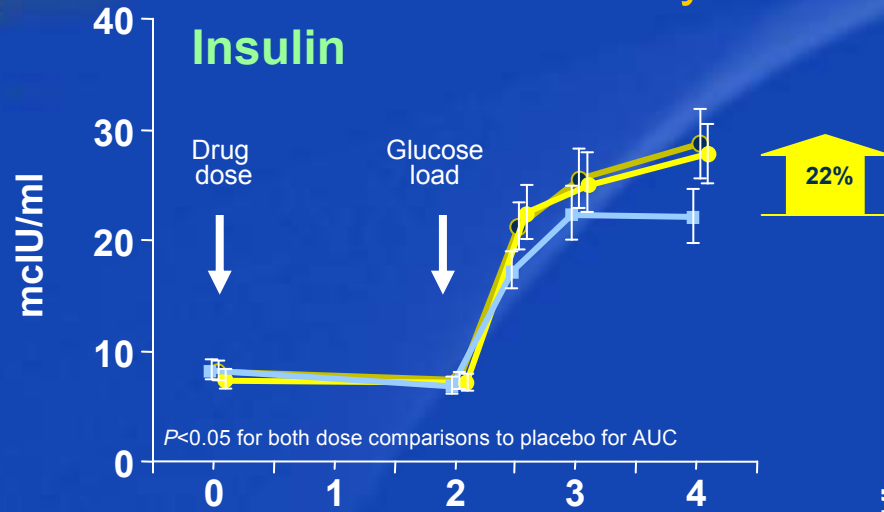
Crossover Study in Patients With Type 2 Diabetes



Herman et al. *Diabetes*. 2005; Stein. ADA. 2006. Late-breaking clinical presentation

Sitagliptin increased insulin, decreased glucagon, and reduced glycaemic excursion after a glucose load

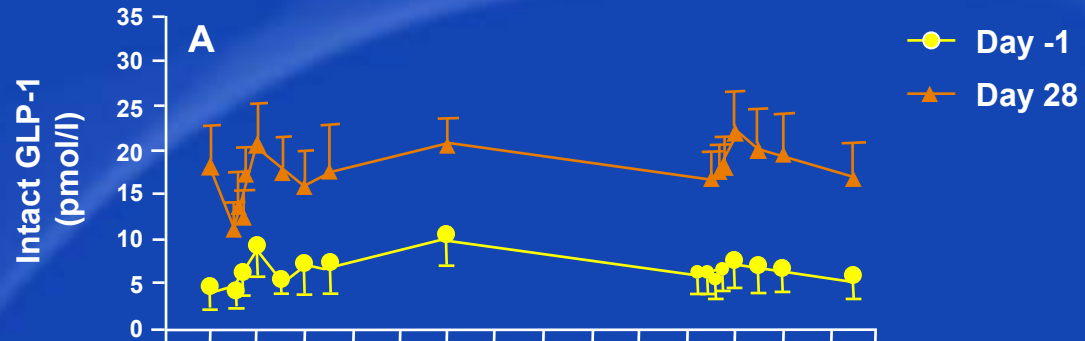
Crossover Study in Patients With Type 2 Diabetes



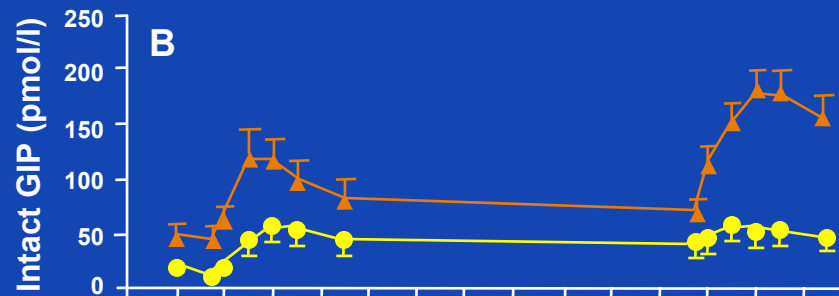
Stein. ADA. 2006. Late-breaking clinical presentation

Vildagliptin increased GLP-1 and GIP and decreased blood glucagon hormone concentrations

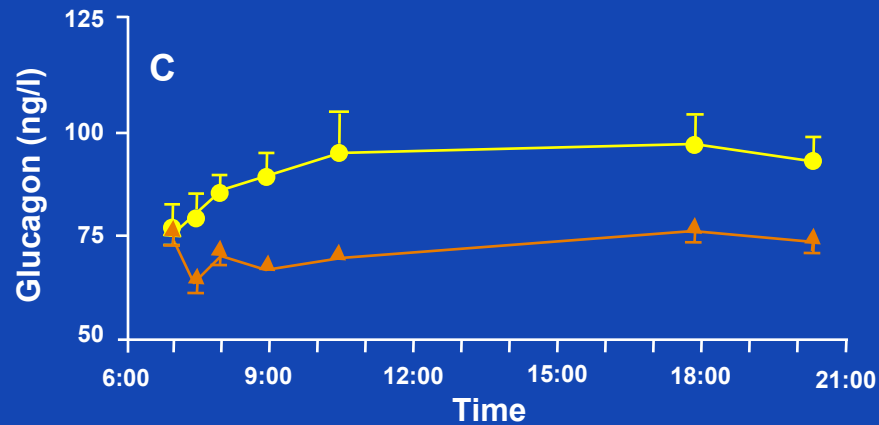
GLP-1



GIP



Glucagon





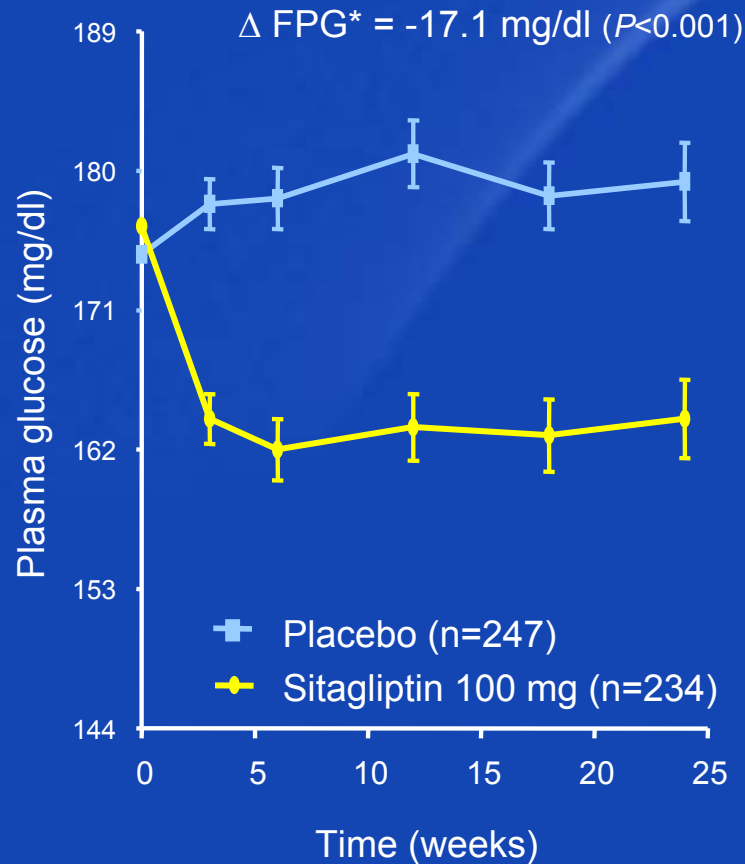
Monotherapy trials

- DPP-4 vs placebo
- DPP-4 vs metformin
- DPP-4 vs TZD

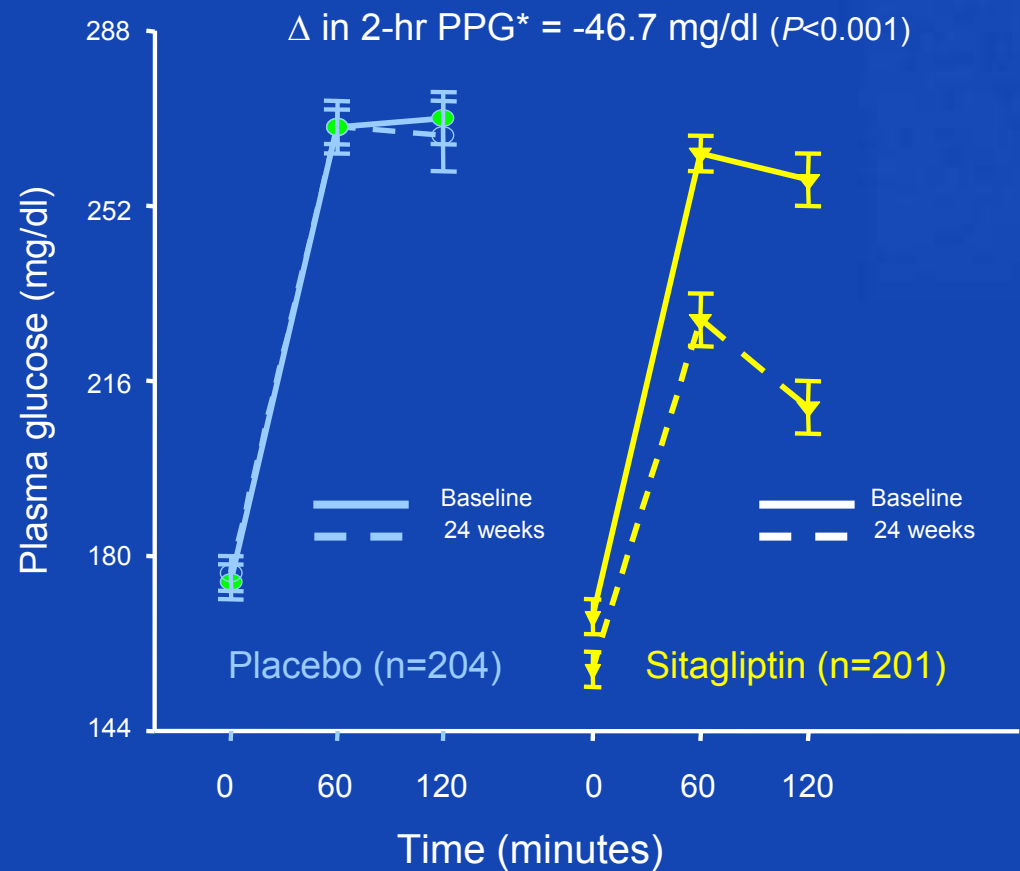
TZD=thiazolidinedione

Sitagliptin improved both fasting and post-meal glucose in monotherapy vs placebo

Fasting Glucose



Post-meal Glucose

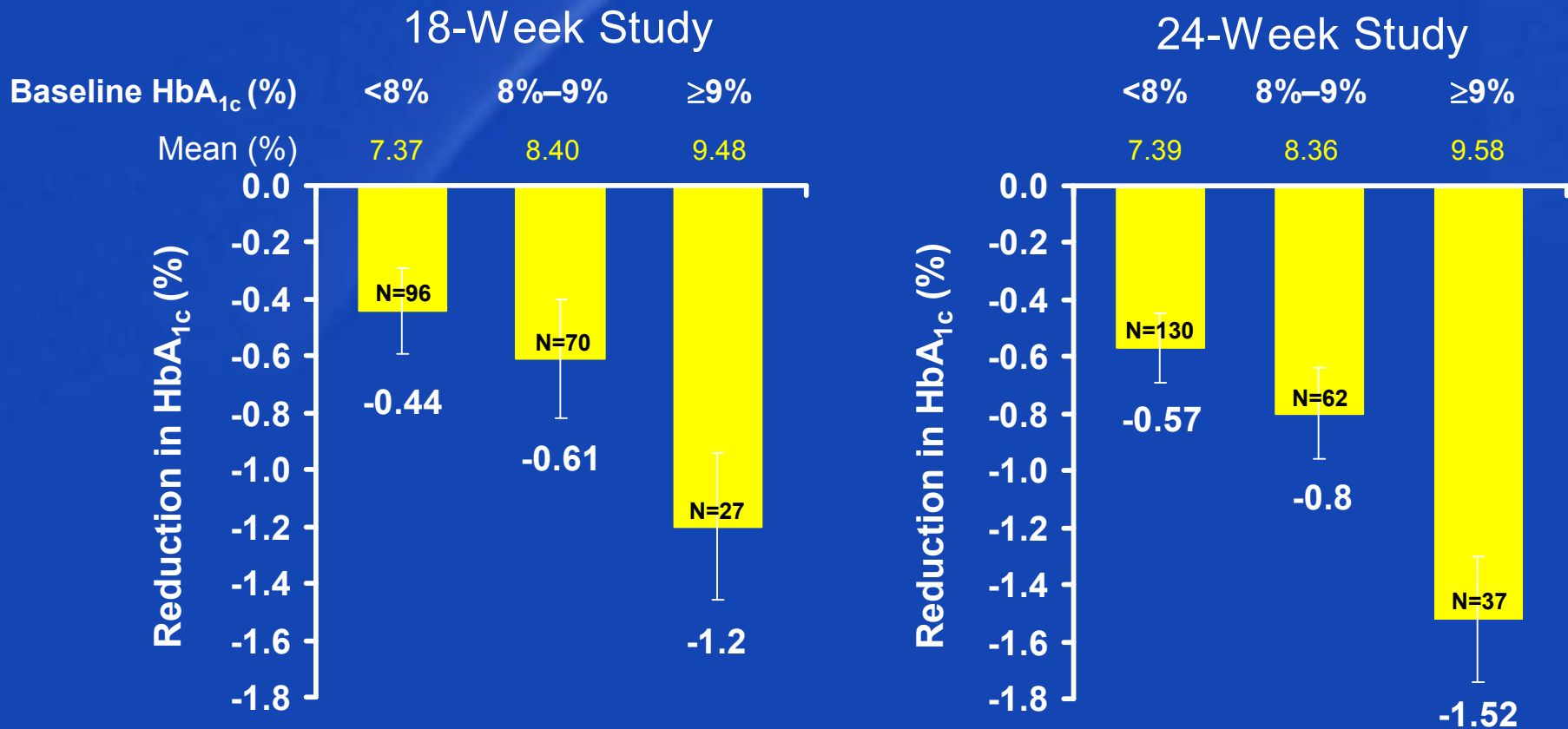


*Least-squares (LS) mean difference from placebo after 24 weeks

Aschner et al. ADA. 2006. Abstract 1995-PO; Stein. ADA. 2006. Late-breaking clinical presentation

DPP-4 inhibitors provide progressively greater reductions in HbA_{1c} with progressively higher baseline HbA_{1c}

Inclusion Criteria: 7%–10%



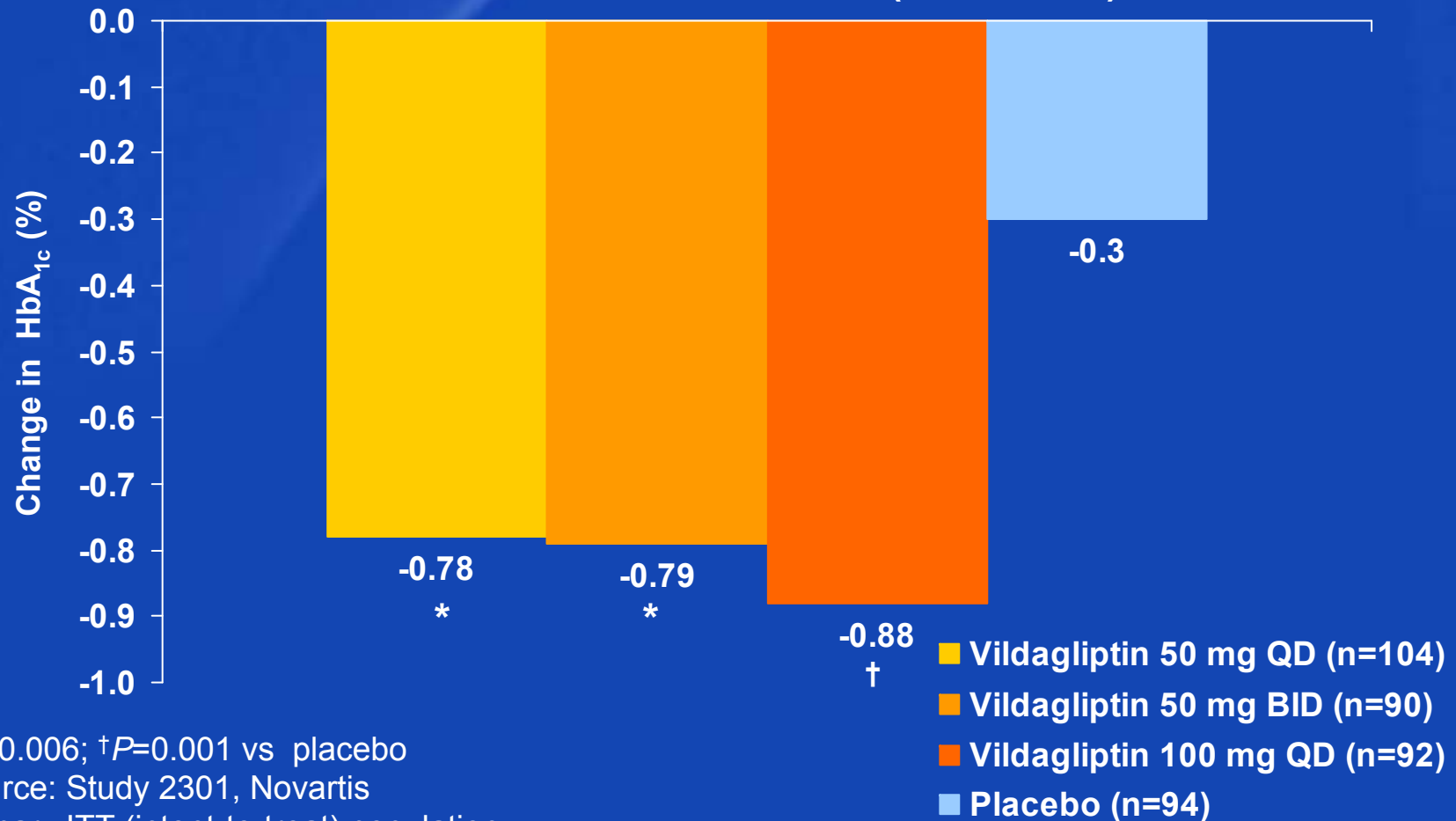
Reductions are placebo-subtracted

Raz et al. ADA. 2006. Abstract 1996-PO; Aschner et al. ADA. 2006. Abstract 1995-PO;

Stein. ADA. 2006. Late-breaking clinical presentation

Vildagliptin monotherapy: similar response to 50 and 100 mg daily

Mean HbA_{1c} reduction from
baseline at 24 weeks (7.5%–11%)

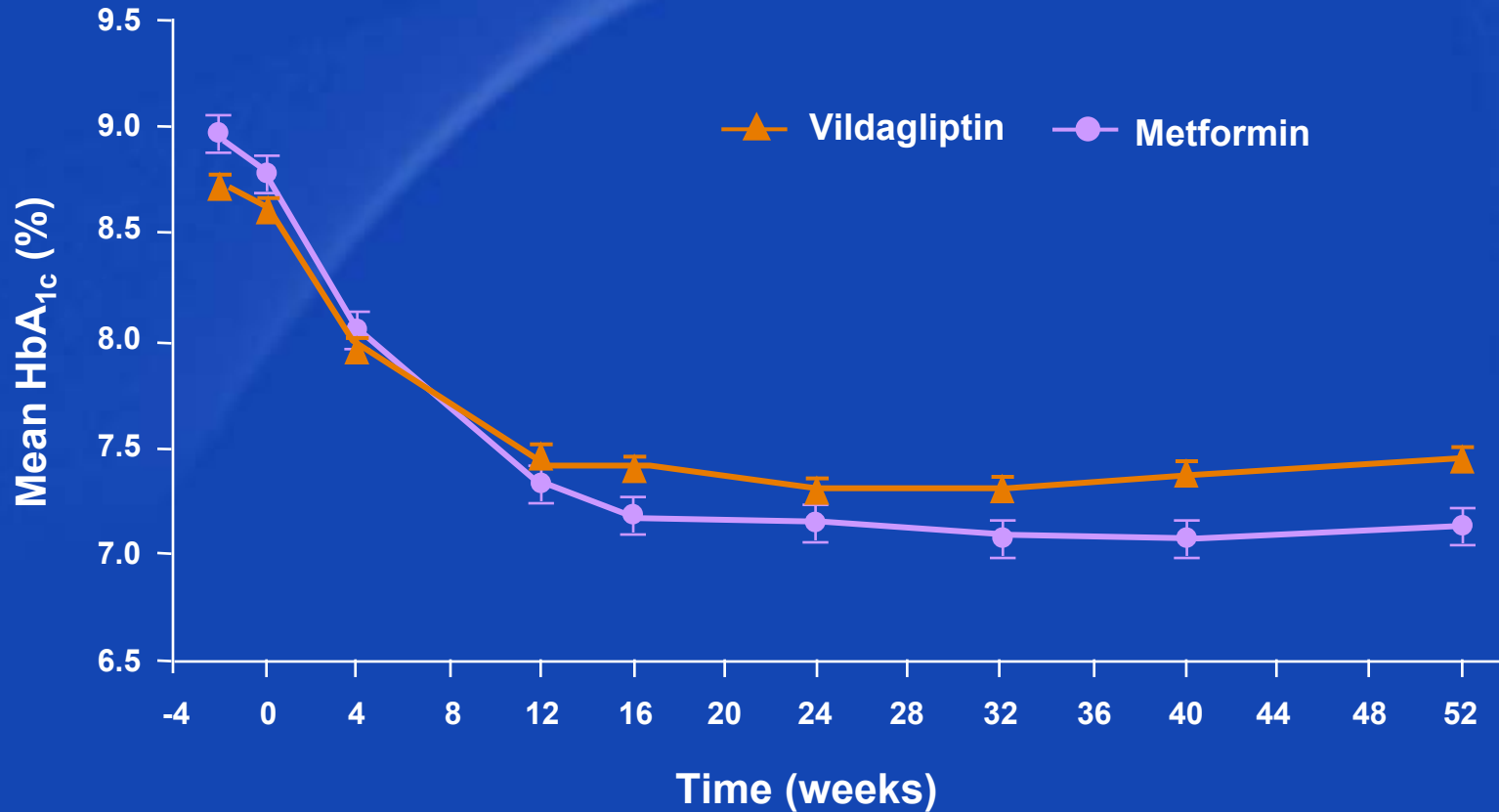


* $P=0.006$; † $P=0.001$ vs placebo

Source: Study 2301, Novartis

Primary ITT (intent-to-treat) population

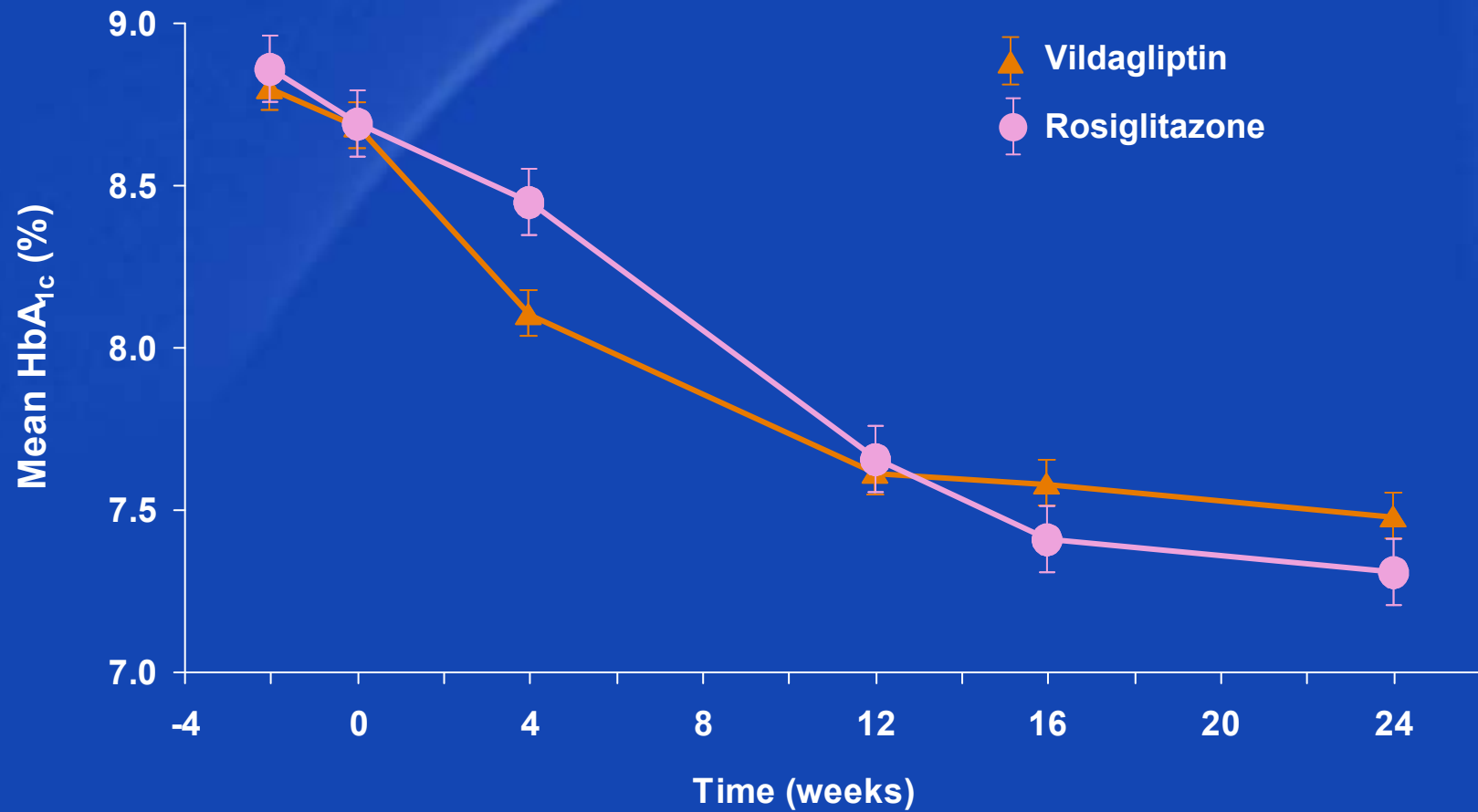
Vildagliptin monotherapy vs metformin



Vildagliptin did not achieve non-inferiority

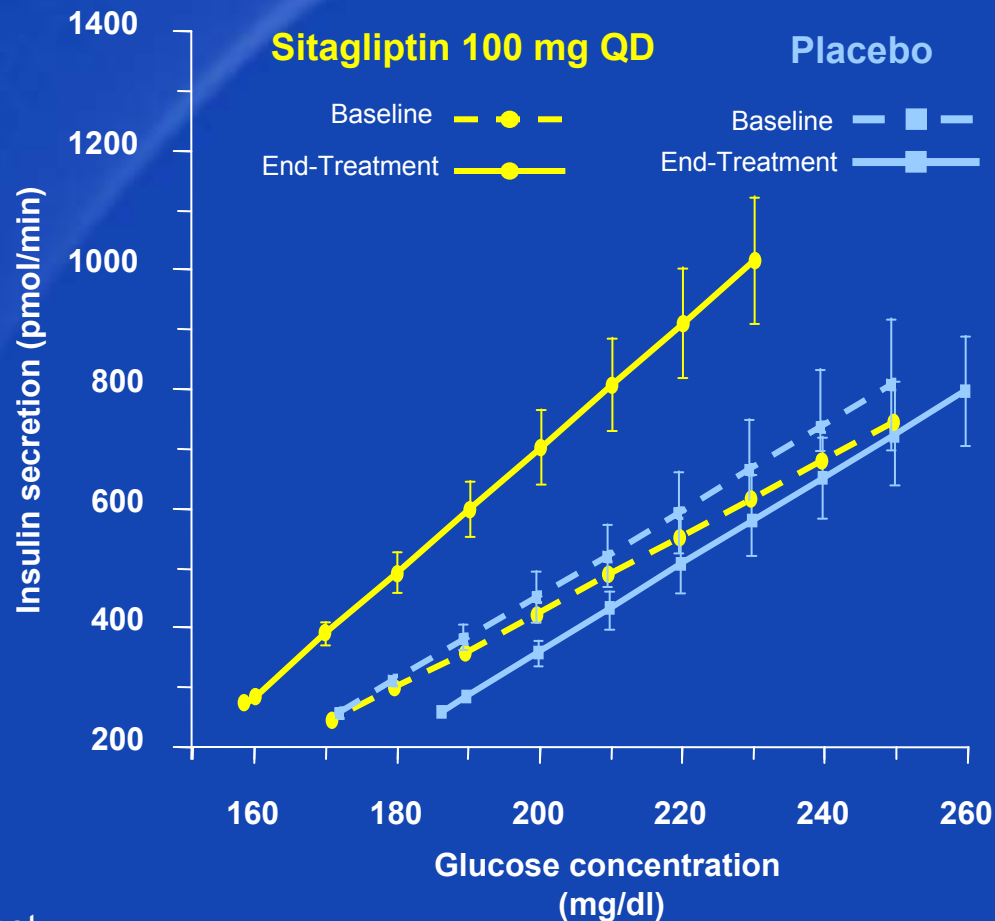
Dejager et al. ADA. 2006. Abstract 120-OR

Vildagliptin monotherapy vs rosiglitazone



Sitagliptin improved the β -cell response to glucose: monotherapy studies

Pooled Monotherapy Studies – Subset of Patients With Frequently Sampled MTT
Model-based assessment of β -cell function

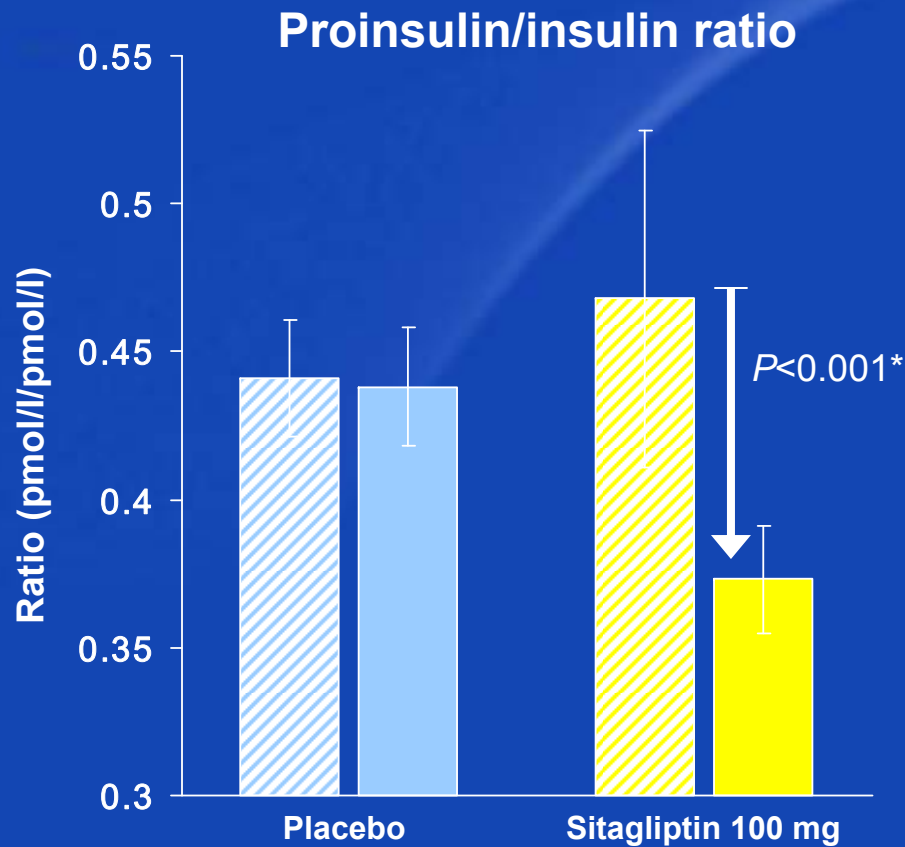


MTT=meal tolerance test

Φ_s =static component; describes relationship between glucose concentration and insulin secretion

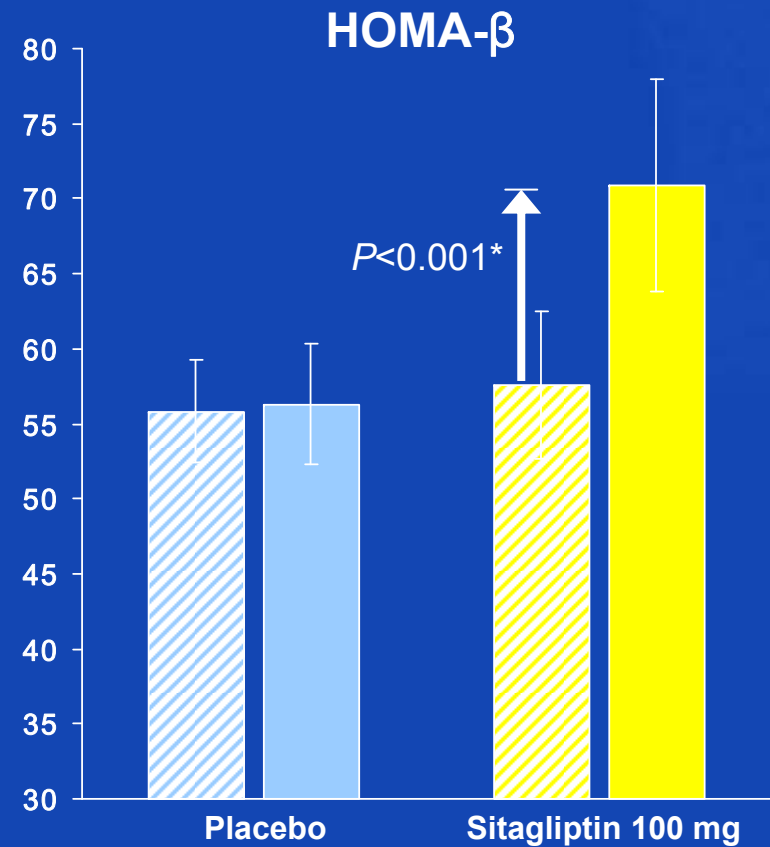
Stein. ADA. 2006. Late-breaking clinical presentation

Sitagliptin improved markers of β -cell function: 24-week monotherapy study



Δ from baseline vs pbo=0.078
(95% CI: -0.114, -0.023)

Hatched=Baseline
Solid=Week 24

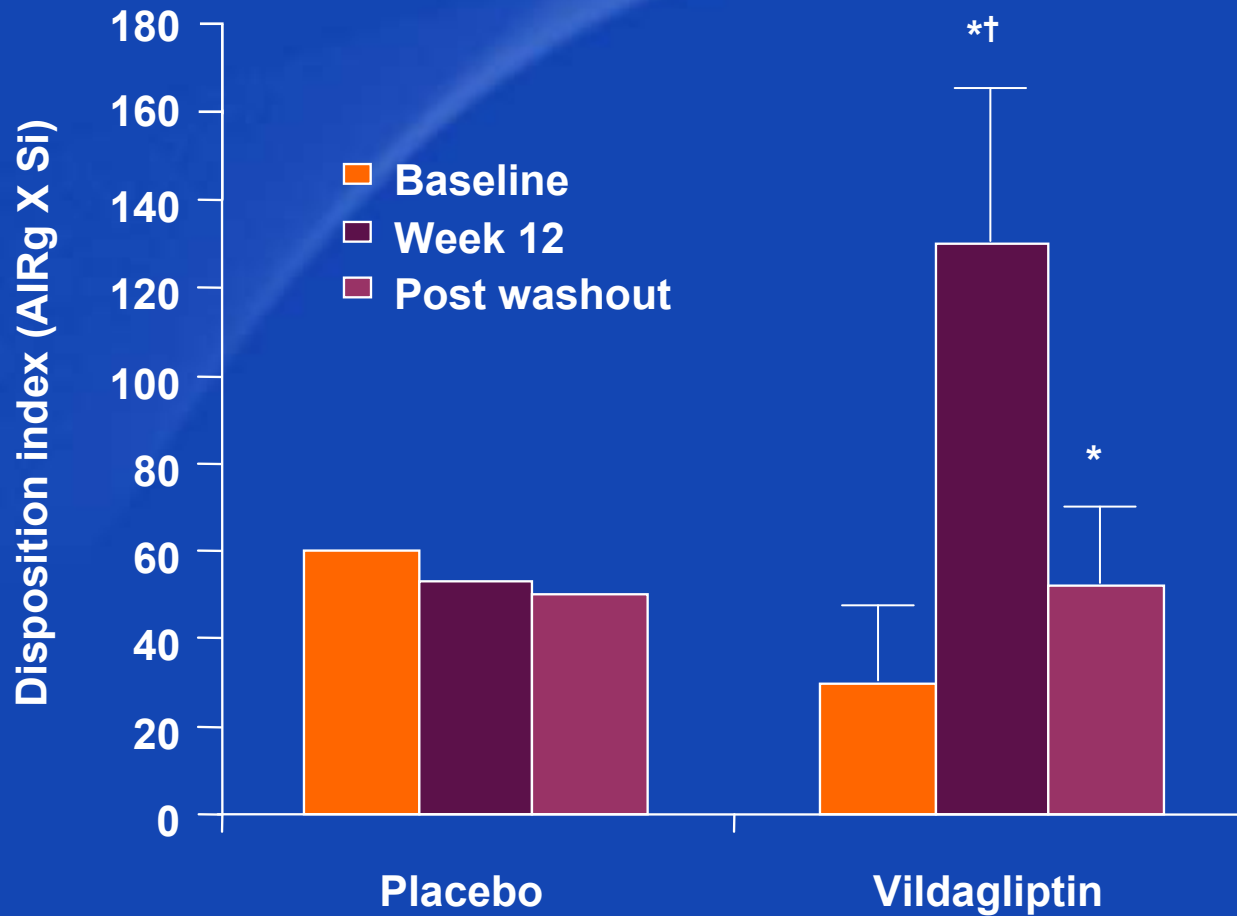


Δ from baseline vs pbo=13.2
(95% CI: 3.9, 21.9)

*P value for change from baseline compared with placebo

Aschner et al. ADA. 2006. Abstract 1995-PO; Stein. ADA. 2006. Late-breaking clinical presentation

Vildagliptin increases disposition index



* $P < 0.05$ vs baseline; † $P < 0.05$ vs placebo
D'Alessio et al. ADA. 2006. Abstract 454-P



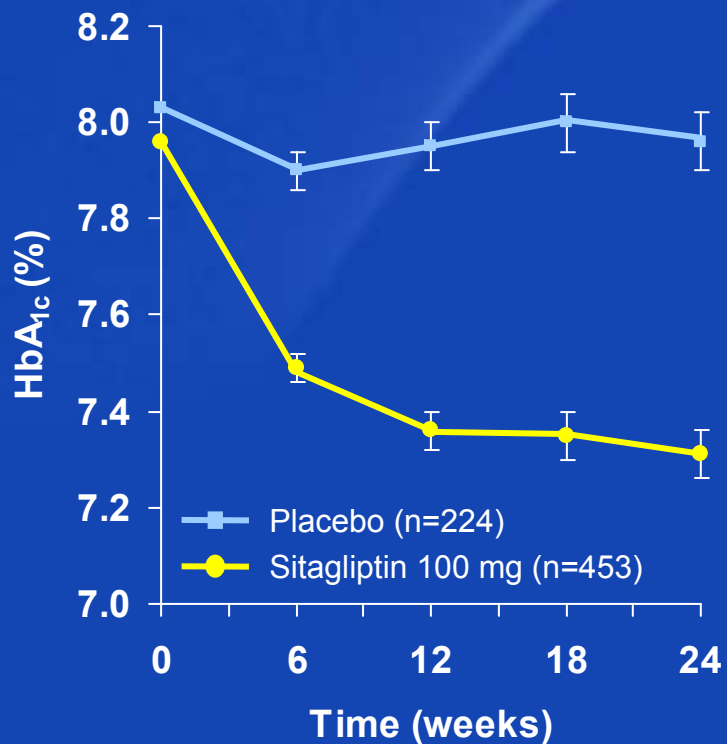
Combination therapy

- Add-on therapy
 - Add-on to metformin
 - Add-on to pioglitazone
 - Add-on to insulin
- Initial combination
 - DPP-4 + metformin
 - DPP-4 + pioglitazone

Sitagliptin once daily lowered HbA_{1c} when added to metformin or pioglitazone

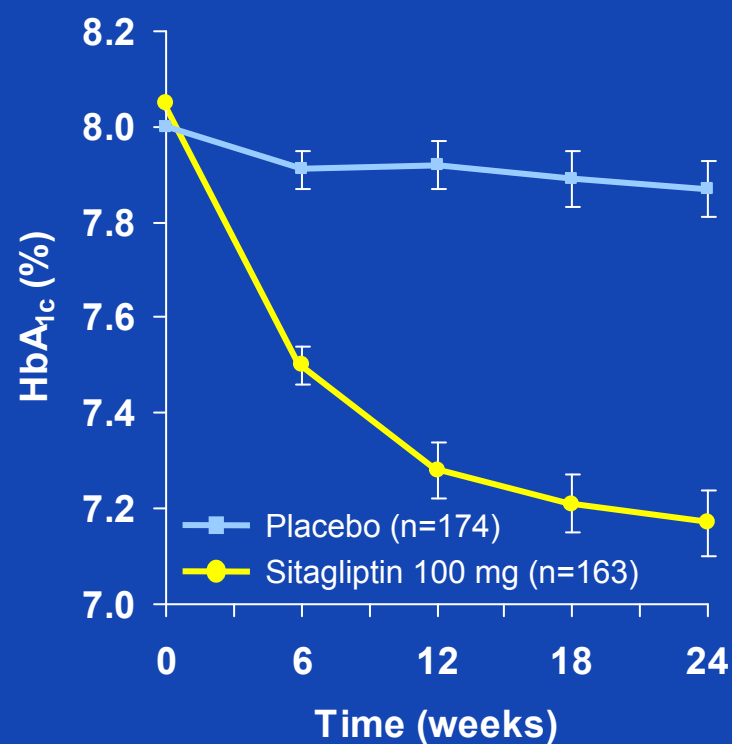
Add-on to Metformin Study

Δ in HbA_{1c} vs Pbo* = -0.65% (P<0.001)



Add-on to Pioglitazone Study

Δ in HbA_{1c} vs Pbo* = -0.70% (P<0.001)



*Placebo-subtracted difference in LS means

Rosenstock et al. ADA. 2006. Abstract 556-P; Karasik et al. ADA. 2006. Abstract 501-P;

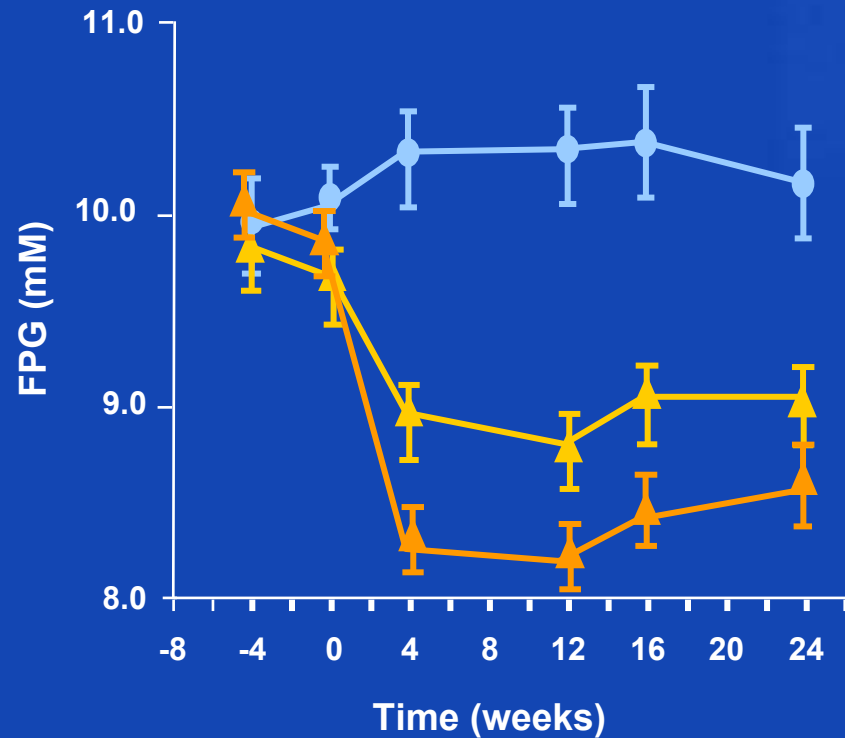
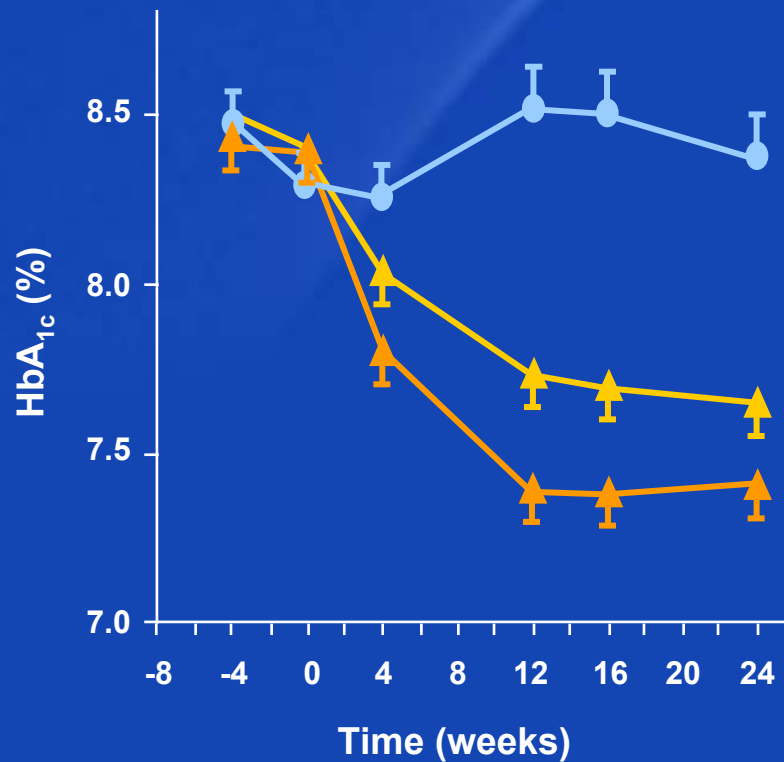
Stein. ADA. 2006. Late-breaking clinical presentation

Vildagliptin added to metformin improved glycaemic control

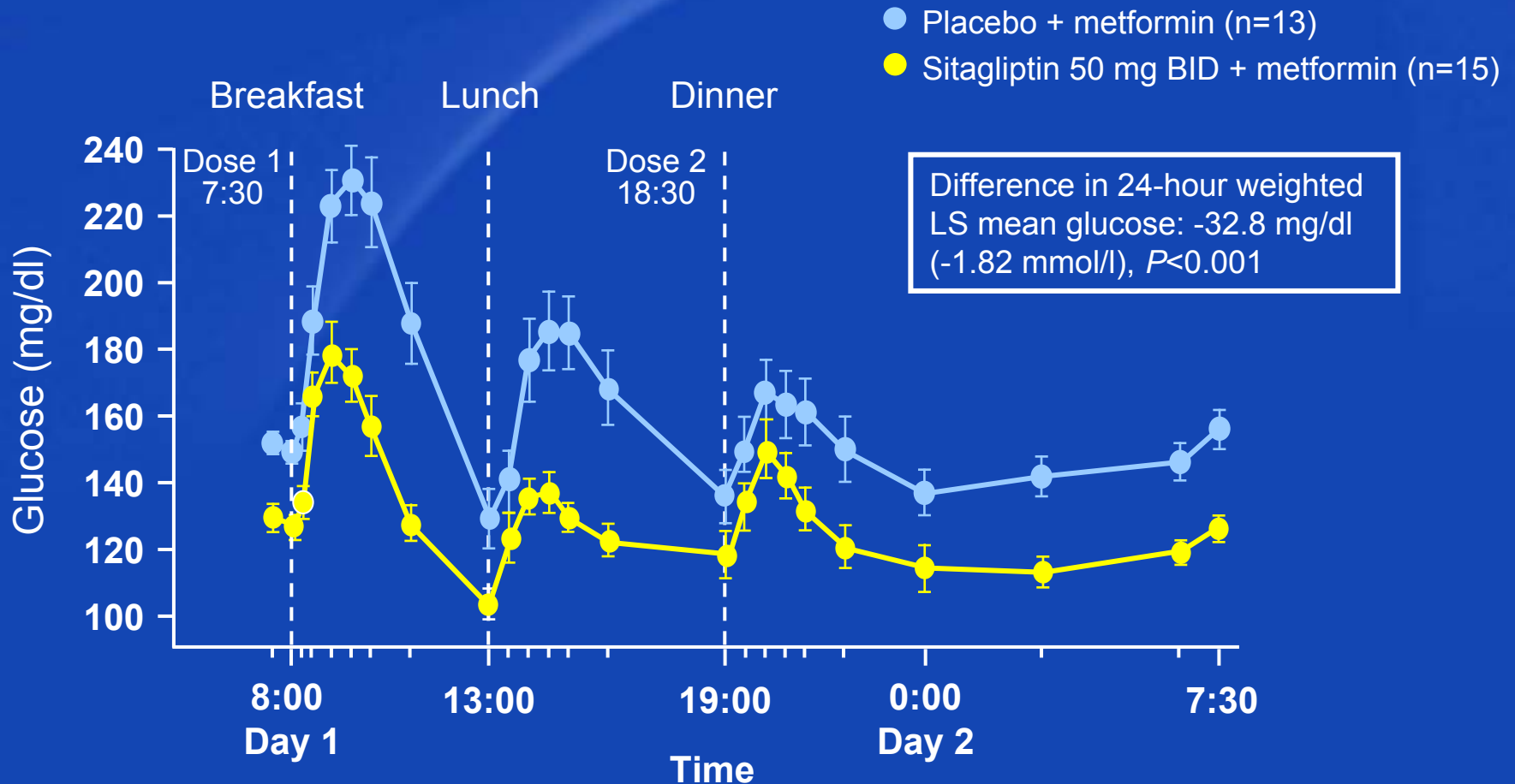
▲ Vildagliptin 50 mg QD & metformin

▲ Vildagliptin 50 mg BID & metformin

● Placebo & metformin

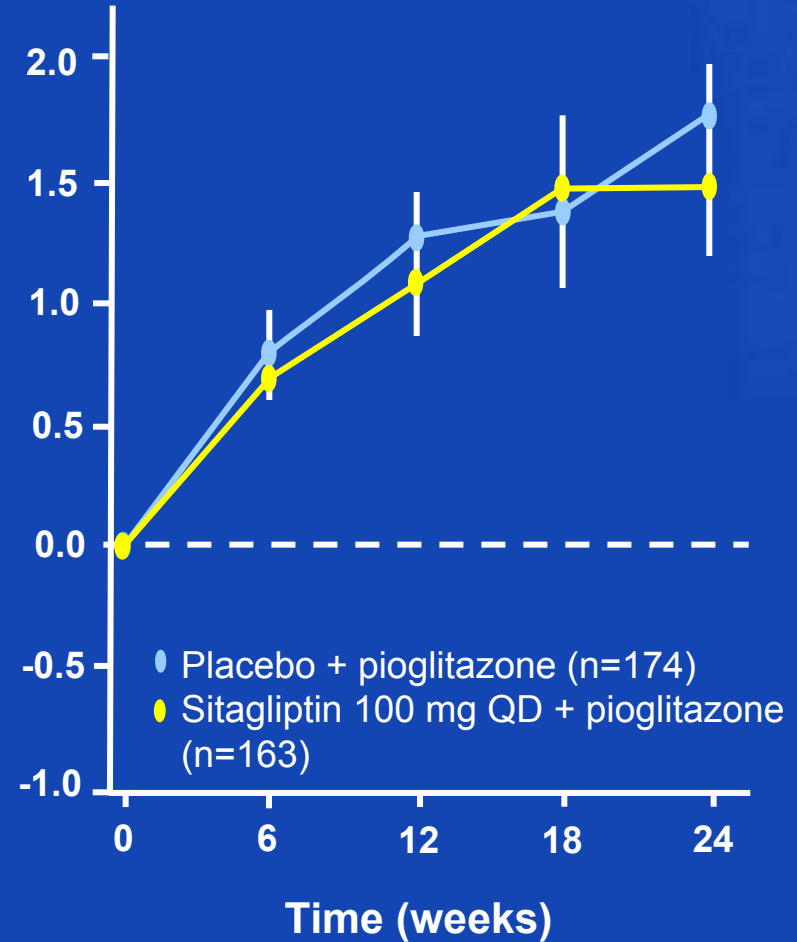
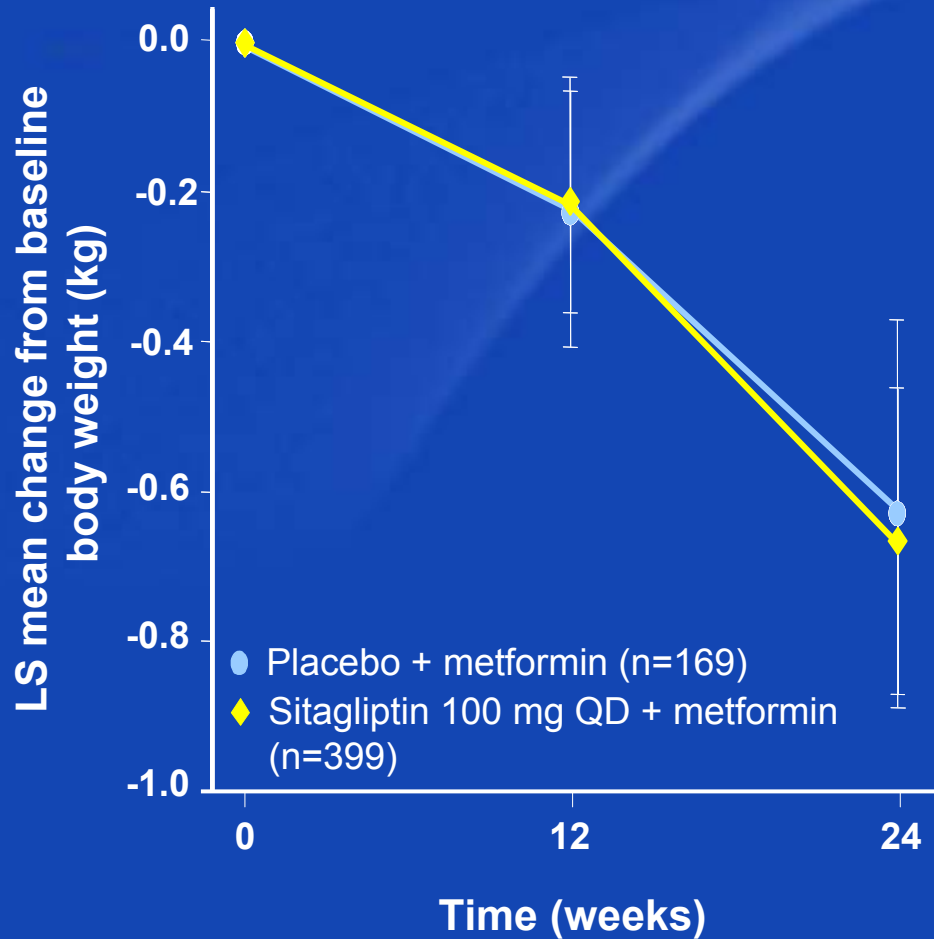


Sitagliptin added to metformin improved 24-hour glucose profile in Type 2 diabetes

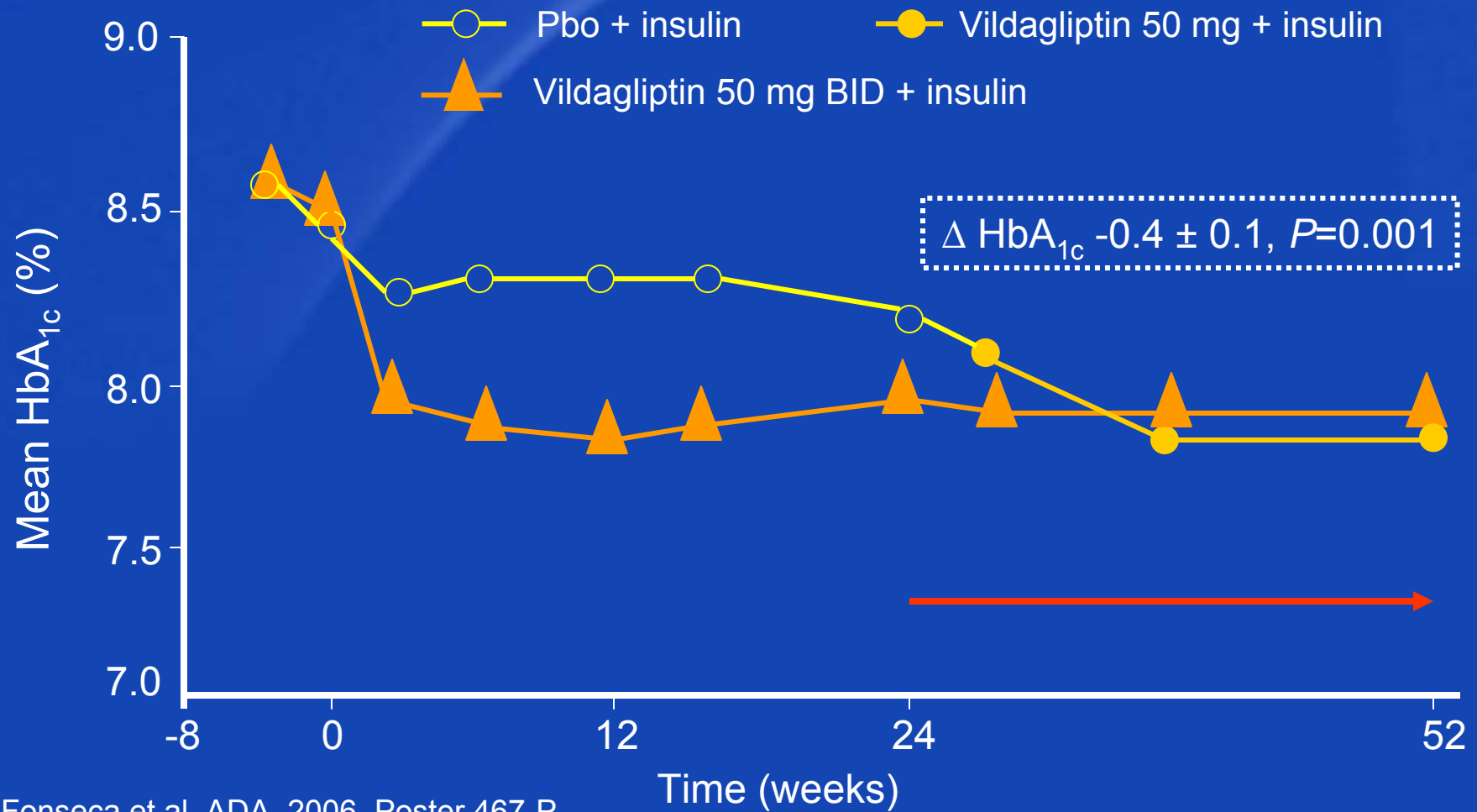


Stein. ADA. 2006. Late-breaking clinical presentation; adapted from Brazg et al. ADA. 2005. Abstract 11-OR

Sitagliptin added to ongoing metformin or pioglitazone: change in body weight over time

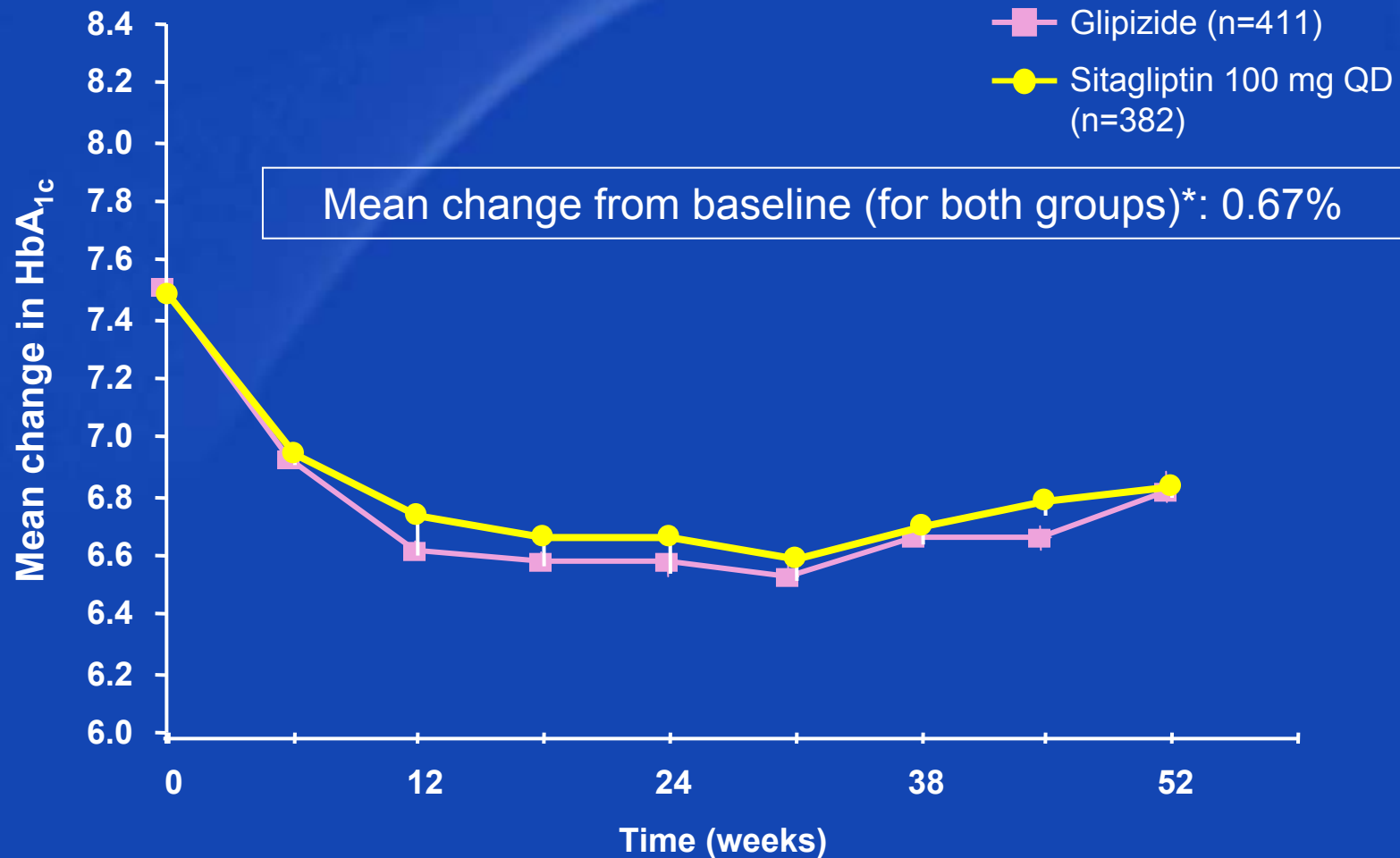


HbA_{1c} during insulin add-on: core and extension study



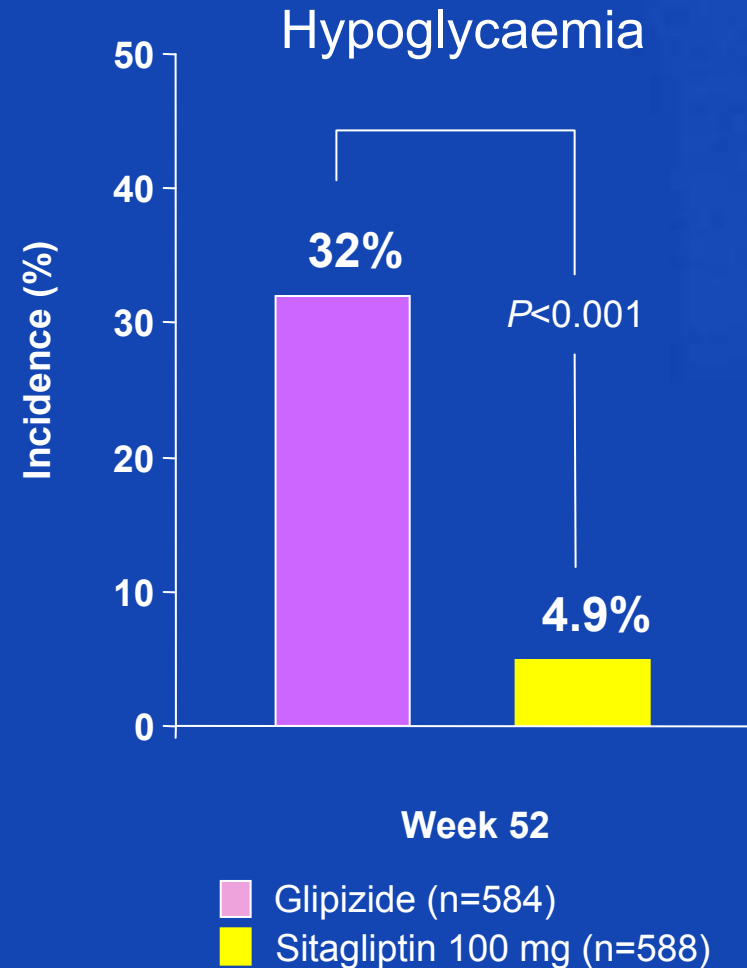
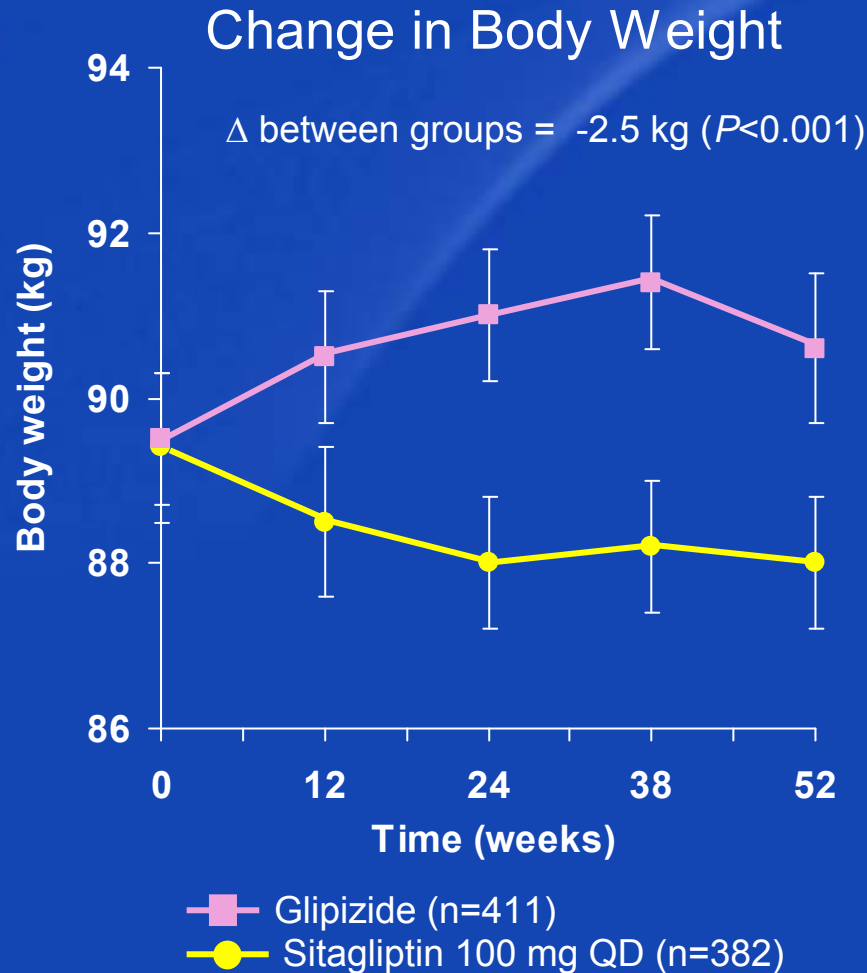
Fonseca et al. ADA. 2006. Poster 467-P
Fonseca et al. EASD. 2006. PS 62. 0802

Sitagliptin once daily showed similar glycaemic efficacy to glipizide when added to metformin (52 weeks)



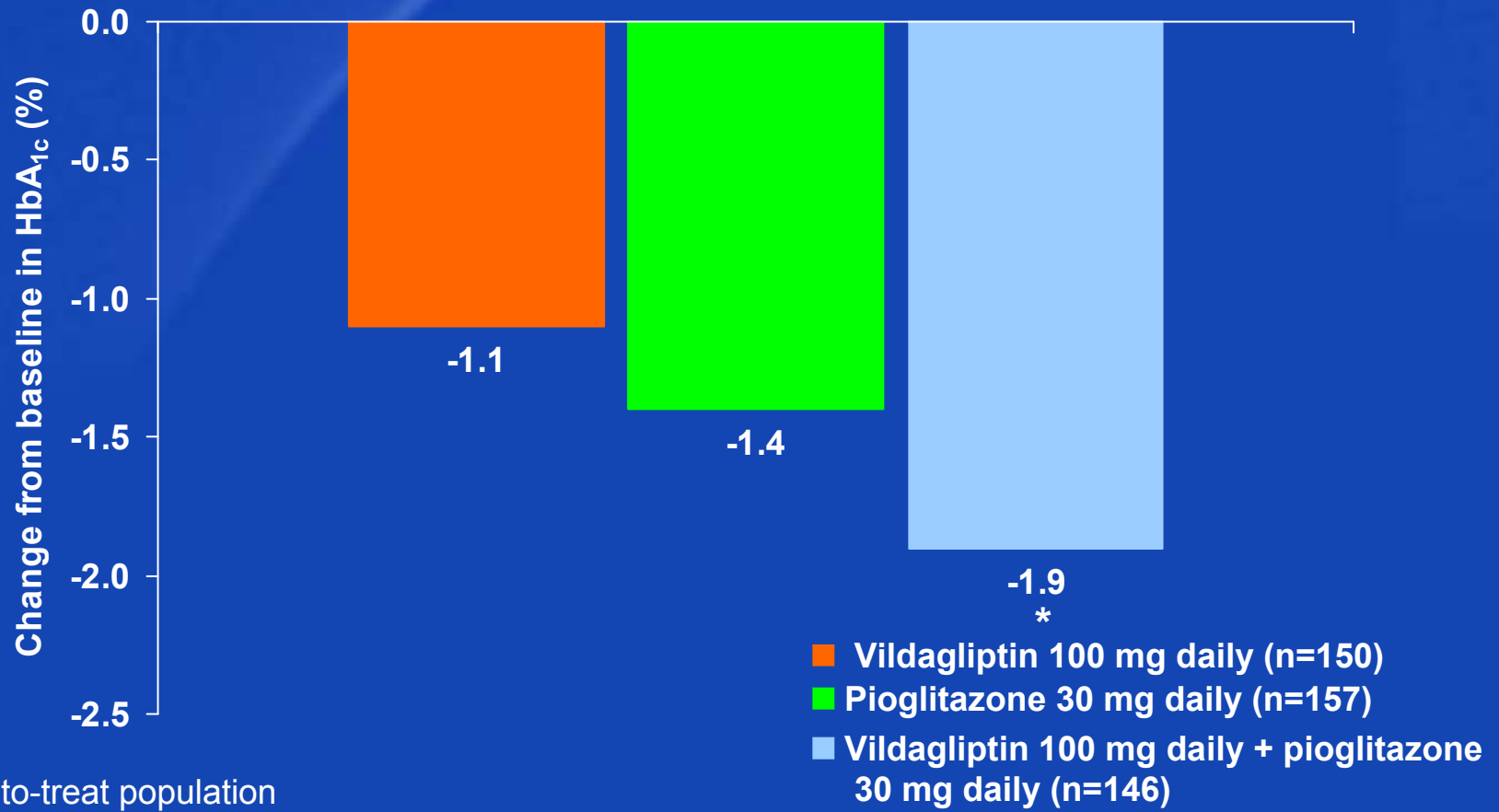
*Per-protocol analysis; -0.51% and -0.56% for sitagliptin and glipizide in LOCF analysis
Stein. ADA. 2006. Late-breaking clinical presentation

Sitagliptin once daily showed better safety and tolerability profile compared with glipizide (52 weeks)



Initial combination of vildagliptin and pioglitazone (24 weeks)

Mean HbA_{1c} reduction from baseline=8.7%



Intention-to-treat population


* $P=0.001$ vs pioglitazone 30 mg; low-dose combination arm is not included

Nathwani. ADA. 2006. Late-breaking clinical presentation



Metabolic effects of DPP-4 inhibitors

- Small decrease in VLDL with corresponding increase in HDL
 - No change in LDL
- Small decrements in blood pressure
- Small decrease in high-sensitivity C-reactive protein
- Animal models may reveal improvement in β -cell mass
 - Studies in humans have not yet been performed to validate these findings



Safety and tolerability overview of DPP-4 inhibitors

- Well tolerated in phase 1-3 trials; in completed and ongoing studies, >4000 patients on sitagliptin (to doses of 200 mg QD in phase 3 studies)
- Pre-specified pooled phase 3 analysis, including monotherapy and combination studies: over 1500 patients on sitagliptin and over 750 patients on placebo
 - Summary measures of adverse experiences (AEs) were similar to placebo
 - Including overall clinical AEs, serious AEs, discontinuations due to AEs, drug-related AEs, laboratory AE summary measures
 - Small differences in incidence of specific AEs
 - Between-group difference (sitagliptin 100 mg and placebo group) in incidence >1% for only 1 specific AE (nasopharyngitis 1.2% difference)

Summary

- DPP-4 inhibitors administered for the treatment of Type 2 diabetes
 - Significant reductions in HbA_{1c} across a range of starting HbA_{1c} levels in monotherapy and combination use
 - Sustained HbA_{1c} reduction to 1 year
 - Improvements in multiple measures of β -cell function
- Compared with a sulfonylurea or TZD, DPP-4 inhibitors provide
 - Similar efficacy
 - Superior improvements in β -cell function, less hypoglycaemia, and weight loss (vs weight gain)
- DPP-4 inhibitors are well tolerated with summary measures of AEs similar to placebo