Napoli 19 ottobre 2012

Gli inibitori del trasporto renale del glucosio
SGLT- 2 inhibitors

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Classi di farmaci per il diabete

1. *Metformina*
2. *Sulfoniluree*
3. *Glinidi*
4. *Glitazoni*
5. *Acarbose*
6. *Insulina*
7. *Inibitori della DPP-4*
8. *Agonisti del GLP-1*
9. ***Inibitori del trasporto renale del glucosio***

Il ruolo del rene nel controllo dell'omeostasi glicemica e nel diabete di tipo 2

Normal glucose homeostasis[1,2]

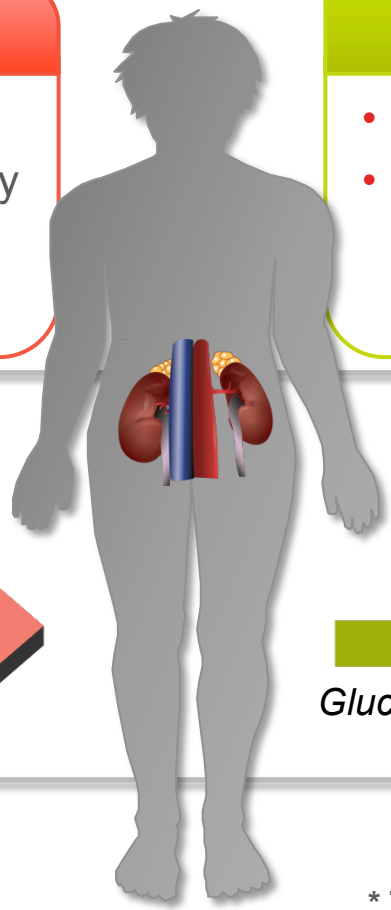
Net balance ~0 g/day

Glucose input ~250 g/day:

- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis*
  - Glycogenolysis

Glucose uptake ~250 g/day:

- Brain ~125 g/day
- Rest of the body ~125 g/day



The kidney filters circulating glucose

Glucose filtered ~180 g/day

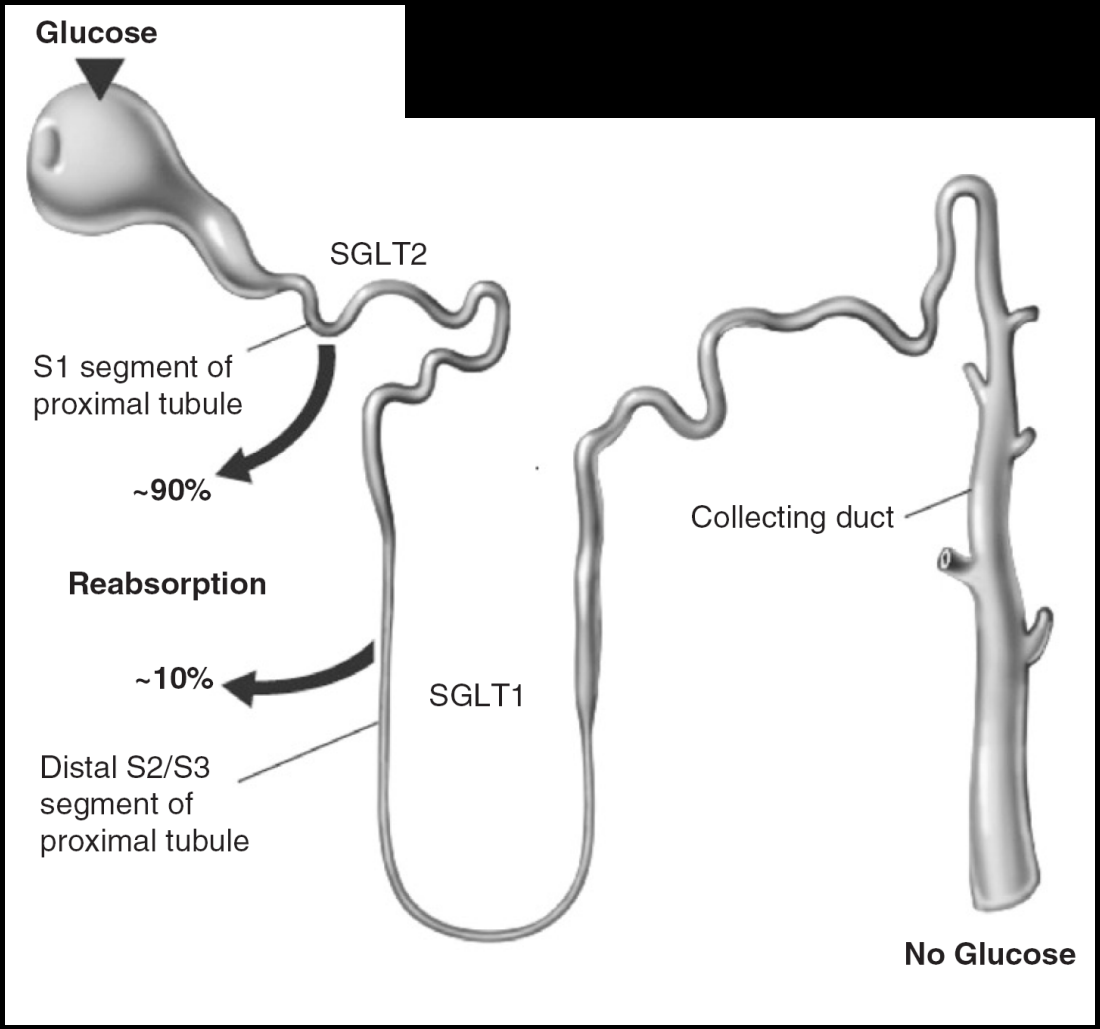
The kidney reabsorbs and recirculates glucose

Glucose reabsorbed ~180 g/day

*** The kidney is responsible for up to 40% of total glucose production by gluconeogenesis**

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18.
2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

Glucose Transporters in the Renal Proximal Tubule in Normal Individuals

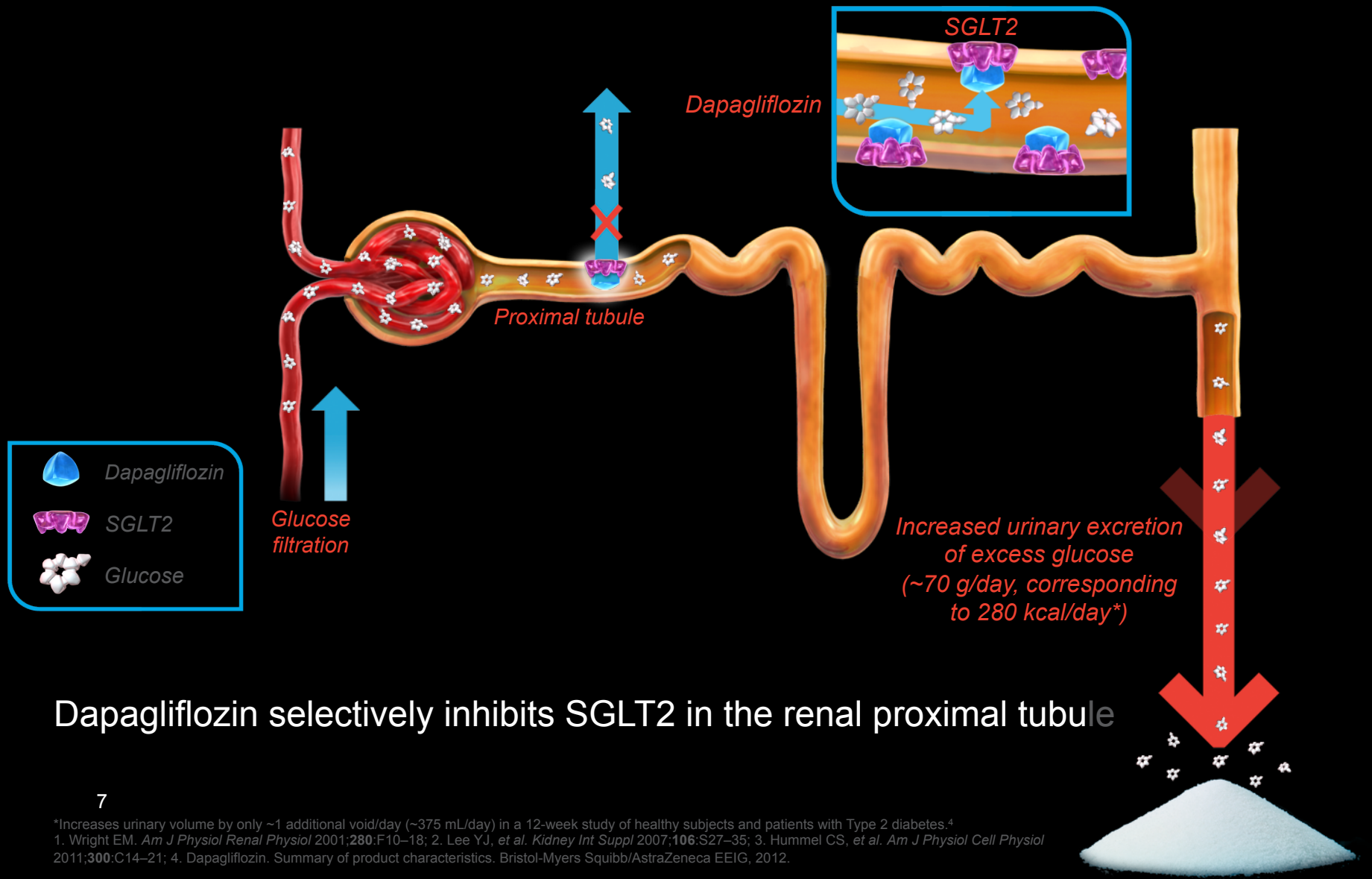


- Volume of plasma kidneys filter/ day = 180 L
- Normal glucose concentration = 1000 mg/L (100 mg/dL)
- Glucose filtered/day = (180 L/ day)(1000 mg/L) = 180 g

Bays H. *CMRO.* 2009;25:671-681.

L’inibizione farmacologica dei trasporatori SGLT2

Dapagliflozin: A novel insulin-independent approach to remove excess glucose



Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule

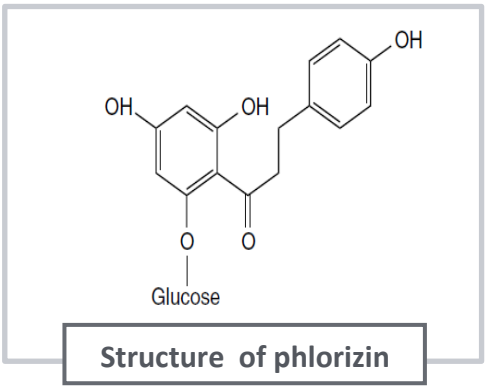
*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35; 3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Sodium Glucose Co-Transporter-2 (SGLT-2) inhibitors

History of SGLT-2 inhibitors

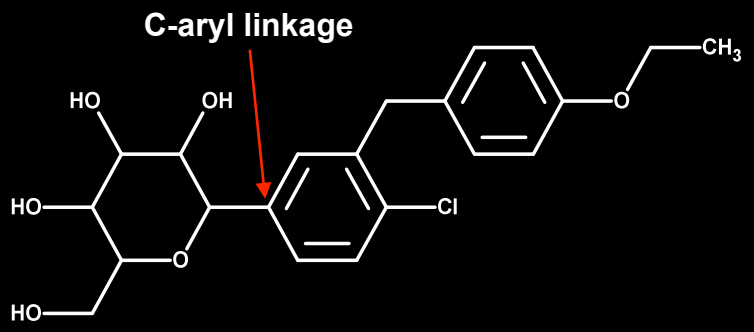
- Sodium Glucose Co-Transporter-2 (SGLT-2) is the most prevalent and functionally important transporter for glucose reabsorption in the kidney
- The compound phlorizin was first isolated in 1835 from root bark of the apple tree by French chemists[1]
- The Merck Index of 1887 lists 'phlorizin' as a 'Glycosid aus der Wurzelrinde des Apfelbaumes' ('glycoside from the bark of apple trees')[1]
- Animal studies demonstrated that phlorizin induced urinary glucose excretion normalised both fasting and post-prandial hyperglycaemia as well as reversing both first and second phase insulin secretory defects[2,3]
- It was found that the mode of action behind that is a selectively and reversibly blocking of the SGLT-2 receptor, which prevents the reabsorption of glucose at the renal proximal tubule
- Therapeutic potential of phlorizin is limited by poor GI absorption and inhibition of both SGLT-1 and SGLT2 transporters[3]
- SGLT-2 inhibitors have been synthesized similar to phlorizin – such as dapagliflozin, canagliflozin and empagliflozin[3]



Structure of phlorizin

1 Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev 2005 Jan;21(1):31-8.
2 Rossetti L, Shulman GI, Zawalich W, DeFronzo RA: Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatomized rats. J Clin Invest 1987; 80(4):1037-44
3 White J. Apple Trees to Sodium Glucose Co-Transporter Inhibitors; A Review of SGLT2 Inhibition. Clinical Diabetes 2010;28(1):5-10.

Dapagliflozin: A Selective SGLT2 Inhibitor



- Highly selective and reversible SGLT2 inhibitor[1]
- Stability
  - C-aryl glycoside less susceptible to O-glucosidase degradation[2,3]
  - Prolonged half-life (~16 hours)[3]
- Main metabolite inactive, eliminated in urine

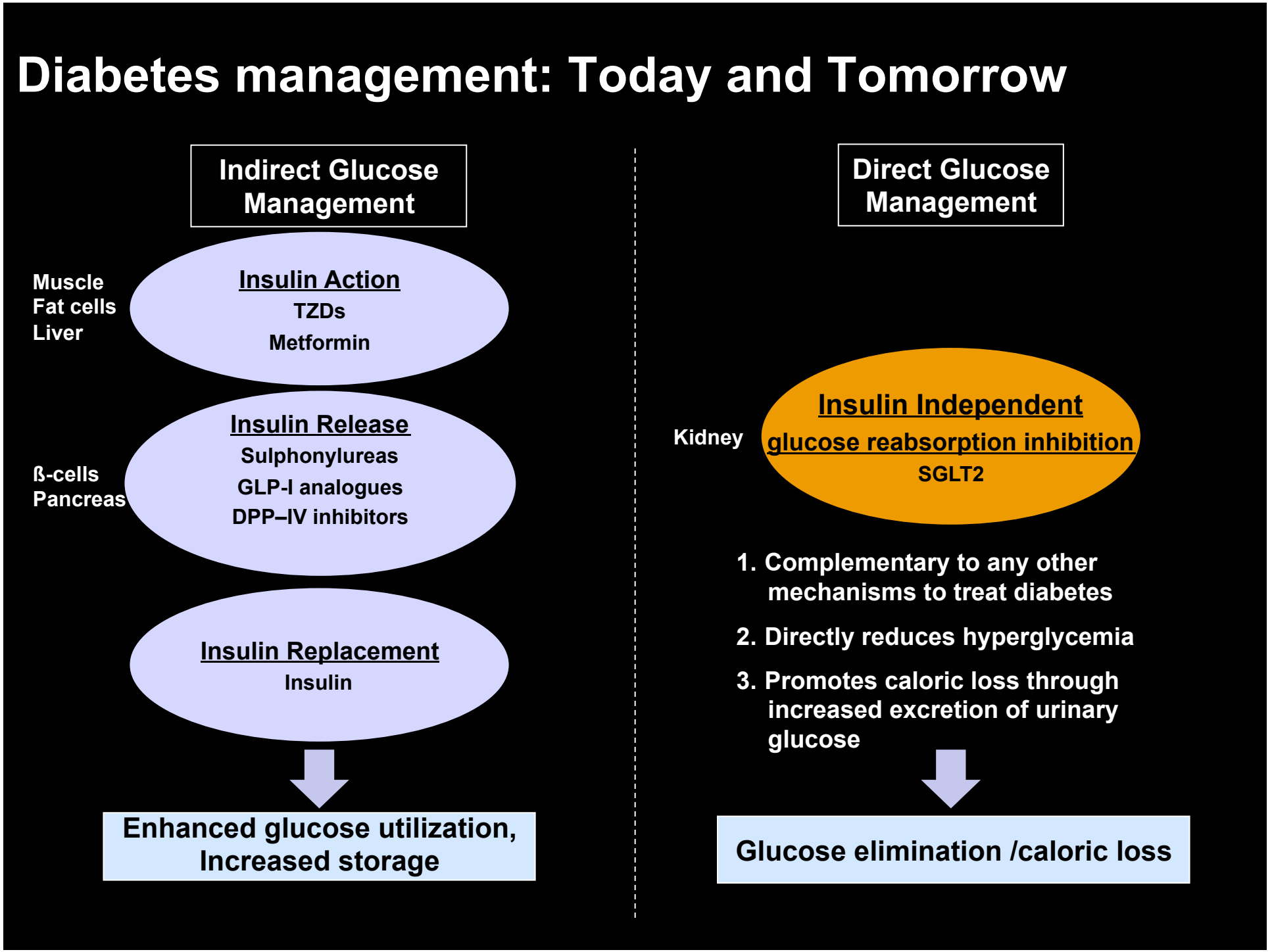
Human Transporters	Dapagliflozin Mean EC_{50}[4] (nM ± SEM)	Dapagliflozin K_i[1] (nM ± SEM)
SGLT2	1.12 ± 0.065	0.2 ± 0.06
SGLT1	1391 ± 7	610 ± 180
Selectivity: SGLT2 vs SGLT1	1200	3000

[1]Bellamine A. Presented at: *BioMedical Transporters 2009*, Thun Switzerland (9 Aug 2008).
[2]Meng W et al, *J Med Chem* (2008) 51:1145. [3]Washburn W, *J Med Chem* (2008) 52:1785.
[4]Radioactive substrate assay; n=16-18 experiments. From Han et al. *Diabetes* (2008) 57:1723.

CANAGLIFOZIN
ENPAGLIFOZIN

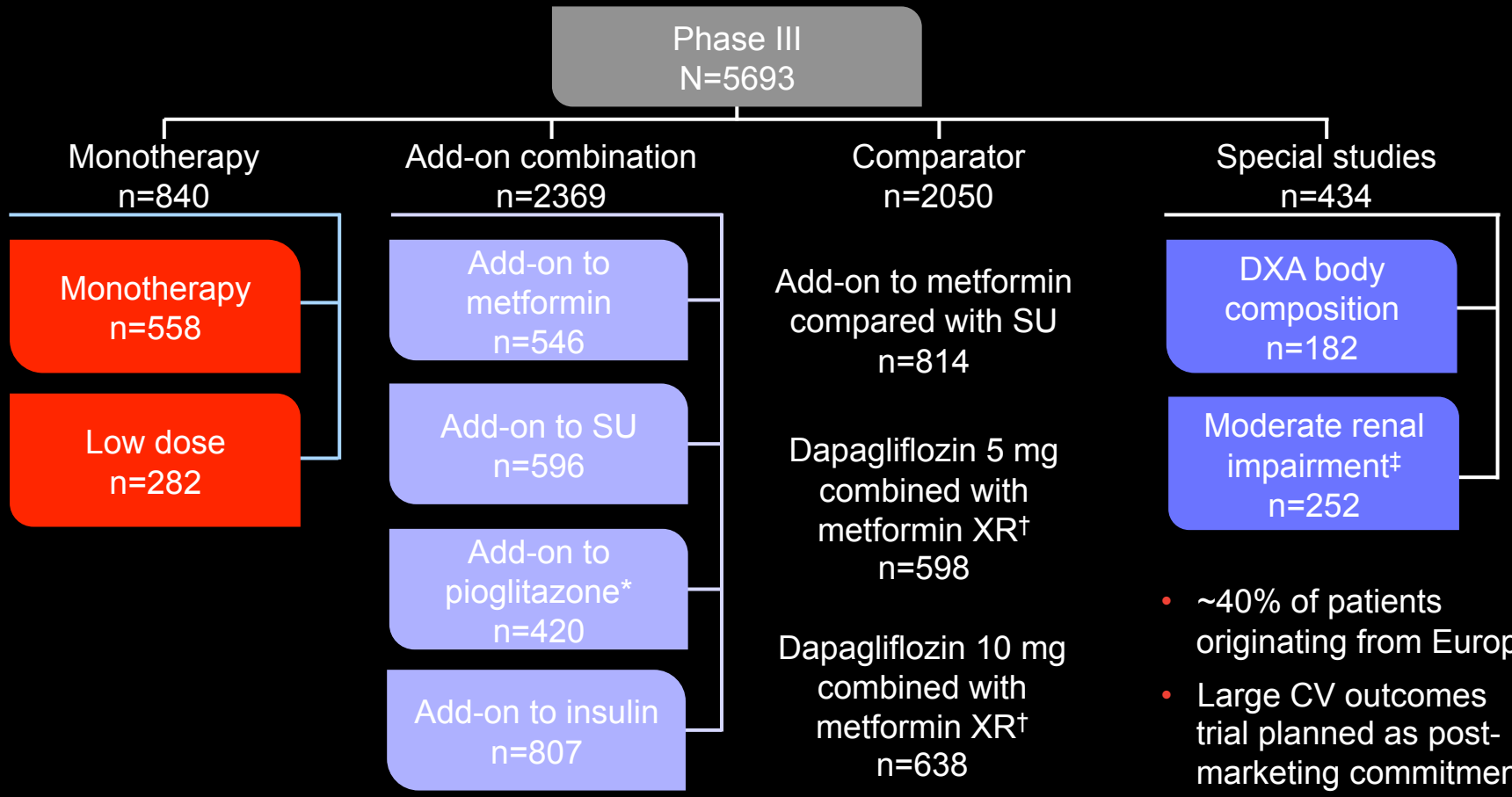
IPRAGLIFOZIN
LUSEOGLIFOZIN
REMOGLIFOZIN
SERGLIFOZIN
TOFOGLIFOZIN

Diabetes management: Today and Tomorrow



L’ efficacia sul controllo glicemico

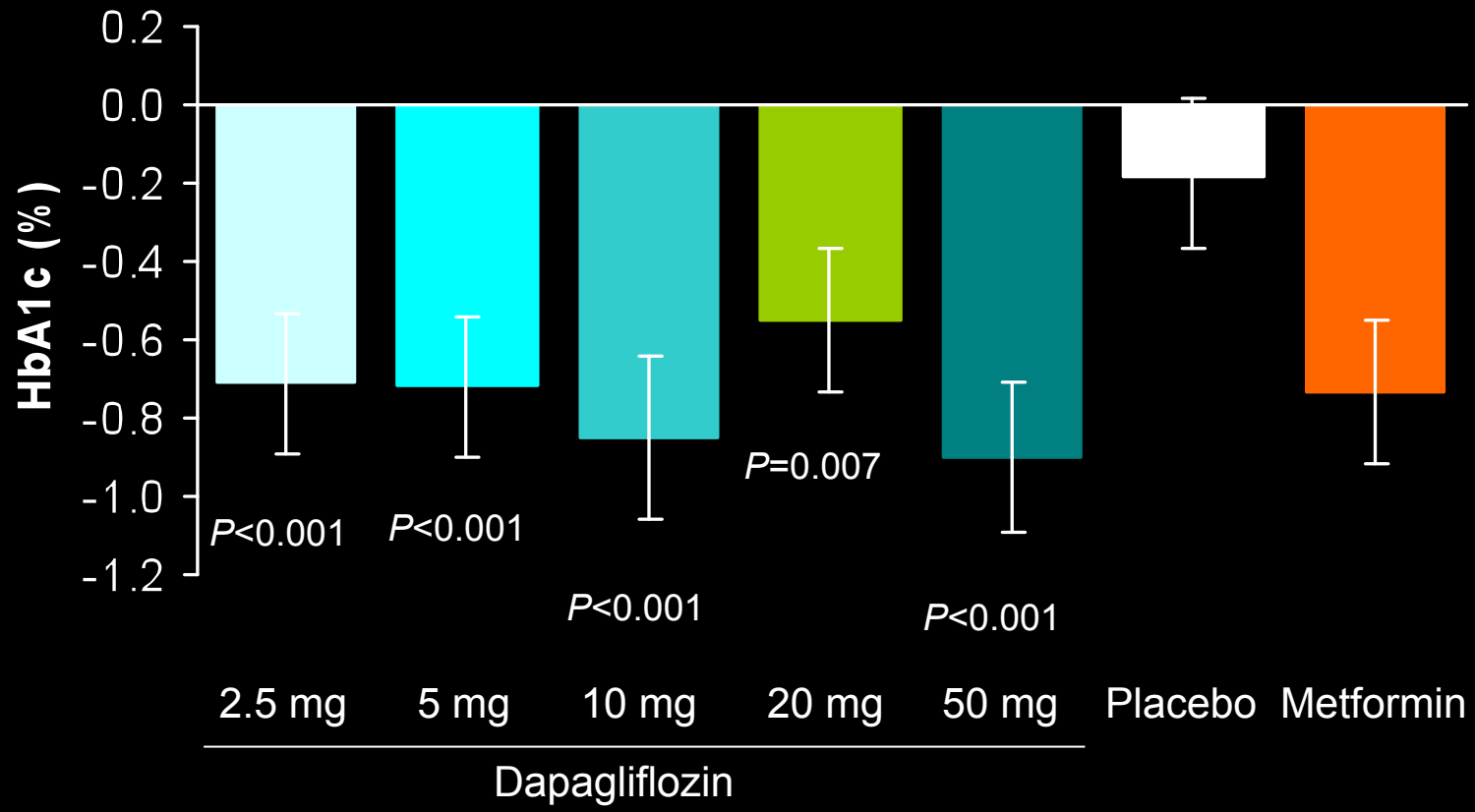
Dapagliflozin Phase III clinical development programme



- ~40% of patients originating from Europe
- Large CV outcomes trial planned as post-marketing commitment

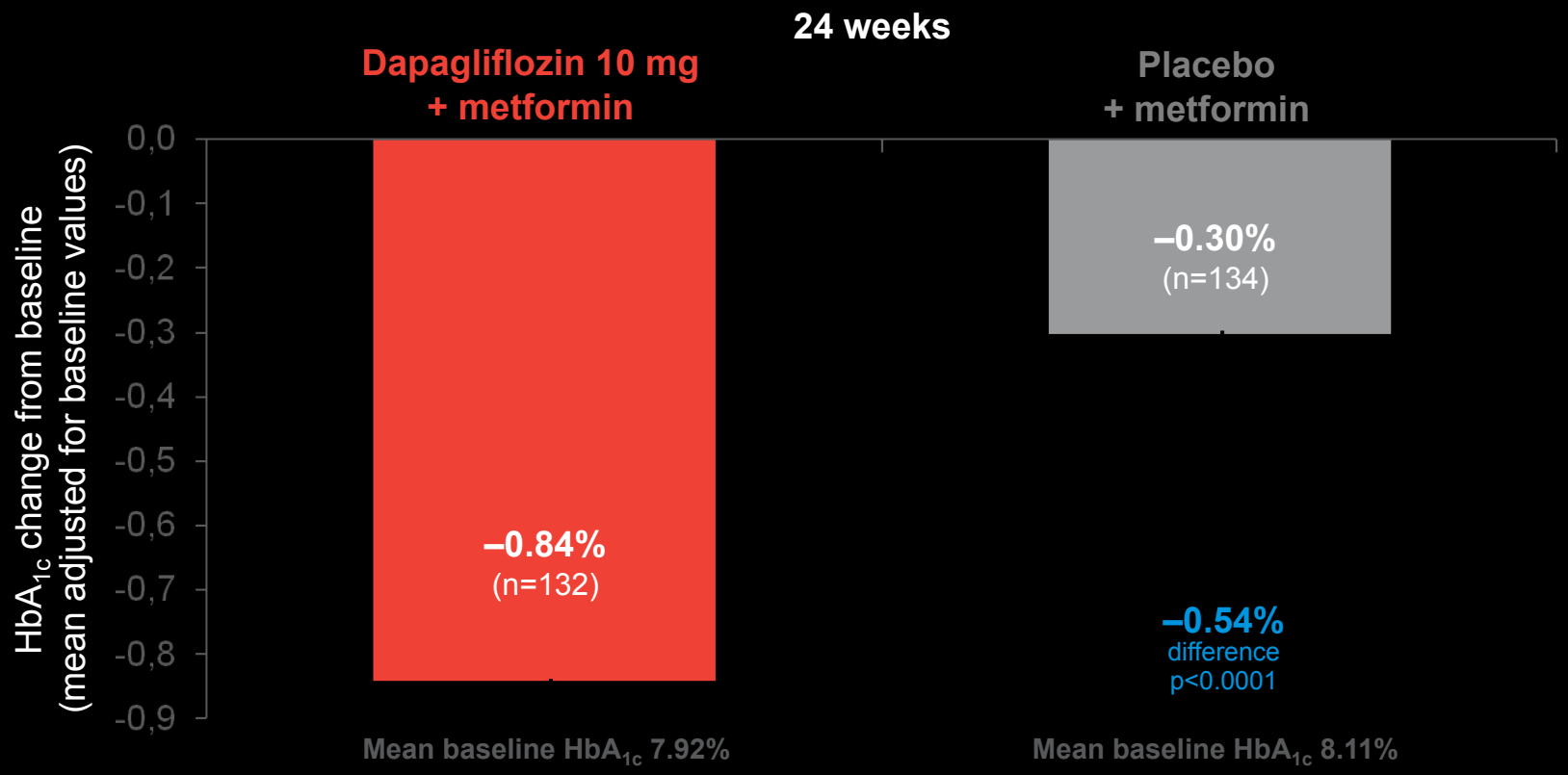
*The use of dapagliflozin with pioglitazone is not recommended; †metformin extended release (XR) is not approved or available in all European countries; ‡Dapagliflozin should not be used in patients with moderate to severe renal impairment (CrCl <60 mL/min or eGFR <60 mL/min/1.73 m^2).
CrCl, creatinine clearance; CV, cardiovascular; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; SU, sulphonylurea.

Phase 2b: HbA1c – Adjusted Mean Changes From Baseline at Week 12 (LOCF)



Data are means and 95% CI.
List JF, et al. *Diabetes Care*. 2009;32:650-657.

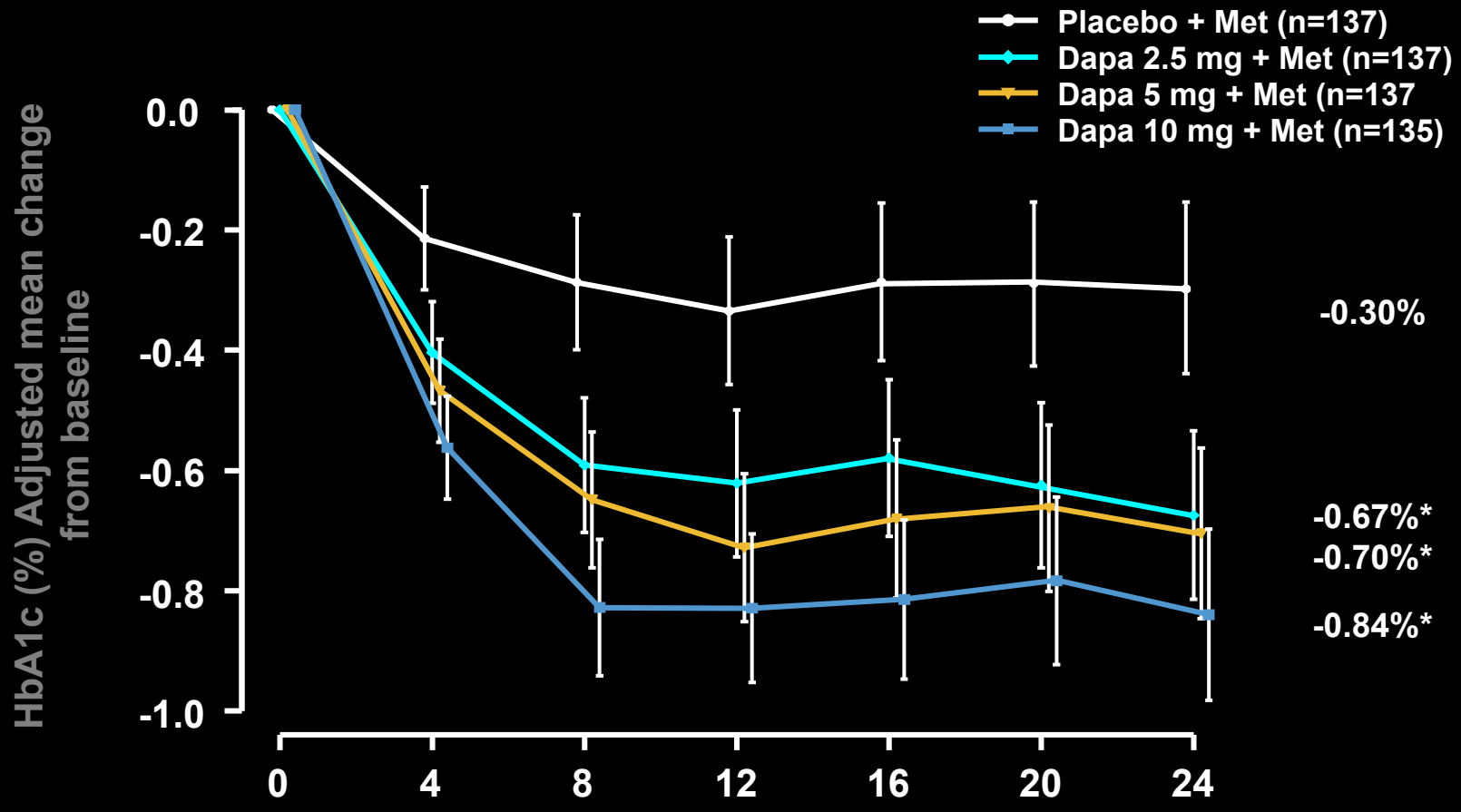
Dapagliflozin: Significant reductions in HbA_{1c} compared with placebo at the 24-week primary endpoint



Changes reported for Week 24 are adjusted for baseline values and are based on last observation carried forward (LOCF).
A Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week clinical study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus placebo + metformin (≥1500 mg/day) in adult patients with Type 2 diabetes who had inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%) on metformin alone. Primary endpoint: HbA_{1c} reduction at 24 weeks.

Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

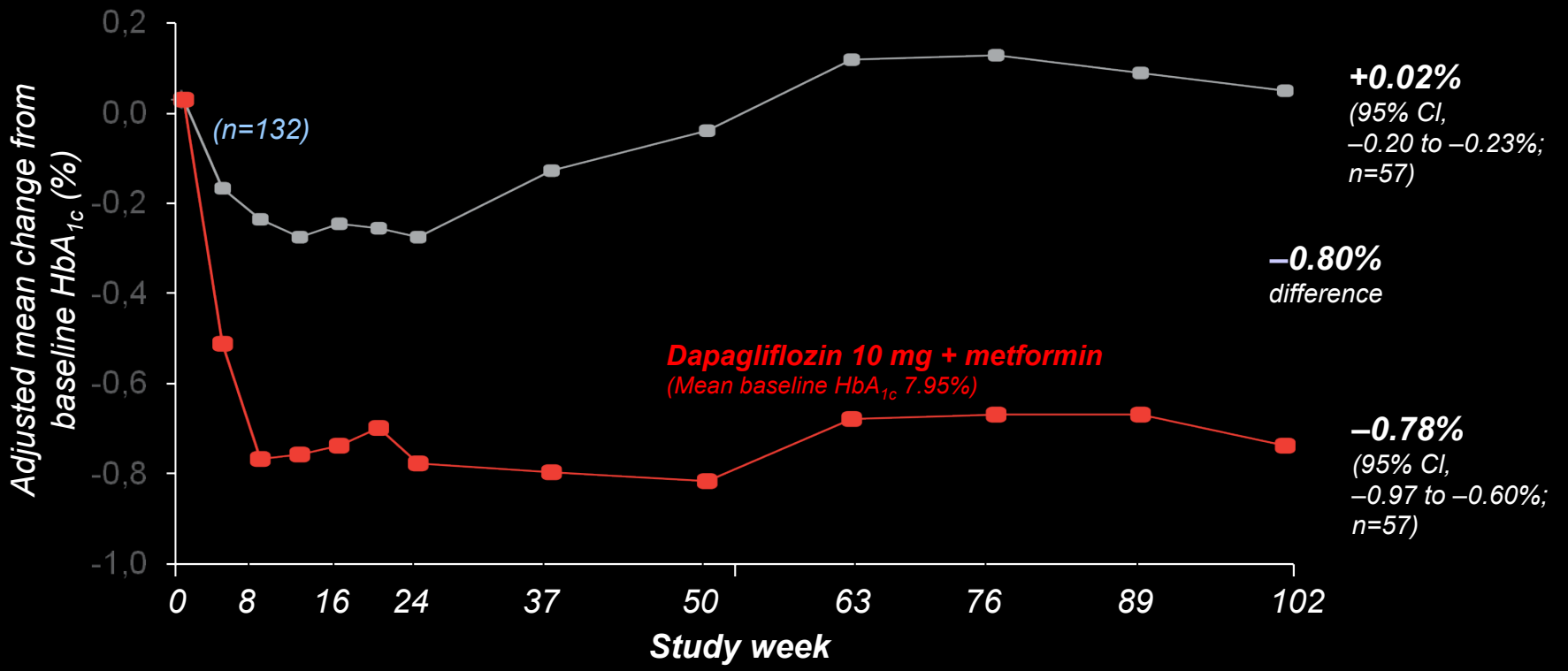
Add-on to Metformin: HbA_{1c} Adjusted Mean Change from Baseline



24-week short-term double-blind treatment period
Excluding data after rescue
Randomized subjects

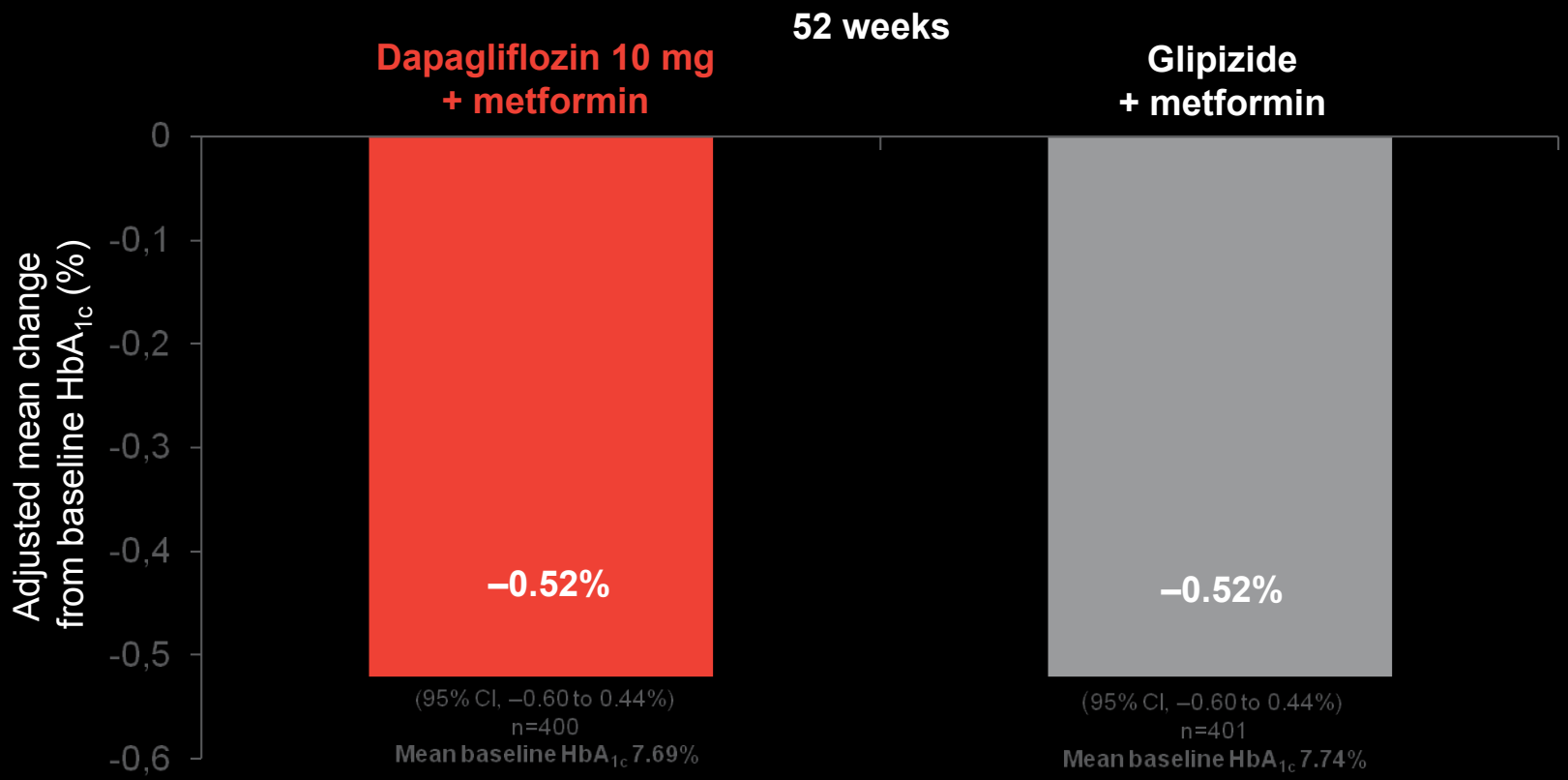
*p<0.05 *vs.* placebo

Dapagliflozin: Reductions in HbA_{1c} were sustained over time



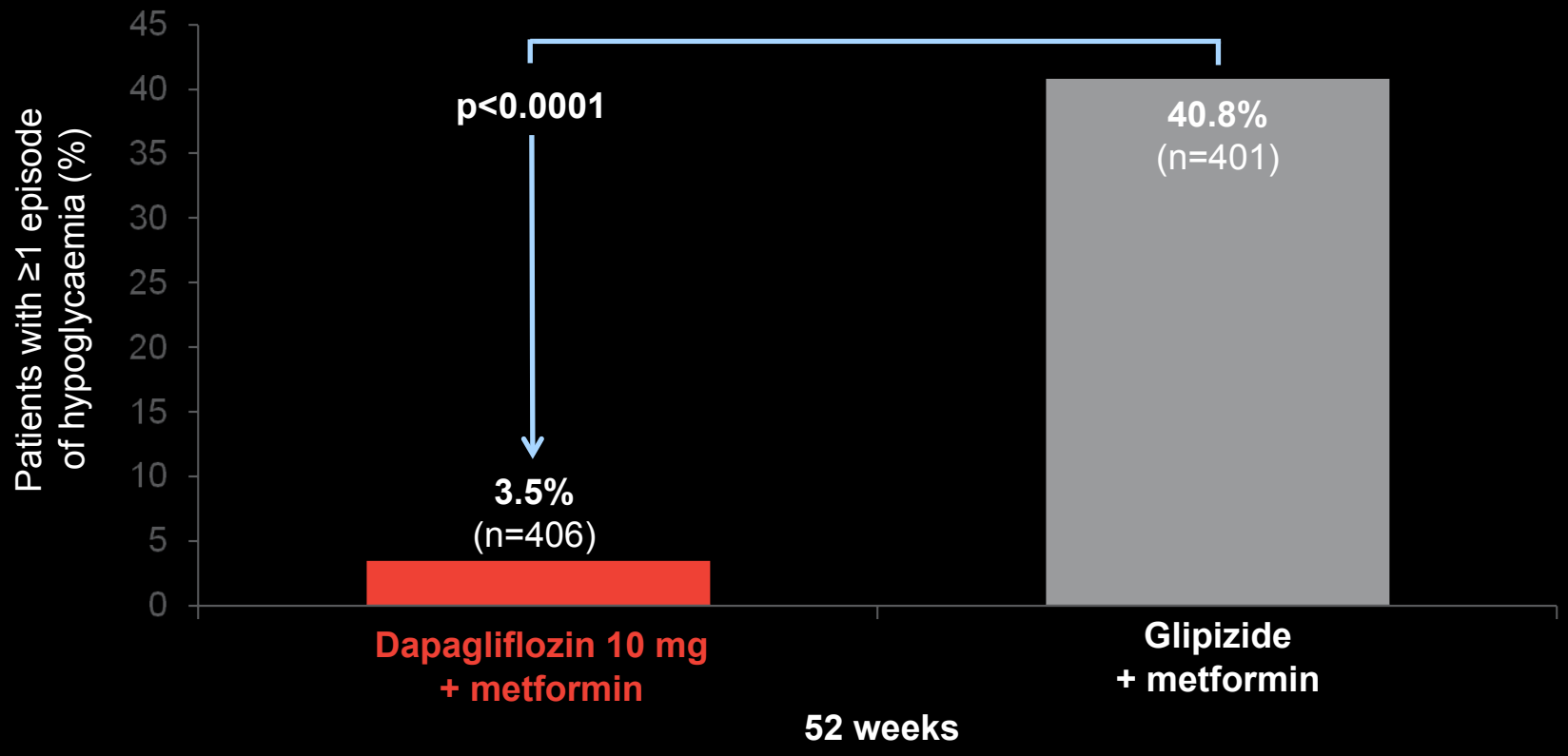
Data are mean change from baseline after adjustment for baseline value. Data after rescue are excluded. Analyses were obtained by longitudinal repeated measures analyses.
CI, confidence interval.
Bailey CJ, et al. Poster 988-P. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011.

Dapagliflozin: Comparable HbA_{1c} reduction to a sulphonylurea at the 52-week primary endpoint



Data are adjusted mean change from baseline and 95% CI derived from analysis of covariance using the full analysis set and LOCF values.
A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled non-inferiority study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus glipizide + metformin (≥1500 mg/day) in patients with inadequate glycaemic control (HbA_{1c} >6.5% and ≤10%) on metformin alone.
Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22.

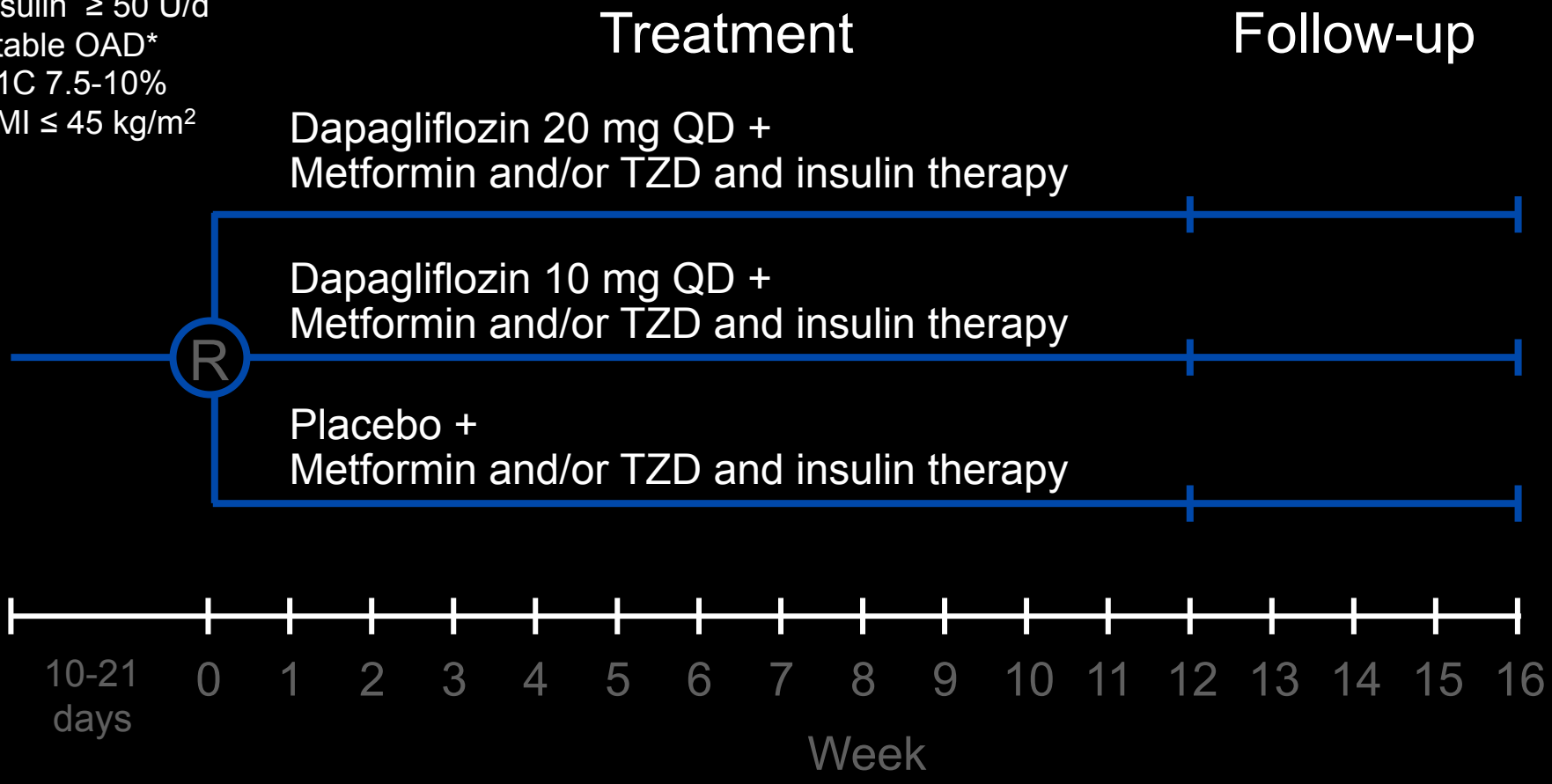
Lower incidence of hypoglycaemia with dapagliflozin compared with a sulphonylurea



Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22.

Add-on to Insulin: Study Design

T2DM
Insulin ≥ 50 U/d
Stable OAD*
A1C 7.5-10%
BMI ≤ 45 kg/m^2



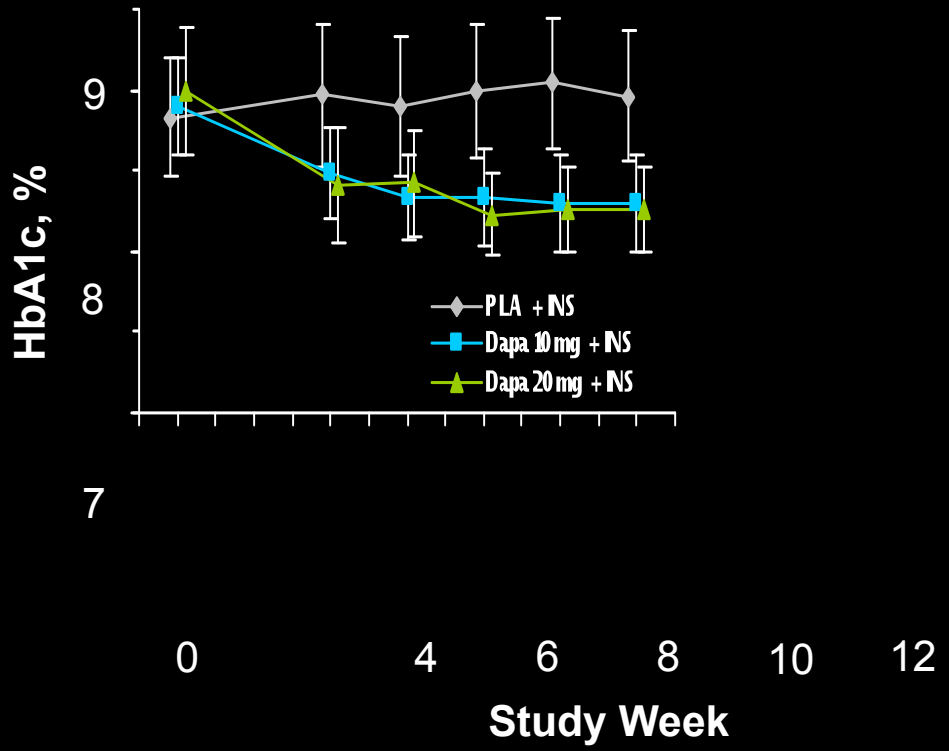
Insulin dose reduced by 50% at study start

* On a stable dose of metformin (daily dose ≥1000 mg), and/or pioglitazone (daily dose ≥30 mg) or rosiglitazone (daily dose of 4 mg)

Wilding JPH, et al. *Diabetes Care.* 2009;32:1656-1662.

Add-on to Insulin: HbA1c

Efficacy with high insulin doses and sensitizer therapy, despite a 50% insulin dose reduction



Data are means based on LOCF, excluding data after insulin up-titration. Error bars represent 95% CIs.

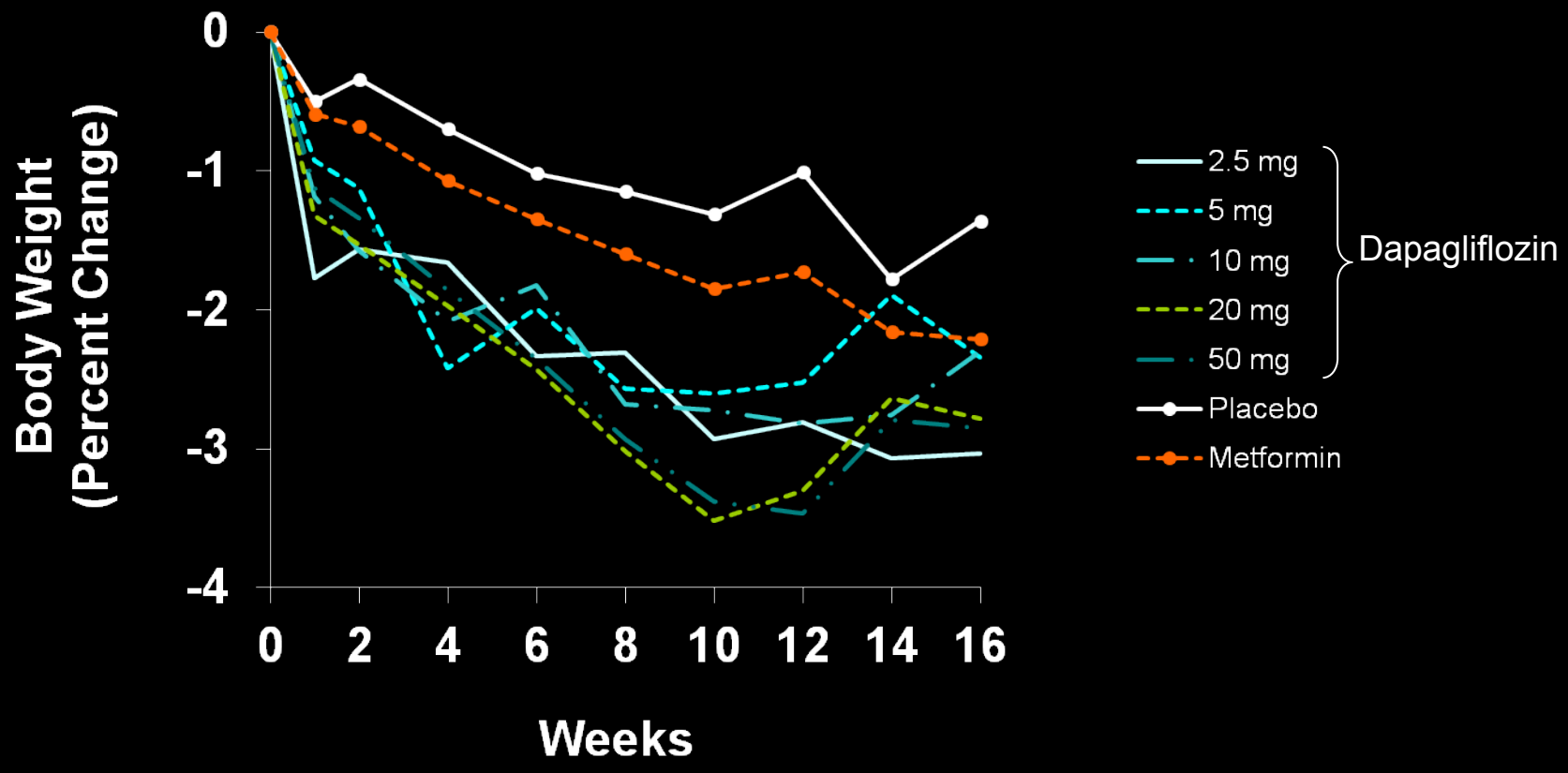
	Change From Baseline	Difference in Change vs Placebo + Insulin
Placebo + insulin (n=19)	0.09 (-0.2 to 0.4)	
Dapagliflozin 10 mg + insulin (n=23)	-0.61 (-0.9 to -0.4)	-0.70 (-1.1 to -0.3)
Dapagliflozin 20 mg + insulin (n=23)	-0.69 (-0.9 to -0.4)	-0.78 (-1.2 to -0.4)

Values are %. Data are means and 95% CI and represent the number of patients with a non-missing baseline and week 12 LOCF value.

Wilding JPH, et al. *Diabetes Care.* 2009;32:1656-1662.

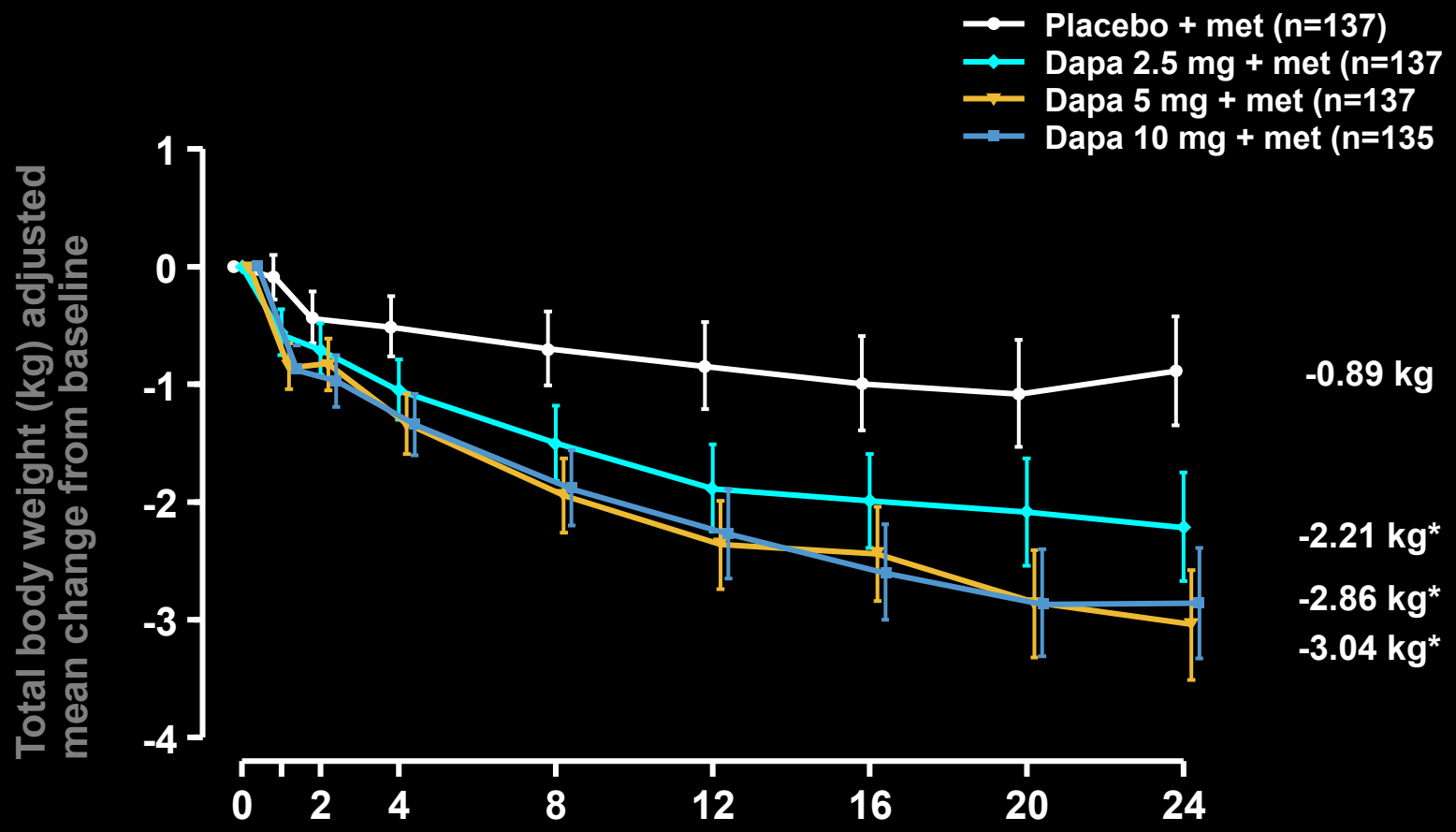
L’ efficacia su altri parametri clinici

Phase 2b: Body Weight – Mean Percent Change Over 12-week Treatment and 4-week Follow-up



List JF, et al. *Diabetes Care*. 2009;32:650-657.

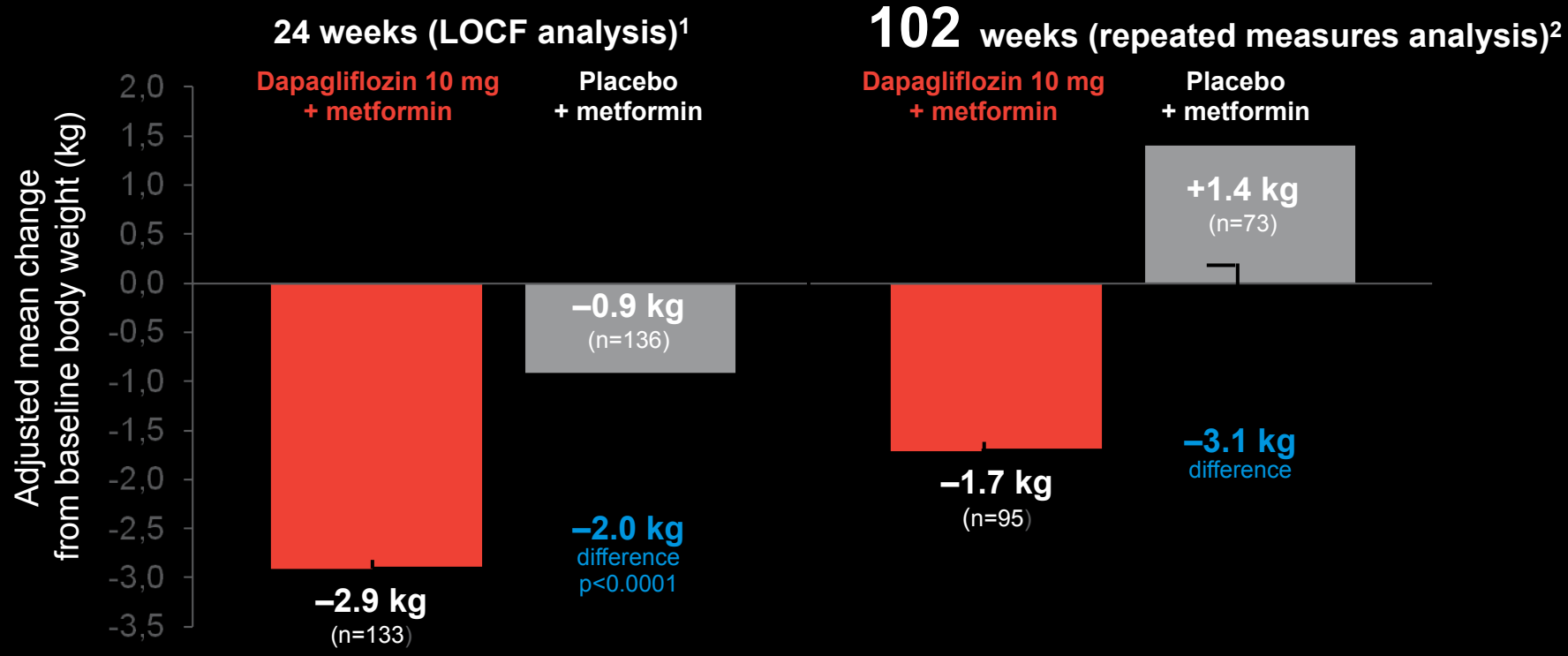
Add-on to Metformin:
Mean Change from Baseline in Total Body Weight



24-week short-term double-blind treatment period
Excluding data after rescue
Randomized subjects; baseline weight: 85-87 kg

*p<0.05 *vs.* placebo

Dapagliflozin also had the additional benefit of weight loss over time

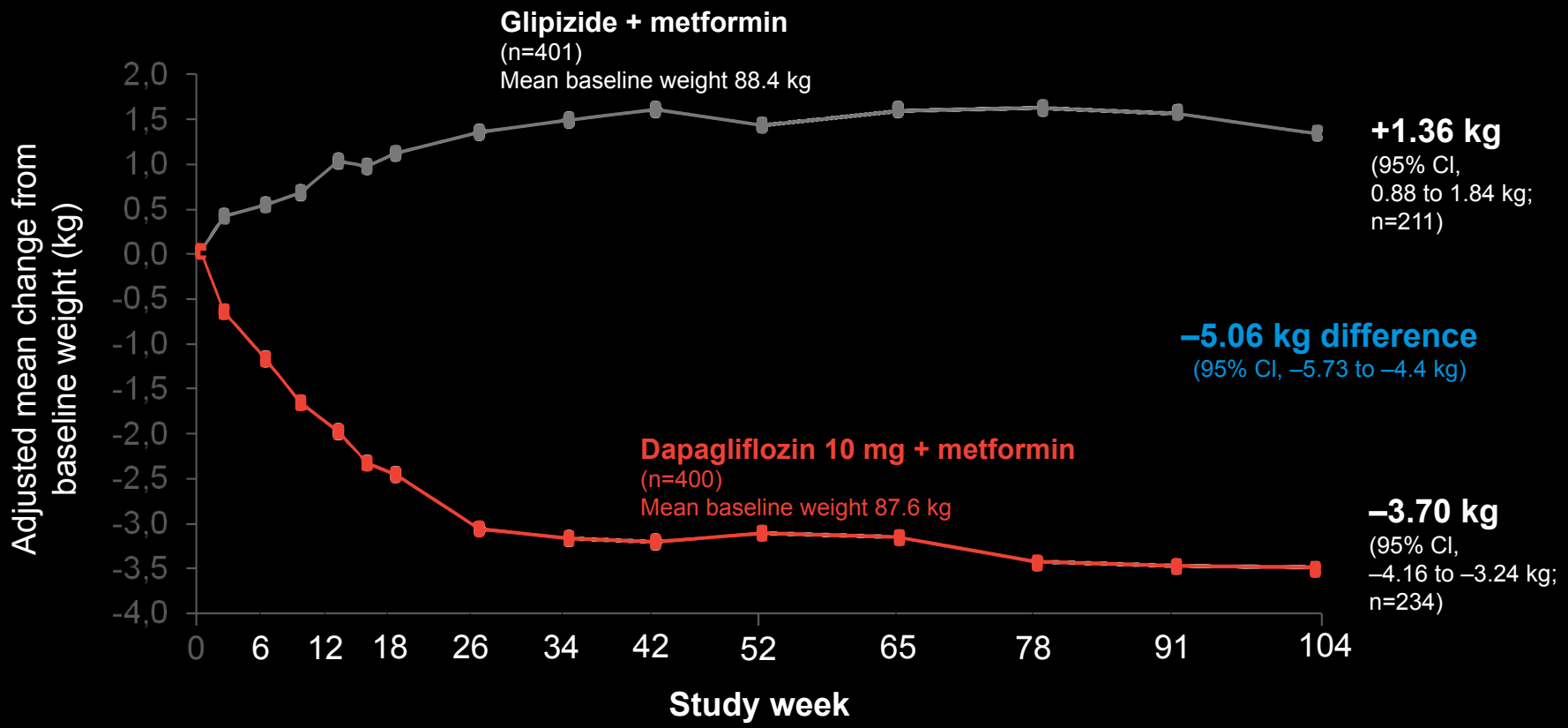


- In a separate dedicated weight loss study, weight loss in patients treated with dapagliflozin came from fat mass reduction[3]

Data are mean change from baseline after adjustment for baseline value (mean baseline weight: Dapagliflozin 86.3 kg, placebo 87.7 kg).
24-week data are based on LOCF analysis excluding data after rescue; 102-week data are based on longitudinal repeated measures analysis and include data after rescue.

1. Bailey CJ, *et al*. *Lancet* 2010;**375**:2223–33; 2. Bailey CJ, *et al*. Poster 988-P. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, June 24–28, 2011; 3. Bolinder J, *et al*. *J Clin Endocrinol Metab* 2012;**97**:1020–31.

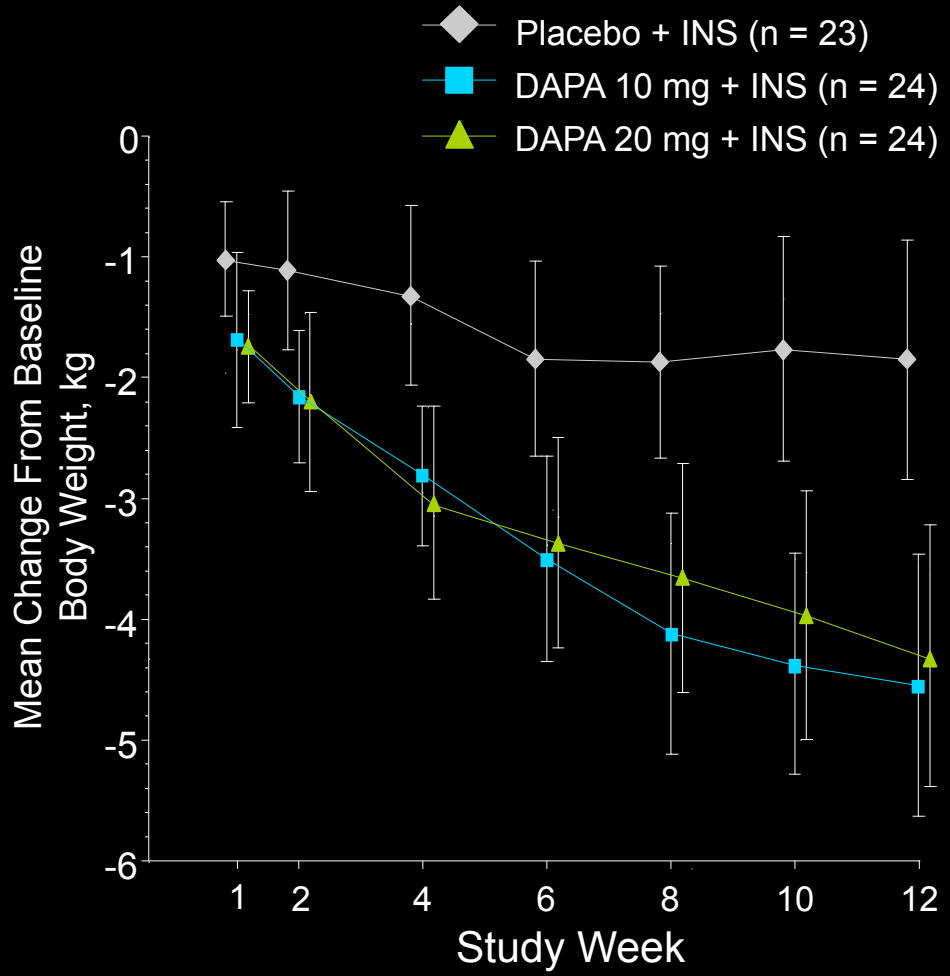
Dapagliflozin: Additional benefit of weight loss sustained over time



Data are adjusted mean change from baseline and 95% CI derived from a repeated measures mixed model.

1. Nauck MA, *et al. Diabetes Care* 2011;**34**:2015–22; 2. Nauck M, *et al.* Poster 40-LB. Poster presented at 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June, 2011.

Add-on to Insulin: Body Weight



Data are means based on LOCF, excluding data after insulin up-titration. Error bars represent 95% CIs.

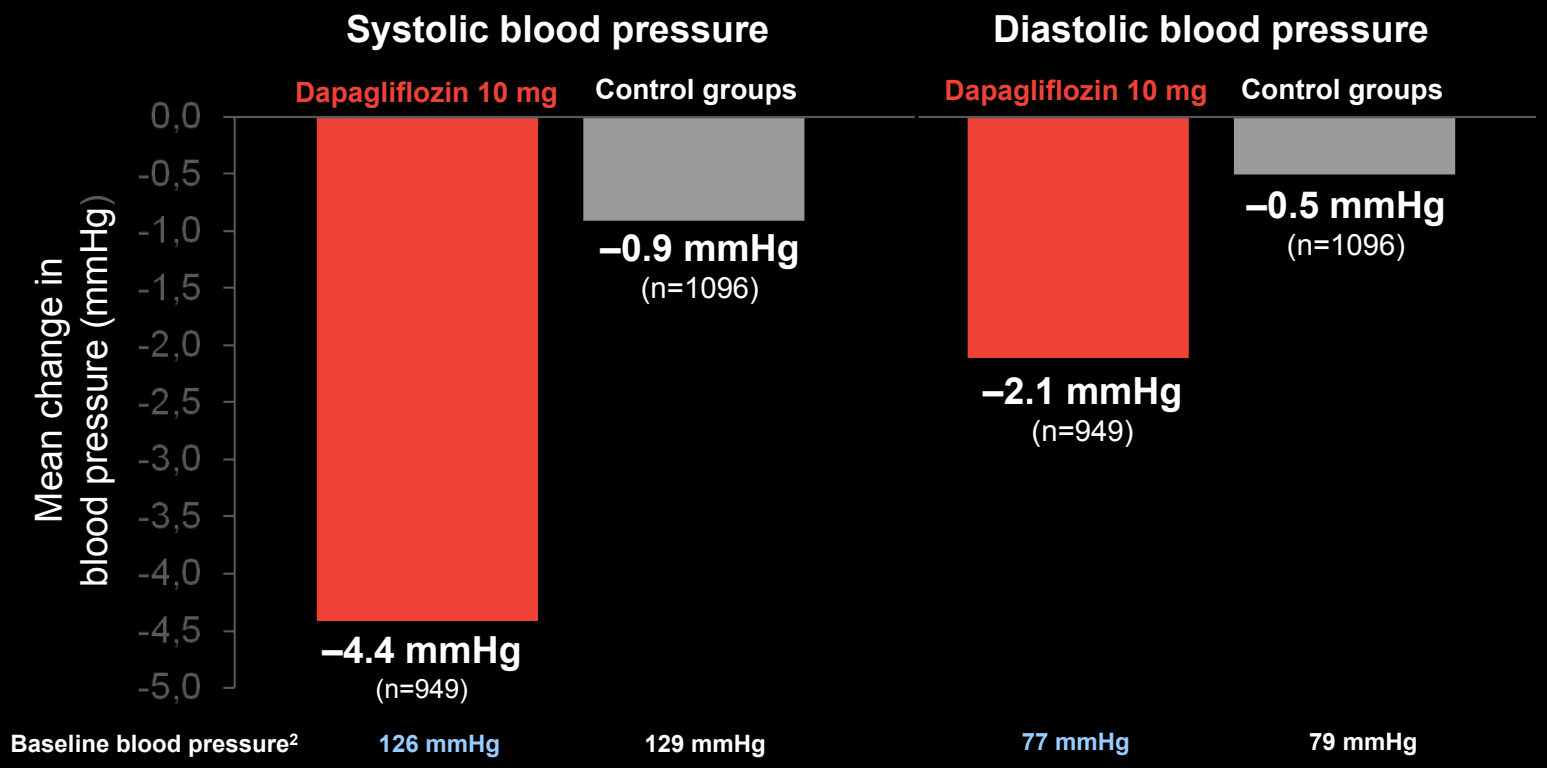
	Change From Baseline	Difference in Change vs Placebo + Insulin
Placebo + insulin (n=22)	-1.9 (-2.9 to -0.9)	
Dapagliflozin 10 mg + insulin (n=23)	-4.5 (-5.5 to -3.5)	-2.6 (-4.0 to -1.2)
Dapagliflozin 20 mg + insulin (n=23)	-4.3 (-5.3 to -3.3)	-2.4 (-3.8 to -1.0)

Values are kg. Data are means and 95% CI and represent the number of patients with a non-missing baseline and week 12 LOCF value.

Wilding JPH, et al. *Diabetes Care.* 2009;32:1656-1662.

Dapagliflozin: Reduction in blood pressure

In a prespecified pooled analysis of 12 placebo-controlled studies, dapagliflozin 10 mg reduced systolic and diastolic blood pressure versus placebo at Week 24[1]



Dapagliflozin is not indicated for the management of high blood pressure. Mean seated systolic and diastolic blood pressure were based on a placebo-controlled, pooled analysis from the 24-week, short-term, double-blind treatment period, including data after rescue. N is the number of subjects with non-missing baseline and Week 24 (LOCF) values in the randomised full analysis set. Change in blood pressure was primarily assessed as safety or exploratory efficacy endpoints in the Phase III clinical programme; therefore, the background antihypertensive medications were not controlled.

1. Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012; 2. BMS/AZ data on file.

Add-on to Metformin: Blood Pressure

- There were mean systolic and diastolic BP decreases in all study groups including placebo
- Decreases were dose-ordered in the dapagliflozin groups

Mean change from baseline at Week 24* in seated BP, mmHg	Placebo + Met (n=119)	Dapa 2.5 mg + Met (n=119)	Dapa 5 mg + Met (n=122)	Dapa 10 mg + Met (n=122)
Systolic BP (SE)	-0.2 (1.2)	-2.1 (1.1)	-4.3 (1.3)	-5.1 (1.3)
Diastolic BP (SE)	-0.1 (0.7)	-1.8 (0.9)	-2.5 (0.8)	-1.8 (0.8)

*Treated subjects with non-missing baseline and Week 24 values, including data after rescue.

- Hypertensive patients not at goal BP† achieving goal at Week 24:

Achieving goal at Week 24	Placebo + Met	Dapa 2.5 mg + Met	Dapa 5 mg + Met	Dapa 10 mg + Met
Number of patients	5 / 57	18 / 61	18 / 59	18 / 49
Percent	8.8%	29.5%	30.5%	37.5%
Difference vs placebo (95% CI)		20.7% (6.7, 34.8)	21.7% (7.3, 36.1)	28.7% (12.7, 44.3)

†BP goal <130 / 80 mmHg.

- No increase over placebo in orthostatic hypotension
  - No change in proportion of patients with orthostatic hypotension at baseline and Week 24 in dapagliflozin groups

Effetti avversi e sicurezza

Safety and tolerability data from a comprehensive clinical programme

dapagliflozin 10 mg

Rate of hypoglycaemia depends on background therapy being

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betwe
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backg
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a

| Freque
episode |
|---|
| Dapagl |
| Placeb |

*In a prespecifie
Dapagliflozin. S

Genital infections and urinary tract infections*

- Most genital infections† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of dapagliflozin
- Events of genita
infections) and U

Frequency at 24 weeks
Dapagliflozin 10 m
Placebo

- Pyelonephritis w
control

*In a prespecified pooled analysis of 12 plac
vaginal infection, balanitis, genital infec
infection, vulvitis, vaginitis bacterial, an
Dapagliflozin. Summary of product characte

Events of volume depletion similar to control at 24 weeks

Frequency of reactions related to volume depletion*	All events
Dapagliflozin 10 mg	0.8%
Control	0.4%

*Including dehydration, hypovolaemia, or hypotension.

- Serious events occurred in <0.2% of patients and were comparable between groups

SU, sulphonylu
Dapagliflozin. Summary of product characteristics. Bristol-Myers S

Rate of hypoglycaemia depends on background therapy being used

- Across all studies, events of hypoglycaemia were comparable between dapagliflozin or placebo*
- The frequency of hypoglycaemia depended on the type of background therapy used in each study
  - Studies of dapagliflozin as add-on to sulphonylurea and add-on to insulin therapies had higher rates of hypoglycaemia

Frequency of minor episodes of hypoglycaemia	All studies	Add-on to sulphonylurea	Add-on to insulin
Dapagliflozin	<4%	6.0%	40.3%
Placebo	<4%	2.1%	34.0%

*In a prespecified pooled analysis of 12 placebo-controlled studies.

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Events of volume depletion similar to control at 24 weeks

Frequency of reactions related to volume depletion*	All events
Dapagliflozin 10 mg	0.8%
Control	0.4%

*Including dehydration, hypovolaemia, or hypotension.

- Serious events occurred in <0.2% of patients and were comparable between groups

Dapagliflozin is not recommended for initiation of therapy in patients who are volume depleted.
Temporary interruption of dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Genital infections and urinary tract infections*

- Most genital infections† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of dapagliflozin

- Events of genital infection (vulvovaginitis, balanitis and related genital infections) and UTIs with dapagliflozin 10 mg versus placebo:

Frequency at 24 weeks	Genital infections		UTIs
	Overall	Female patients	
Dapagliflozin 10 mg	4.8%	9.7%	4.3%
Placebo	0.9%	3.4%	3.7%

- Pyelonephritis was uncommon and occurred at a similar frequency to control

*In a prespecified pooled analysis of 12 placebo-controlled studies; †Genital infection includes the preferred terms, listed in order of frequency reported: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Cardiovascular safety

Dapagliflozin is not associated with an increase in cardiovascular risk in patients with Type 2 diabetes*

	Frequency of primary episodes†	Hazard ratio (95% CI)
Dapagliflozin	1.64% per patient year	0.82 (0.58 to 1.15)
Control	1.99% per patient year	

*In a meta-analysis of cardiovascular events in 19 double-blind clinical studies of dapagliflozin 2.5–10 mg adjudicated by an independent committee.

†Cardiovascular death, stroke, myocardial infarction or hospitalisation for unstable angina.

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Malignancies

- During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data
- Imbalances were observed for breast and bladder cancers
  - Newly diagnosed cases of bladder cancer were reported in 0.16% of subjects treated with dapagliflozin and 0.03% of subjects treated with placebo / comparator
    - After excluding subjects in whom exposure to study medicinal product was less than 1 year at the time of diagnosis of bladder cancer, there were four (0.07%) cases with dapagliflozin and no cases with placebo/comparator
  - Breast cancer in female subjects was reported in 0.40% of females treated with dapagliflozin and 0.22% of females treated with placebo/comparator, all were diagnosed within 1 year
- Causality has not been established

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Considerations for dapagliflozin dosage and administration

- The efficacy of dapagliflozin **is dependent on renal function**
- Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (CrCl <60 mL/min or eGFR <60 mL/min/1.73 m^2)

- The monitoring of renal function is recommended as follows:
  - Prior to initiation of dapagliflozin and at least yearly, thereafter
  - Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter
  - For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl <60 mL/min or eGFR <60 mL/min/1.73 m^2, dapagliflozin treatment should be discontinued

*eGFR calculated with Modification of Diet in Renal Disease Formula.

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Altri SGLT-2 inhibitors a ruota

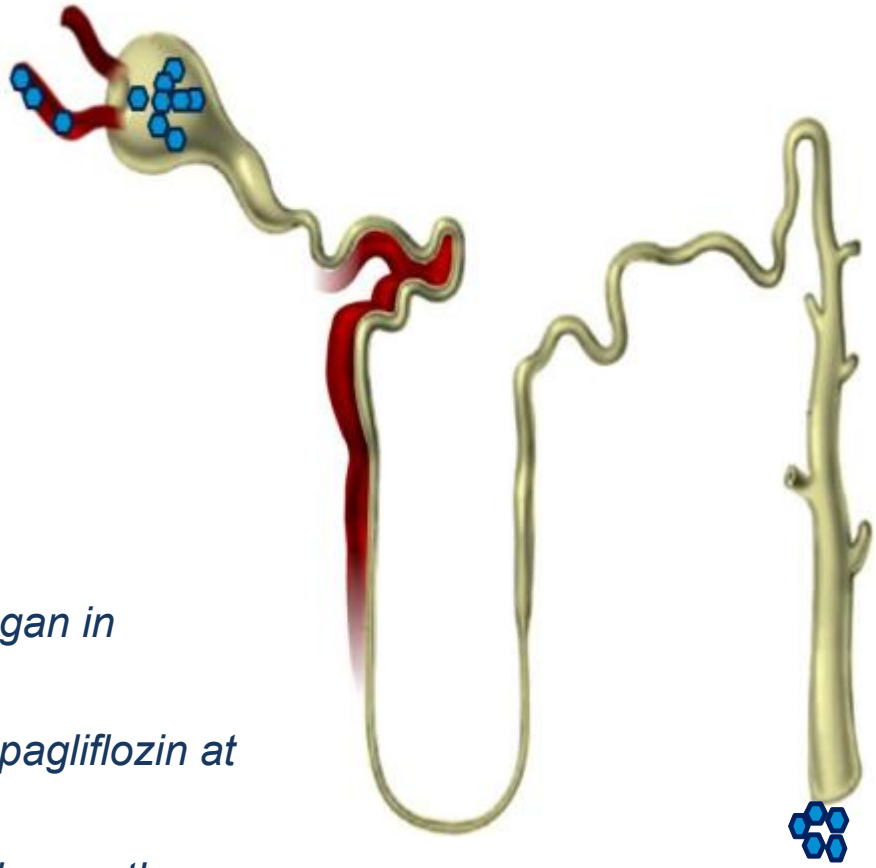
CANAGLIFOZIN
ENPAGLIFOZIN

IPRAGLIFOZIN
LUSEOGLIFOZIN
REMOGLIFOZIN
SERGLIFOZIN
TOFOGLIFOZIN

Empagliflozin overview[1,2,3]

Empagliflozin is a potent (IC_{50} = 3.1 nM) and selective (>2,500-fold over SGLT-1) SGLT-2 inhibitor

- *Phase I and II clinical trial results show:*
  - *Increase in urinary glucose excretion (UGE)*
  - *FPG reductions*
  - *HbA1c reductions*
  - *body weight reductions*

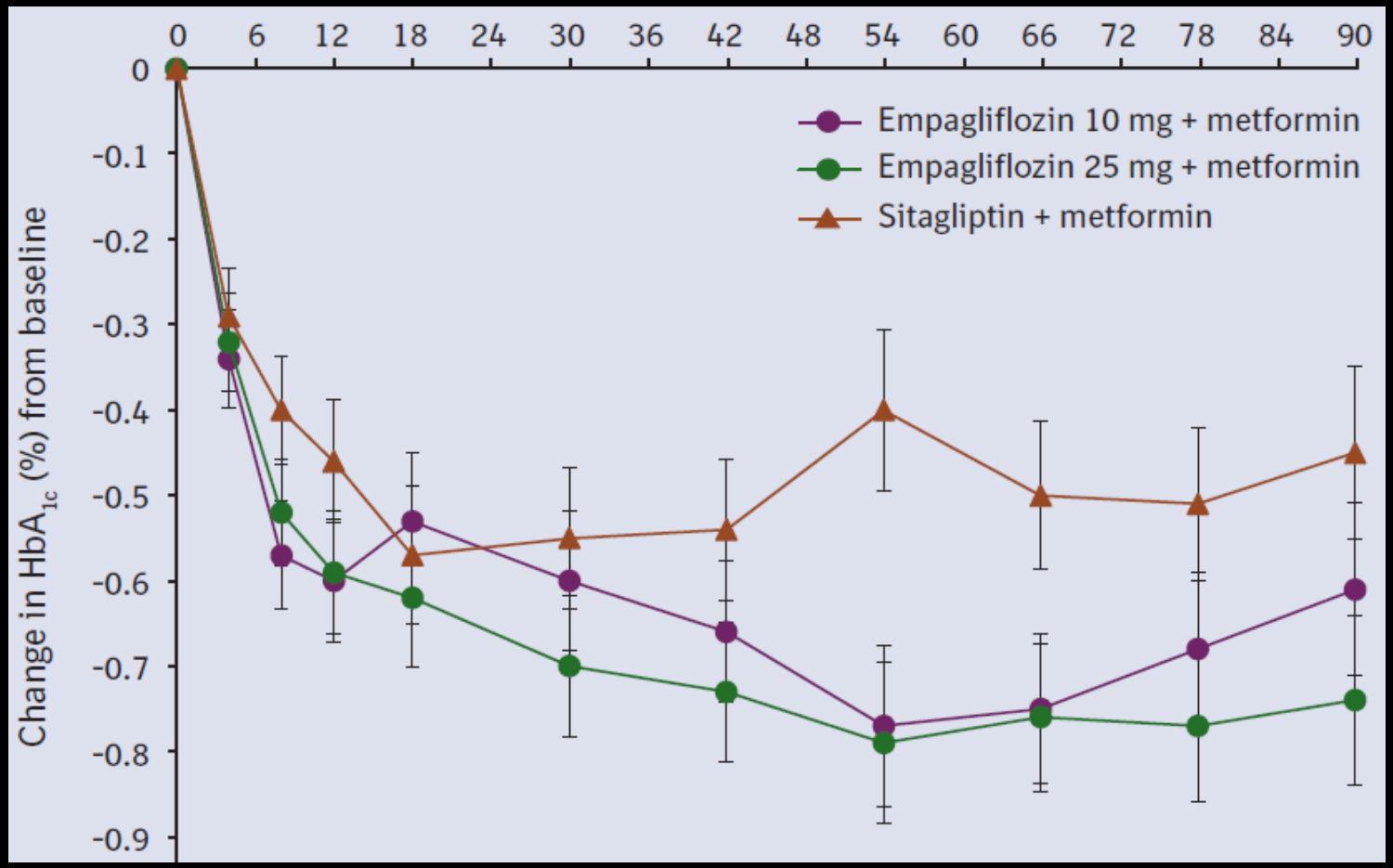


- *Phase III clinical testing of empagliflozin began in mid-2010:*
  - *Phase III clinical program evaluates empagliflozin at 10 mg and 25 mg doses*
  - *In total, the Phase III program will enroll more than 14,500 patients, including a large CV outcome trial*

BI-10773, a sodium-glucose cotransporter 2 inhibitor for the potential oral treatment of type 2 diabetes mellitus

Empagliflozin 78 week extension

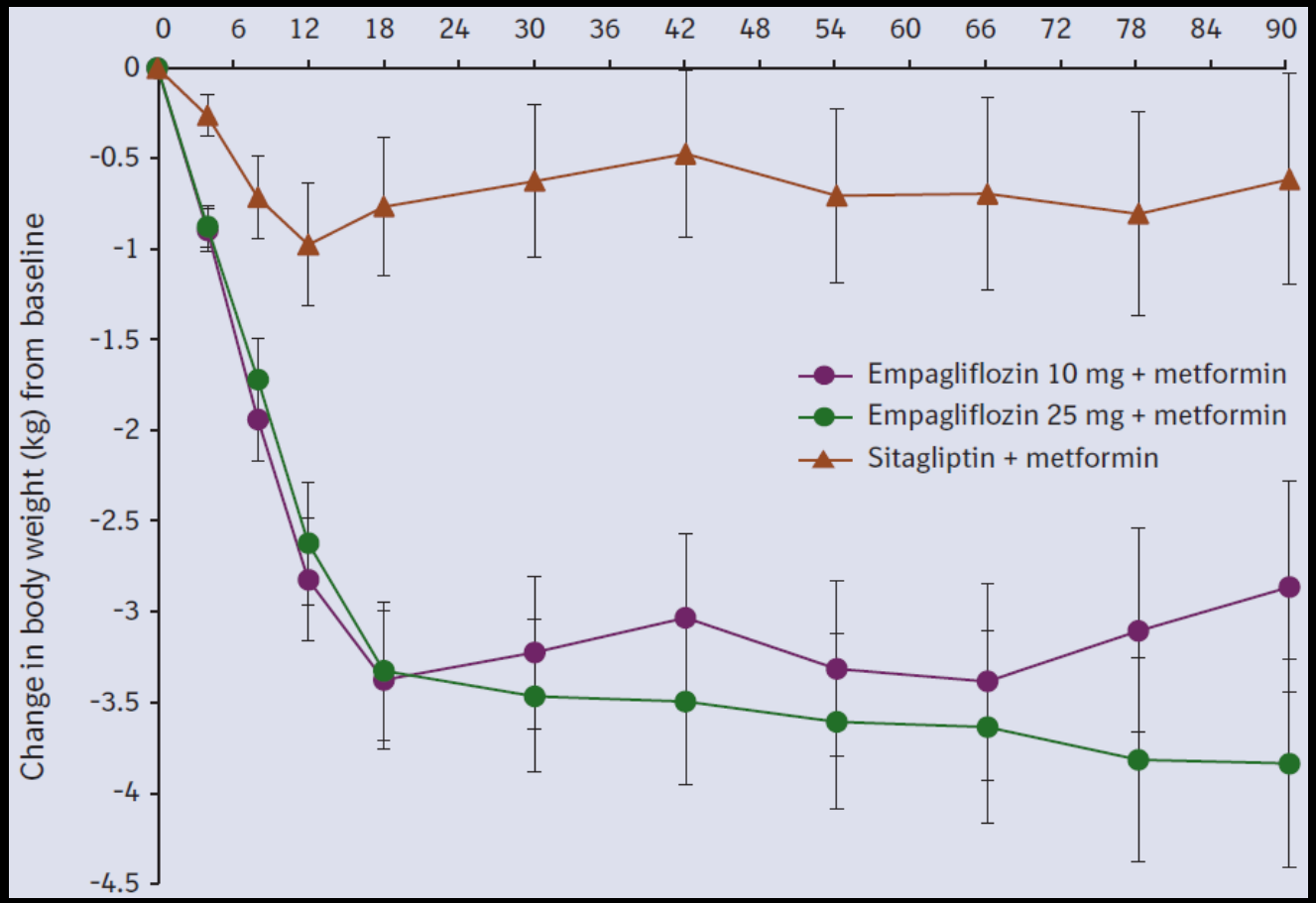
Efficacy - HbA1c reduction in add on to MET vs. SITA+MET



Hans J. Woerle et al., ADA 2012; Diabetes, June 2012; 61 (Suppl 1A): LB13 [49-LB]

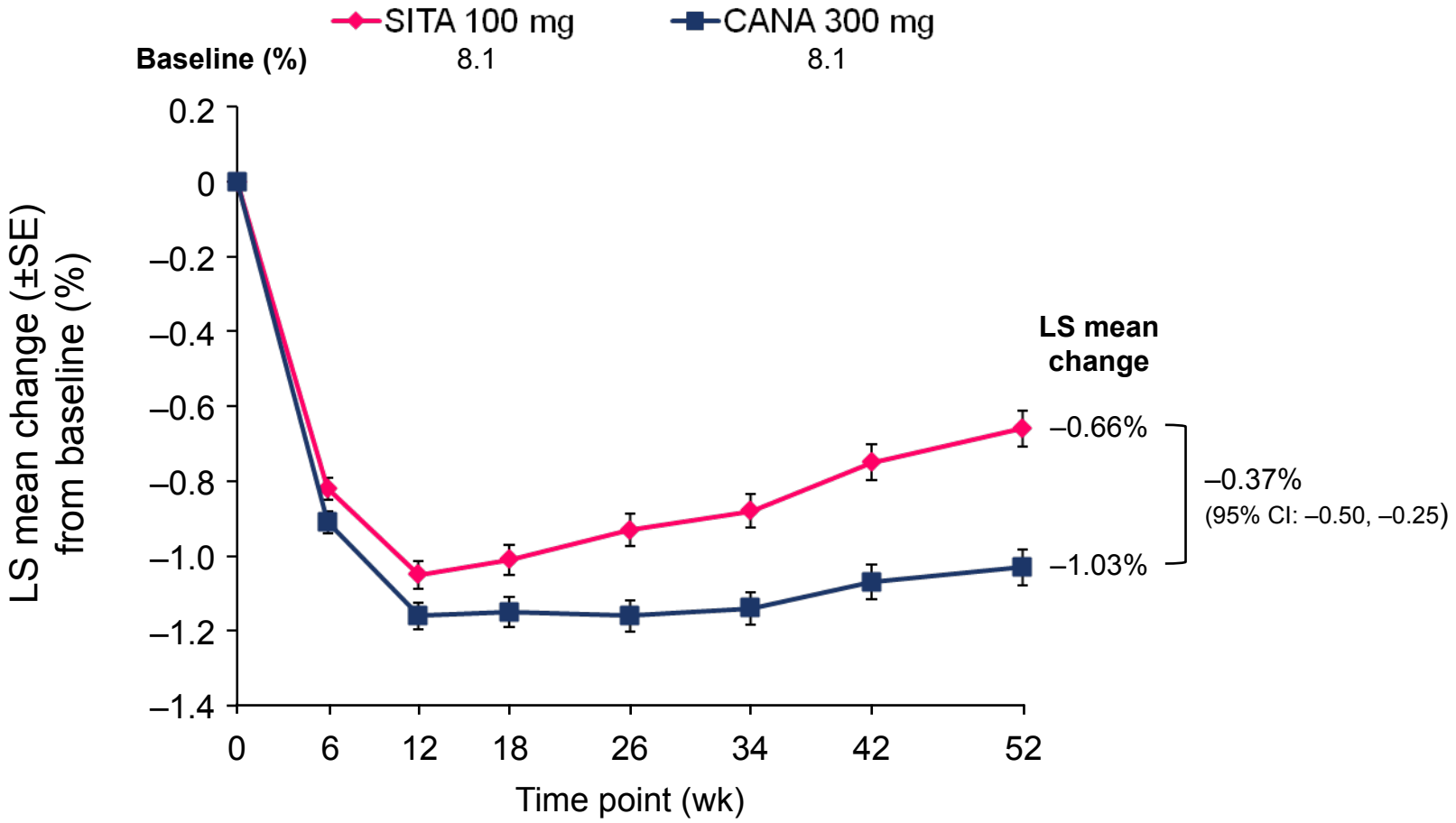
Empagliflozin 78 week extension

Efficacy – weight reduction in ad on to MET vs. SITA + MET



Hans J. Woerle et al., ADA 2012; Diabetes, June 2012; 61 (Suppl 1A): LB13 [49-LB]

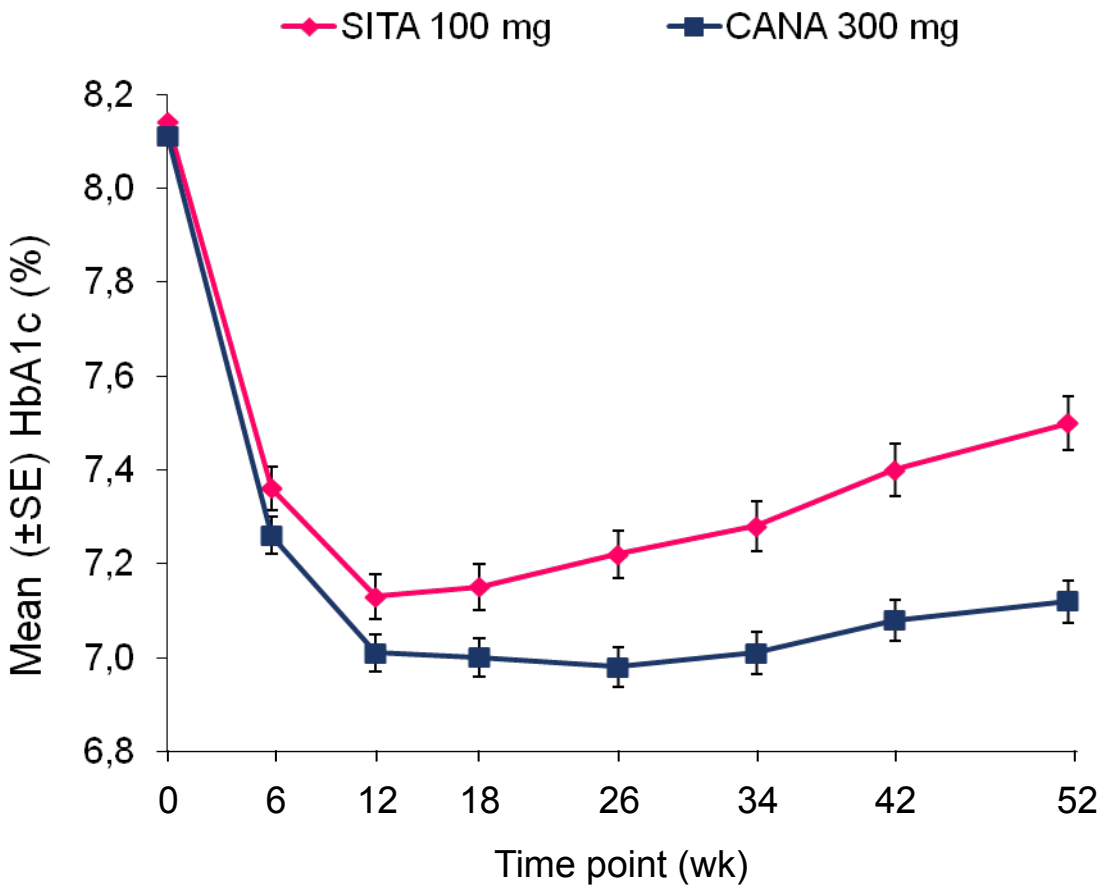
Canaglifozin change in HbA1c (LOCF)



LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Gross J, et al. Poster presented at 72nd ADA, 2012 (50-LB).

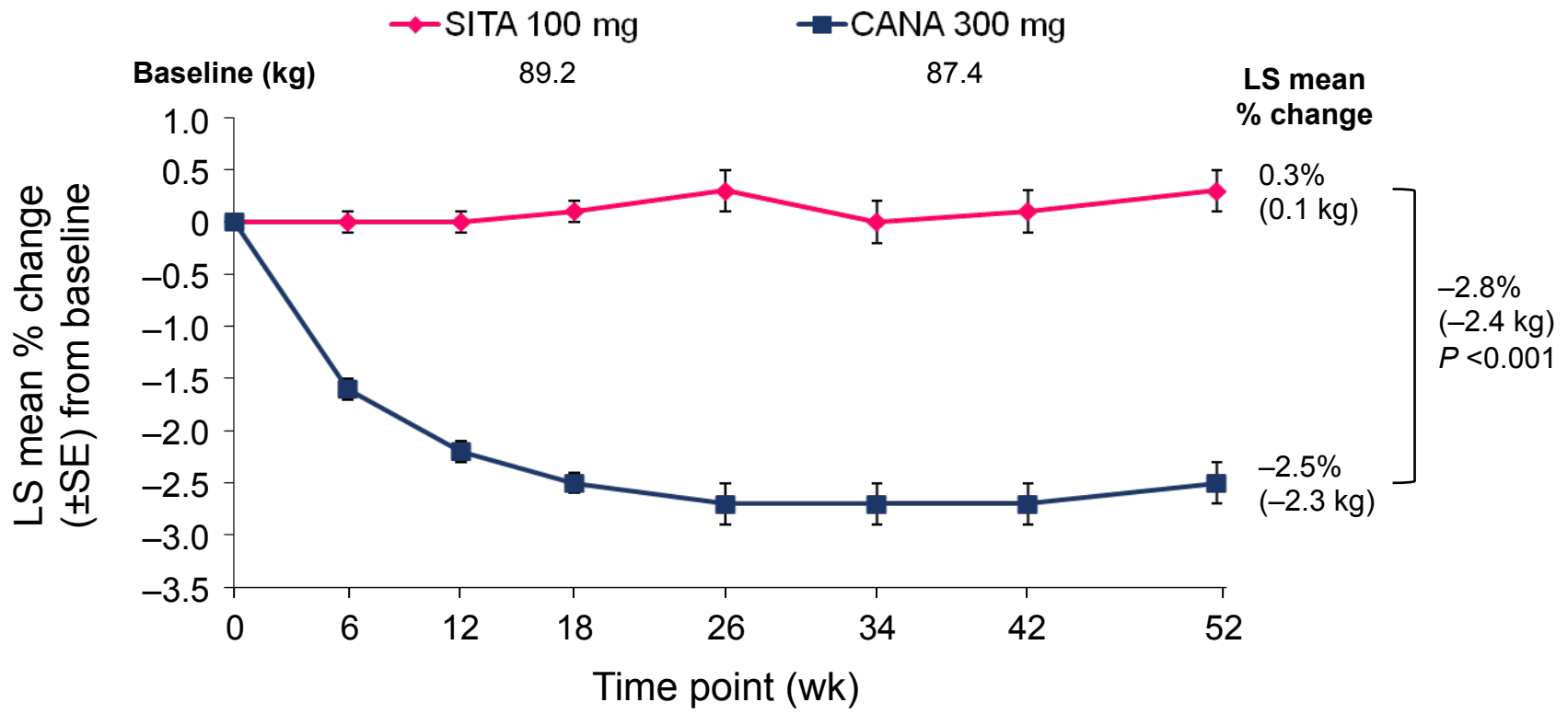
Canaglifozin Mean HbA1c (LOCF)



LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; SE, standard error.

Gross J, et al. Poster presented at 72nd ADA, 2012 (50-LB).

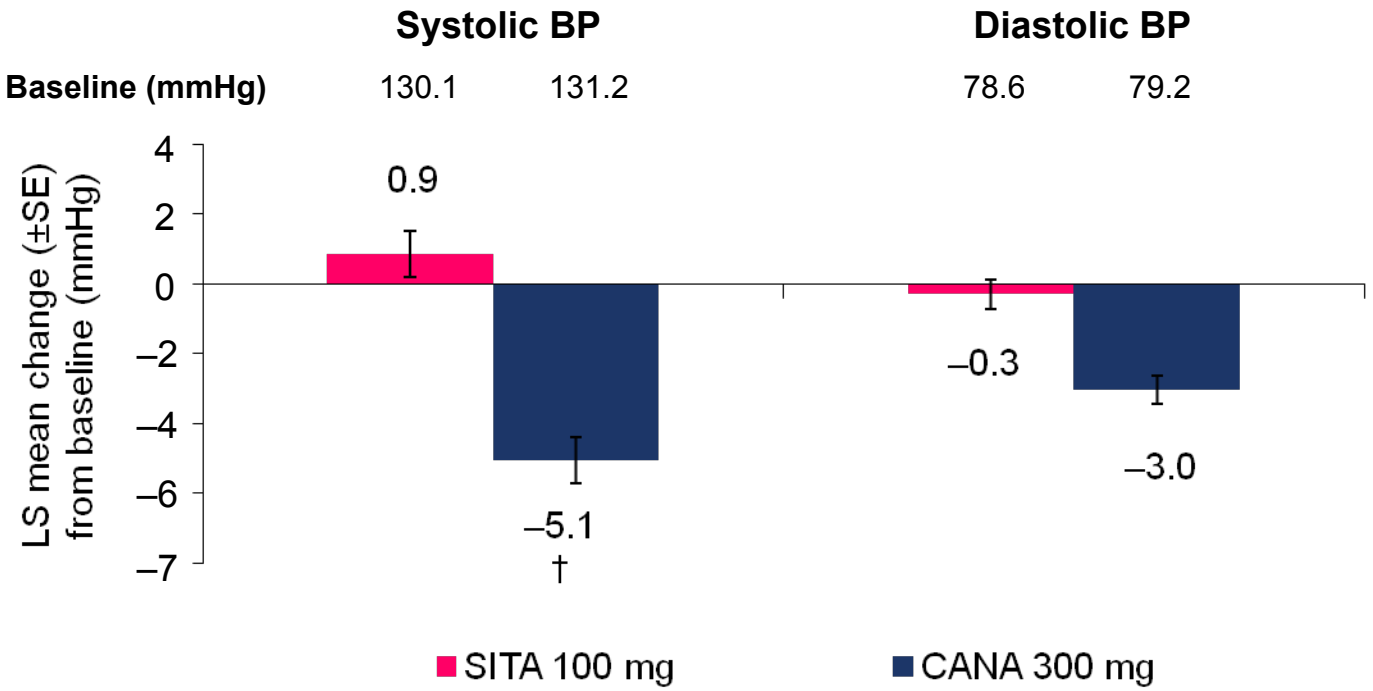
Percent Change in Body Weight (LOCF)



LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error.

Gross J, et al. Poster presented at 72nd ADA, 2012 (50-LB).

Canaglifozin change in BP at Week 52 (LOCF)*



BP, blood pressure; LOCF, last observation carried forward; LS, least squares; SE, standard error; SITA, sitagliptin; CANA, canagliflozin.
*Statistical comparison vs Sitagliptin 100 mg not performed (not pre-specified) for diastolic BP.
†*P* <0.001 vs Sitagliptin 100 mg.

- No change in heart rate was associated with the decrease in BP with Canagliflozin (mean change of –0.1 and 0.7 beats/min for Canagliflozin and Sitagliptin, respectively)

Gross J, et al. Poster presented at 72nd ADA, 2012 (50-LB).

Conclusioni

Stato dell'arte 2012

La "nuova" terapia diabete richiede precocità, intensità ed efficacia del trattamento per mirare a livelli bassi di HbA1c.

Una nuova (nona) classe di farmaci compare sulla scena : gli inibitori del SGLT-2

Classe efficace, non provoca aumento di peso, migliora il controllo pressorio.

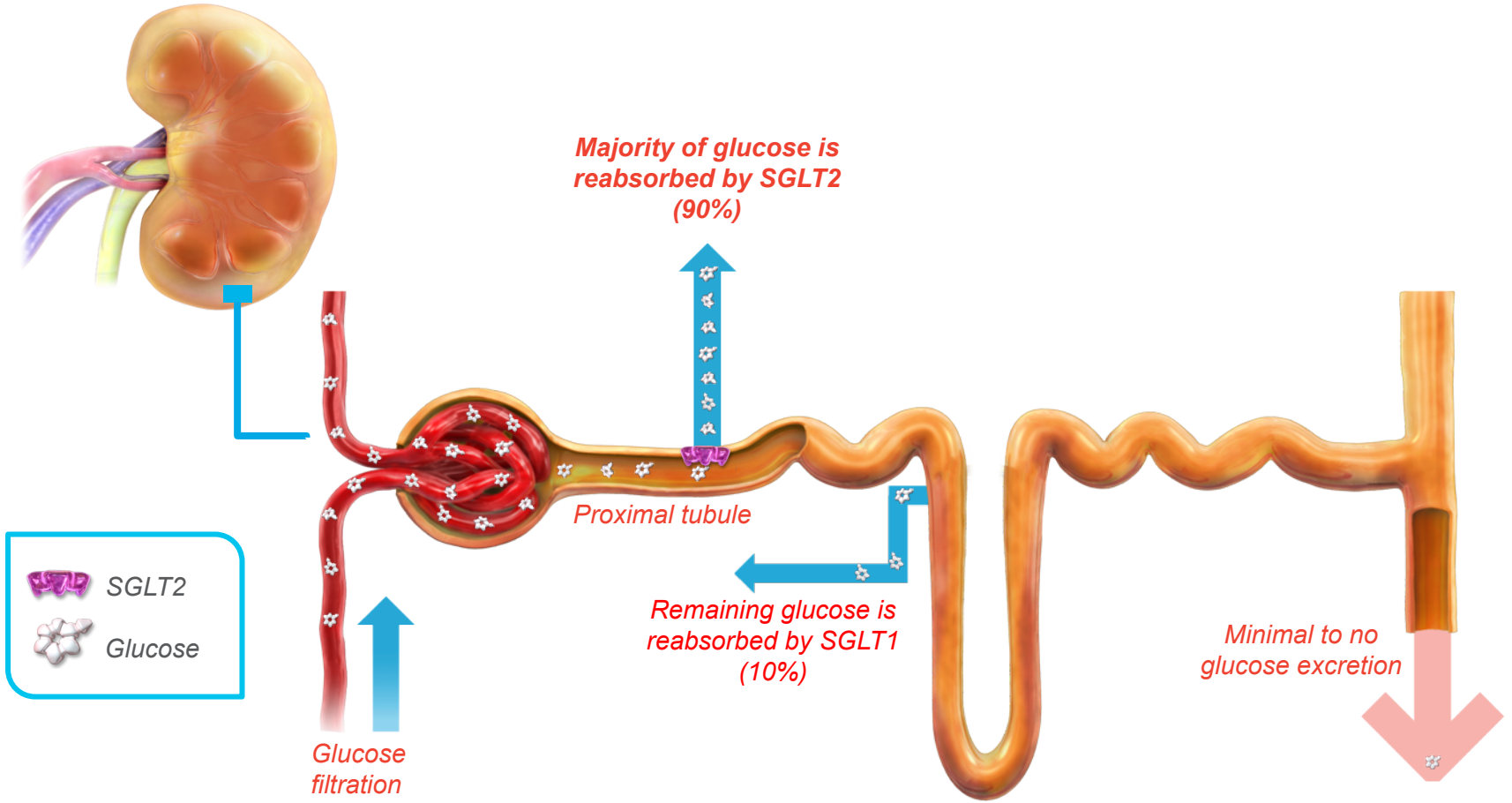
Grazie per l'attenzione

Considerations for dapagliflozin dosage and administration (2)

- Dapagliflozin is not recommended in:
  - Patients aged ≥75 years or <18 years
  - Patients treated concomitantly with pioglitazone
  - Patients receiving loop diuretics
- Dapagliflozin is also not recommended for initiation of therapy in patients who are volume depleted
  - Temporary interruption of dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected
- Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk
- A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin

Dapagliflozin. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2012.

Normal renal glucose handling[1–3]



SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35; 3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

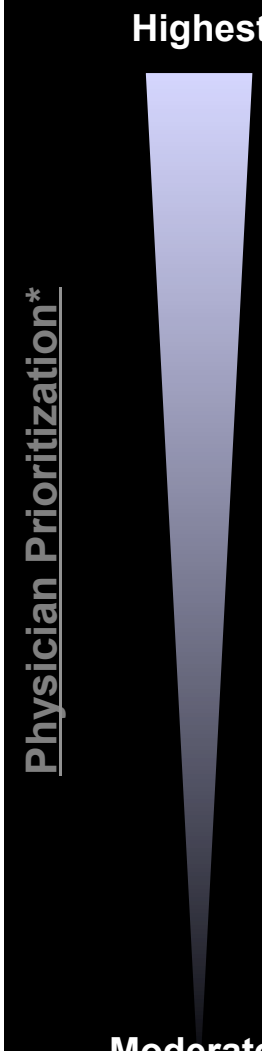
Dapagliflozin: Overall Summary

Dapagliflozin has the potential to help control hyperglycaemia in diabetes

CURRENT DATA SHOW:

- Mean HbA_{1c} reduction from baseline of ~ 0.7%
- Rapid reduction in FPG
- Weight reduction of 2-4% (via loss of calories in the urine)
- Small BP reduction (possibly via diuretic effect)
- Complementary to metformin and insulin
- Low risk of hypoglycemia
- Generally safe and well tolerated

Target profile for a new diabetes drug



- Good HbA_{1c} effect
- Efficacy at any stage of the disease
- Can be combined with other oral anti-diabetic agent
- Acceptable safety/tolerability profile
- Low risk of hypoglycemia
- Broad utility / No contraindication in special populations
- No weight gain
- Oral, once a day dosing, regardless of meals or time of day
- Beneficial effects on microvascular and macrovascular outcomes
- No adverse effect on co-morbid conditions (e.g. HTN)
- No adverse effect on lipid profile
- Fast onset of action and therapeutic effect