SCIENTIFIC
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DIABETES

Do we need another DPP4 inhibitor?

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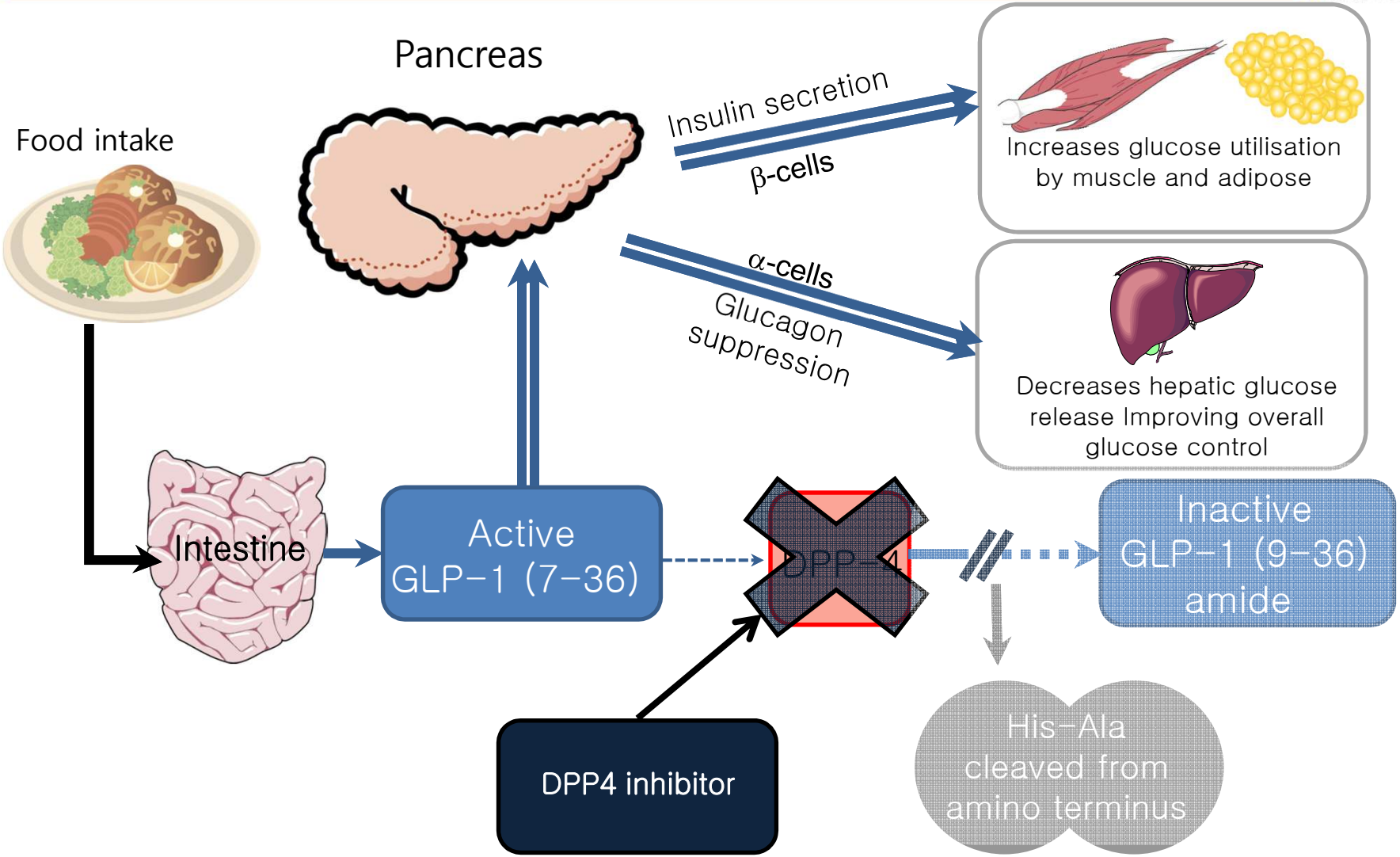
2012년 당뇨병학회 춘계 **symposium**

Boehringer Ingelheim

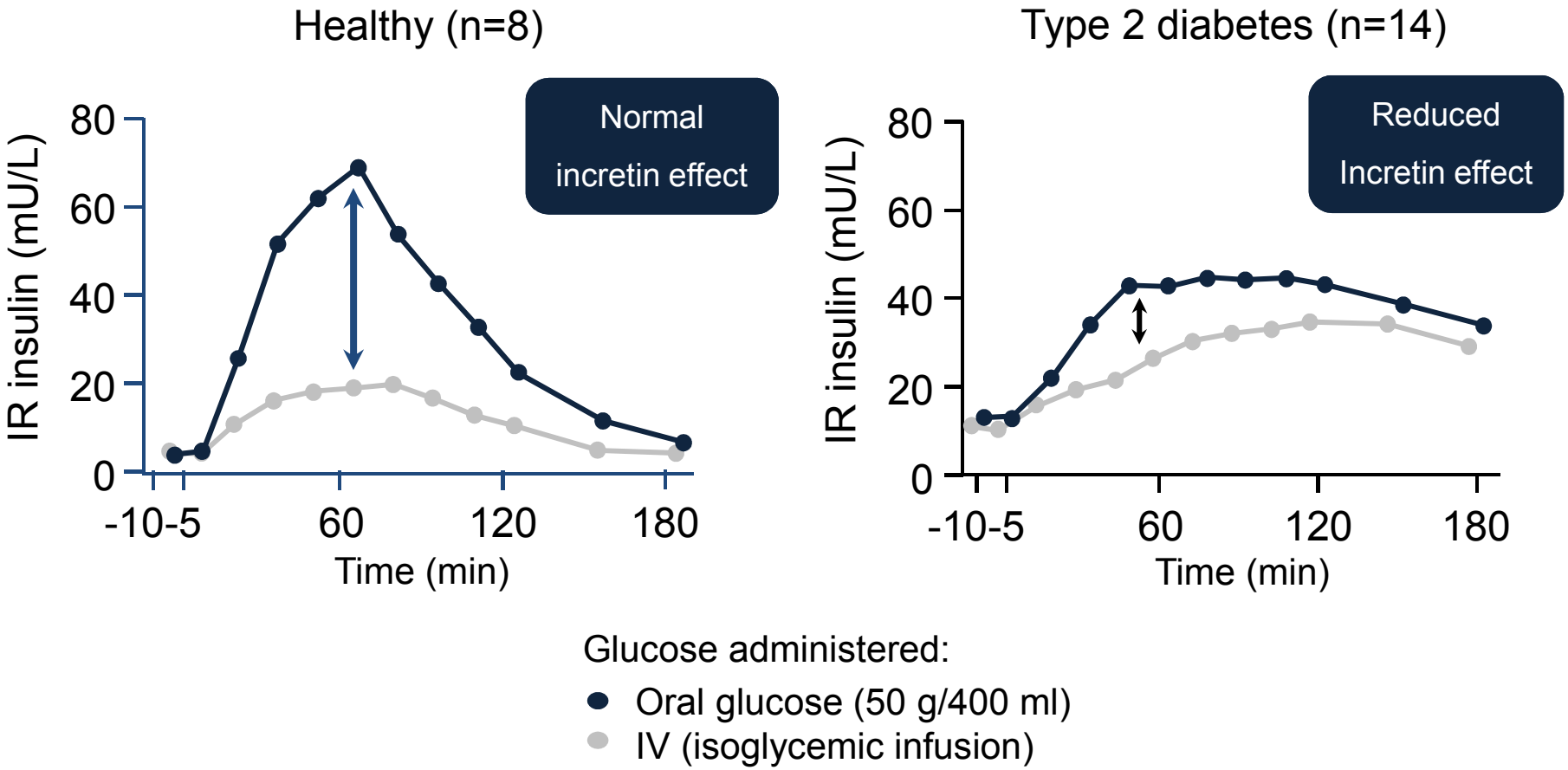
Lilly

DPP4 inhibitor – Mechanism of action



Adapted from Drucker DJ. Expert Opin Invest Drugs. 2003;12(1):87-100
Ahrén B. Curr Diab Rep. 2003;3:365-372

The incretin effect is reduced in type 2 diabetes



Nauck M, et al. *Diabetologia*. 1986;29:46–52.

DPP-4 inhibitors available in Korea

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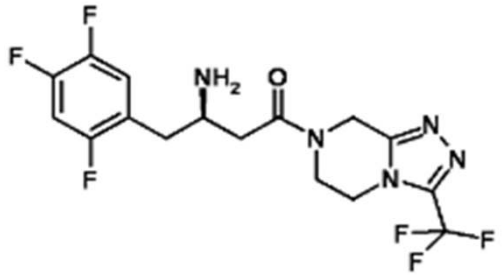
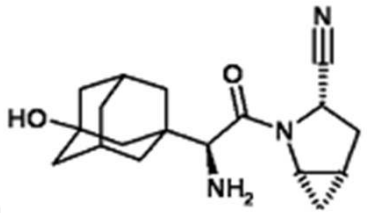
DPP-4 inhibitors mimicking dipeptides

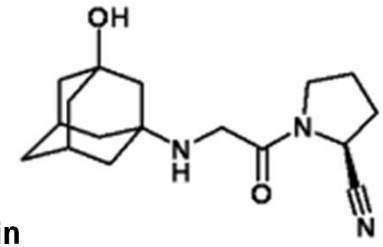
Sitagliptin



Saxagliptin

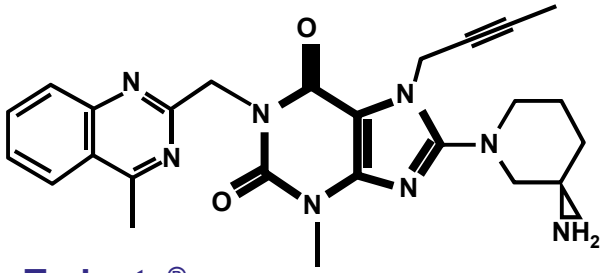


Vildagliptin



Peptidomimetic DPP-4 inhibitors

DPP-4 inhibitors directly binding to the active site of the enzyme



Trajenta®

Xanthine-based structure

- Elongate half life of drug
- Tight binding to DPP4

Non-peptidomimetic DPP-4 inhibitors

Adapted from Deacon CF. *Diabetes Obes Metab*. 2011;13:7–18.

Characteristics of DPP-4 Inhibitors in Clinical Use in Korea

	Chemistry	Metabolism	Elimination route
Linagliptin	Xanthine-based	**Not appreciably metabolised**	**Biliary (unchanged as parent); <5% via kidney**
Sitagliptin	β-amino acid-based	Not appreciably metabolised	Renal (~80% unchanged as parent)
Vildagliptin	Cyanopyrrolidine	Hydrolysed to inactive metabolite (P_{450} enzyme independent)	Renal (22% as parent, 55% as metabolite)
Saxagliptin	Cyanopyrrolidine	Hepatically metabolised to active metabolite (via P_{450} 3A4/5)	Renal (12-29% as parent, 21-52% as metabolite)

Deacon; Diabetes Obes Metab 2011

Characteristics of DPP-4 Inhibitors in Clinical Use in Korea (cont'd)

	Compound t½	Dosing#	DPP-4 inhibition*
Linagliptin	**10 – 40 h**	5 mg qd	Max ~80%; ~70% 24 h post-dose
Sitagliptin	8 – 24 h	100 mg qd	Max ~97%; >80% 24 h post-dose
Vildagliptin	1½ – 4½ h	50 mg bid	Max ~95%; >80% 12 h post dose
Saxagliptin	2 – 4 h (parent) 3 – 7 h (metabolite)	5 mg qd	Max ~80%; ~70% 24 h post-dose

Potency (ie dose) is not the same as efficacy

* No direct comparisons of degree of inhibition attained by different inhibitors with the therapeutic doses

Deacon; Diabetes Obes Metab 2011

DPP-4 Inhibitors: Selectivity for DPP-4

Selectivity for DPP-4 compared to the DPP gene family

	QPP*/DPP-2	DPP-8	DPP-9
Linagliptin	> 100,000	40,000	> 10,000
Sitagliptin	> 5,500	> 2,660	> 5,500
Vildagliptin	> 100,000	270	32
Saxagliptin	> 50,000	390	77

* Quiescent cell proline dipeptidase

Deacon CF. *Diabetes, Obes Metab.* 2011;13(1):7–18.

DPP-4 Inhibitors – Similarities and Differences

Differences	Similarities
Chemical structures	Efficacy (HbA_{1c} lowering)
in vitro selectivity	Tolerability
Metabolism (changed/unchanged; active/inactive metabolite)	Clinical safety profile
Elimination (renal/hepatic)	
Preclinical toxicities	
Potency (therapeutic dose)	
Dosing frequency (once/twice daily)	
Use in special populations (eg impaired renal/hepatic function)	

Deacon; Diabetes Obes Metab 2011

DPP-4 Inhibitors: Other Differences

Vildagliptin and saxagliptin (but not sitagliptin or linagliptin) reported to be associated with adverse skin toxicology in cynomolgus monkeys.

…. but no reports of skin problems in any of the clinical trials

Saxagliptin: Small, reversible, reductions in absolute lymphocyte count in some clinical trials (more apparent at doses ≥20 mg; remained within normal limits)

…. but no effect on white blood cell or neutrophil count; no evidence of altered immune function. Clinical significance (if any) unknown

Vildagliptin: 100 mg qd reported to be associated with small numerical elevations in liver transaminases (vs placebo or 50 mg bid). Therapeutic dose changed to 50 mg bid; liver function tests required before initiation and periodically thereafter.

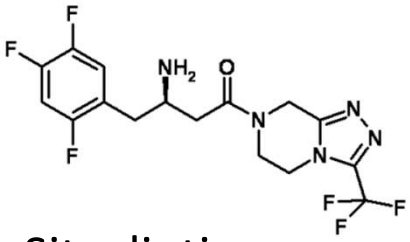
…. subsequently, larger pooled safety analysis confirms trend for mild increases (≥3x ULN) (Ligueros-Saylan et al, Diabetes Obes Metab 2010) – not associated with increased incidence of actual hepatic adverse events; liver function tests still recommended

Linagliptin reported to improve wound healing in *ob/ob* mice (Linke et al, ADA 2009; 596-P)

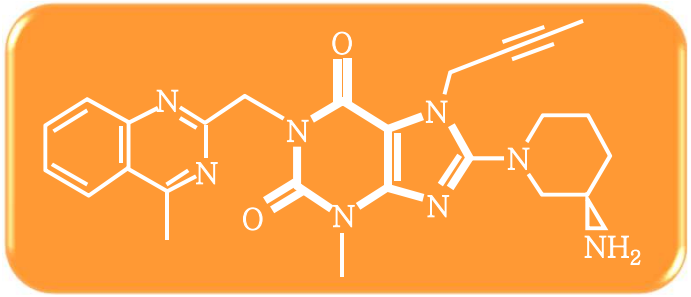
…. unclear whether this is related to inhibition of DPP-4 or FAPα (or both). Unknown at present whether other DPP-4 inhibitors share this property

Deacon; Diabetes Obes Metab 2011

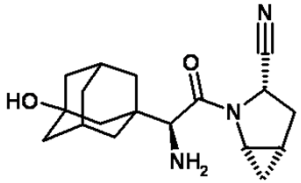
Trajenta® – Unique Xanthine-Based Structure



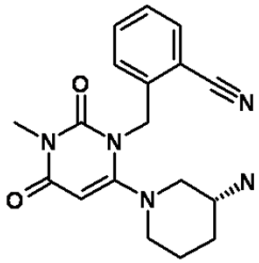
Sitagliptin



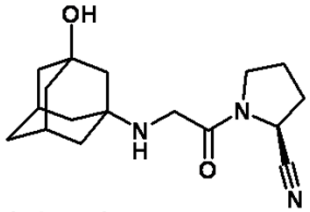
Trajenta®



Saxagliptin

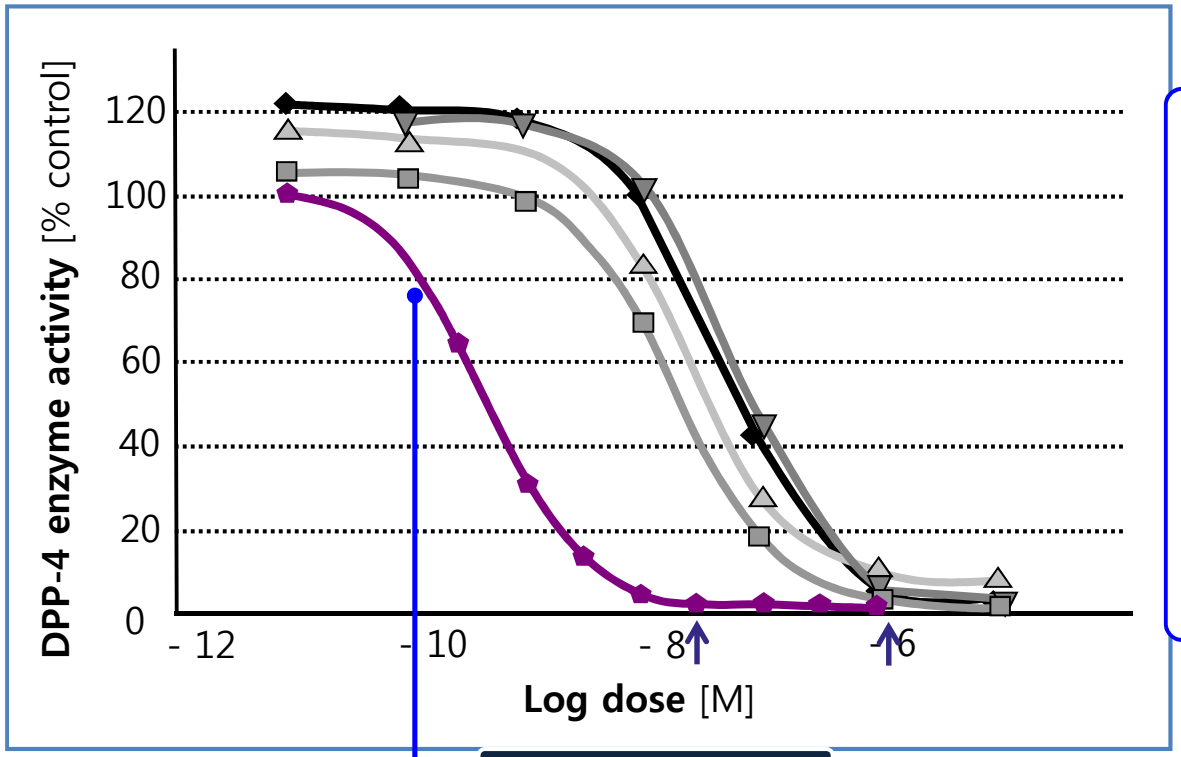


Alogliptin



Vildagliptin

Trajenta®– highest potency to inhibit DPP-4 enzyme activity in direct comparison to other DPP-4 inhibitors



	IC50[1] [nM] mean	Therapeutic dose [mg]
Linagliptin	1	5
Saxagliptin	9	5
Sitagliptin	19	100
Alogliptin	24	25
Vildagliptin	62	2x50

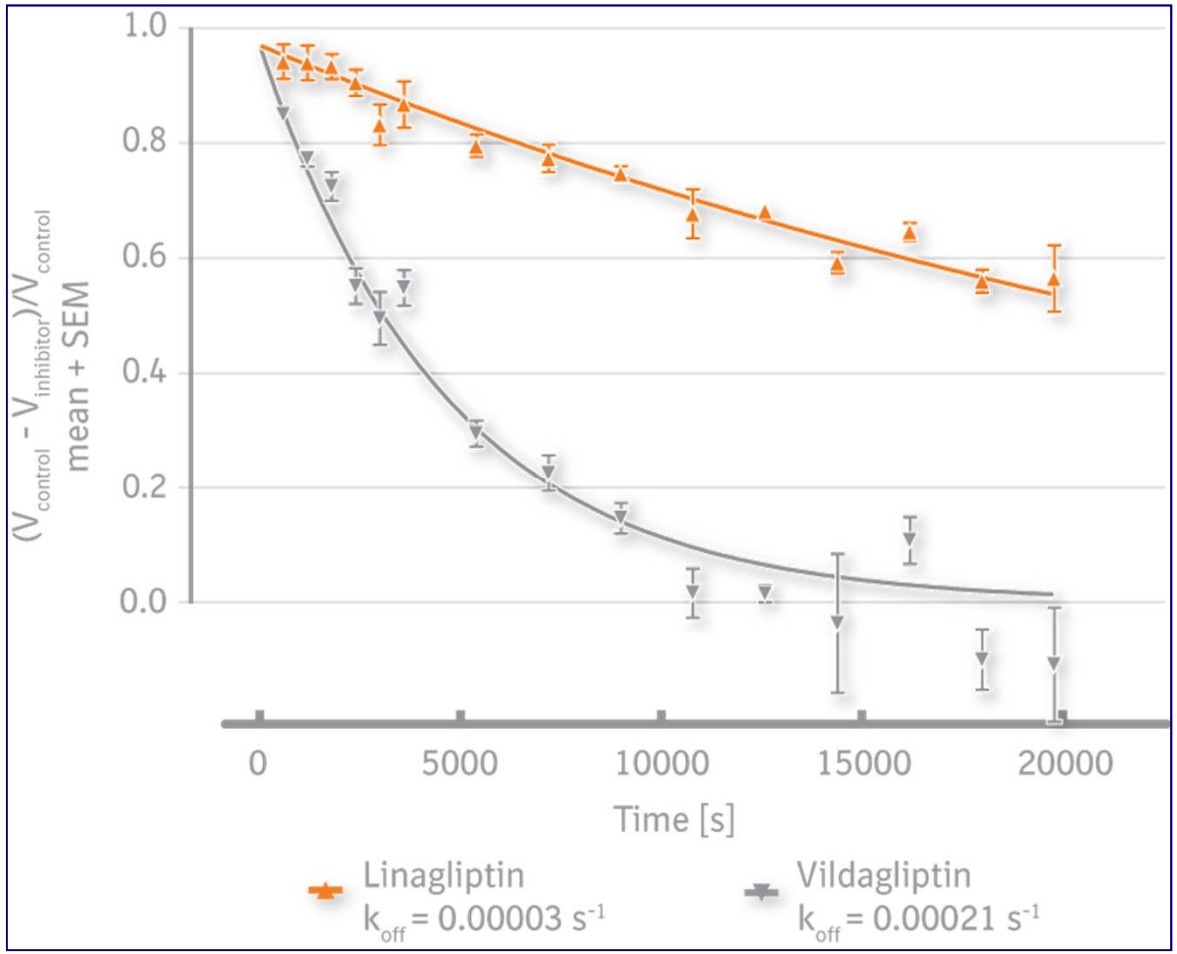
Linagliptin concentration in clinical use is 6-8 nmol/L, resulting in >80% DPP-4 inhibition over 24 hours

1 Concentration of compound needed to inhibit 50% of DPP-4 activity, i.e. the lower the IC50, the higher the potency to inhibit DPP-4 activity

Source: Thomas et al., J Pharmacol Exp Ther. 2008;325(1):175–82

Trajenta®– Tight binding and slow dissociation from the DPP-4 Enzyme

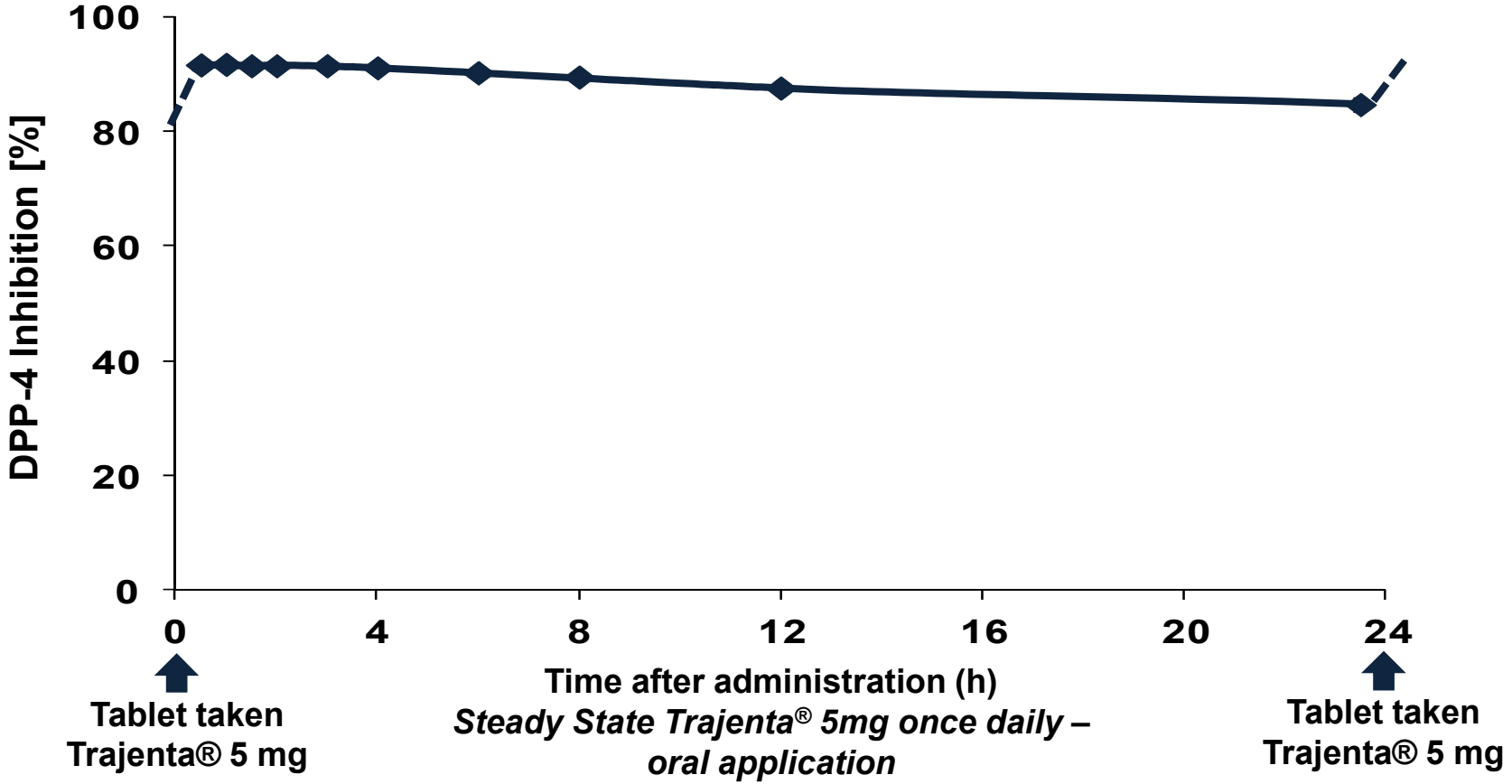
- DPP4 enzyme extracted from human Caco-2 cell were preincubated with inhibitor concentrations (30 nM for linagliptin and 3 µM for vildagliptin) high above the respective k_i values
- The calculated k_{off} rate for linagliptin was ~10-fold slower than the off-rate for vildagliptin



Thomas et al., J Pharmacol Exp Ther. 2008;325(1):175–82.

Trajenta® provides long-lasting DPP-4 inhibition in patients with type 2 diabetes

Steady-state plasma levels are achieved after the third dosing interval providing >91% of DPP-4 inhibition at peak levels



Adapted from Heise T et al. *Diabetes Obes Metab.* 2009;11(8):786–94

Linagliptin : Large safety margin in animals

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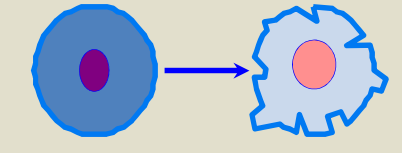
Carcinogenesis



- No increased incidence of tumours in rats after 2 years (up to 418 times the clinical dose)
- No increased incidence of tumours in male mice after 2 years (up to 270 times the clinical dose); high doses of Trajenta® in female mice increased incidence of lymphoma (at 215 times the clinical dose)

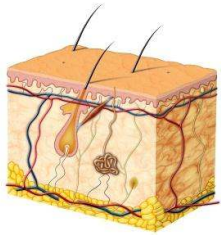
Mutagenesis

- Trajenta® was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay

Impairment of fertility

- Trajenta® had no adverse effects on early embryonic development, mating, fertility, or bearing live young (up to 943 times the clinical dose)

Skin and vascular lesions



- No skin or vascular lesions observed in cynomolgus monkeys[1] at > 1,000-fold therapeutic exposure

1 Cynomolgus monkeys showed severe skin lesions for vildagliptin and saxagliptin (13 weeks' exposure)

Source: Trajenta® US PI; Trajenta® data on file

Linagliptin (Trajenta®) is primarily excreted unchanged via bile and gut

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Absorption

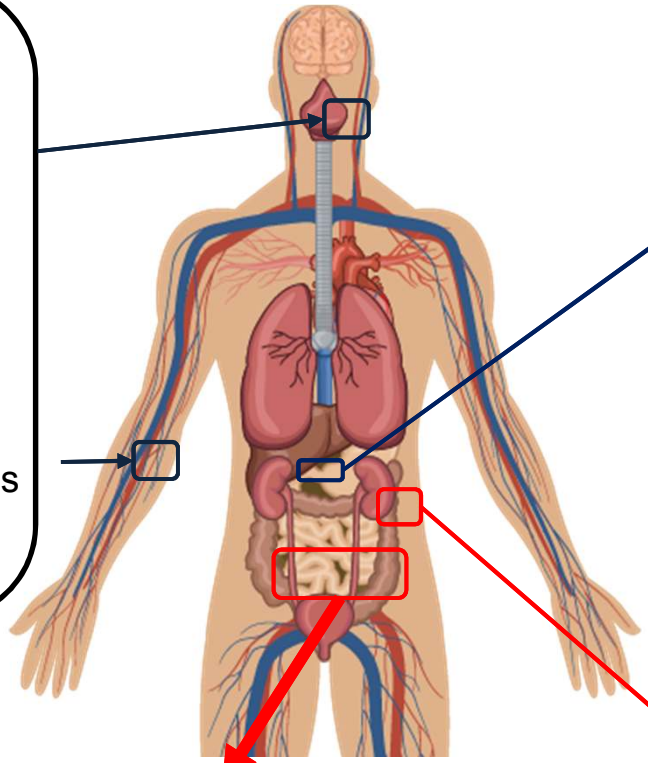
Tablet intake: 5 mg QD, independent of food

↓

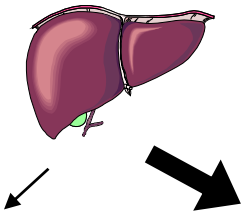
Absolute bioavailability: ~30%, with or without food

↓

~95% bound to plasma proteins (in essence DPP-4)



Metabolism



~10% (inactive) metabolite

~90% transferred **unchanged**

Excretion[1]**:**

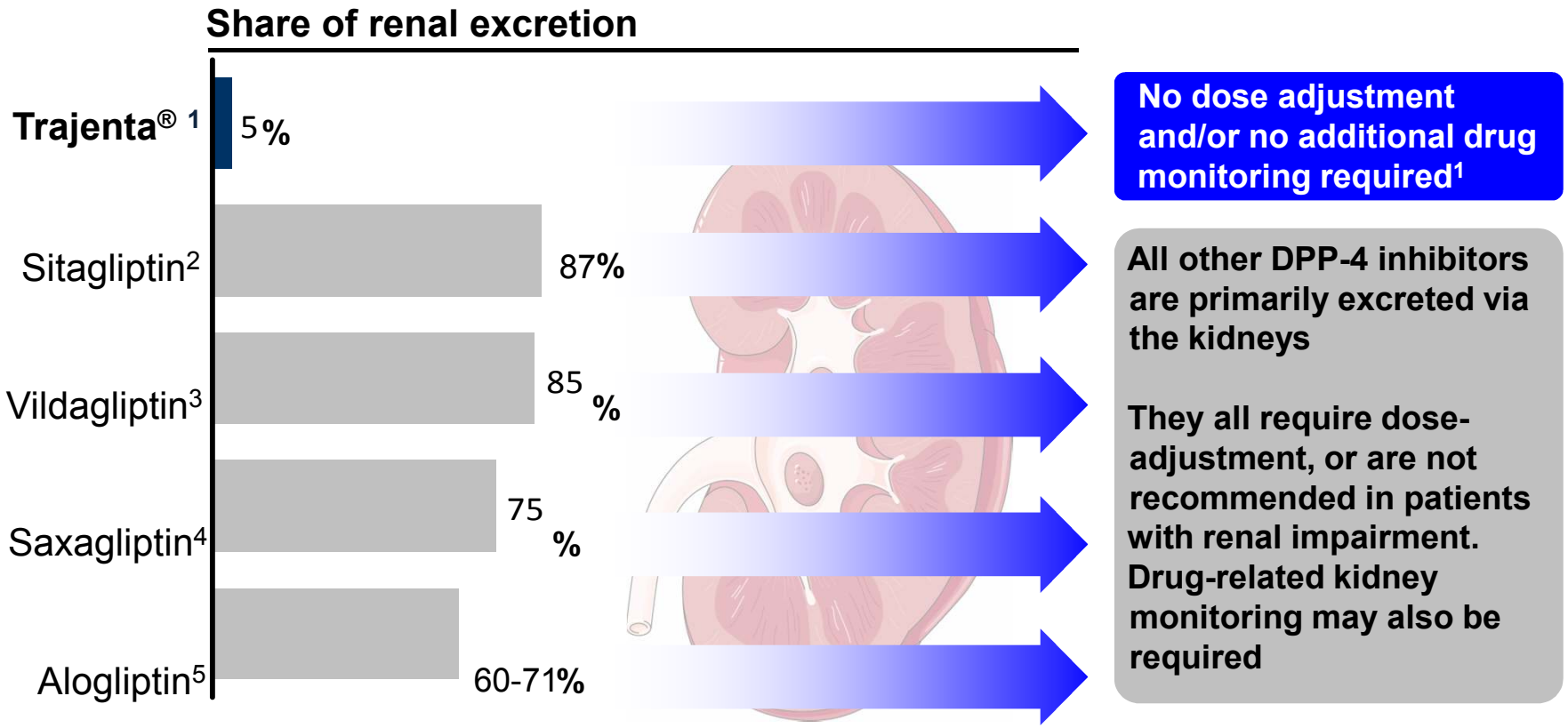
~ 95% of orally administered Trajenta® is excreted **via the bile and gut**

~ 5% of orally administered Trajenta® is excreted via the kidneys

1 At steady state

Source: EU/US prescribing information

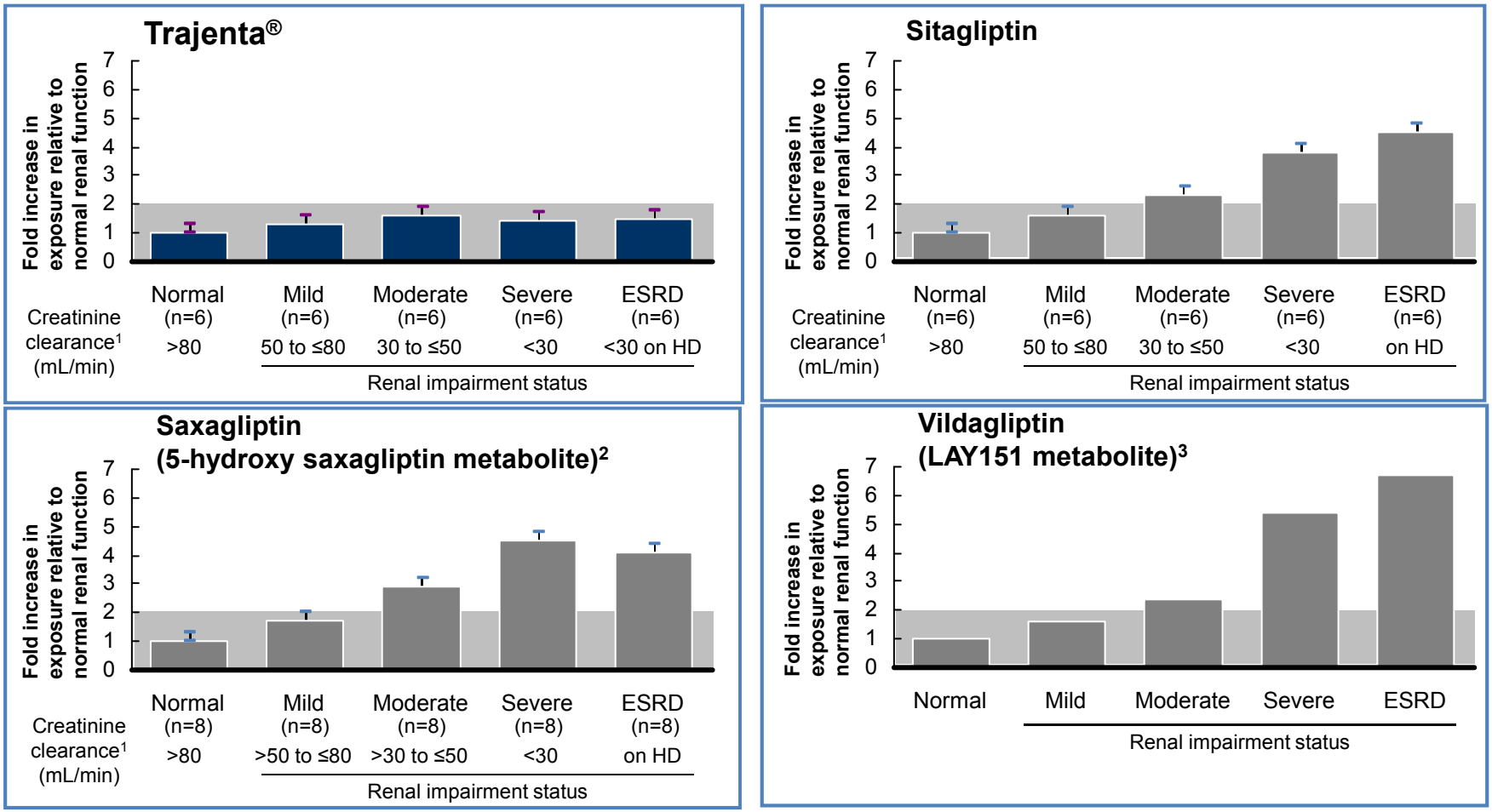
Percent renal excretion of DPP-4 inhibitors



* of currently globally approved DPP-4 inhibitors
Data from multiple trials, includes metabolites and unchanged drug; excretion after single dose administration of [14C] labeled drug

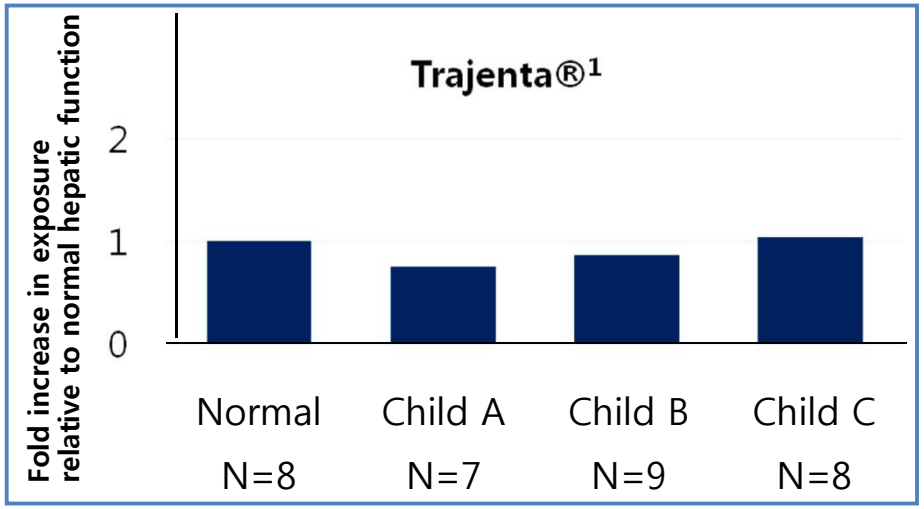
1. Linagliptin EU/US PI; 2. Vincent SH et al. *Drug Metab Dispos.* 2007;35(4): 533–538
3. He H, et al. *Drug Metab. Dispos.*2009 37(3):545–554; 4. Saxagliptin US PI
5. Christopher R et al. *Clin Ther*. 2008;30(3):513–527.

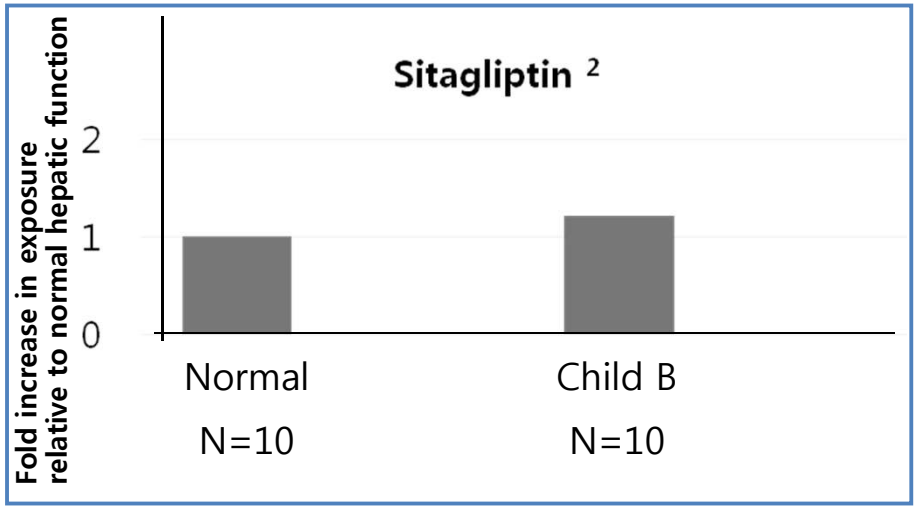
DPP-4 inhibitor exposure in patients with various level of renal function

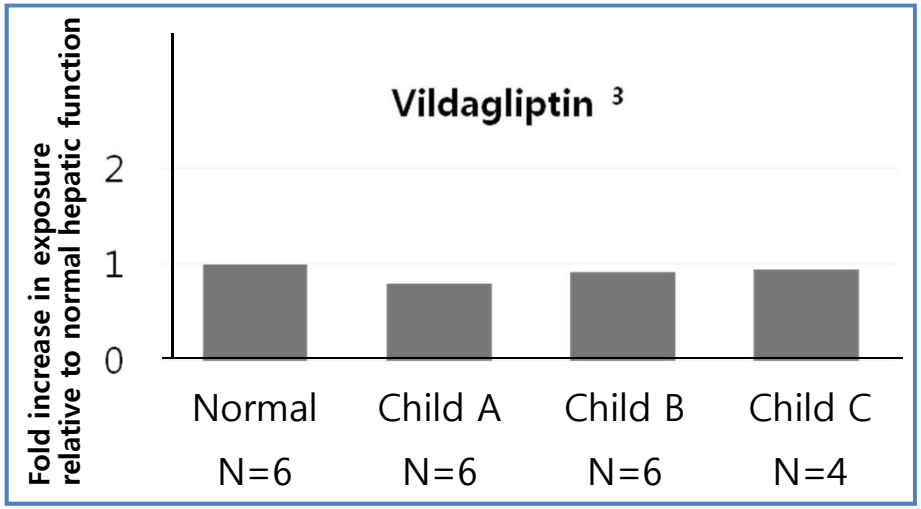


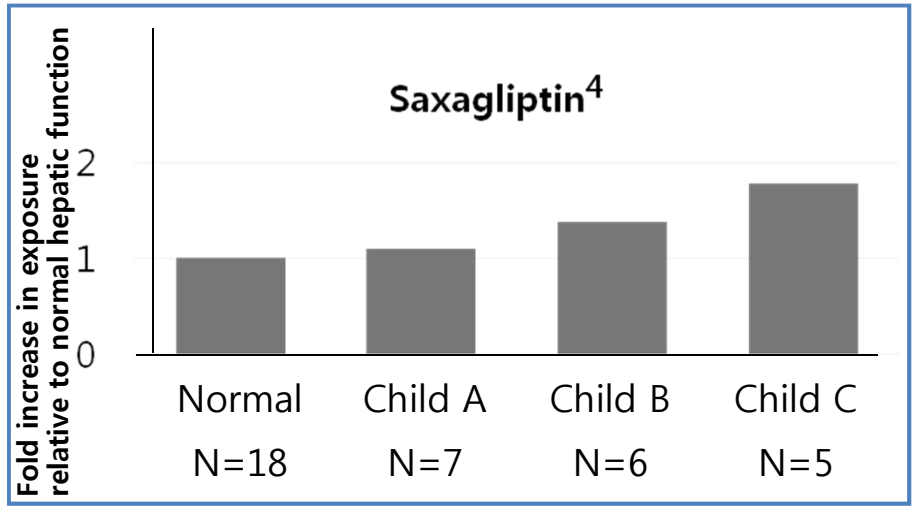
Source: Graefe-Mody et al. 1011 DOM in press, Bergman et al. *Diabetes Care* 2007, 30:1862-1864; Boulton et al. *Clin Pharmacokinet* 2011, 50:253-265; European Medicines Agency (EMEA). Galvus (vildagliptin). European Public Assessment Report (EPAR)

Linagliptin (Trajenta®) : no dose adjustment required regardless of the degree of hepatic impairment







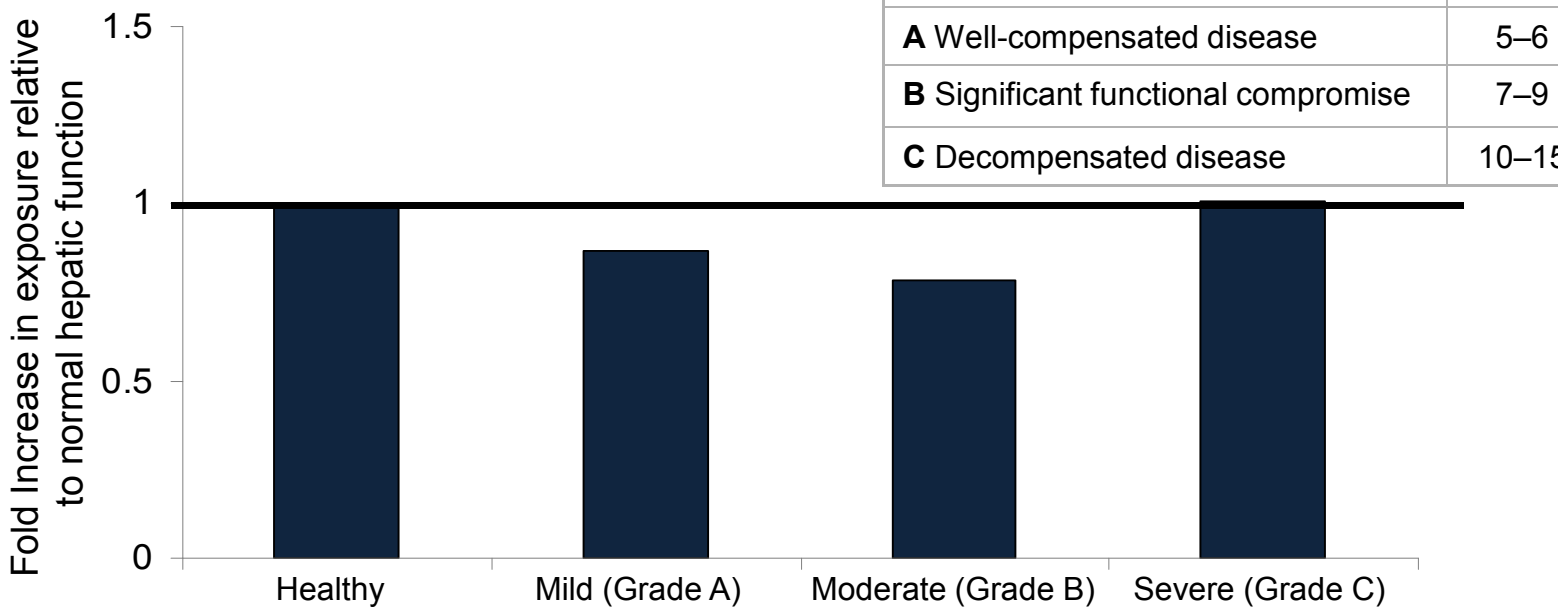


1.Br J of Clin Pharmacol 2012 epub, ahead of print. 2. Januvia US PI 2011
3 Eur J Clin Pharmacol (2007) 63:677–686 4.Clin Pharmacokinet. 2011Apr 1;50(4):253-65.

Influence of hepatic impairment on pharmacokinetics and exposure of Linagliptin (Trajenta®)

No dosage adjustment for Trajenta® is necessary for patients with mild, moderate or severe hepatic impairment

Child-Pugh Grade	*Points*
A Well-compensated disease	5–6
B Significant functional compromise	7–9
C Decompensated disease	10–15



Hepatic impairment (Child-Pugh classification)

n = 8 n = 7 n = 9 n = 8

Patients with mild moderate and severe hepatic impairment

Graefe-Mody et al. 4th International Congress on Prediabetes and the Metabolic Syndrome, Madrid, Spain, April 6-9, 2011.

Prescribing characteristics of DPP-4 inhibitors

Inhibitor	Renal Impairment*			Hepatic Impairment	
	Mild (CrCl ≥ 50 ml/min)	Moderate (CrCl ≥30-<50 ml/min)	Severe/ESRD (CrCl <30 ml/min)	Mild/ Moderate	Severe
Trajenta®	✓	✓	✓	✓	✓
Sitagliptin	✓	½ dose	¼ dose	✓	Not recommended[1]
Vildagliptin[2]	✓	½ dose (not approved in the US) [1]	½ dose (not approved in the US) [1]	Not recommended	Not recommended
Saxagliptin[3]	✓	½ dose (EU) ½ dose (US)[1]	½ dose (use with caution) not recommended in ESRD (EU) ½ dose (US)[1]	✓ (Moderate: use with caution)	Not recommended[1]

CrCl = Creatinine clearance; ESRD = end-stage renal disease
* Assessment of renal function recommended prior to initiation of treatment and periodically thereafter
1. Not studied/no clinical experience
2. Assessment of hepatic function recommended prior to initiation of vildagliptin and periodically thereafter
3. Dose reduction (2.5 mg) when saxagliptin co-administered with strong CYP450 3A4/5 inhibitors (e.g. ketoconazole)

Adapted from Deacon CF. *Diabetes, Obes Metab.* 2011;13(1):7–18.

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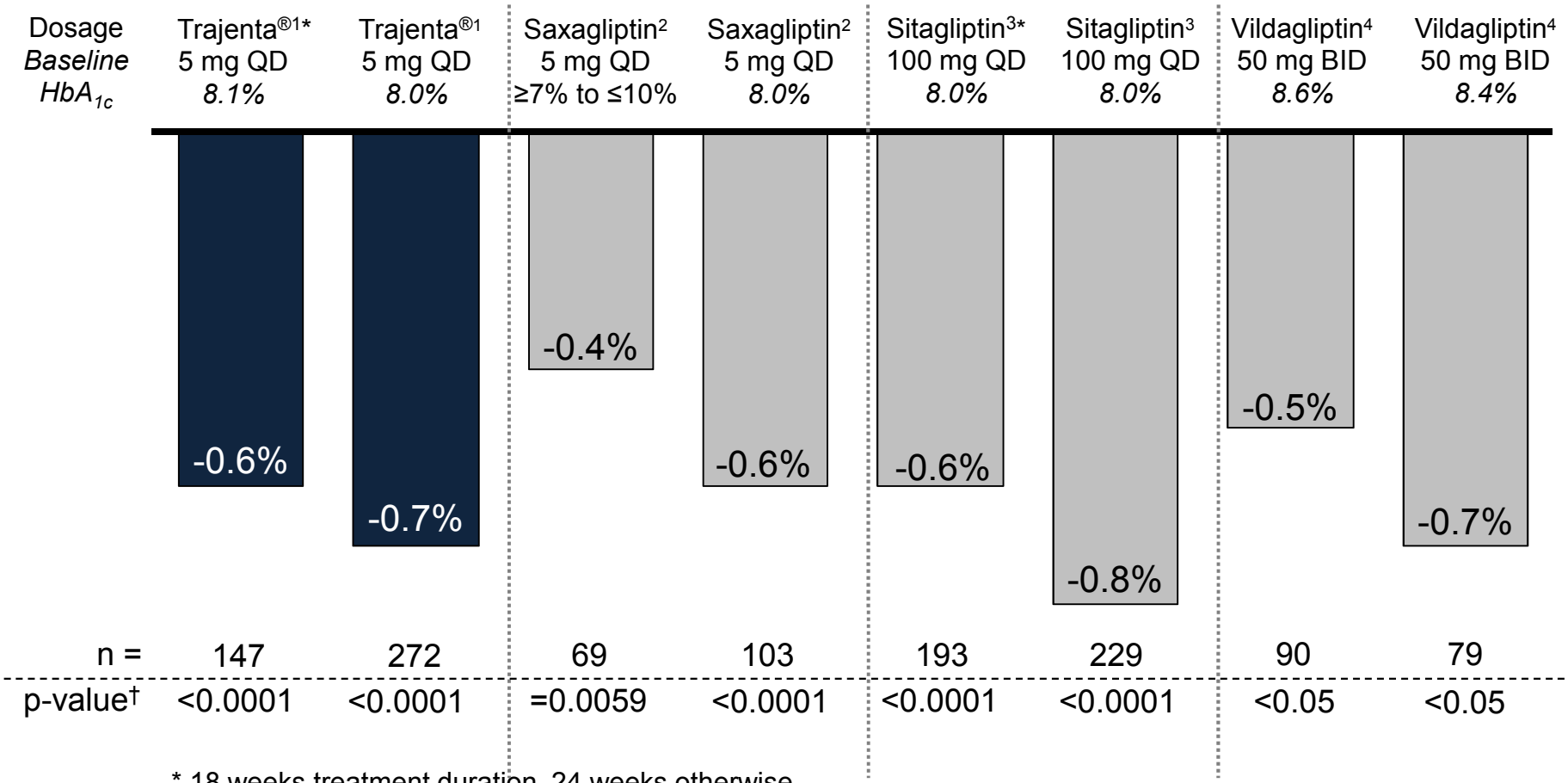
Clinical Data

Linagliptin (Trajenta)

Efficacy of DPP-4 inhibitors in monotherapy trials

Placebo-corrected, adjusted mean change from baseline HbA_{1c}

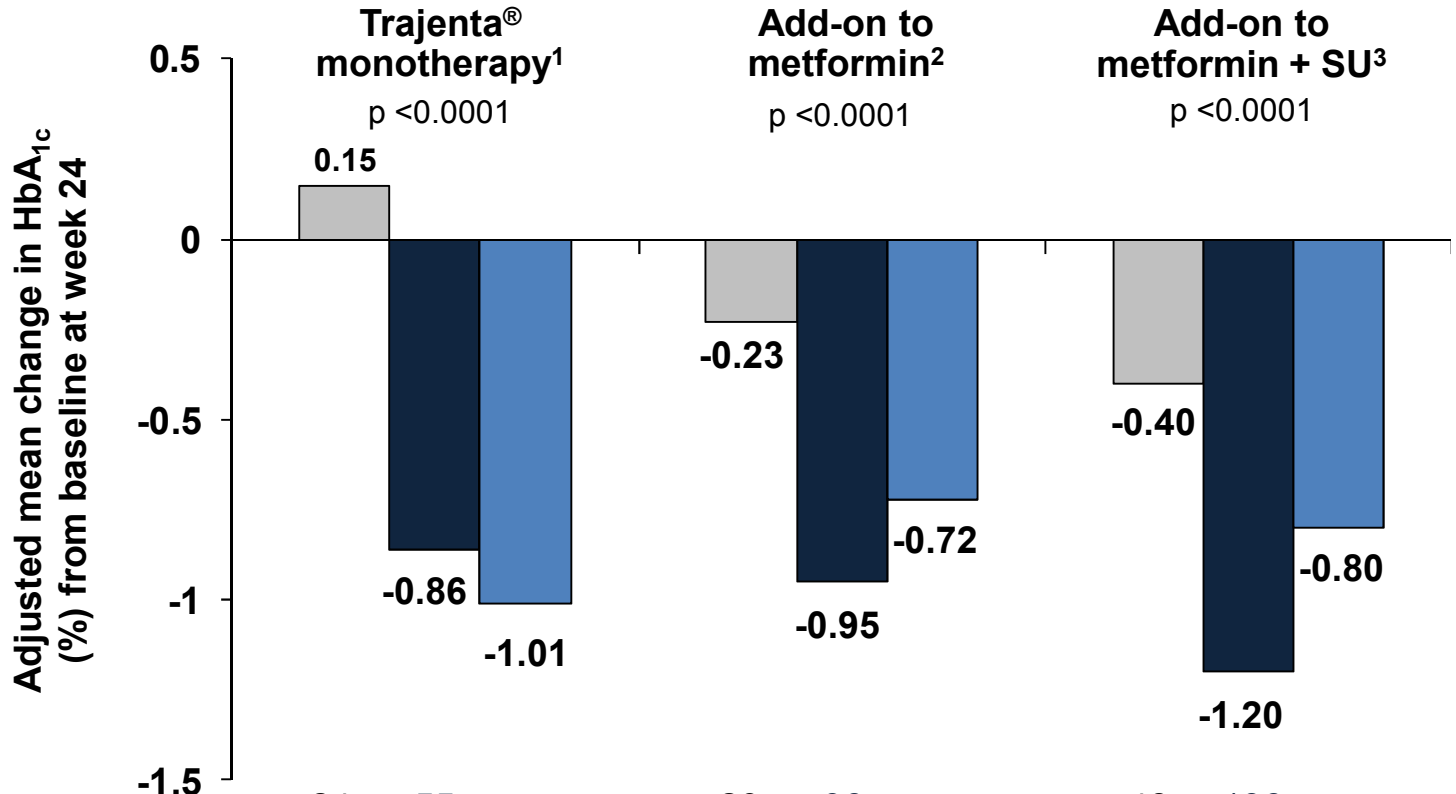


* 18 weeks treatment duration, 24 weeks otherwise
† Between group difference versus placebo

Sources: 1– 4, EU SmPC for Trajenta® , saxagliptin, sitagliptin and vildagliptin

Trajenta®: HbA_{1c} changes in poorly controlled patients

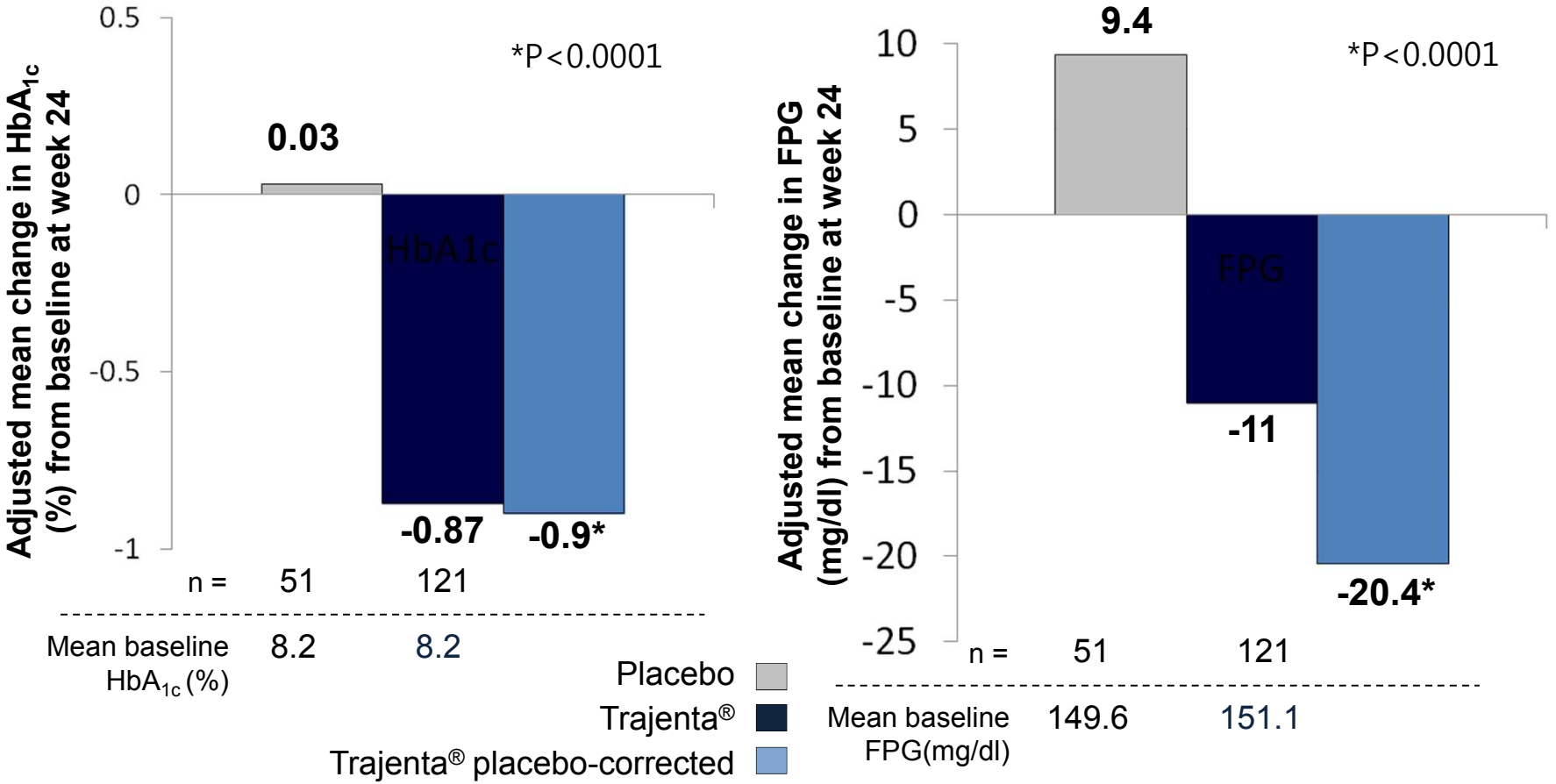
Significant HbA_{1c} reductions in **type 2 diabetes patients with baseline HbA_{1c} ≥ 9%**



1. Del Prato S, et al. *Diabetes Obesity and Metabolism* 2011;13(3):258–267.
2. Taskinen M-R, et al. *Diabetes Obesity and Metabolism* 2011;13(1):65–74.
3. Owens DR, et al. *Diabetic Medicine* (in press) 2011

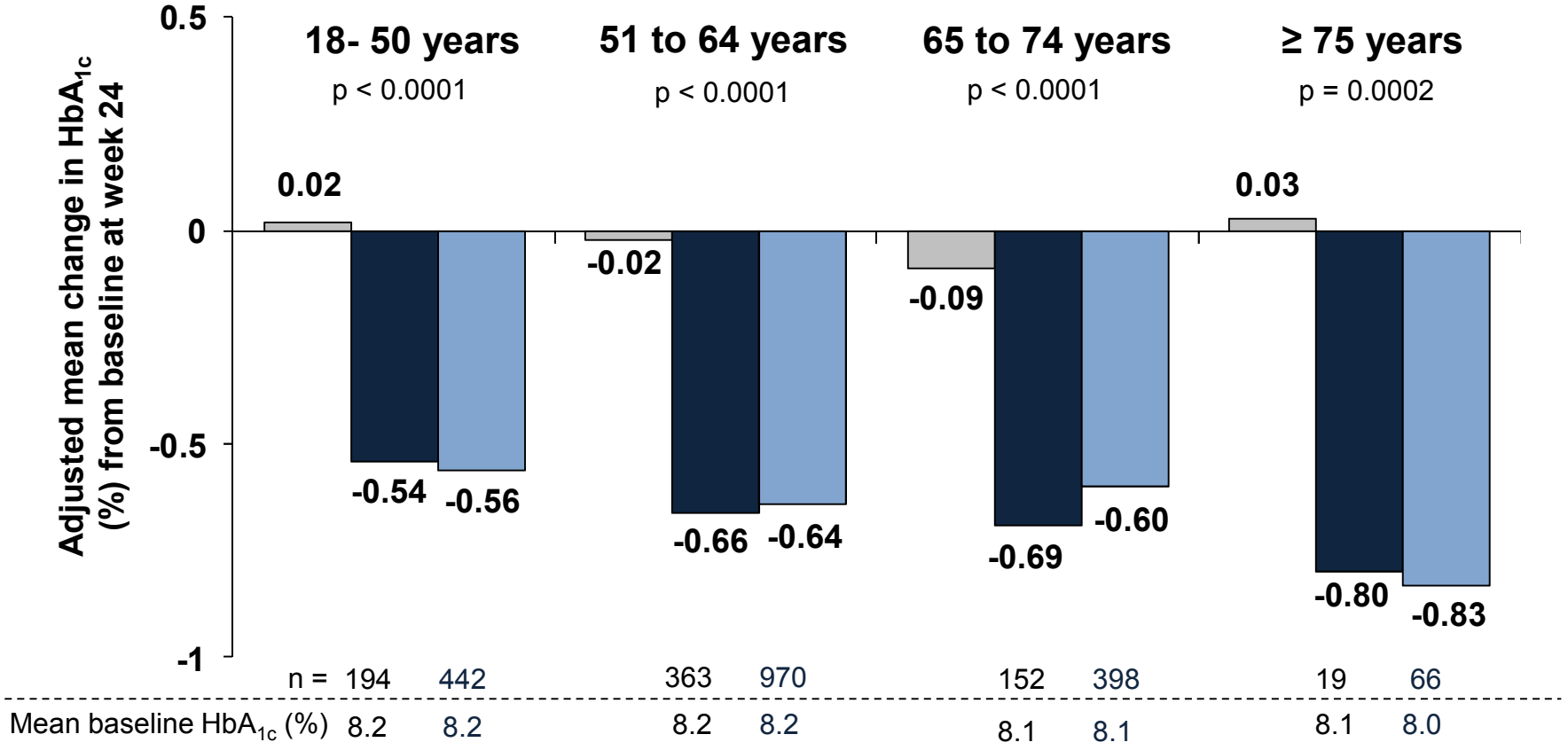
Trajenta®: Meaningful efficacy in Korean subgroup

Significant HbA_{1c} and FPG reductions in **Korean** subgroup with Trajenta®
combined with Metformin and Sulfonylurea



International Conference on Diabetes and Metabolism, 12 Nov 2011 OP7-5 * Changes vs placebo
Linagliptin in Combination with Metformin and a Sulfonylurea in Type 2 Diabetes,, Korean subgroup analysis

Trajenta® : HbA1c reductions and patient age

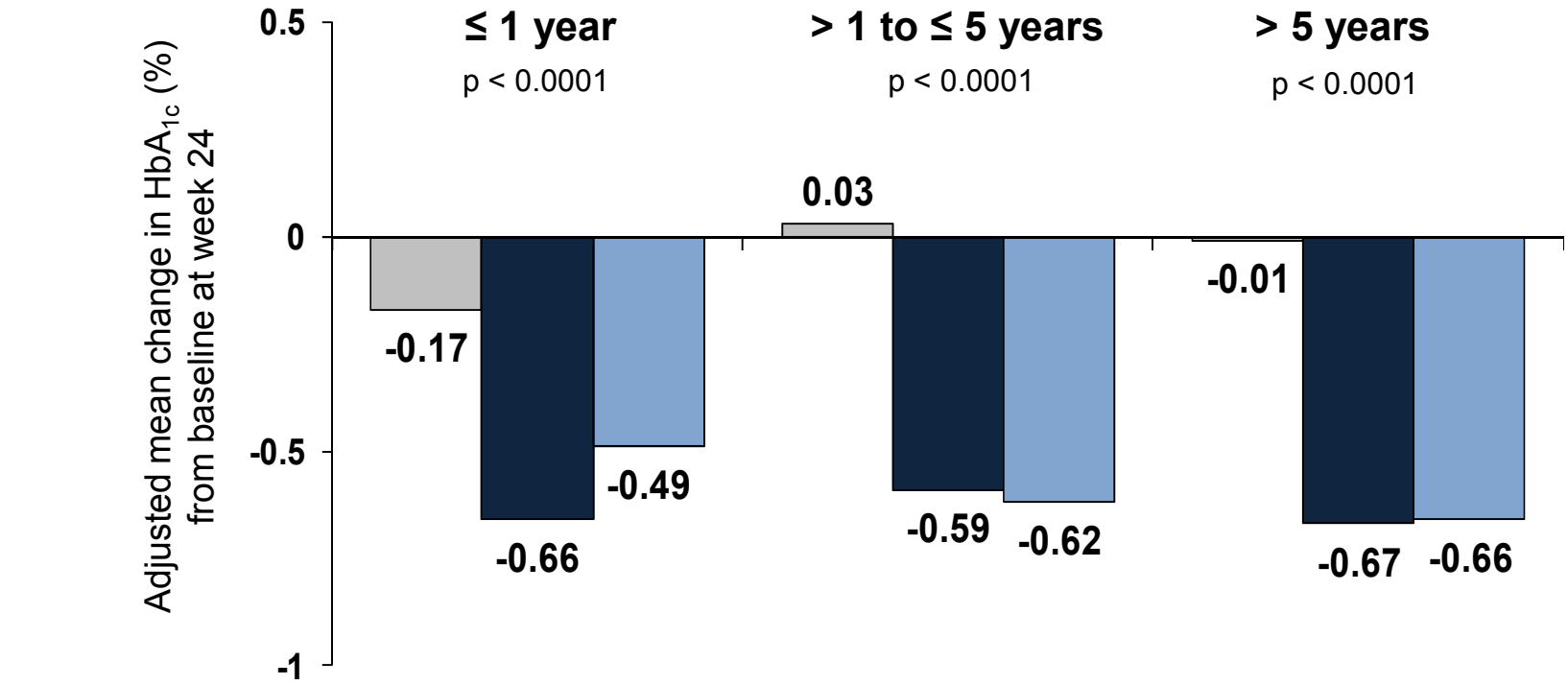


Pre-specified sub-group analysis on pooled data from four pivotal phase III randomized placebo-controlled trials: treatment in monotherapy, add-on to metformin, add-on to metformin + SU, initial combination with pioglitazone. p-values for between-group difference (versus placebo)

Placebo
Trajenta®
Trajenta® placebo-corrected

Source: Patel 2011 EASD Poster P-832

Trajenta® : HbA1c reductions and time of diagnosis



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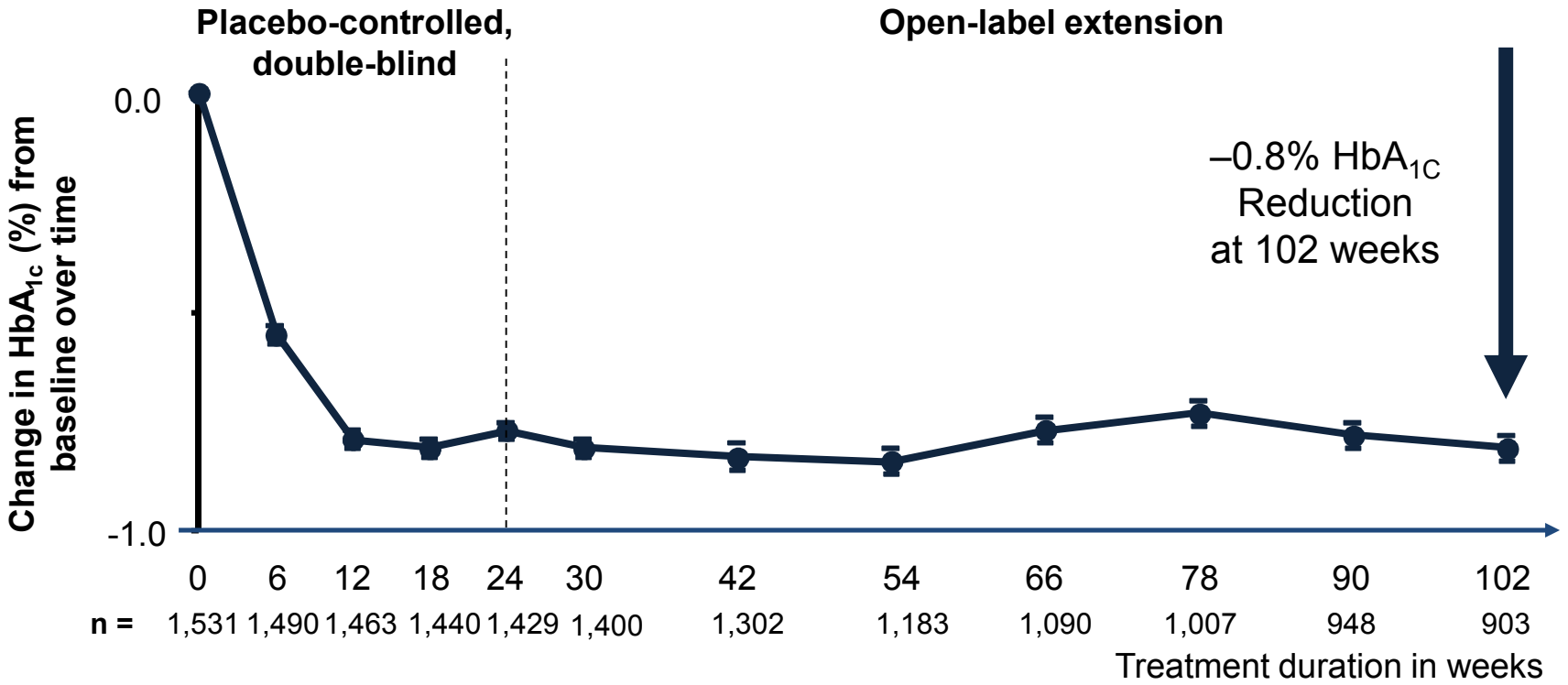
Placebo
Trajenta®
Trajenta® placebo-corrected

Source: Patel 2011 EASD Poster P-832

Durability



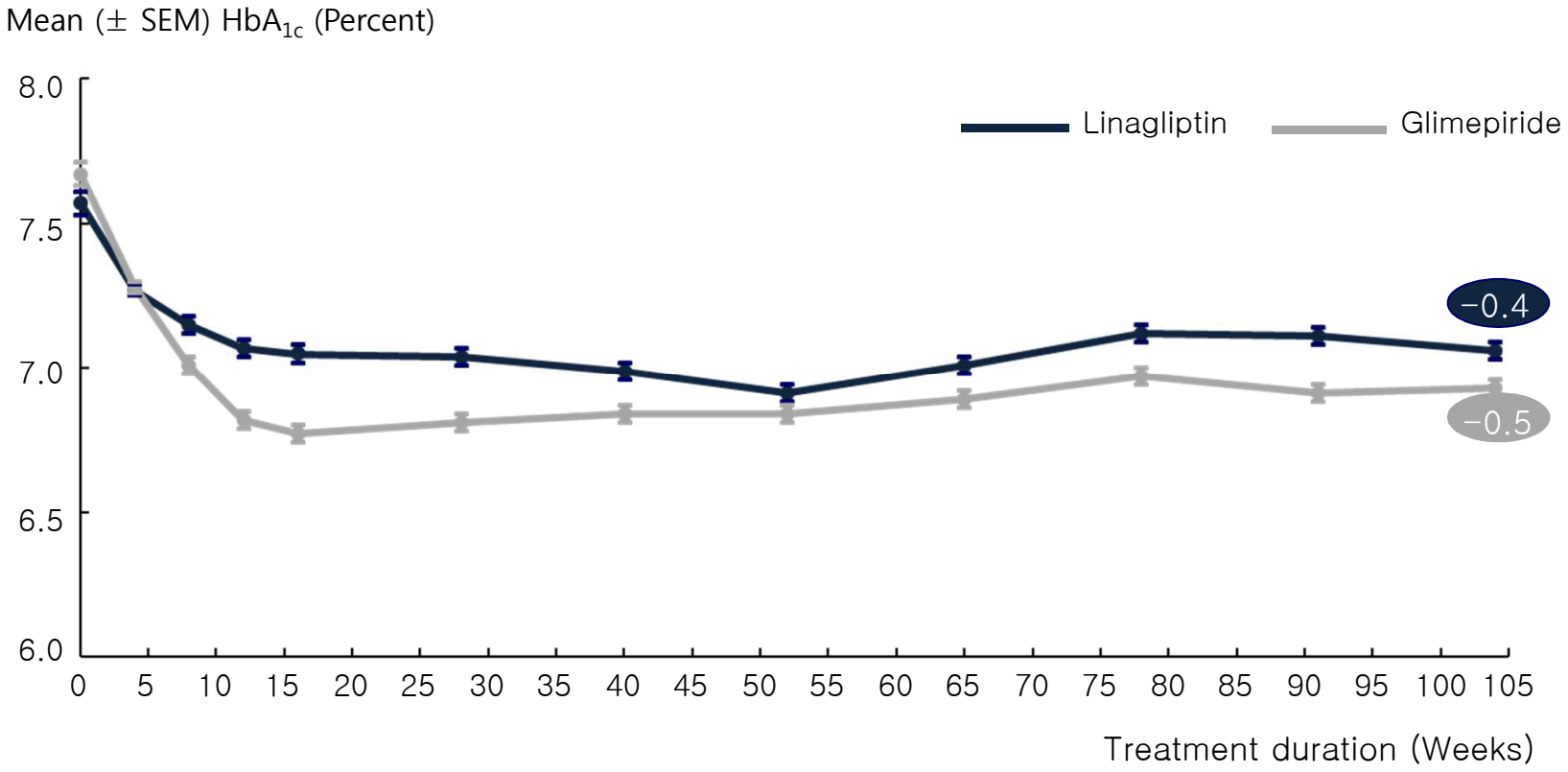
After 24 weeks double-blind, 78-week, open-label extension of four randomized, controlled trials. Patients were on four treatment regimens: Trajenta® monotherapy (n = 296); combination with metformin (n = 457); combination with metformin and SU (n = 544) and initial combination with pioglitazone (n = 234).

1. Pre-specified analysis of Trajenta® treatment in oral mono-, dual and triple combination therapy (full analysis set, observed cases).

Source: Schlosser et al EASD 2011 OP43: 242

Trajenta® compared to glimepiride – similar mean change in HbA_{1c} from baseline

HbA_{1c} change over 2 years
Mean over time ± SEM, percent



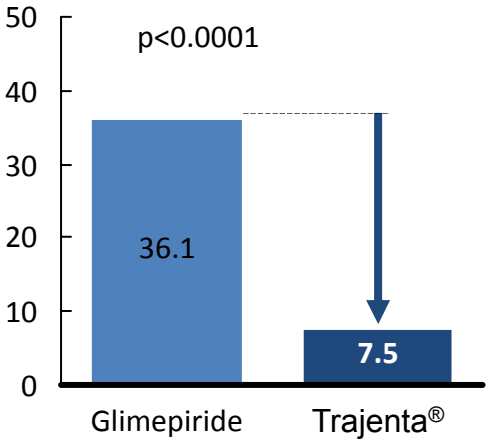
1 Per Protocol Set Completers linagliptin n=447, glimepiride n=458

Gallwitz B., et al. ADA 2011 Late Breaker 39-LB

Trajenta® compared to glimepiride – incidence of hypoglycemia, weight change and rate of patients achieving HbA1c target <7%

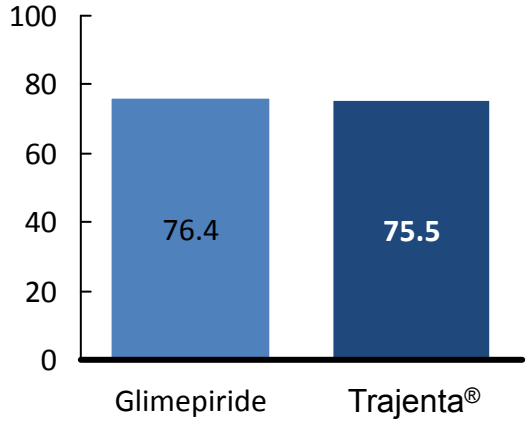
Incidence of hypoglycemia

Percent of patients - Treated set[1]



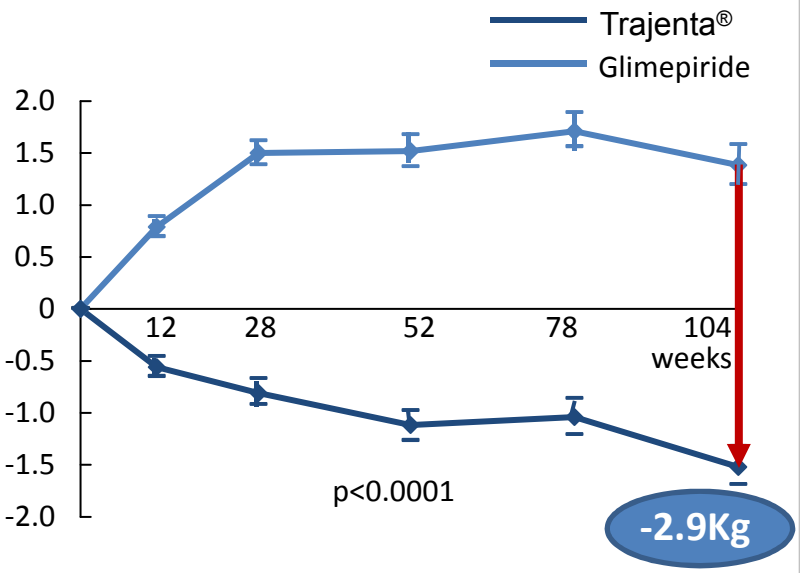
Rate of patients achieving HbA1c target <7%

Percent of patients at week 104 completers cohort[2]



Adjusted3 means for body weight change from baseline ± SE

Kg - FAS (OC)



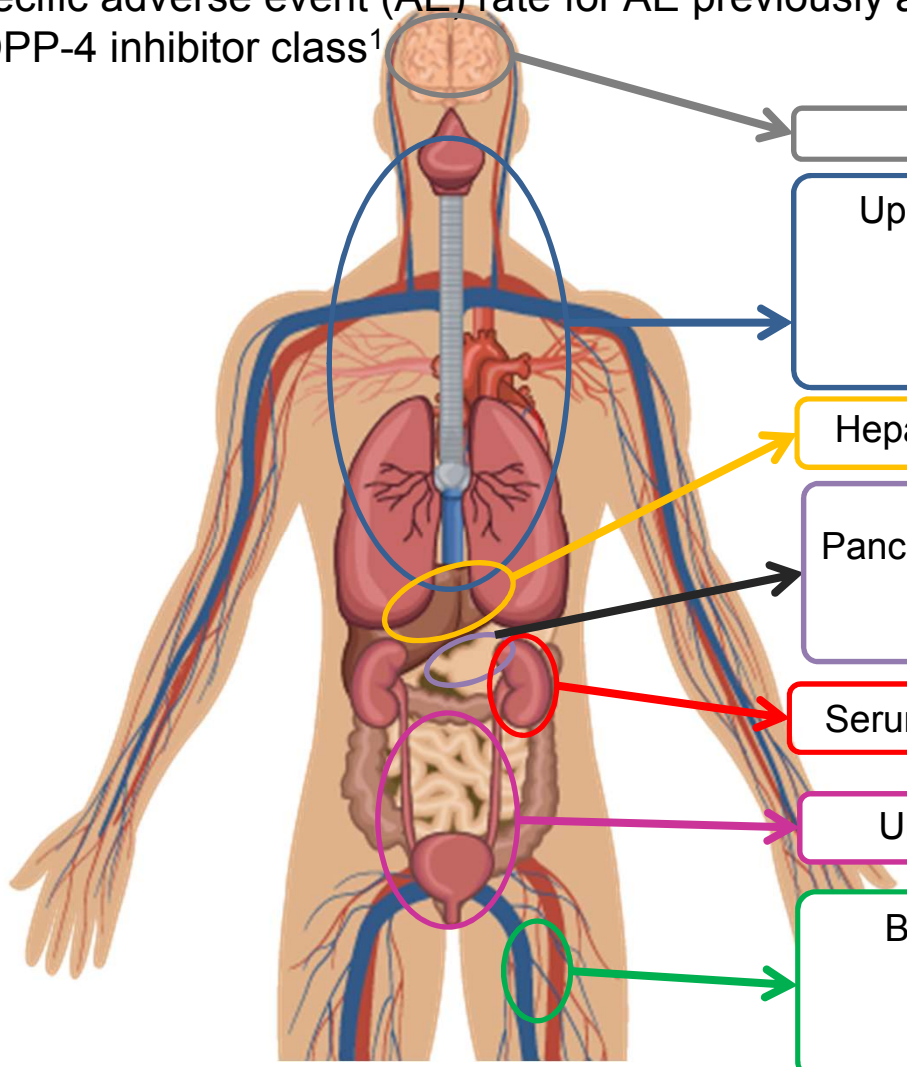
Trajenta® brings patients to target (HbA1c <7%) with significantly less hypoglycemia and relative weight loss compared to glimepiride

1 Treated Set: Trajenta® n=776, glimepiride n=775
2 Completers cohort: Trajenta® n=233, glimepiride n=271
3 Model includes baseline HbA1c, baseline weight, no. prior OADs, treatment, week repeated within patients and week by treatment interaction

Source: Gallwitz et al. American Diabetes Association, 71th Scientific Sessions, San Diego, CA, June 24-28, 2011; 39-LB

Trajenta® is well tolerated

Organ-specific adverse event (AE) rate for AE previously associated with the DPP-4 inhibitor class[1]



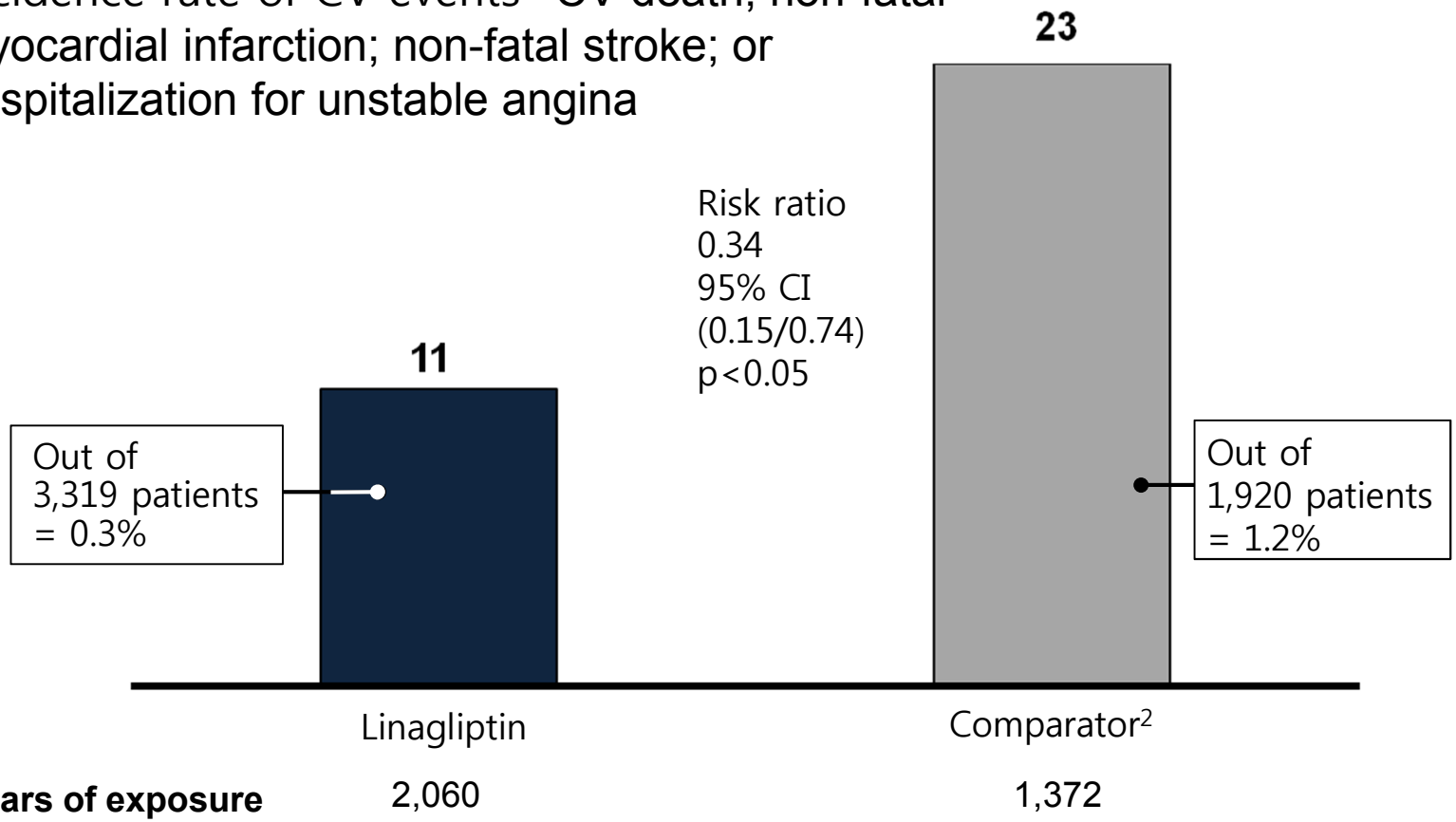
	Linagliptin	Placebo
n	2,523	1,049
Headache	2.9%	3.1%
Upper respiratory tract infection	3.3%	4.9%
Nasopharyngitis	5.9%	5.1%
Cough	1.7%	1.0%
Hepatic enzyme increase	0.1%	0.1%
Pancreatitis: 1 per 538 person years versus for Linagliptin zero in 433 person years for comparator		
Serum creatinine increase	0.0%	0.1%
Urinary tract infection	2.2%	2.7%
Blood and lymphatic system disorders	1.0%	1.2%
Hypersensitivity	0.1%	0.1%

1. Organ-specific adverse events taken from label of currently marketed DPP-4 inhibitor in the US; * Linagliptin US PI
Schernthaner G., et al. ADA 2011 Abstract 2327-PO. Pooled data from 8 studies

Trajenta® was not associated with an increased CV risk

In a prospective, pre-specified meta-analysis,

Incidence rate of CV events[1] :CV death; non-fatal myocardial infarction; non-fatal stroke; or hospitalization for unstable angina

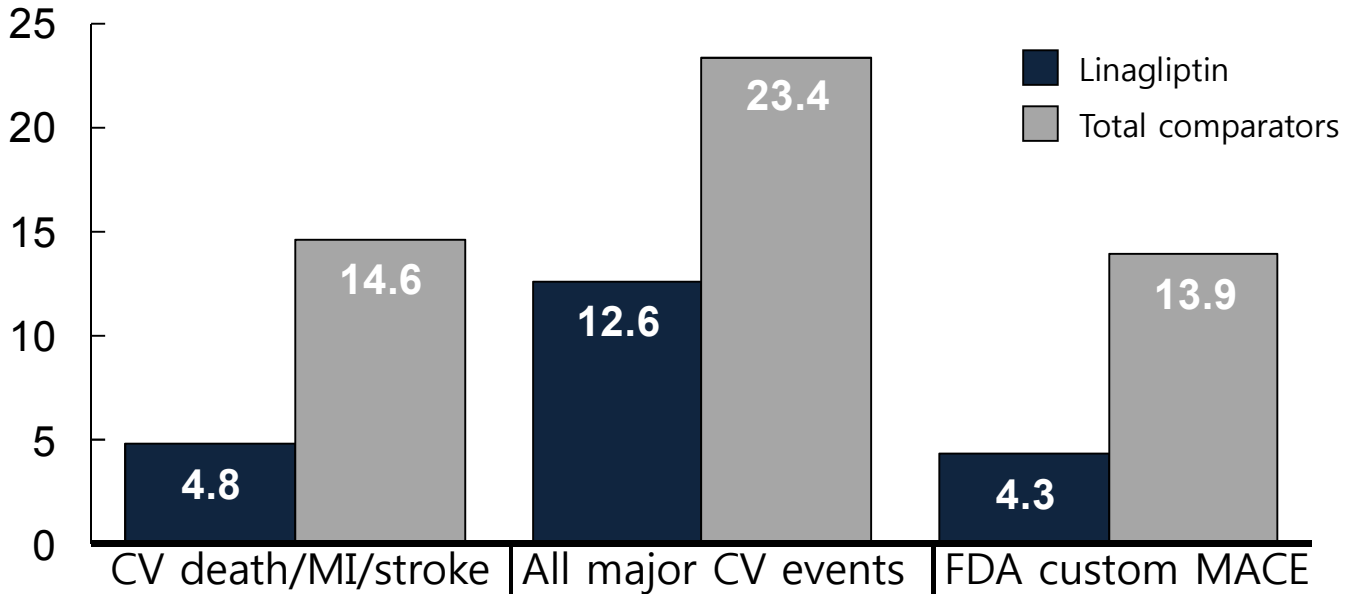


1. CV events as defined as primary endpoint; 2. 977 patients receiving placebo, 781 glimepiride, 162 voglibose

Johansen OE, et al. *Cardiovasc Diabetol* . 2012; 11:epub
Johansen O-E., et al. ADA 2011 Late breaker 30-LB

Linagliptin CV meta-analysis: Incidence for secondary composite CV endpoints

Incidence rate per 1,000 patient-years[1,2]



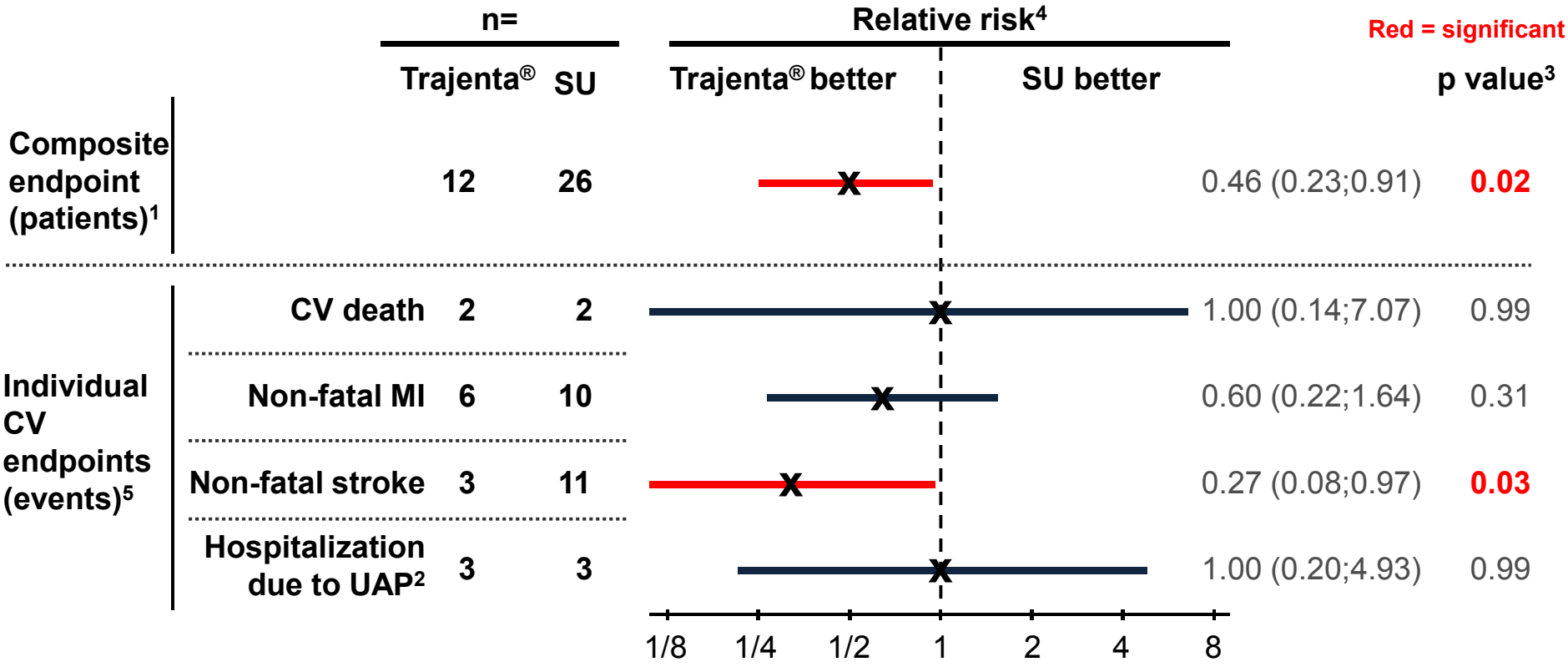
	CV death/MI/stroke		All major CV events		FDA custom MACE	
CV events	10	20	26	32	9	19
Exposure, years	2,060	1,372	2,060	1,372	2,060	1,372
Patient	3,319	1,920	3,319	1,920	3,319	1,920

Hazard ratio[2]	0.36	0.56	0.34
95% CI	0.17/0.78	0.33/0.94	0.15/0.75

1. Johansen OE, et al. *Cardiovasc Diabetol* . 2012; 11:epub;2. Johansen O-E., et al. ADA 2011 Late breaker 30-LB

Trajenta® compared to glimepiride – CV relative risk reduction

Trajenta® *vs.* glimepiride on metformin background over 2 years



Treated set: All events independently adjudicated by CEC, all endpoints pre-specified (also for individual studies) from CV-meta-analysis statistical plan. Patients may have suffered more than one individual CV endpoint event and therefore the number of patients reaching the composite end-point is less than the total number of events.

1. CV death, MI, stroke, hosp. due to unstable angina pectoris; 2. UAP = Unstable angina pectoris; 3. Chi-squared test
4. 2-sided 95% confidence interval on a logarithmic scale; 5. Individual CV endpoints do not numerically add up to composite endpoint since a patient may experience more than one event; CEC = clinical events committee

Gallwitz B., et al. ADA 2011 Late Breaker 39-LB

CAROLINA will evaluate CV safety of Trajenta® in patients with T2DM at high CV risk[1]

SCIENTIFIC INTERCHANGE ON DIABETES

Inclusion if at least one of the following is fulfilled

1. Previous vascular complications
2. Evidence of end organ damage, e.g. albuminuria
3. Age > 70 years
4. Two or more specified traditional CV risk factors

With or without metformin background therapy (including patients with contraindication to metformin use in renal impairment)

Trajenta® 5mg vs. Glimepiride 1-4mg[2]

n= 6,000; approx. 6-7 year follow up

Primary endpoint: Time to the first occurrence of the primary composite endpoint

1. CV death (including fatal stroke and fatal MI)
2. Non-fatal MI
3. Non-fatal stroke
4. Hospitalization for unstable angina pectoris

1. Rosenstock J., et al. ADA 2011 Poster 1103-P; Clinicaltrial.gov NCT01243424
2. 16 weeks titration phase of glimepiride up to 4mg/day

CAROLINA has a unique trial design

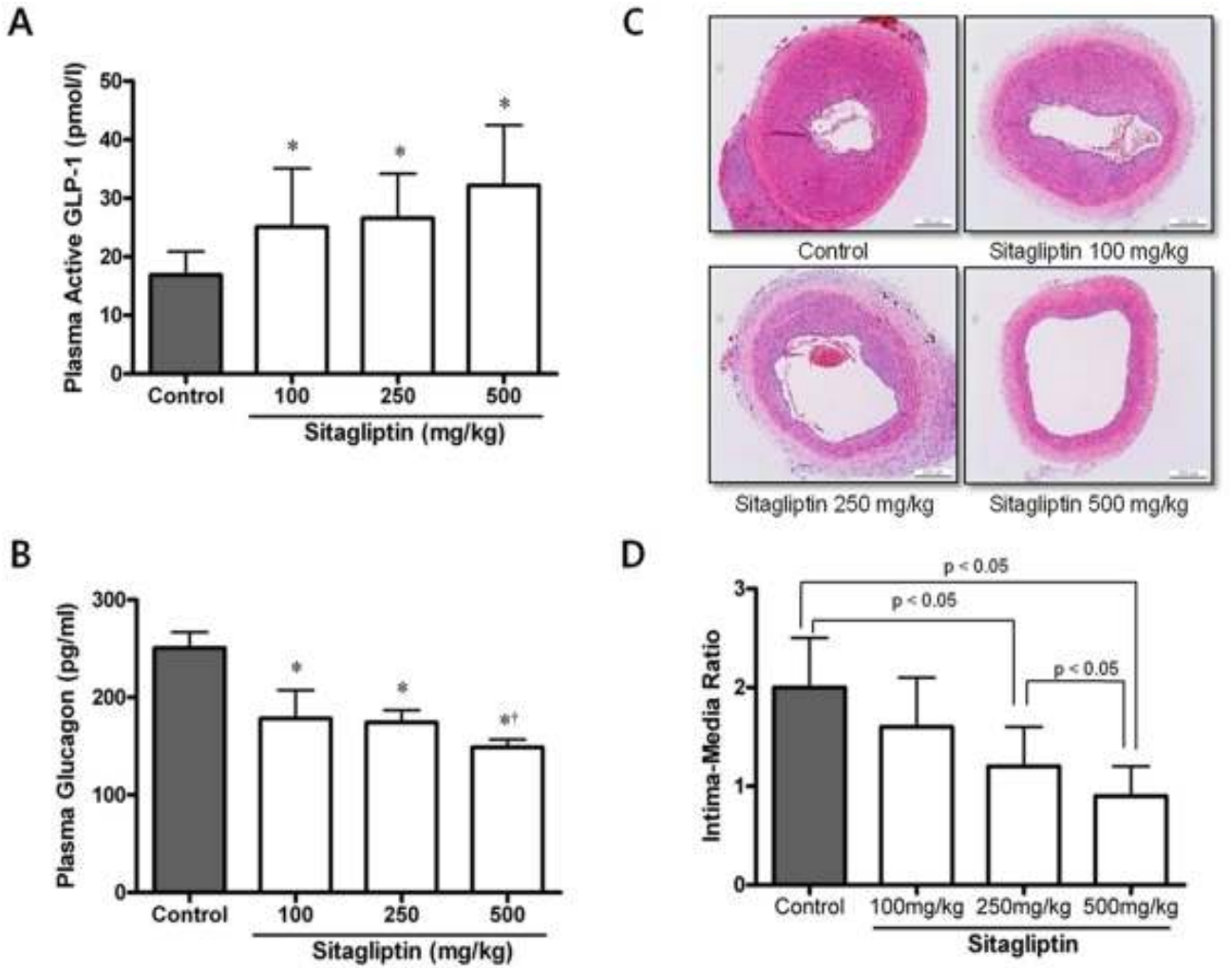
	CAROLINA[1]	TECOS[2]	SAVOR-TIMI53[3]	EXAMINE[4]
DPP-4 inhibitor	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin
Comparator	SU (Active)	Placebo	Placebo	Placebo
Number of patients	6,000	14,000	16,500	5,400
Trial initiation	Oct 2010	Nov 2008	May 2010	Sept 2009
Background diabetes therapy per protocol	Predominantly on metformin	Any	Any	Any
Expected diabetes focus stage	Early	Advanced	Advanced	All, but limited to CV events

PRIMARY ENDPOINTS:
1,2,4 CV death, non-fatal MI, non-fatal stroke, hospitalization due to unstable angina pectoris
3 Major Adverse Cardiovascular Events (CV death, non-fatal MI, non-fatal stroke)

ClinicalTrials Identifiers: 1. NCT01243424, 2. NCT00790205, 3. NCT01107886, 4. NCT00968708

Effect of a Dipeptidyl Peptidase-IV Inhibitor, Des-Fluoro-Sitagliptin, on Neointimal Formation after Balloon Injury in Rats

Soo Lim,[1,2*] Sung Hee Choi,[1,2] Hayley Shin,[3] Bong Jun Cho,[1] Ho Seon Park,[2] Byung Yong Ahn,[2] Seon Mee Kang,[1,2] Ji Won Yoon,[1,2] Hak Chul Jang,[1,2] Young-Bum Kim,[4] and Kyong Soo Park[2,5]



PLoS One. 2012; 7(4): e35007.

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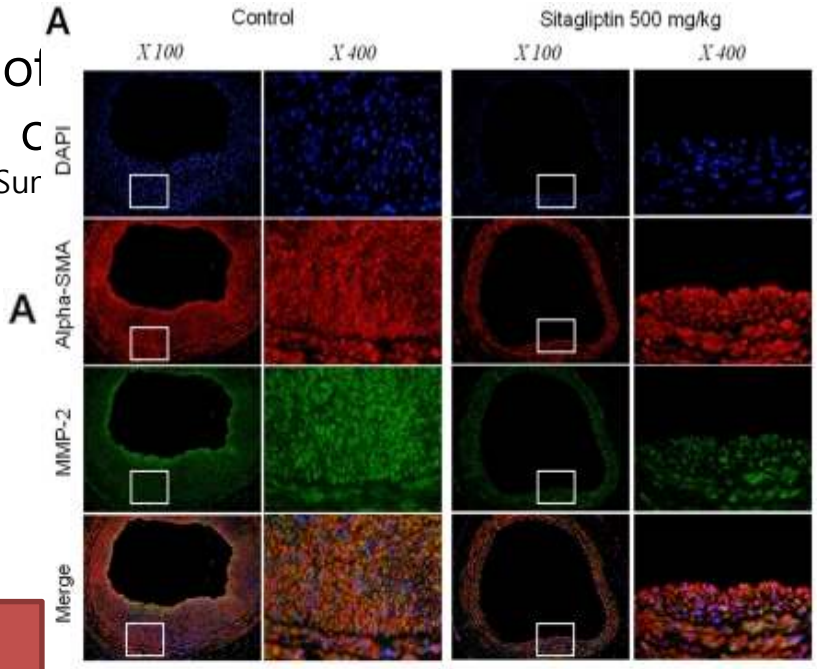

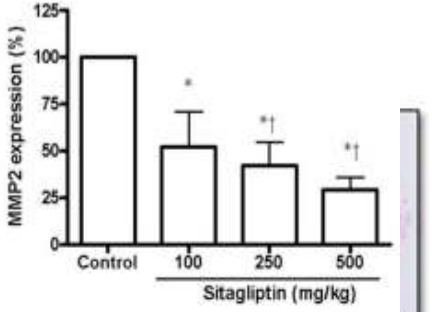

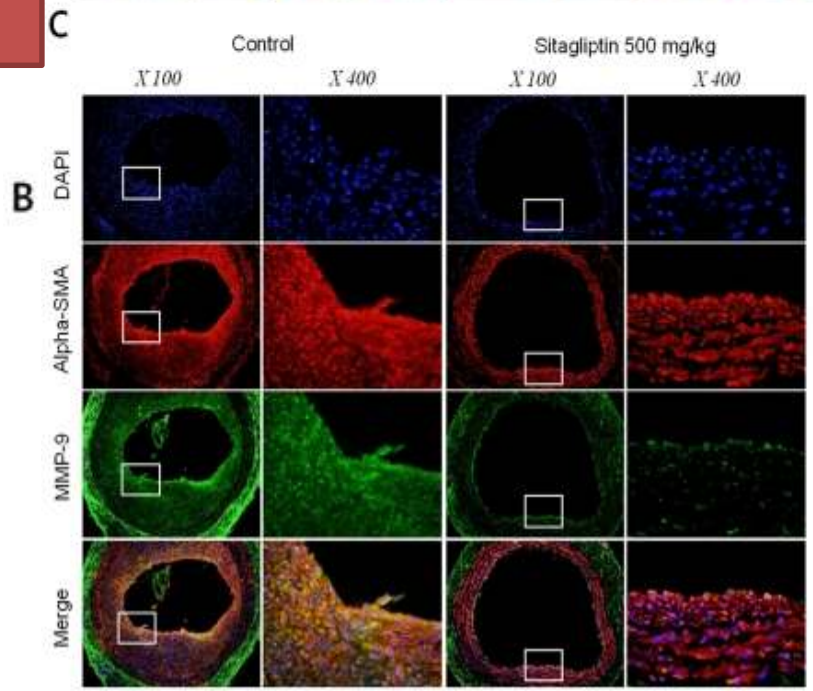

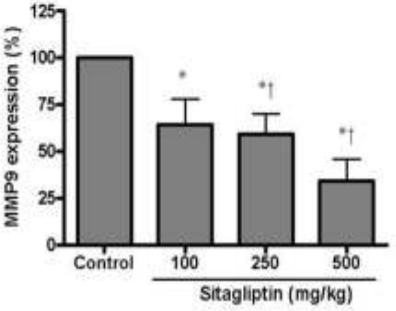

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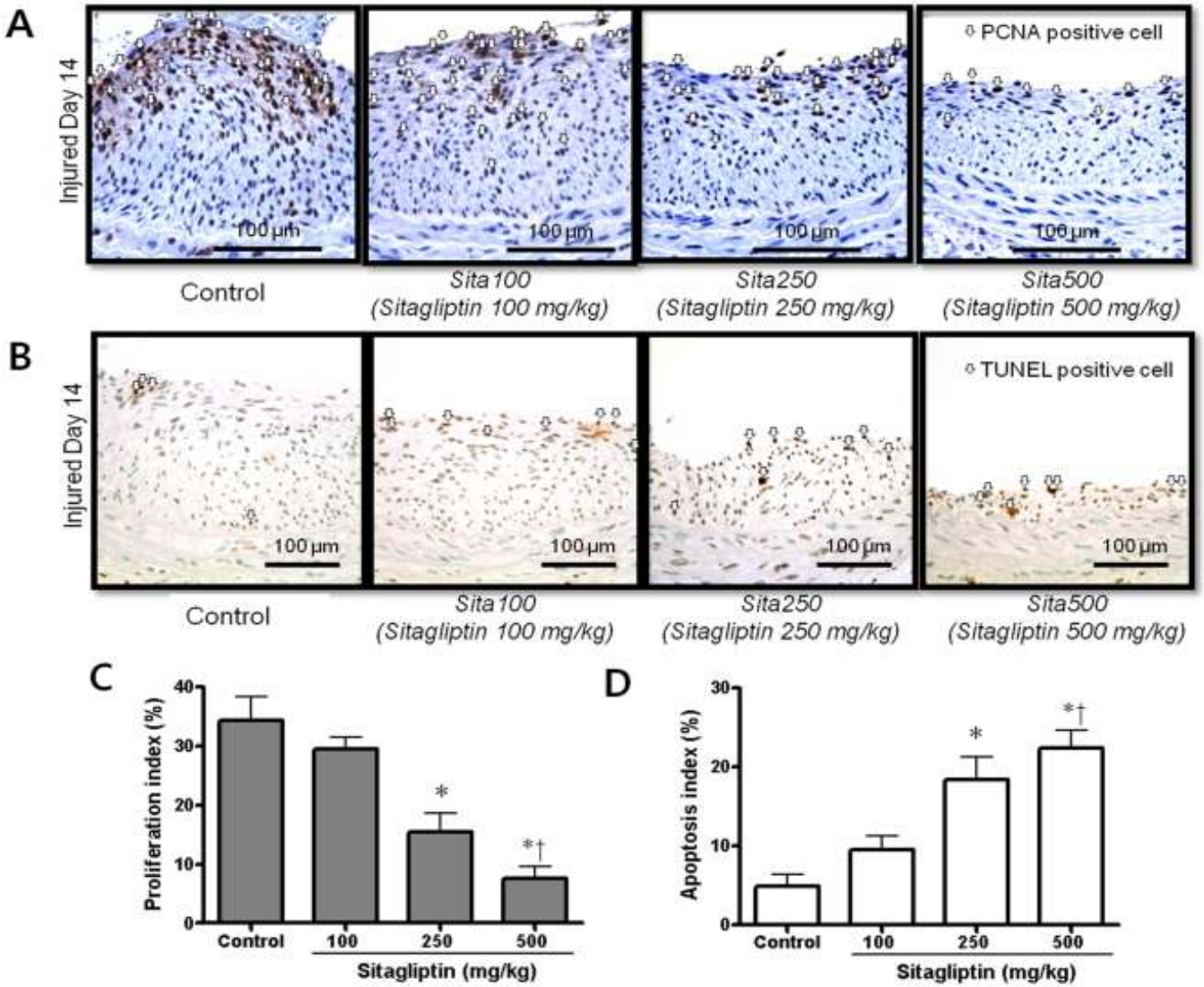
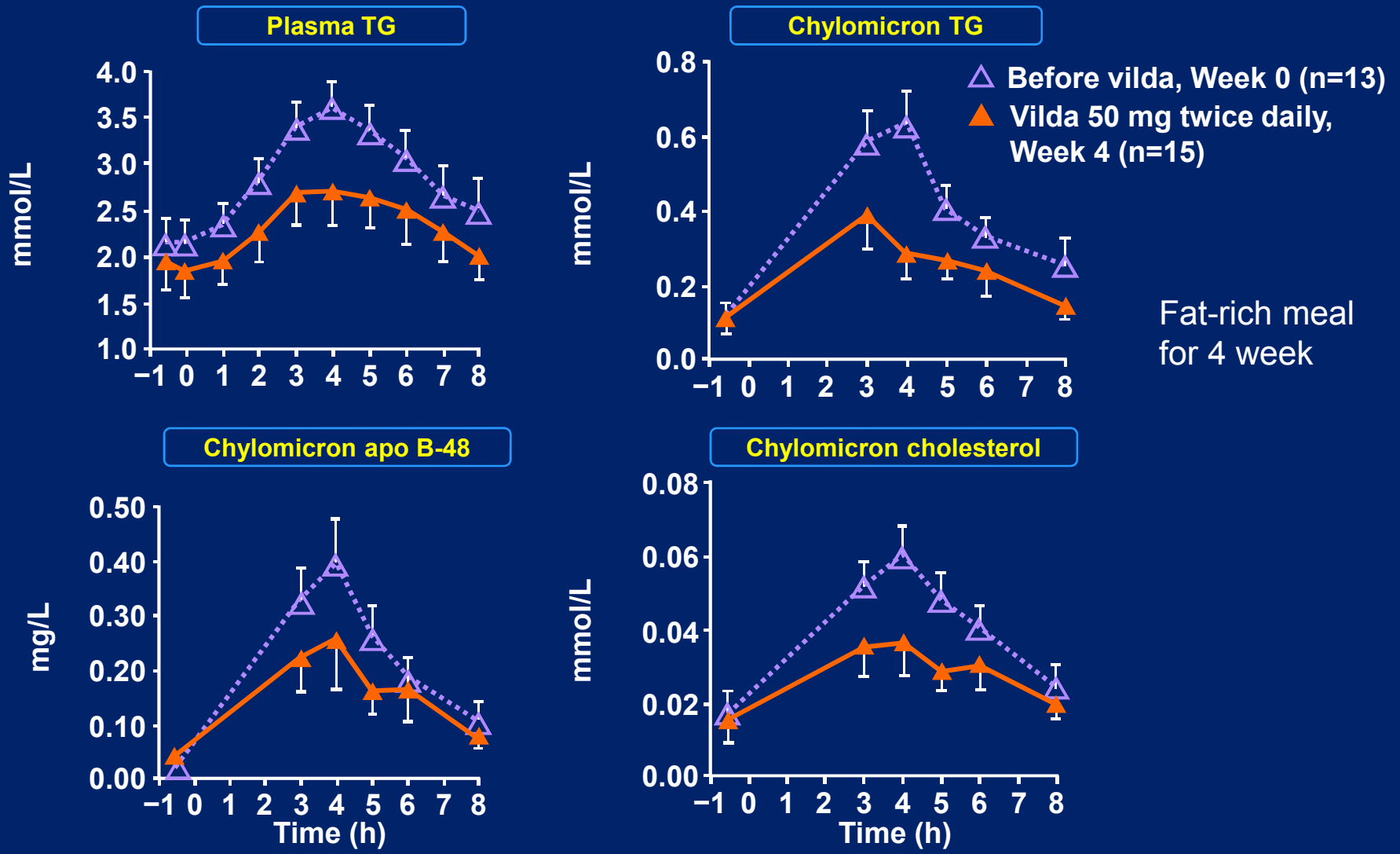


hsCRP, MCP-1감소, adiponectin 증가

PLoS One. 2012; 7(4): e35007.

Effects of Vildagliptin on Postprandial Lipid and Lipoprotein Metabolism

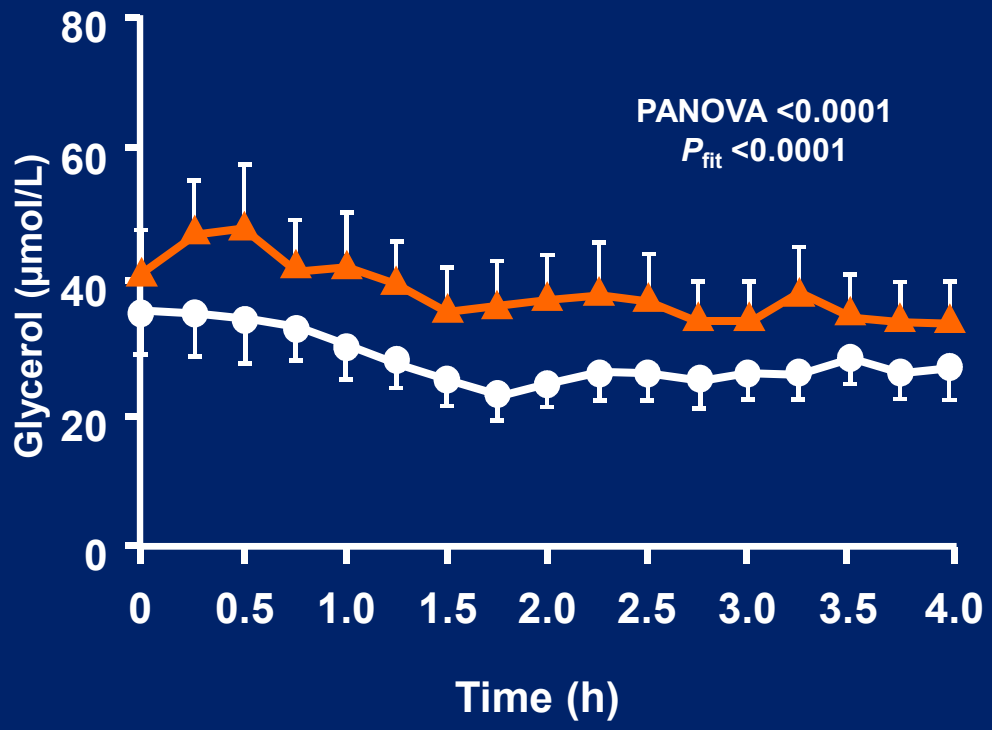


TG=triglyceride; Vilda=vildagliptin.

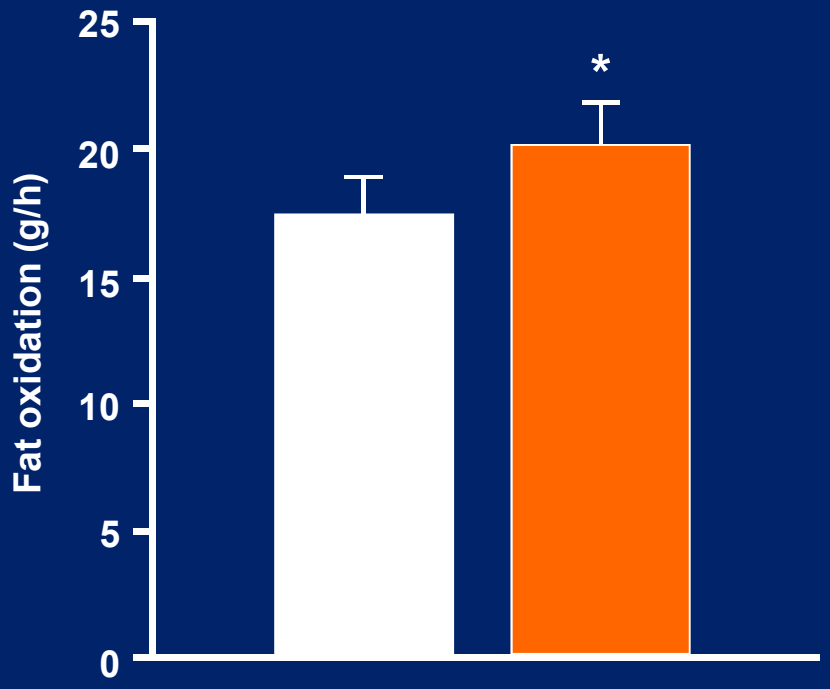
Matikainen N, et al. *Diabetologia.* 2006; 49: 2049–2057.

Vildagliptin increases postprandial lipolysis and enhances fat oxidation

Lipolysis



Fat oxidation



Vildagliptin 100 mg qd N = 20, 7d

Placebo N = 20

Galvus (vildagliptin 100 mg qd is not approved); # in patients with low baseline HbA1c levels

PANOVA: P value by two ways ANOVA. Pfit: P value for global fitting, *P <0.05.

Boschmann M, et al. *J Clin Endocrinol Metab.* 2009; 94: 846–852.

Sitagliptin Pooled Safety Analysis

Adverse Experience	Incidence Rate per 100 Patient-Years			
	Sitagliptin n=5,429	Non-exposed n=4,817	Between-Groups Difference (95% CI)[b]	Relative Risk Ratio (95% CI)
MACE	0.6	0.9	–0.3 (–0.7, 0.1)	0.68 (0.41, 1.12)

- Custom MACE analysis with terms similar to those requested by the US FDA for recent MACE analyses with other antihyperglycemic agents
- Total of 64 patients with at least 1 MACE-related event

Williams-Herman D et al. BMC Endocr Disord. 2010;10:7.

Cardiovascular Safety of Sitagliptin vs. SU in Patients with type 2 DM: a Pooled Analysis

- Post hoc CV safety analysis performed with patient-level data (N = 2,451)
- Results from 3 randomized, double-blind clinical trials comparing sitagliptin and a sulfonylurea were pooled

Characteristic	Sitagliptin (n = 1226)	Sulphonylurea (n = 1225)
Cumulative exposure, PY	1269	1274
MACE, n	0	11
Incidence rate per 100 PY	0	0.9

PY = patient-years.

Difference in incidence rate (95% CI) = -0.9 (-1.6, -0.5)
Risk ratio = 0.00 (0.00, 0.31)

MACE

CV death

Characteristic	Sitagliptin (n = 1226)	Sulphonylurea (n = 1225)
Cumulative exposure, PY	1269	1277
CV deaths, n	0	5
Incidence rate per 100 PY	0	0.4

PY = patient-years.

Difference in incidence rate (95% CI) = -0.4 (-0.9, -0.1)
Risk ratio = 0.00 (0.00, 0.81)

Goldstein BJ, et al. 2012 IDF

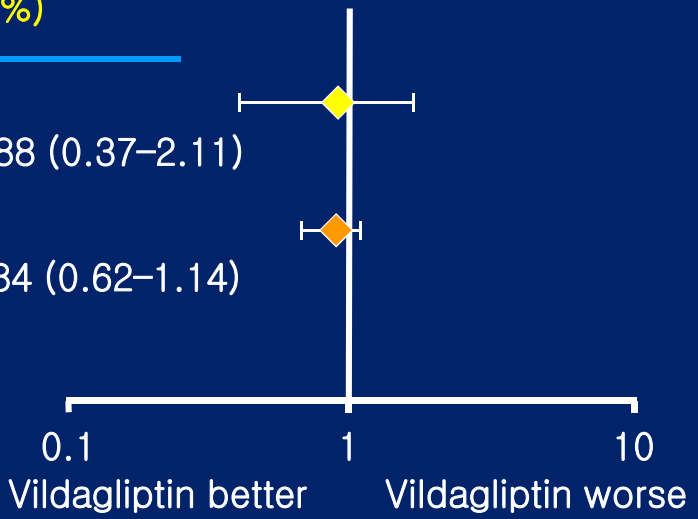
No Increased Risk for Adjudicated CV Events, Relative to All Comparators*

75세 이상 환자군

Incidences and Odds Ratios for Adjudicated CV Events by Treatment

	Vildagliptin n / N (%)	Reference n / N (%)	M-H RR (95% CI)
Vilda 50 mg qd#	10 / 1393 (0.72)	14 / 1555 (0.90)	0.88 (0.37–2.11)
Vilda 50 mg bid#	81 / 6116 (1.32)	80 / 4872 (1.64)	0.84 (0.62–1.14)

Risk Ratio



#Meta-analysis of vildagliptin 50 mg bid data vs all comparators according to the methodology set by the US Food and Drug Administration‡ [50 mg bid odds ratio = 0.84 (95% CI 0.62–1.14)].

AEs=adverse events; bid=twice daily; CI=confidence interval; CV=cardiovascular; M-H RR=Mantel-Haenszel risk ratio; qd=once daily; vilda=vildagliptin.

#Vs comparators (all non-vildagliptin treatment groups). All-study safety population.

‡Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), December 2008.

Schweizer A, et al. Diabetes Obesity Metabolism 2010;

Summary

Trajenta (Linagliptin) is a novel DPP4 inhibitor

Pharmacologically

- Unique structure – the only **xanthine-based DPP-4 inhibitor**
- Very **potent** – which translates into a low dose and suitability for FDCs
- **Binds DPP-4 avidly and tightly** – low plasma levels

Clinically

- Meaningful, durable and reliable efficacy in all clinical studies to date
- Approximately 1% of HbA1c reduction combined with metformin and sulf onylurea compare to placebo in Korean population.
- **Non-renal excretion route, mostly excreted unchanged – no dose adj ustments necessary in patients with renal or liver impairment**
- **One dose fits all – the only DPP-4 inhibitor with only one dose streng th on the market**
- **CV meta-analysis shows no increased CV risk with linagliptin**
- A unique CV outcome study CAROLINA has been already initiated.

SCIENTIFIC
INTERCHANGE ON
DIABETES

Thank you for your attention

Boehringer Ingelheim

Lilly