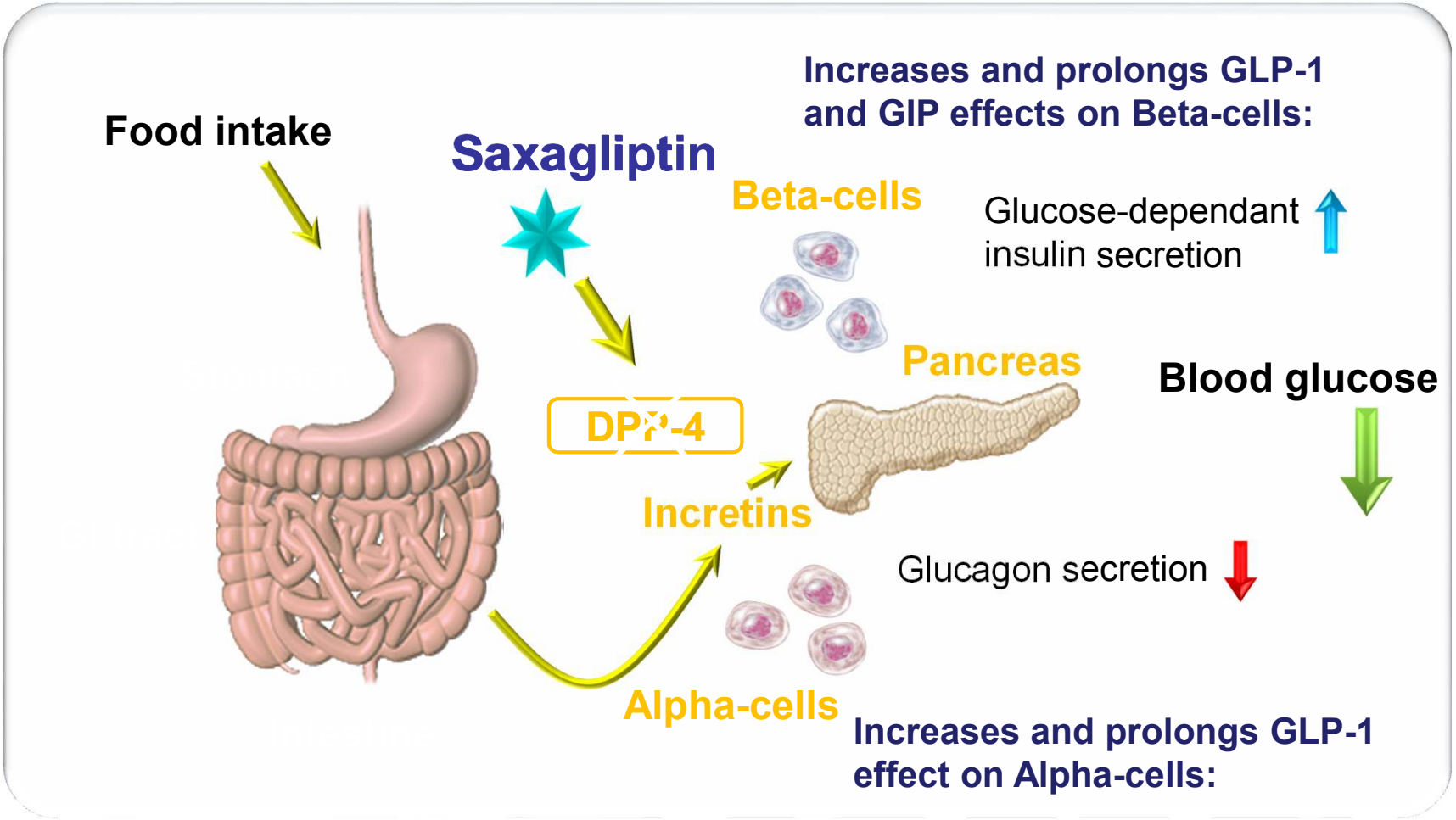
What are the Advantages of Saxagliptin for the Treatment of Type 2 Diabetes Mellitus?

Jeong H. Park, M.D., Ph.D.

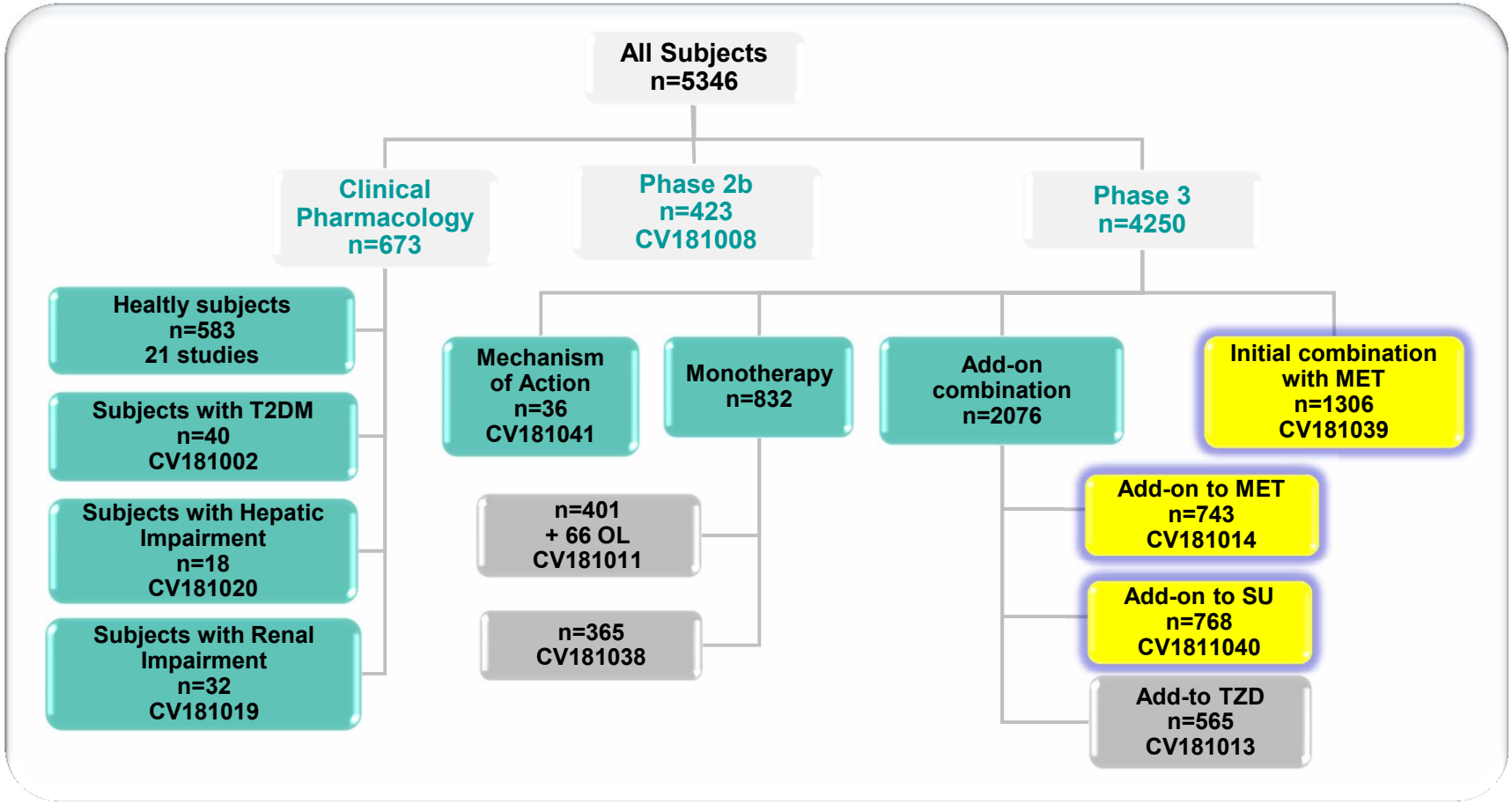
Department of Internal Medicine, College of Medicine, Inje University, Busan

Saxagliptin enhances incretin activity



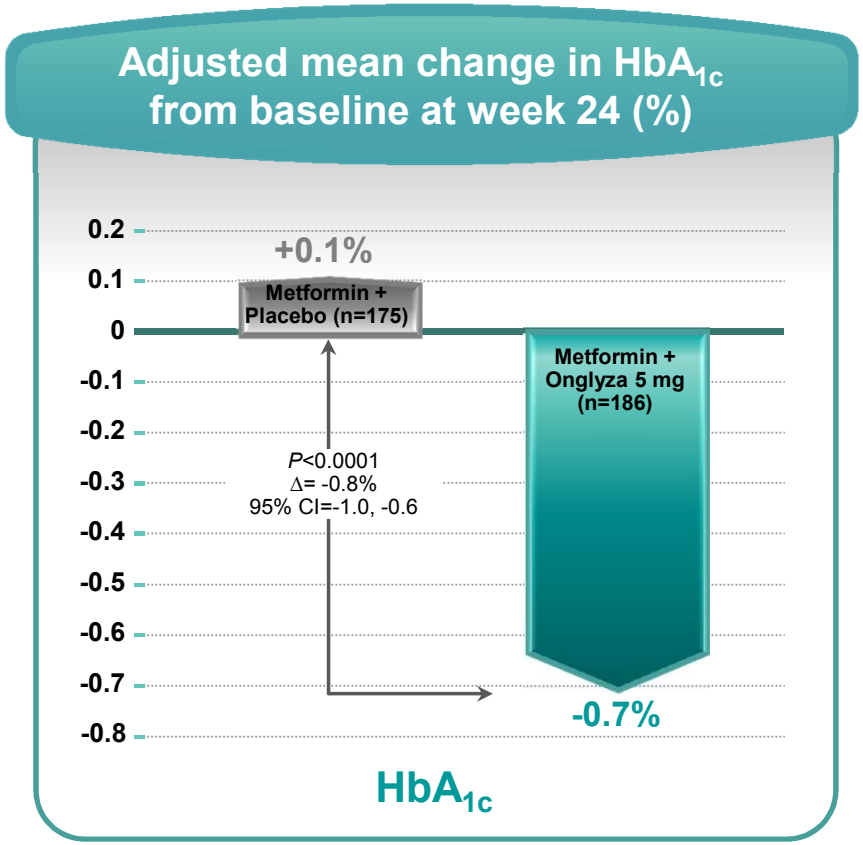
FDA Briefing Document. April 2009. Available at: http://www.fda.gov/OHRMS/DOCKETS/ac/09/briefing/2009-4422b1-02-Bristol.pdf. Accessed on 7 May 2009.

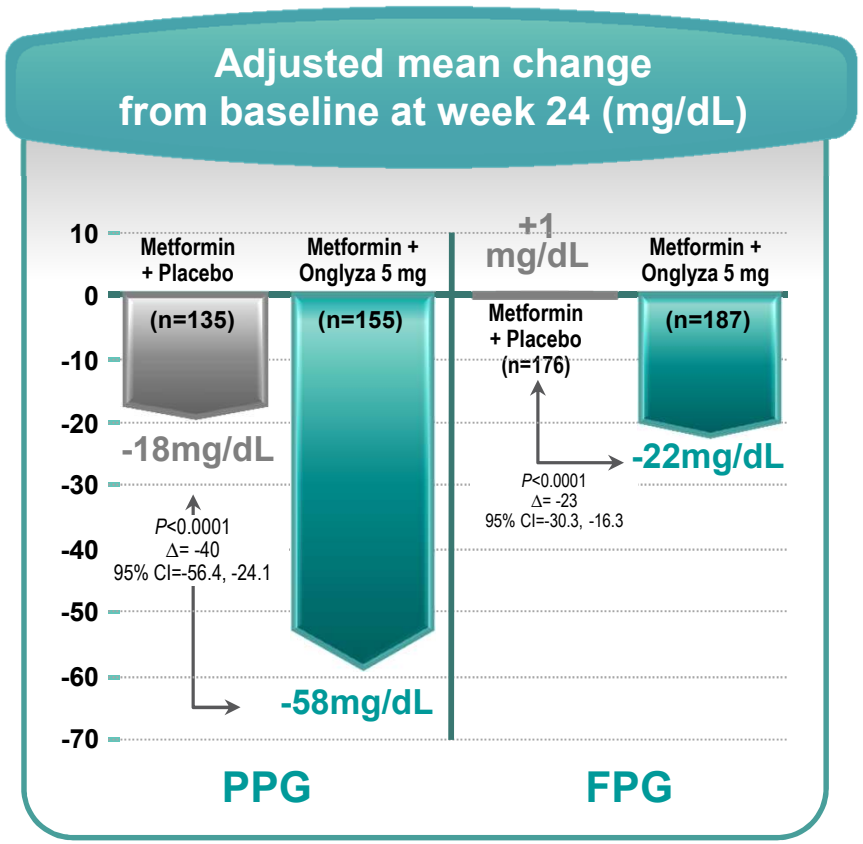
Clinical development program for Saxagliptin



FDA Briefing Document. April 2009. Available at: http://www.fda.gov/OHRMS/DOCKETS/ac/09/briefing/2009-4422b1-02-Bristol.pdf. Accessed on 7 May 2009.

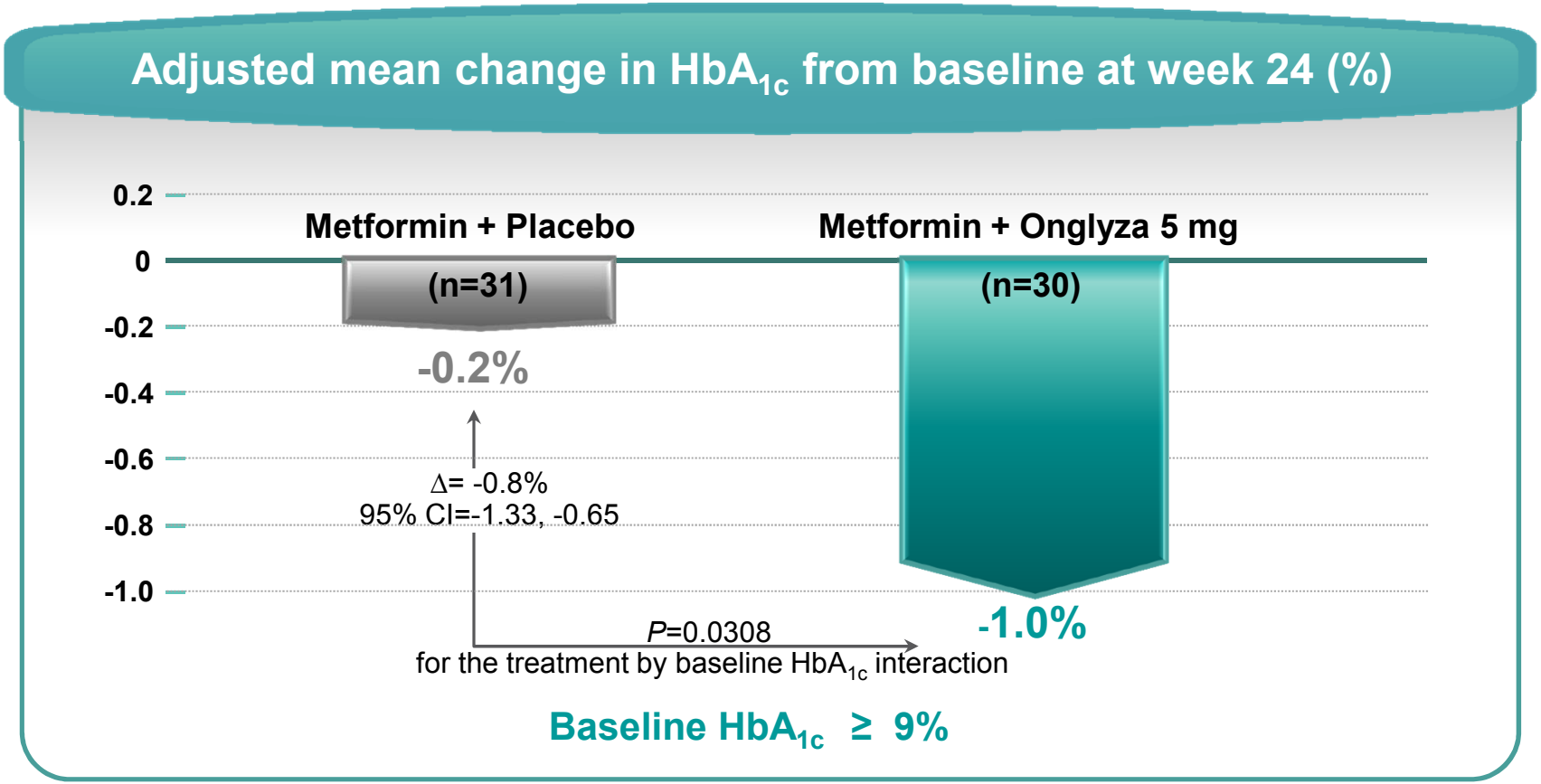
Saxagliptin results in significant reductions in HbA_{1c}, PPG and FPG when added to metformin alone





DeFronzo RA, et al. Diabetes Care. 2009;32(9):1649-55. 2. Data on File. SAXA 004. Bristol-Myers Squibb Company/AstraZeneca.

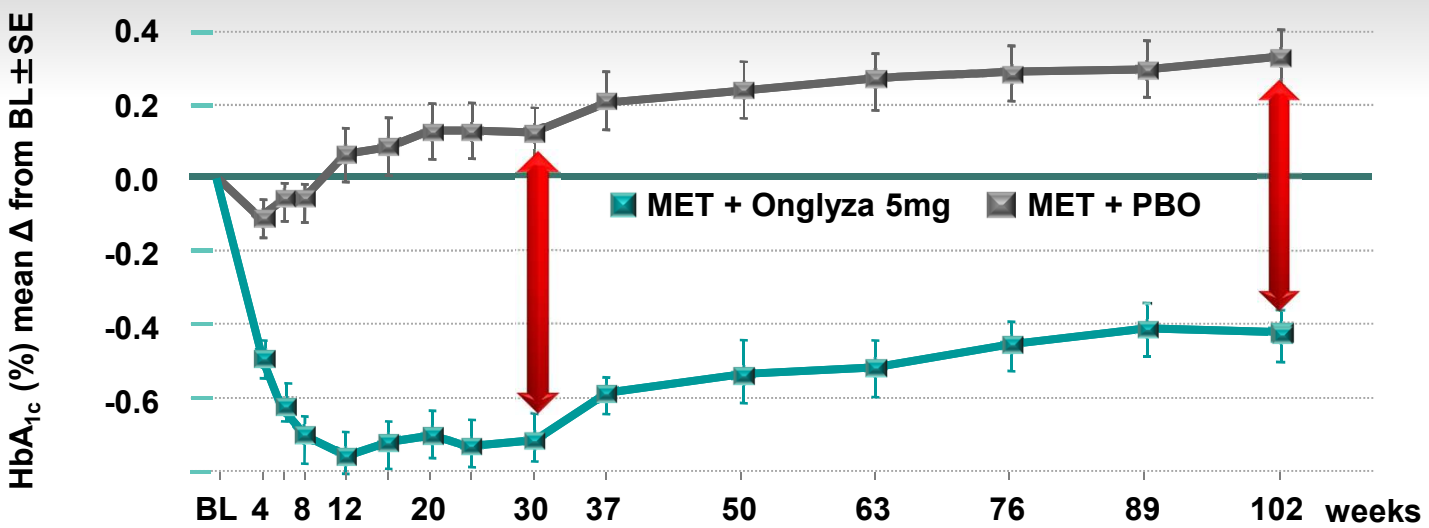
Saxagliptin provides greater reductions in HbA_{1c} in patients with higher baseline HbA_{1c}



Data on File. SAXA 034. Bristol-Myers Squibb Company/AstraZeneca.

Saxagliptin 5mg provides sustained glycaemic benefits when added to metformin over 2 years

HbA_{1c} mean change from baseline (LOCF)



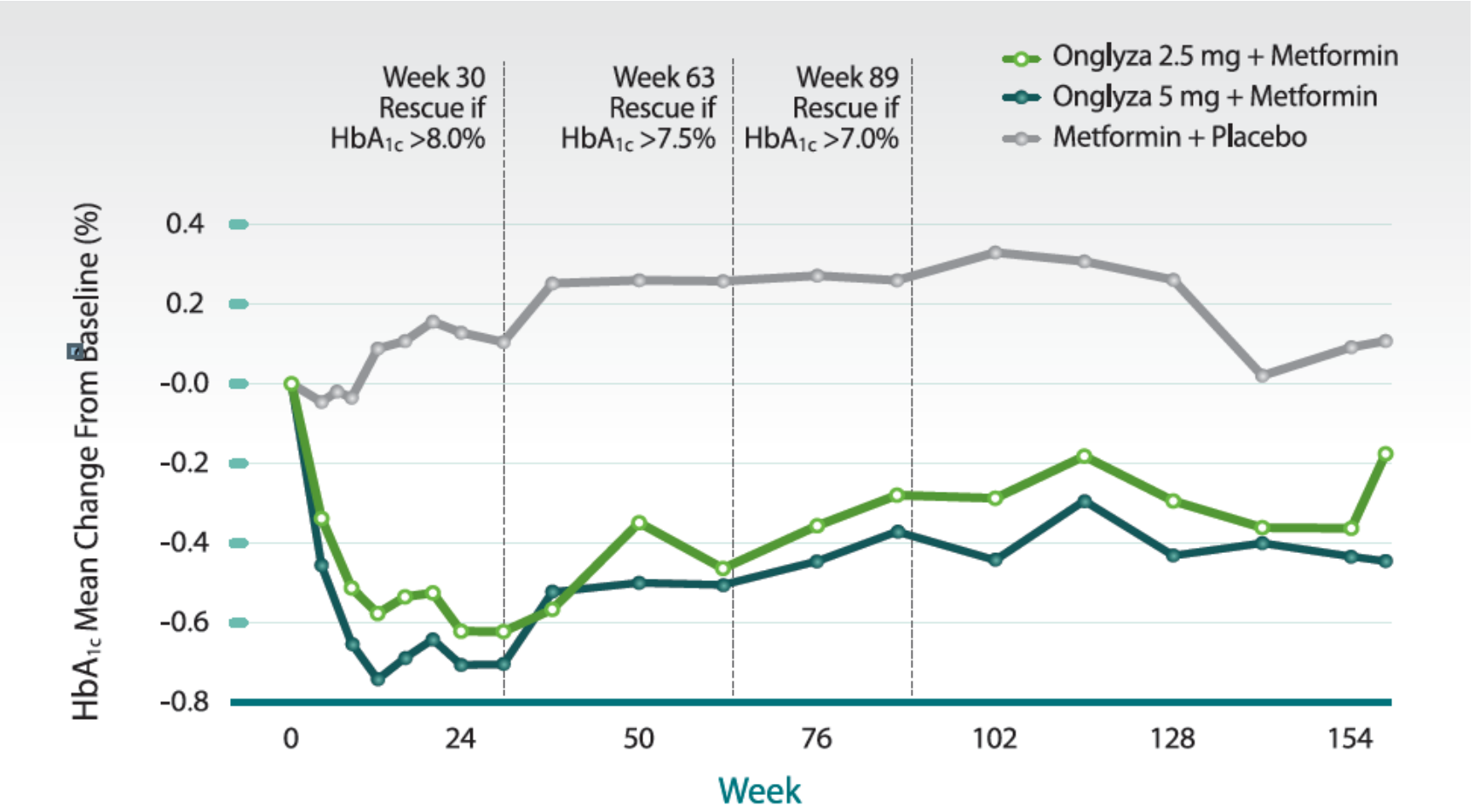
Patients (n observed):

MET + Onglyza 5 mg	**191**	**146**	**116**	**99**	**89**	**70**	**58**	**25**
MET + PBO	**179**	**111**	**72**	**60**	**52**	**33**	**25**	**15**

BL: Baseline; MET: Metformin; PBO: Placebo; Onglyza (Saxagliptin)

Ravichandran S, et al. Diabetologia 2009; 52(Suppl. 1):S60 [Abstract 132]. Presented as an Oral Presentation at the European Association for the Study of Diabetes Congress, Vienna, Austria, September 2009 [Presentation no. 132]

Saxagliptin provides sustained glycaemic benefits when added to metformin for up to 3 years[1]

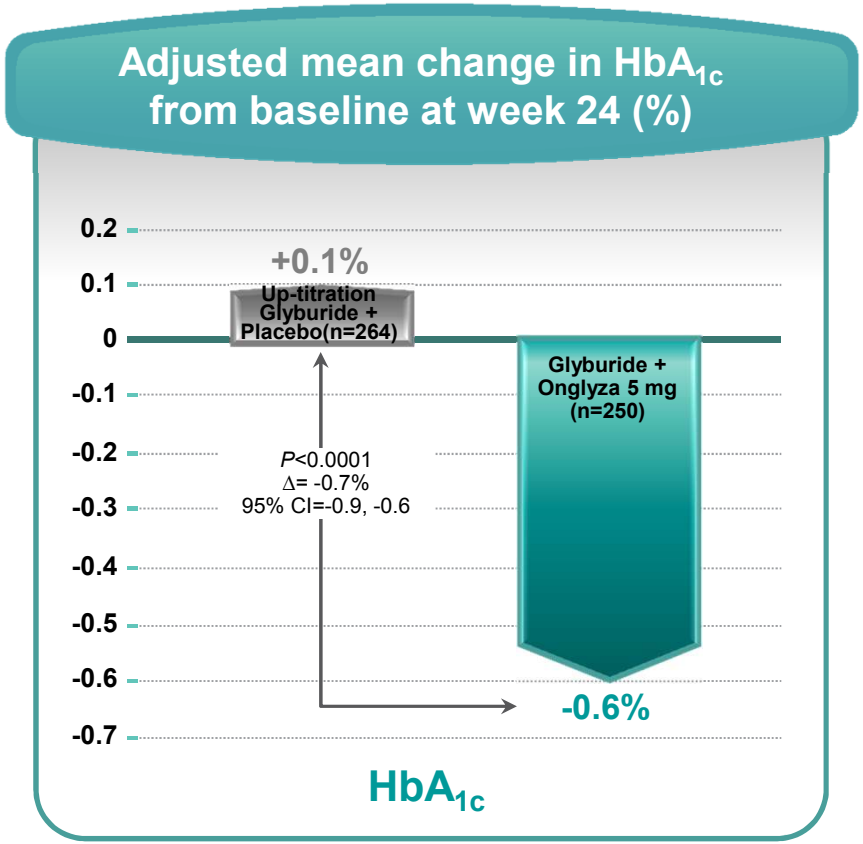


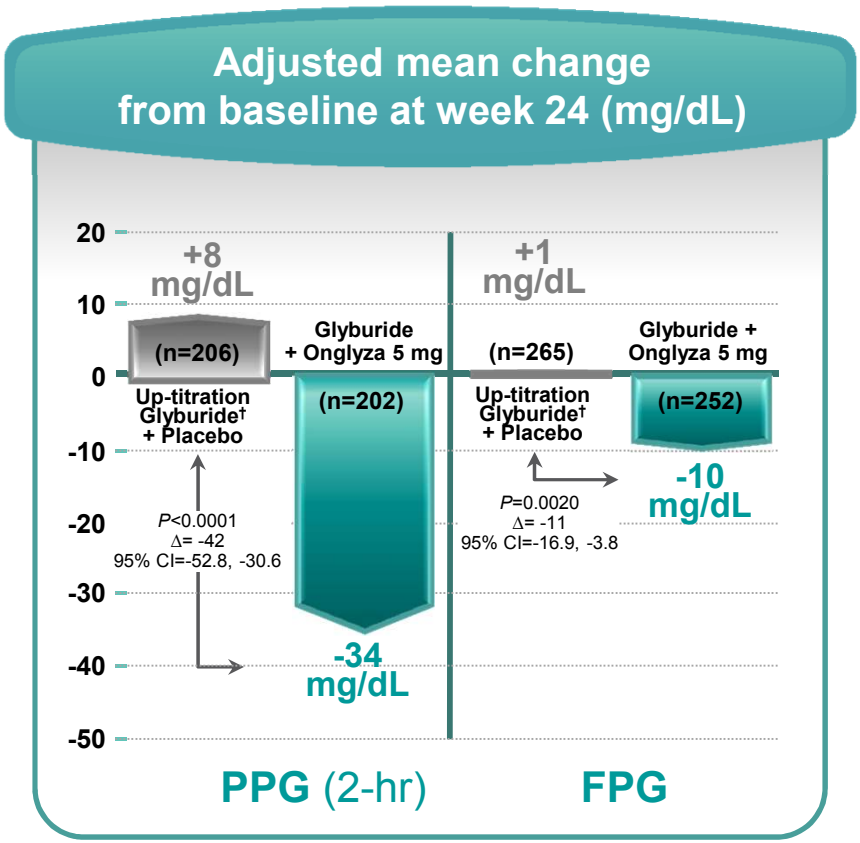
Number of patients with observed data

Onglyza 2.5 mg + MET	192	147	104	50	45	26	21
Onglyza 5 mg + MET	191	144	100	70	44	34	28
Onglyza 10 mg + MET	181	137	114	79	44	34	30
PBO + MET	179	110	59	33	16	10	9

1.Rosenstock J et al. Poster presented at the ADA 71st ADA Scientific Sessions, June 24-28, 2011. San Diego, USA

Saxagliptin results in significant reductions in HbA_{1c}, PPG and FPG when added to SU alone





Chacra AR, et al. Int J Clin Pract. 2009;63(9):1395-406.

Most common adverse events are comparable between saxagliptin and placebo over 4 years[1]

AEs reported in >10% of patients with saxagliptin add-on to metformin Vs. placebo at 4 years

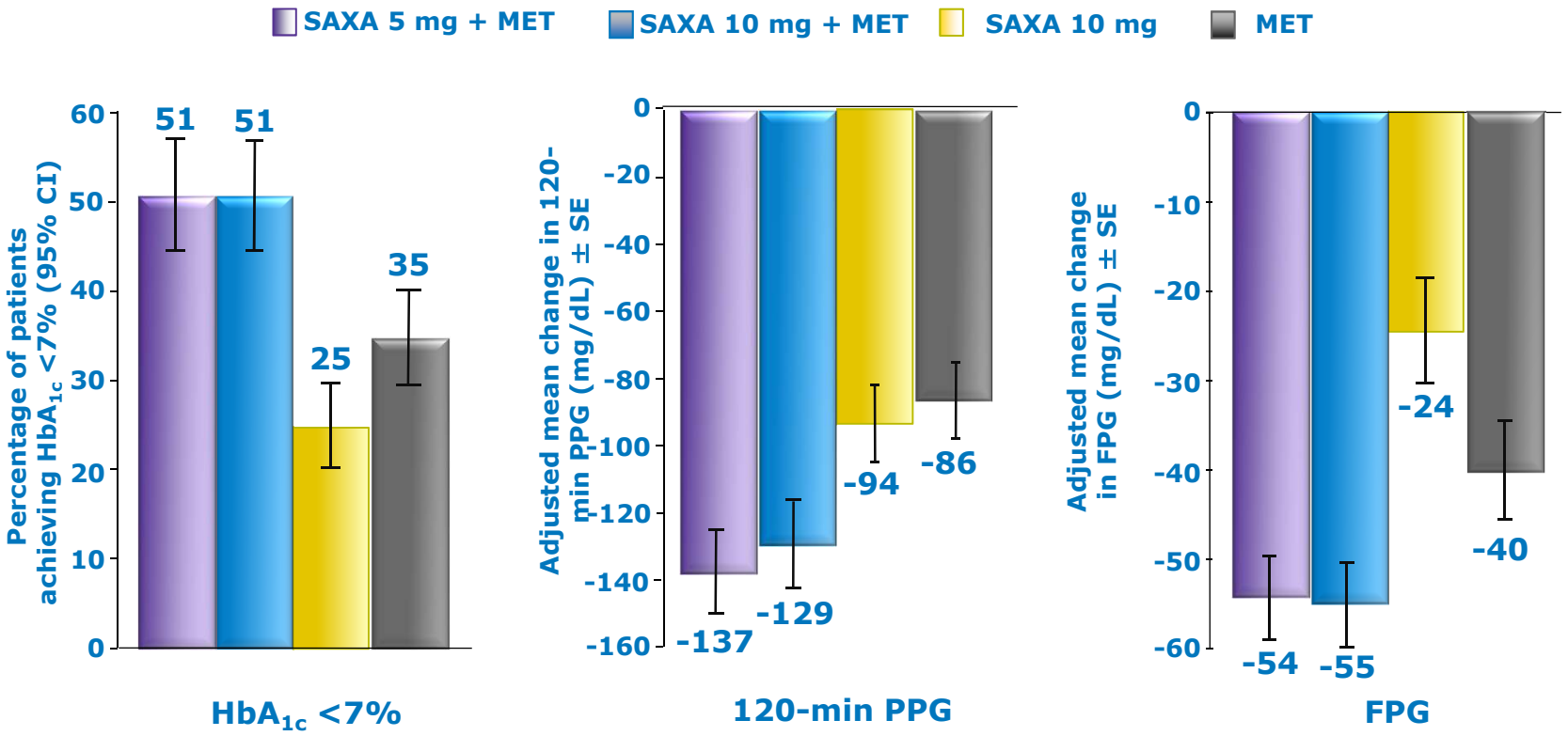
	Patients, n (%)	
	SAXA + MET 5 mg (n=564)	PBO & MET (n=179)
Influenza	86 (15)	27 (15)
Diarrhea	67 (12)	23 (13)
Upper respiratory tract infection	66 (12)	17 (10)
Urinary tract infection	65 (12)	15 (8)
Arthralgia	66 (12)	12 (7)

MET=metformin; PBO=placebo; PBO/MET=placebo in the core study switched to metformin in the extension; SAXA=saxagliptin.

- **Most adverse events were mild to moderate**
- **Serious adverse events were infrequent and balanced**
- **Confirmed hypoglycaemic episodes were infrequent (0-1.4%)**
- **No clinically meaningful changes in body weight**

1. Rosenstock J, et al. Poster presented at the 71st ADA Scientific Sessions, June 24 - 28, 2011. San Diego, USA.

Initial combination with metformin: 76-week extension Key glycaemic control parameters



	5 + MET	10 + MET	SAXA 10	MET
n =	307	315	320	314
BL mean	9.4	9.5	9.6	9.4

	5 + MET	10 + MET	SAXA 10	MET
n =	150	143	124	135
BL mean	334	345	343	344

	5 + MET	10 + MET	SAXA 10	MET
n =	315	317	327	320
BL mean	199	204	201	199

BL, baseline; FPG: Fasting Plasma Glucose; MET: Metformin; PPG: Post-Prandial Glucose; SAXA: Saxagliptin.

Pfützner A, et al. Diabetes Obes Metab. 2011;13(6):567-76.

Initial combination with metformin: 76-week extension Safety and tolerability

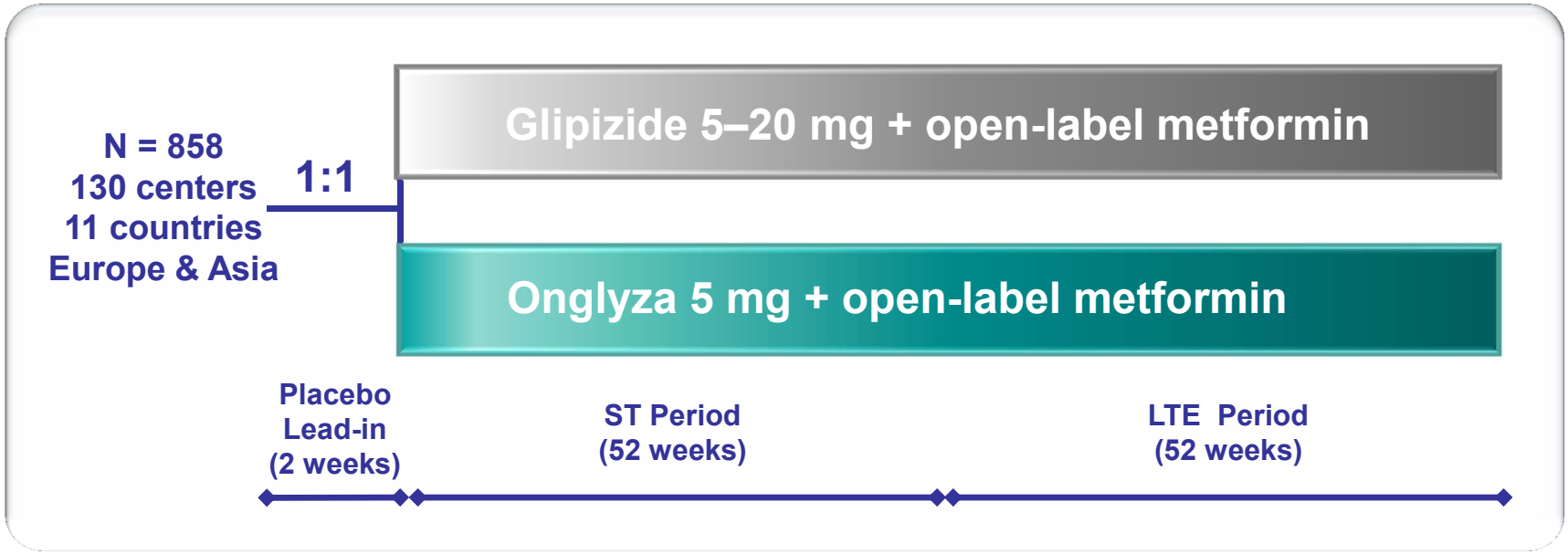
Most common adverse events* and incidence of hypoglycaemia, by treatment

n (%)	SAXA 5 mg + MET n=320	SAXA 10 mg + MET n=323	SAXA 10 mg n=335	MET n=328
Headache	31 (9.7)	36 (11.1)	31 (9.3)	18 (5.5)
Nasopharyngitis	29 (9.1)	19 (5.9)	24 (7.2)	19 (5.8)
Hypertension	27 (8.4)	21 (6.5)	19 (5.7)	17 (5.2)
Diarrhoea	26 (8.1)	41 (12.7)	12 (3.6)	30 (9.1)
Influenza	20 (6.3)	13 (4.0)	17 (5.1)	19 (5.8)
URTI	15 (4.7)	19 (5.9)	14 (4.2)	10 (3.0)
UTI	13 (4.1)	22 (6.8)	23 (6.9)	25 (7.6)
Reported hypoglycaemia	15 (4.7)	22 (6.8)	7 (2.1)	20 (6.1)
Confirmed hypoglycaemia†	0 (0)	3 (0.9)	0 (0)	2 (0.6)

***Occurring in >5% of patients in any treatment group.**
†Confirmed hypoglycaemia: symptoms of hypoglycaemia with fingerstick glucose ≤50 mg/dL.
MET, metformin; SAXA, saxagliptin; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Pfützner A, et al. Diabetes Obes Metab. 2011;13(6):567-76.

Saxagliptin+Metformin vs Glipizide+Metformin: 52-Week Non-inferiority Trial (added to metformin)

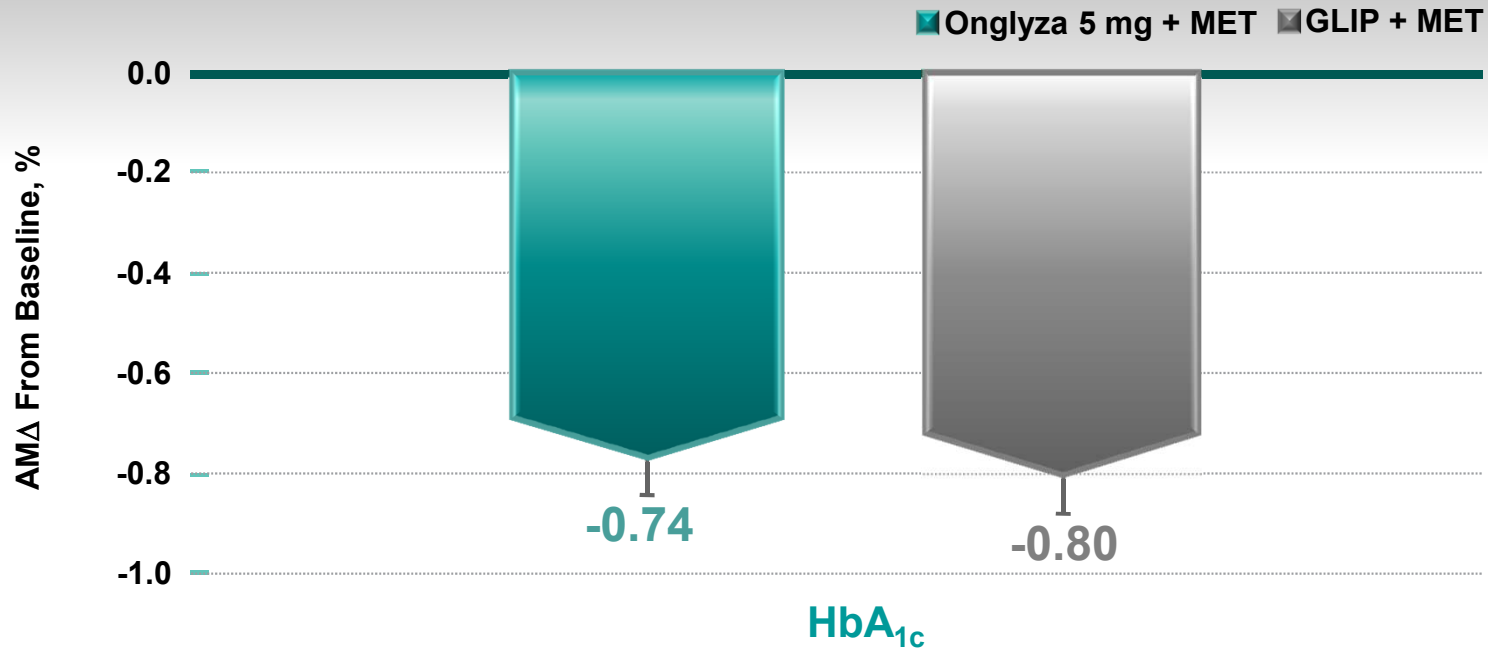


- Glipizide started at 5 mg at randomization; assessment for titration during Weeks 3–18 of ST period.
- Glipizide dose may be downtitrated if medically indicated.
- Note: All patients received diet and lifestyle advice from lead-in through LTE period.

LTE, long-term extension; ST, short-term.

Göke B et al. Int J Clin Pract. 2010 Nov;64(12):1619-31

Saxagliptin+Metformin vs Glipizide+Metformin: 52-Week Non-inferiority Trial (added to metformin)

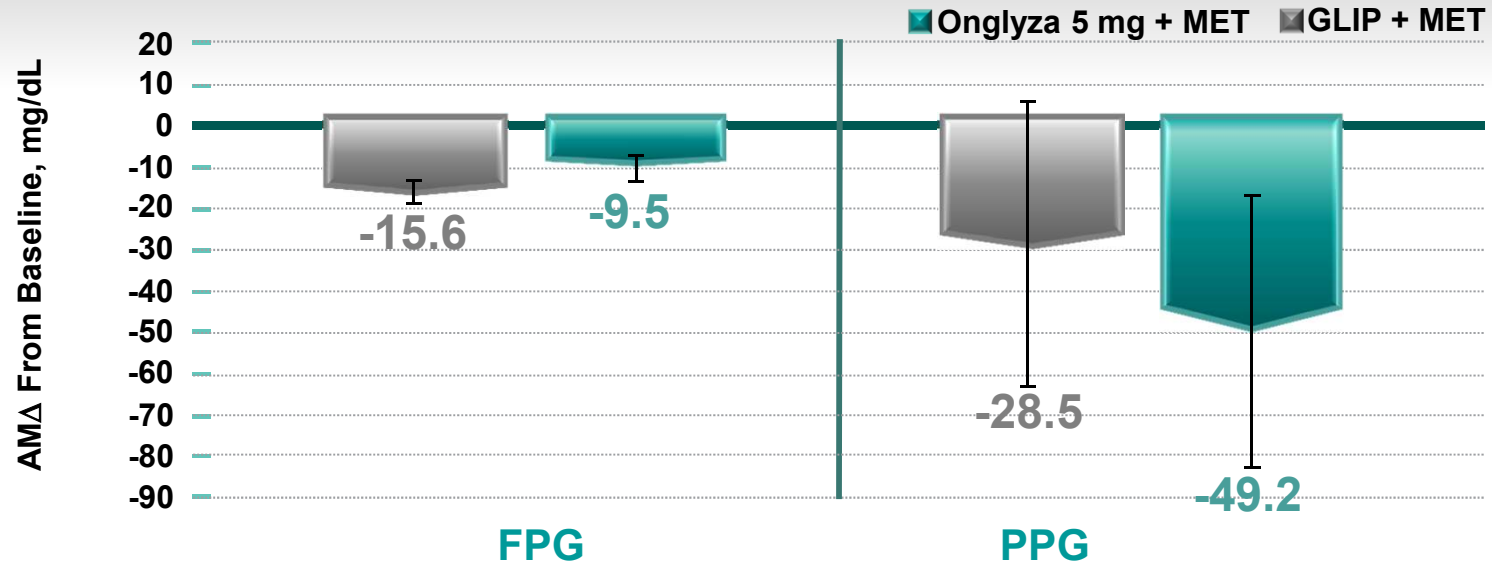


n	293	293
Baseline A1c	7.5	7.5

Göke B et al. Int J Clin Pract. 2010 Nov;64(12):1619-31

Saxagliptin+Metformin vs Glipizide+Metformin: 52-Week Non-inferiority Trial (added to metformin)

Changes in PPG and FPG at week 24 compared to placebo when Onglyza is added to metformin alone

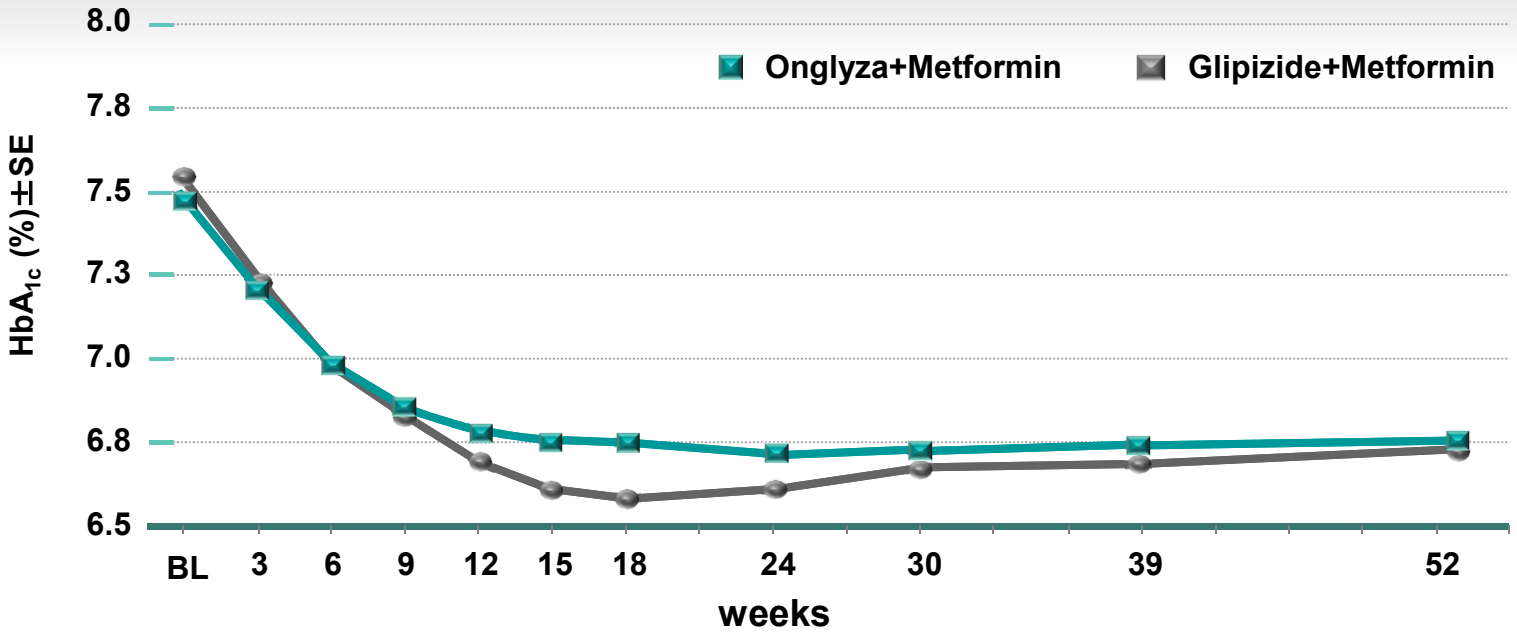


n	424	426	18	17
Baseline	162	161	285	280

Göke B, et al. Presented at: 70th Annual Meeting of the American Diabetes Association; June 25-29, 2010. Orlando, FL. Abstract 578-P.
AstraZeneca. Data on file, Study D1680C00001.

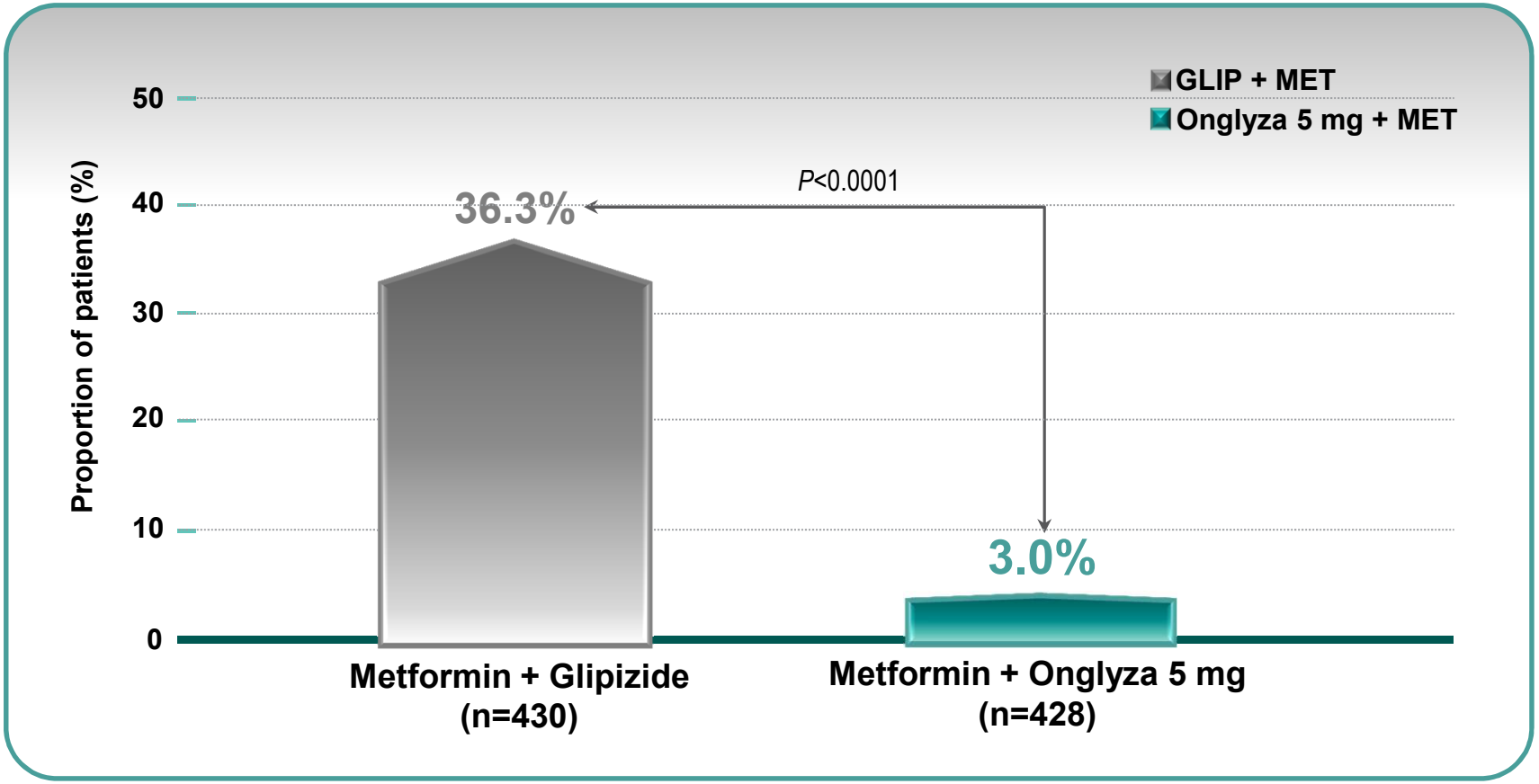
Saxagliptin+Metformin vs Glipizide+Metformin: change of HbA_{1c} by time

Mean HbA_{1c} values over 52 weeks when Onglyza 5mg or Glipizide is added to metformin



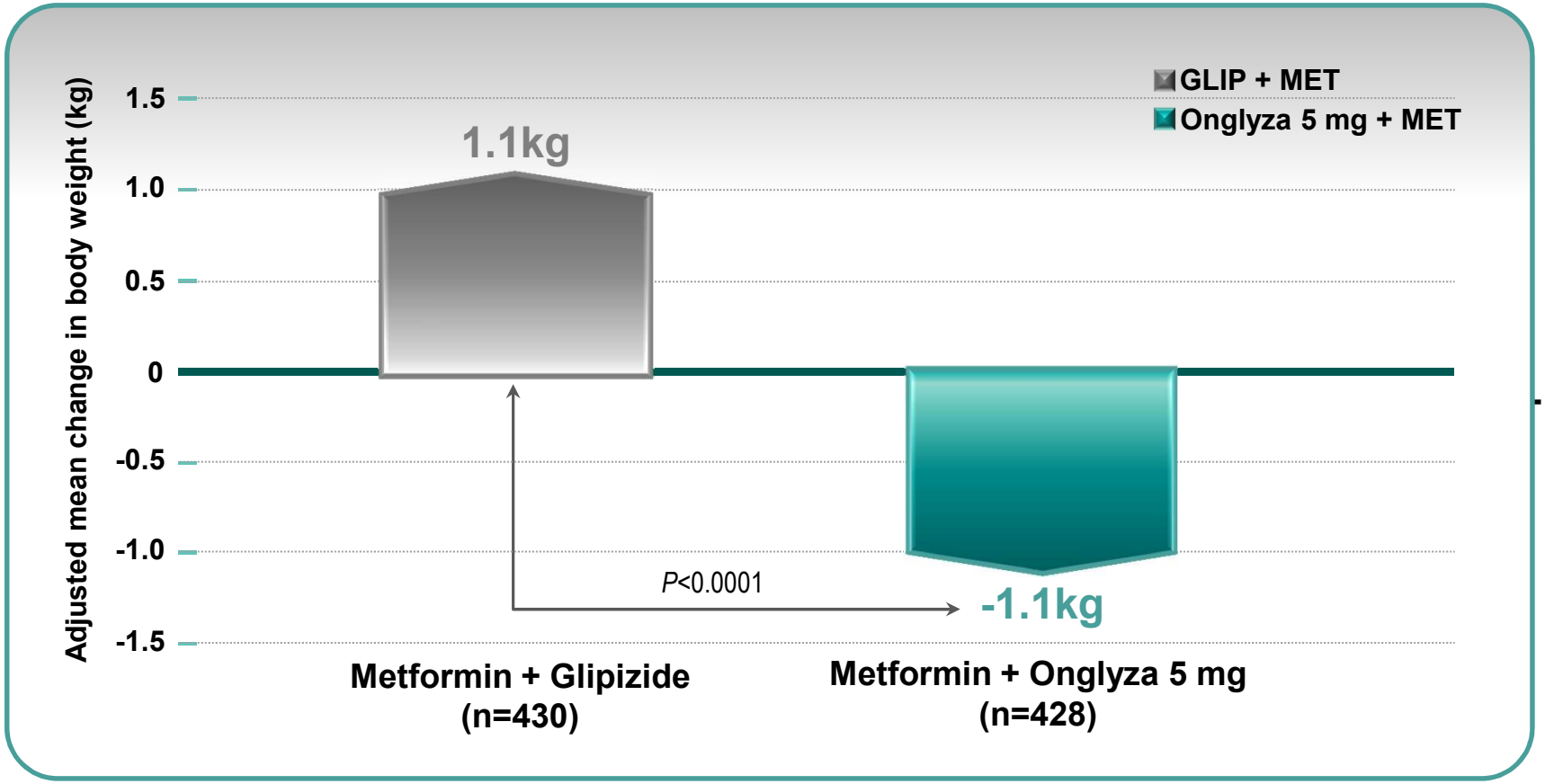
Göke B et al. Int J Clin Pract. 2010 Nov;64(12):1619-31

Saxagliptin+Metformin vs Glipizide+Metformin: Difference in Hypoglycemia



Göke B et al. Int J Clin Pract. 2010 Nov;64(12):1619-31

Saxagliptin+Metformin vs Glipizide+Metformin: Difference in Weight Change



Göke B et al. Int J Clin Pract. 2010 Nov;64(12):1619-31

DPP-4 Inhibition and Binding Potency

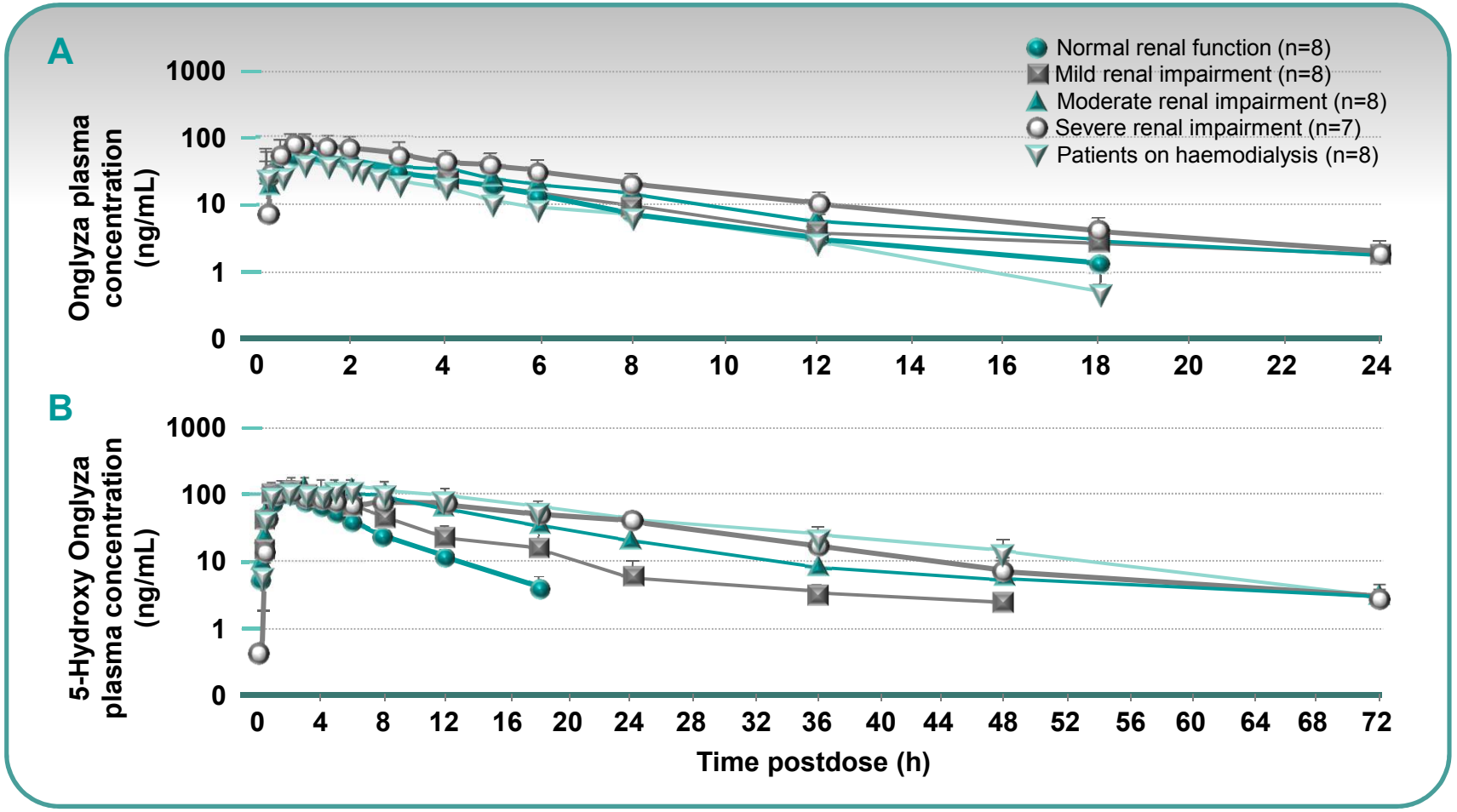
DPP-4 inhibition: binding potency

Inhibitor	Dissociation constant for inhibitor binding (*Ki*)	Binding Potency
saxagliptin	**1.3±0.3 nM**	**1**
Sitagliptin	18±2 nM	1/14
Vildagliptin	13±3 nM	1/10

Gallwitz B et al. Diabetes, Metabolic syndrome and Obesity: Target and Therapy 2010:3 117-124

Efficacy & safety in special populations

Saxagliptin in patients with renal impairment



Boulton et al. Clin Pharmacokinet 2011; 50 (4): 253-265

Pharmacokinetics of DPP-4 inhibitors in renal impairment

Degree of renal impairment		Increase of AUC_{∞}		
		Onglyza	Sitagliptin	Vildagliptin
	CCr 50-80 ml/min	**1.2 fold**	1.6 fold	32-134% increase; change did not correlate with severity of renal impairment
	30-50 ml/min	**1.4 fold**	2.3 fold	
	< 30 ml/min)	**2.1 fold**	3.8 fold	
			4.5 fold	

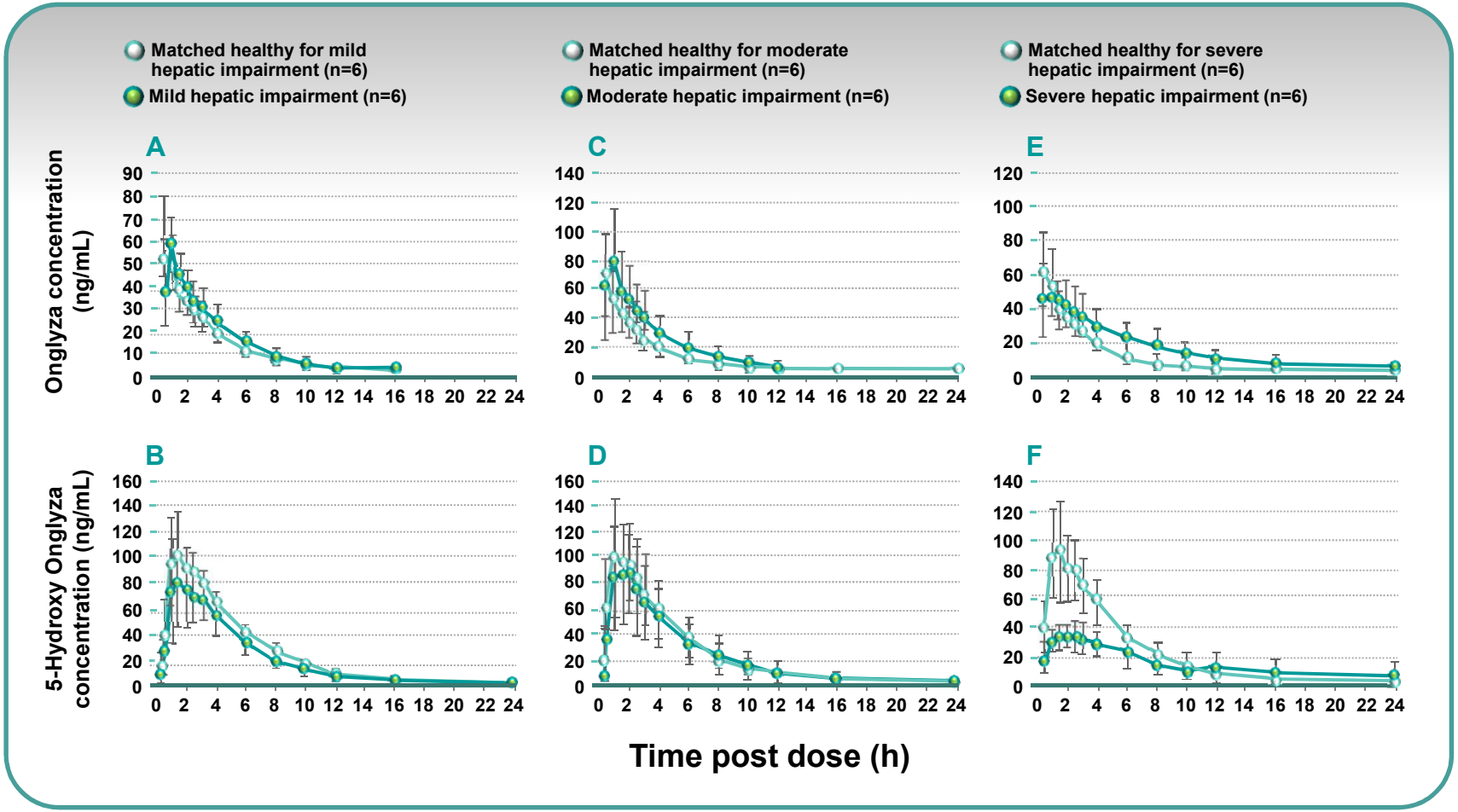
Scheen et al. Diabetes, Obesity and Metabolism 12: 648-658, 2010 et al. Clin Pharmacokinet 2011; 50 (4): 253-265

Diabetes control in renal impairment

Use of DPP-4 inhibitors by renal function according to KFDA label

Inhibitor	Renal Impairment		
	Mild	Moderate	Severe/ESRD
Saxagliptin	**5mg q.d.**	**2.5mg q.d.**	**2.5mg q.d.**
Sitagliptin	100mg q.d.	50mg q.d.	25mg q.d.
Vildagliptin	50mg b.i.d.	50mg q.d.	50mg q.d.

Saxagliptin in patients with hepatic impairment



Boulton et al. Clin Pharmacokinet 2011; 50 (4): 253-265

Diabetes control in hepatic impairment

Use of DPP-4 inhibitors by hepatic function according to KFDA label

Inhibitor	Hepatic insufficiency		Liver enzyme monitoring
	Mild/moderate	Severe	
Onglyza (saxagliptin)	**Can be used**	**Can be used**	**Not required**
Sitagliptin	Can be used	Can be used	Not required
Vildagliptin	Not recommended in patients with ALT or AST > 2.5 x the upper limit of normal		Prior to initiation/every three month during first year/periodically thereafter

Saxagliptin 2.5 mg in patient with renal impairment

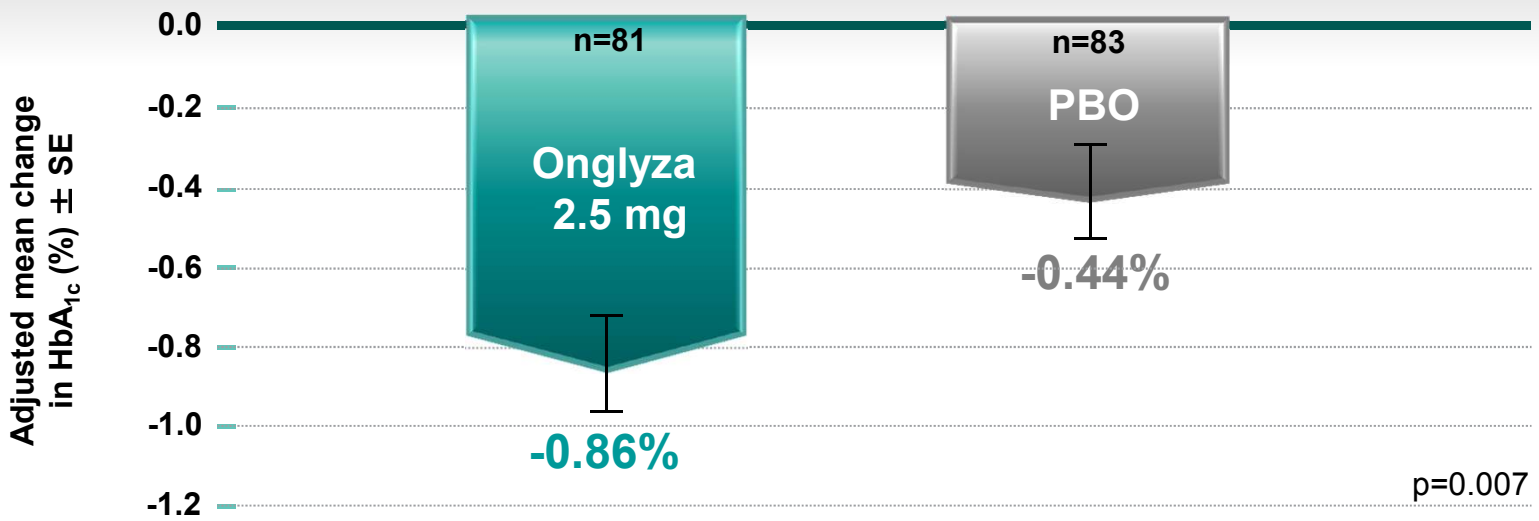
- **43% Male; 85% White**; mean age 66.5 years; mean BMI: 30.7 kg/m^2
- **Mean duration of type 2 diabetes**: 16.7 years
- 83.5% of Onglyza patients and 67.1% of PBO patients were receiving background insulin therapy

Baseline renal impairment category, n (%)	Onglyza 2.5 mg (n=85)	PBO (n=85)
CrCl ≥30 to <50 ml/min	48 (56.5)	42 (49.4)
CrCl <30 ml/min not receiving dialysis	18 (21.2)	23 (27.1)
Haemodialysis-dependent	19 (22.4)	20 (23.5)

Nowicki M, et al. Diabetes Obes Metab. 2011;13(6):523-32.

Saxagliptin 2.5 mg is effective in patients with renal impairment

Adjusted mean change in HbA_{1c} from baseline at week 12

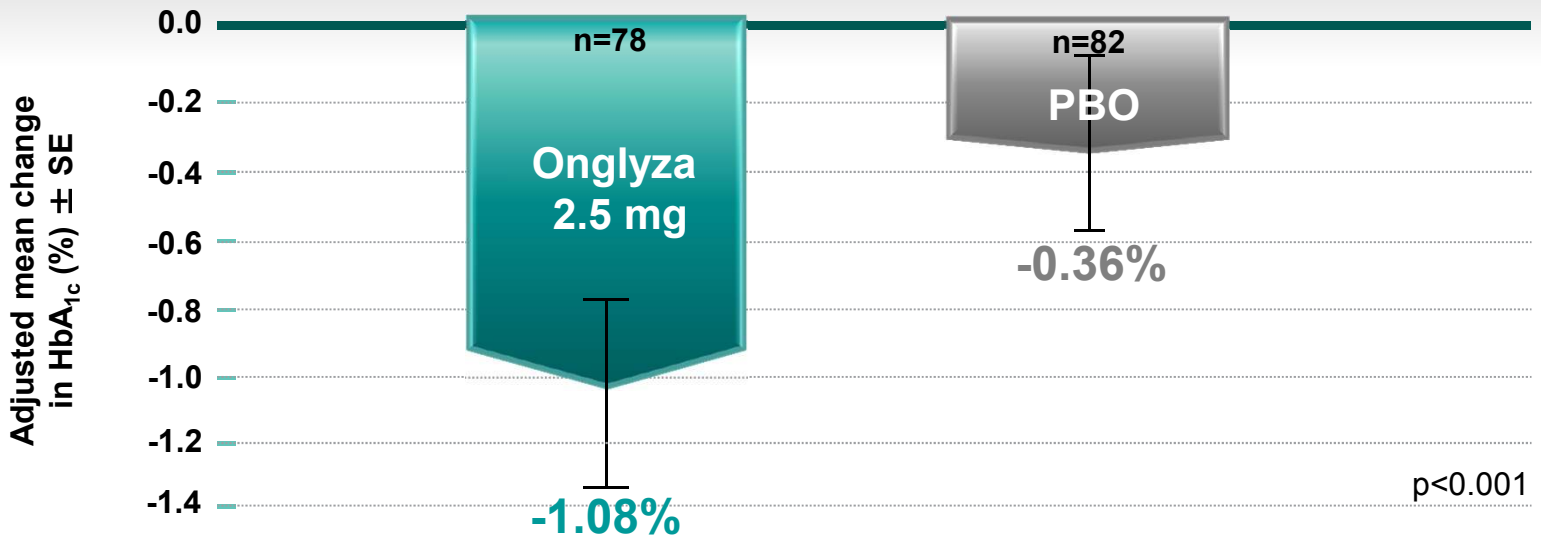


A similar trend was observed in the subgroups with moderate or severe renal impairment

Nowicki M, et al. Diabetes Obes Metab. 2011;13(6):523-32.

Saxagliptin 2.5 mg is effective in patients with renal impairment (Long-term)

Adjusted mean change in HbA_{1c} from baseline at week 52

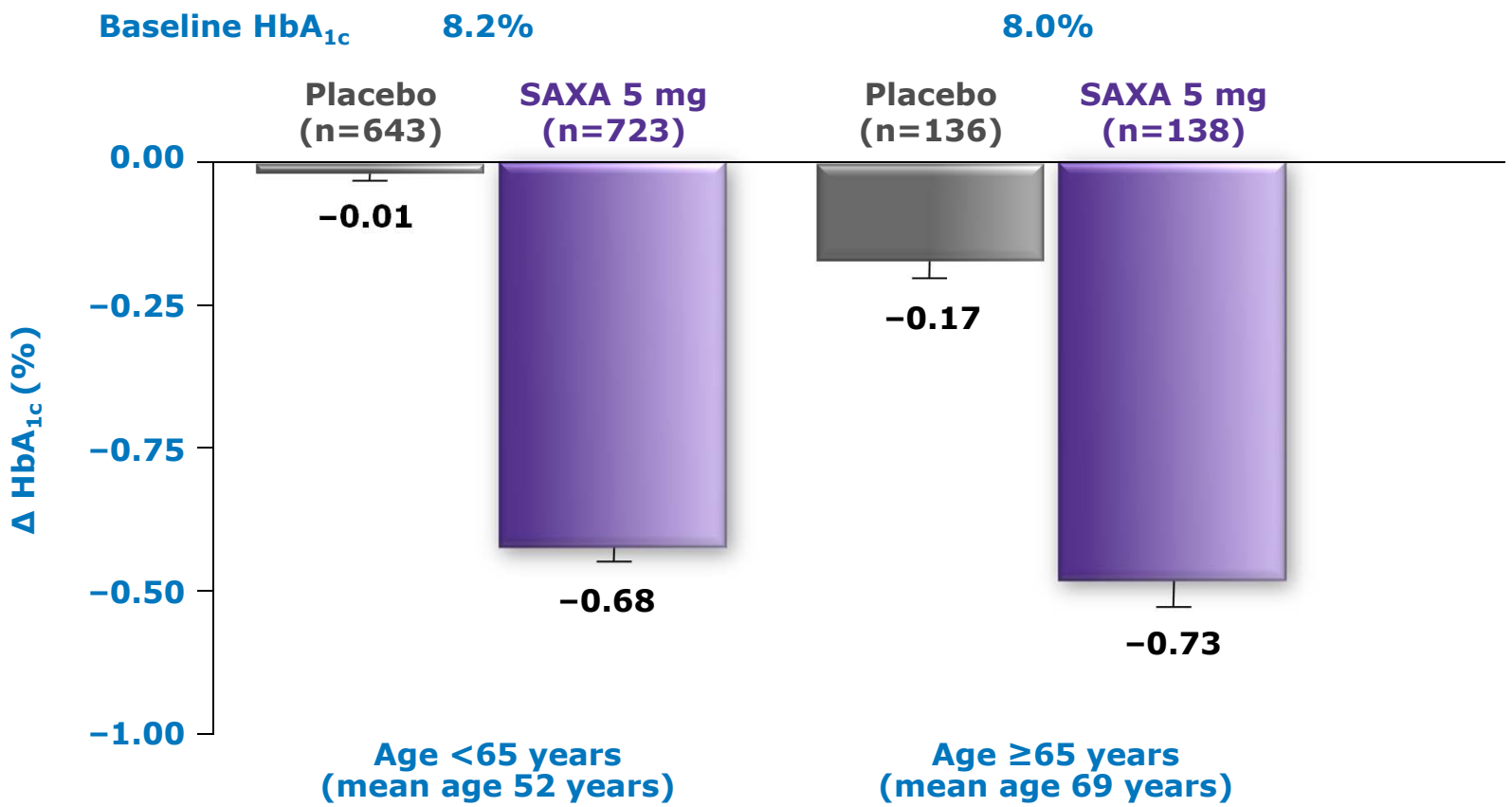


A similar trend was observed in the subgroups with moderate or severe renal impairment

Nowicki M, et al. *Int J Clin Pract,* Oct 7 (Epub ahead of Print)

Saxagliptin in elderly patients : Change from baseline in HbA_{1c}[1]

Retrospective analysis of pooled data, 24 weeks



1. Maheux P, et al. Diabetologia 2009; 52(Suppl. 1):S302.

Saxagliptin in elderly patients
Most common (>5%) AEs during the 24-week treatment period[1]

Safety analysis set	Age <65 years		Age ≥65 years	
	SAXA 5 mg (n=740)	**PBO** (n=662)	**SAXA 5 mg** (n=142)	**PBO** (n=137)
Adverse event ≥5%, n (%)*				
URTI	62 (8.4)	51 (7.7)	6 (4.2)	10 (7.3)
UTI	52 (7.0)	41 (6.2)	8 (5.6)	8 (5.8)
Nasopharyngitis	42 (5.7)	44 (6.6)	7 (4.9)	10 (7.3)
Influenza	26 (3.5)	24 (3.6)	4 (2.8)	11 (8.0)
Bronchitis	17 (2.3)	7 (1.1)	2 (1.4)	7 (5.1)
Diarrhoea	30 (4.1)	39 (5.9)	6 (4.2)	10 (7.3)
Back pain	27 (3.6)	35 (5.3)	11 (7.7)	6 (4.4)
Pain in limbs	24 (3.2)	26 (3.9)	3 (2.1)	7 (5.1)
Headache	52 (7.0)	38 (5.7)	5 (3.5)	9 (6.6)
Dizziness	17 (2.3)	19 (2.9)	4 (2.8)	10 (7.3)
Cough	21 (2.8)	25 (3.8)	3 (2.1)	11 (8.0)

***Excludes hypoglycaemia.**
AE: adverse events; PBO: placebo; URTI: upper respiratory tract infection; UTI: urinary tract infection.

1. Maheux P, et al. Diabetologia 2009; 52(Suppl. 1):S302.

CV Safety

Cardiovascular Outcomes in Saxagliptin

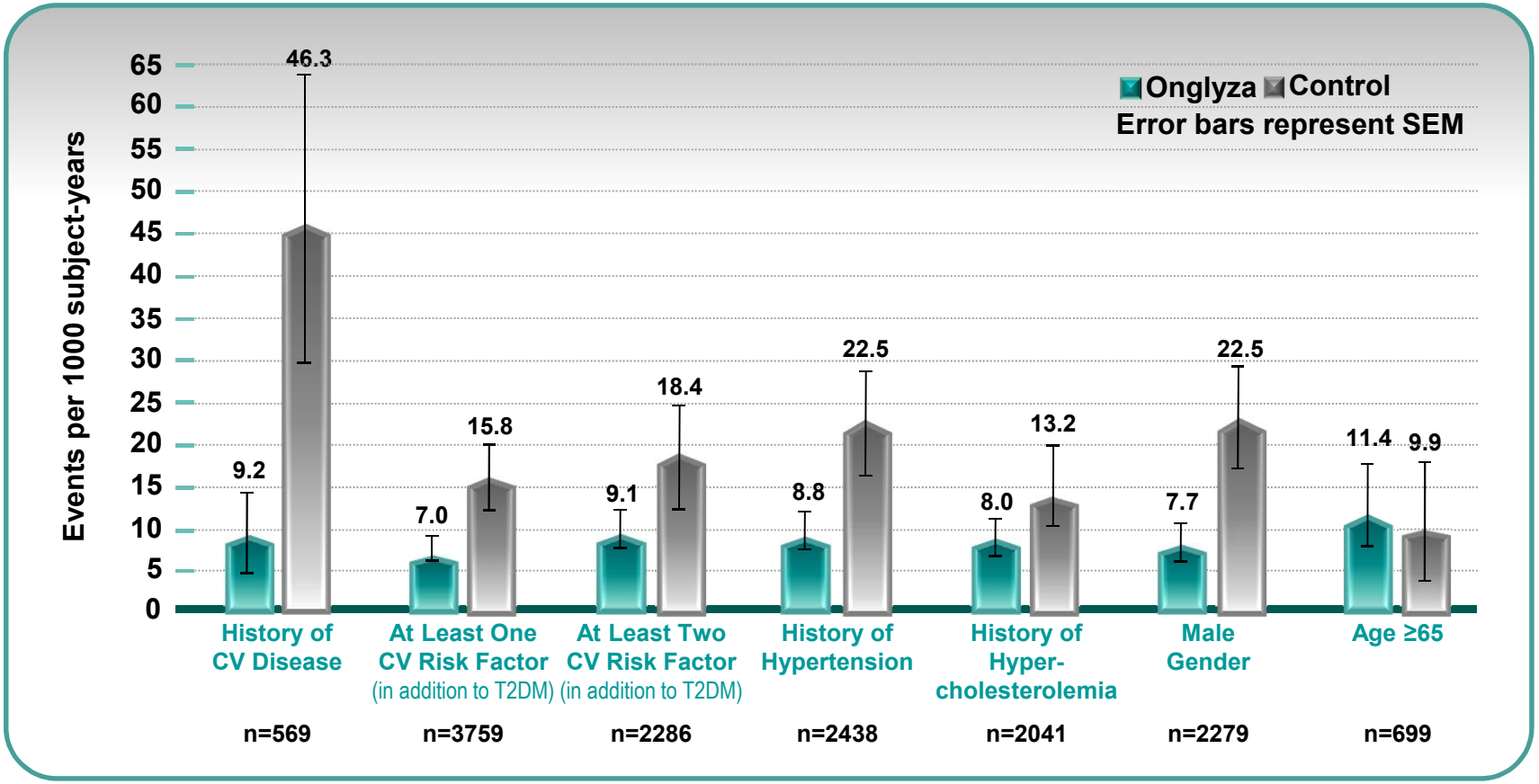
- **Cardiovascular events(death, myocardial infarction, stroke, revascularization procedures and cardiac ischemia) were reported as adverse events and death, myocardial infarction and stroke were blindly adjudicated post hoc by an independent clinical events committee.**

- **3356 Onglyza treated patients were compared to 656, placebo, 328 metformin, and 267 glyburide treated patients.**

	Onglyza (3356)	Comparator (1251)
Cardiovascular events	38 (1.1%)	23 (1.8%)
CV death, MI & Stroke	22 (0.7%)	18 (1.4%) **RR = 0.43 (0.23-0.80)**

Frederich R et al.Postgrad Med 122:16-27, 2010

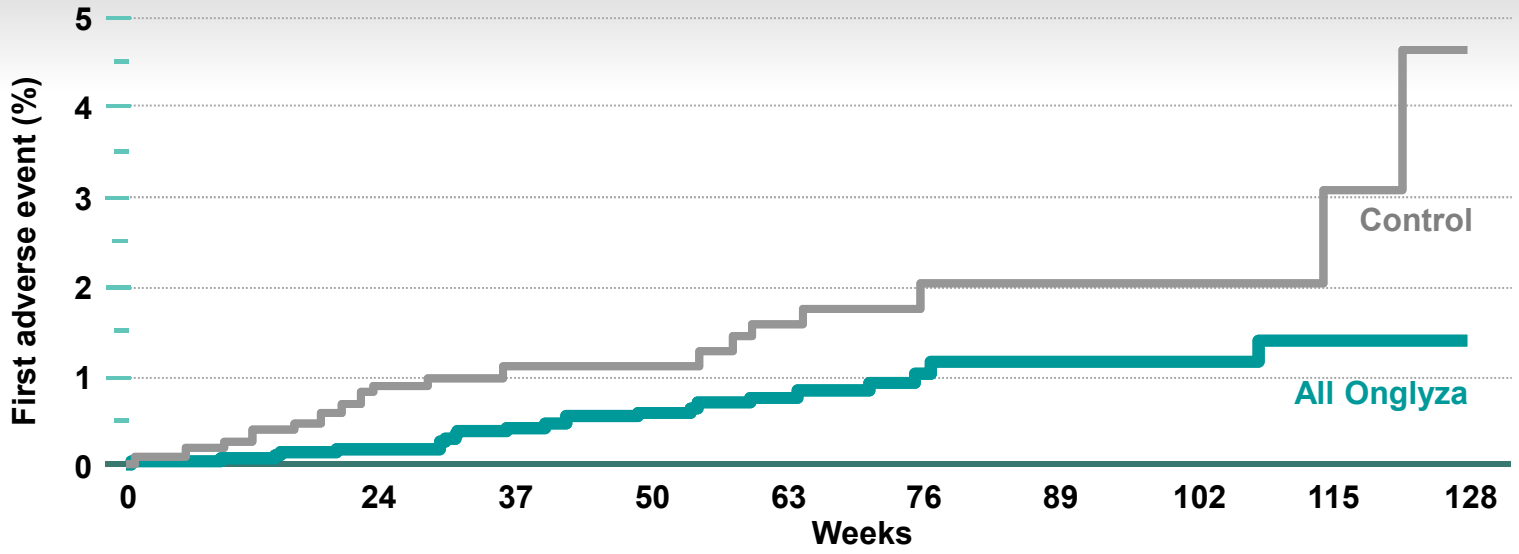
Incidence rate for primary MACE by subgroup



Frederich R, et al. Postgrad Med. 2010;122(3):16-27.

Cardiovascular events

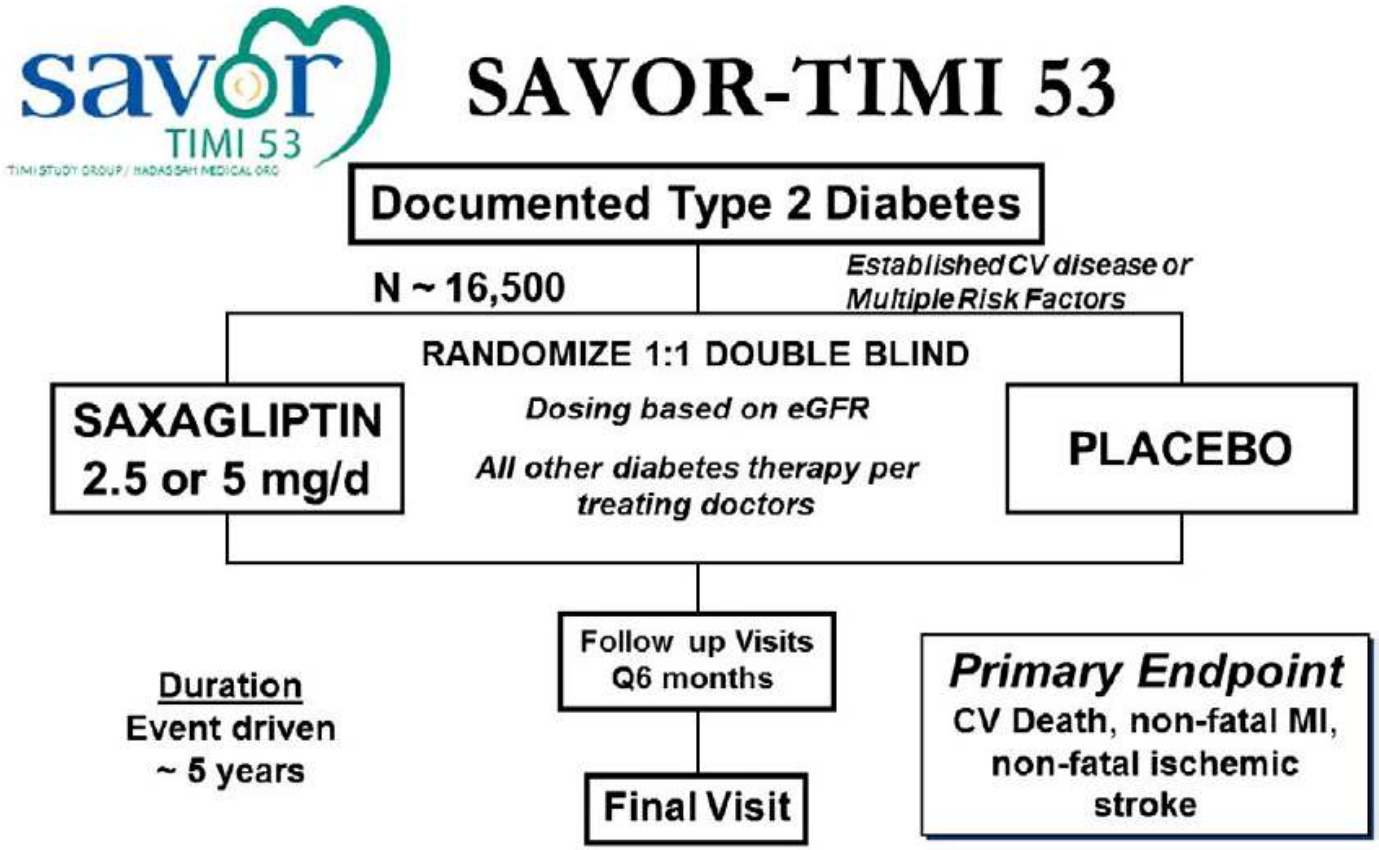
Time to onset of first primary Major Adverse Cardiovascular Event (MACE)*



Patients at risk										
Control	1,251	935	860	774	545	288	144	123	102	57
All Onglyza	3,356	2,615	2,419	2,209	1,638	994	498	436	373	197

Frederich et al. Postgrad Med 122:16-27, 2010.

SAVOR STUDY



Trial schema of the SAVOR-TIMI 53 Trial.

Am Heart J 2011;162:818-825.e6.)

Drug-drug interaction

Metabolism of saxagliptin

- **Saxagliptin is metabolised by cytochrome P450 3A4/5 (CYP3A4/5)**
- **Strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite**

No dosing adjustments required for the following drugs

Co-administered drug	AUC* of saxagliptin	AUC* of 5-hydroxy saxagliptin
Metformin	0.98	0.99
Glyburide	0.98	ND
Pioglitazone	1.11	ND
Digoxin	1.05	1.06
Simvastatin	1.12	1.02
Diltiazem	2.09	0.66
Rifampin	0.24	1.03
Omeprazole	1.13	ND
famotidine	1.03	ND

*** Ratio with/without co-administered drug; No effect=1.00**

Saxagliptin prescribing information

No effect of saxagliptin on the following drugs

Co-administered drug	AUC* of co-administered drugs
Metformin	1.20
Glyburide	1.06
Pioglitazone	1.08
Digoxin	1.06
Simvastatin	1.04 / 1/16 (simvastatin acid)
Diltiazem	1.10
Ketoconazole	0.87

*** Ratio with/without saxagliptin; No effect=1.00**

Saxagliptin prescribing information

Drug-drug interaction of saxagliptin

- **No dose adjustment is needed with antidiabetic drugs (metformin, glyburide, pioglitazone), diltiazem, statin, omeprazole, digoxin, rifampin, famotidine.**
- **Saxagliptin 2.5mg is recommended with strong CYP3A4/5 inhibitors like ketoconazole, clarithromycin, erithromycin.**

Saxagliptin prescribing information

Summary

Saxagliptin 5 mg offers

- **Comprehensive glycaemic control through consistent, clinically meaningful and significant reductions in HbA_{1c}, PPG and FPG**
- **A favourable safety and tolerability profile with a low risk of hypoglycaemia and minimal weight changes when added to metformin (a fixed dose combination was approved in Korea)**
- **Comparable efficacy to SU with significantly less hypoglycaemia and beneficial effect on weight**
- **Benefit to various types of patients (with renal/hepatic impairment, elderly patients)**
- **Reassurance on cardiovascular safety with no signal identified in a retrospective analysis of the clinical development programme**