Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Dapagliflozin
BMS-512148

July 19, 2011

Bristol-Myers Squibb

AstraZeneca

Dapagliflozin

Introduction

Amy Jennings, PhD

Bristol-Myers Squibb

Dapagliflozin – Proposed Indication

Indication

- Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Treatment Settings

- Monotherapy
- Add-on combination to MET, SU, PIO, insulin
- Initial combination with MET

MET = metformin; SU = sulfonylurea; PIO = pioglitazone

Dapagliflozin – Presentation Outline

Introduction	Amy Jennings, PhD BMS, Director, Global Regulatory Sciences - US
Medical Need for New Anti-Diabetic Treatments	John Buse, MD, PhD Professor of Medicine, Division of Endocrinology and Metabolism, University of North Carolina at Chapel Hill
Overview of Mode of Action / Introduction to Development Program	Elisabeth Svanberg, MD, PhD BMS, Vice President, Development Lead, Dapagliflozin
Clinical Efficacy	Shamik Parikh, MD AZ, Executive Director, Cardiovascular / Metabolics
Safety	James List, MD, PhD BMS, Executive Director, Cardiovascular / Metabolics
Overall Benefit-Risk	James Gavin, MD, PhD CEO and Chief Medical Officer, Healing Our Village, Inc.
Proposed Dapagliflozin Label and Post-Approval Benefit/Risk Assessment	Brian Daniels, MD BMS, Senior Vice President, Global Development & Medical Affairs

Consultants Available to the Committee

Philippe L'Allier, MD
Clinical Event Committee (CEC) Chair,
Montreal Heart Institute Coordinating Center

Dean Bajorin, MD
Medical Oncologist, specializing in Bladder Cancer
Memorial Sloan Kettering Cancer Center

Tomas Berl, MD
Professor of Medicine, Division of Renal Diseases and Hypertension, University of Colorado, Denver

John Buse, MD, PhD
Professor of Medicine
Chief, Division of Endocrinology
Director, Diabetes Care Center
Executive Associate Dean for Clinical Research
University of North Carolina School of Medicine

Maura Dickler, MD
Associate Attending Physician
Breast Cancer Medicine Service
Memorial Sloan-Kettering Cancer Center

James Gavin, MD, PhD
CEO and Chief Medical Officer
Healing Our Village, Inc.

Robert Lindsay, MD
Professor of Clinical Medicine
Columbia University
New York, NY

Willis C. Maddrey, MD
University of Texas
Southwestern Medical Center at Dallas

Brian L. Strom, MD, MPH
George S. Pepper Professor of
Public Health & Preventive Medicine in
Biostatistics and Epidemiology
University of Pennsylvania School of Medicine

Lee-Jen Wei, PhD
Professor of Biostatistics
Harvard University

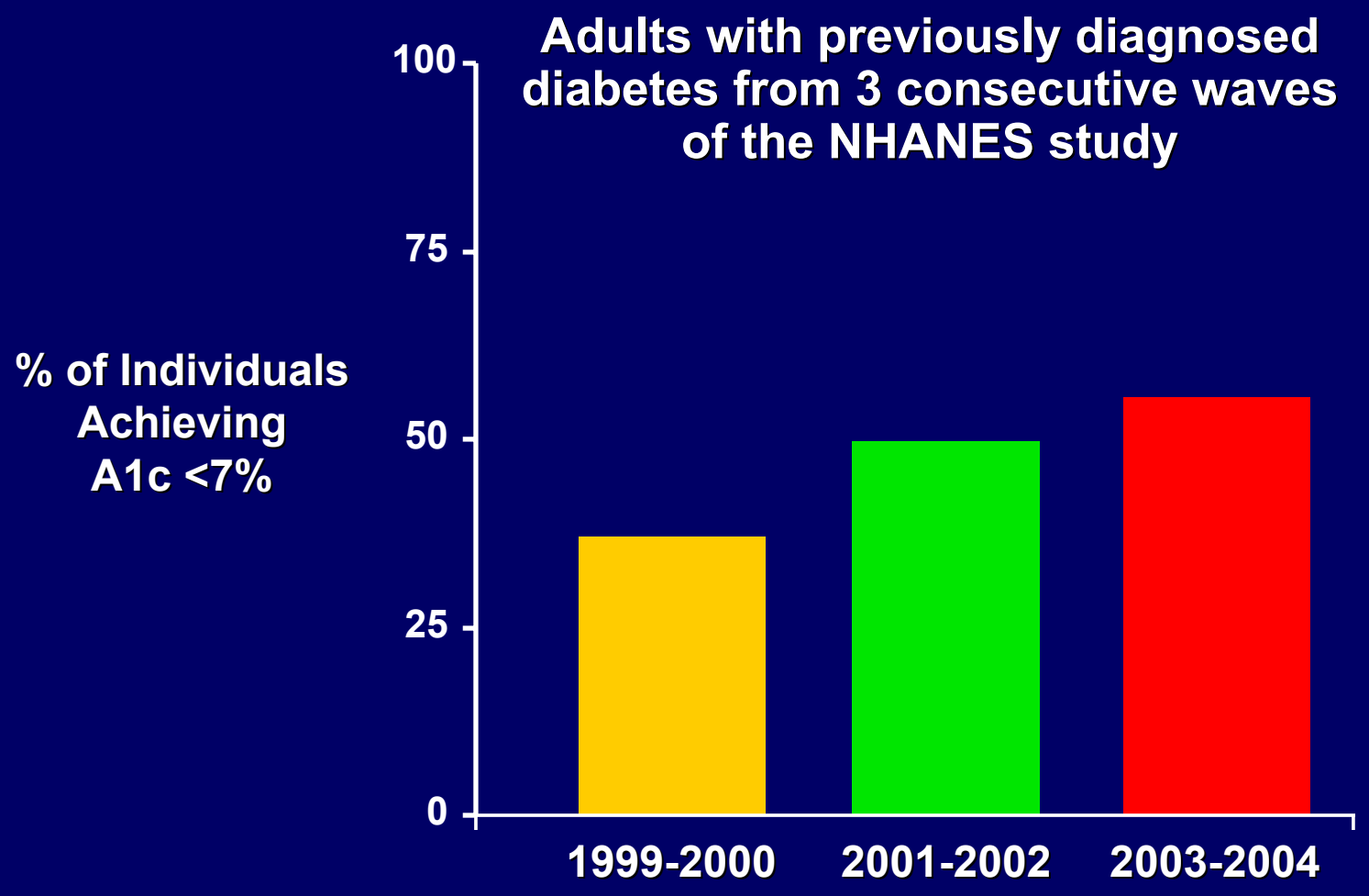
Dapagliflozin

Medical Need

John Buse, MD, PhD

University of North Carolina School of Medicine

Glycemic Control Has Improved



Hoerger TJ, et al. *Diabetes Care.* 2008;31:81-86.

Centers for Disease Control and Prevention: 2011 National Diabetes Fact Sheet

Epidemiology

- 25.8 million people, 8.3% of the U.S. population
- 1.9 million new cases in 2010

Expenses

- More than 2X higher than for people without diabetes, $174 billion in 2007

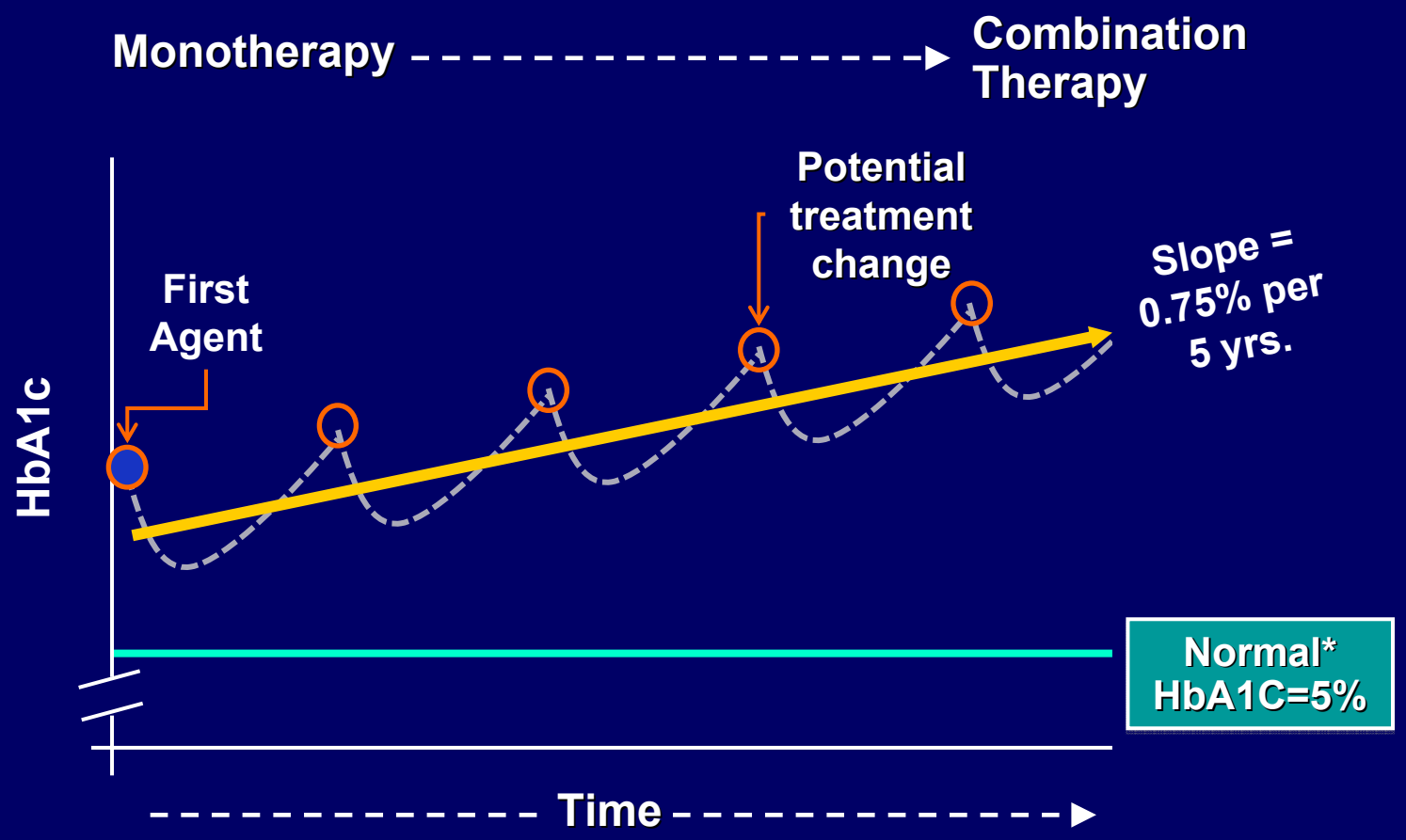
Clinical Consequences of Diabetes

- Risk for death about twice that of people of similar age
- In 2005–2008, > 4.2 million with diabetic retinopathy
  - 655,000 advanced cases that could lead to severe vision loss
- In 2008, 202,290 with end-stage kidney disease
  - 48,374 began treatment
- In 2006, about 65,700 nontraumatic lower-limb amputations performed

Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

The Progressive Nature of Type 2 Diabetes Ultimately Overwhelms Medications

Glycemic Control in an Illustrative Patient

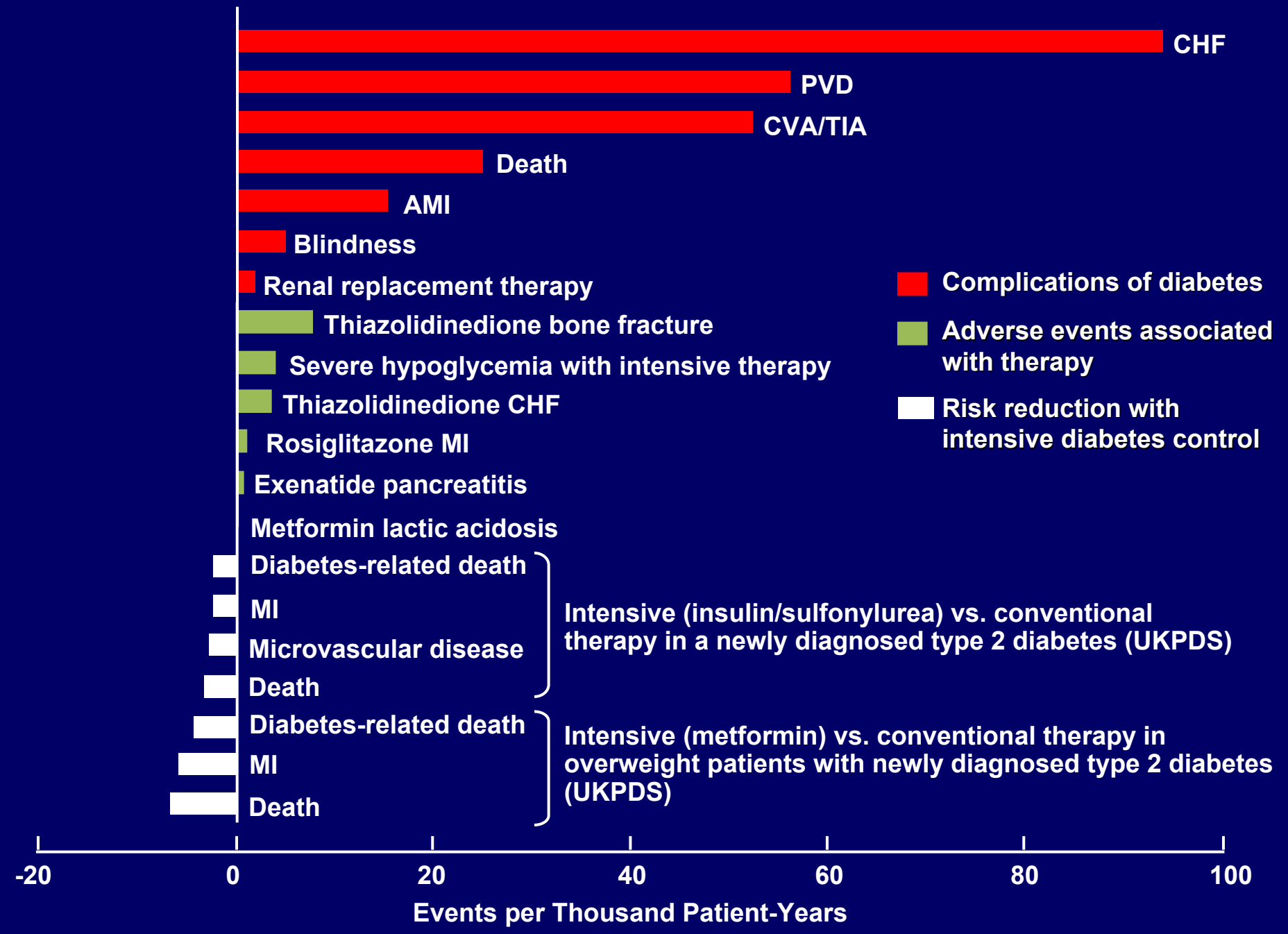


Sources: ADOPT, UKPDS
* according to the NIH

Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Severe Hypo-glycemia	Weight Change	Usual Dosing (times/day)	Injected or Oral	Other Safety Concerns
Metformin	1.5	No	Neutral	1-2	Oral	Lactic acidosis, B12 deficiency
NPH, Glargine, Detemir	1.5 - 2.5	Yes	Gain	1	Injected	
R, Lispro, Aspart, Glulisine	1.5 - 2.5	Yes	Gain	2-4	Injected	
Glipizide ER, Glimepiride	1.5	Yes	Gain	1	Oral	CVD
Pioglitazone	0.5 - 1.4	No	Gain	1	Oral	CHF, Fractures, Bladder Ca
Repaglinide	1 - 1.5	Yes	Gain	3	Oral	
Nateglinide	0.5 - 0.8	Rare	Gain	3	Oral	
Acarbose, Miglitol	0.5 - 0.8	No	Neutral	3	Oral	
Pramlintide	0.5 – 0.9	No	Loss	3	Injected	
Exenatide	0.5 - 1.0	No	Loss	2	Injected	Pancreatitis, acute renal failure
Sita-, saxa-, lina- gliptin	0.6 - 0.8	No	Neutral	1	Oral	Pancreatitis
Colesevelam	~0.5	No	Neutral	1-2	Oral	Hypertriglyceridemia
Bromocriptine QR	~0.6	No	Neutral	1	Oral	Various from bromocriptine
Liraglutide	~1.5	No	Loss	1	Injected	Pancreatitis, MTC

Adapted from: Nathan DM, et al. ADA. *Diabetes Care.* 2010;33:S11-S61.
WelChol PI. 1/2008. Cycloset PI. 10/2010. Victoza PI. 1/2010.



Bergenstal RM, Bailey CJ, Kendall DM. *Am J Med* 2010;123:374.e9-374.e18.

Dapagliflozin Addresses Unmet Needs

- Novel mechanism of action independent of insulin
- Good efficacy in lowering A1C
  - Equivalent to metformin or sulfonylurea
- No intrinsic increased risk of hypoglycemia
- Weight loss
- 10 mg, once daily, oral dosing, irrespective of meals
- Effective in a broad spectrum of patients
  - Independent of background therapy
  - Independent of duration of diabetes
- Safety on par with other approved agents

Dapagliflozin

Overview of Mode of Action / Introduction to Development Program

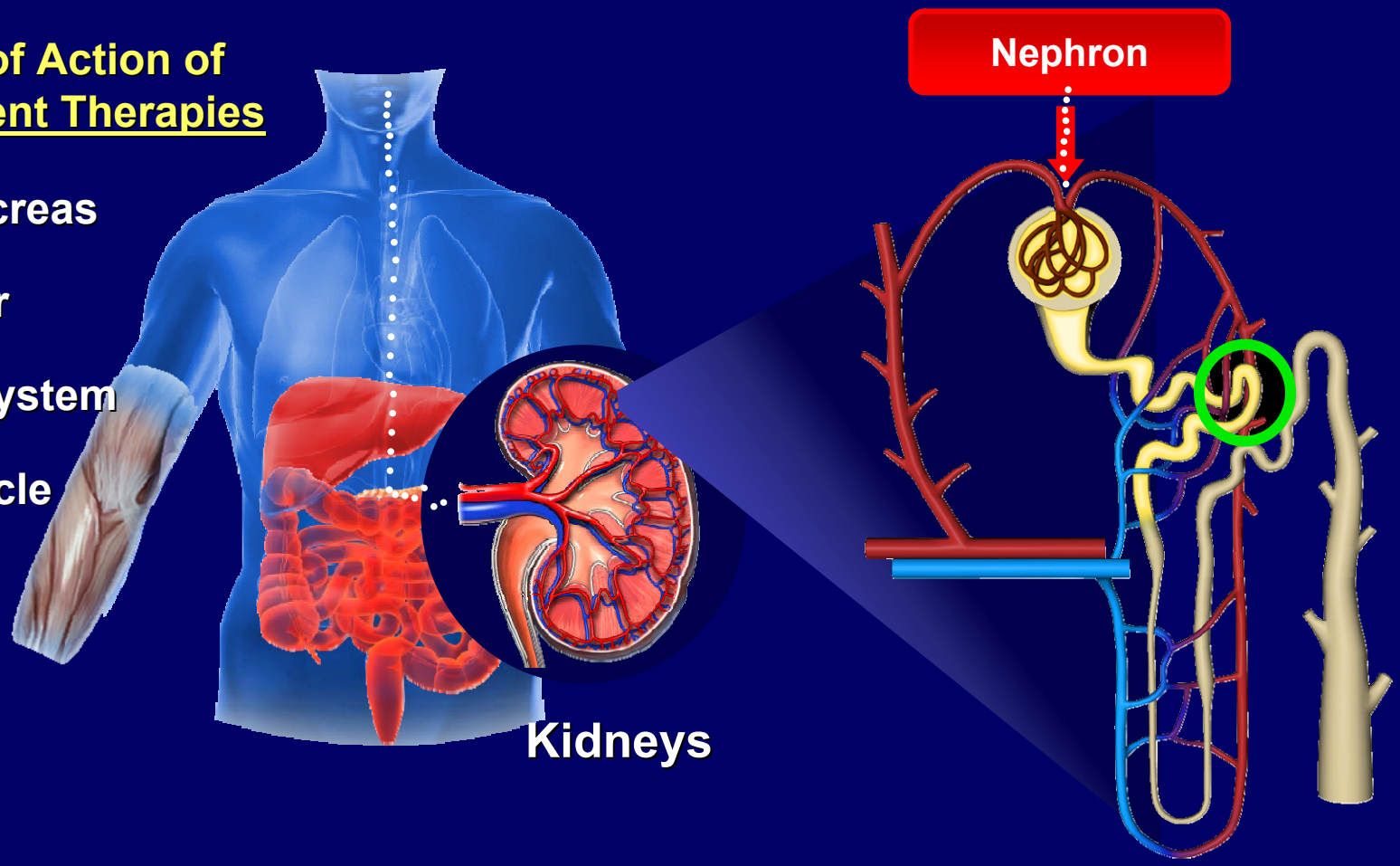
Elisabeth Svanberg, MD, PhD

Bristol-Myers Squibb

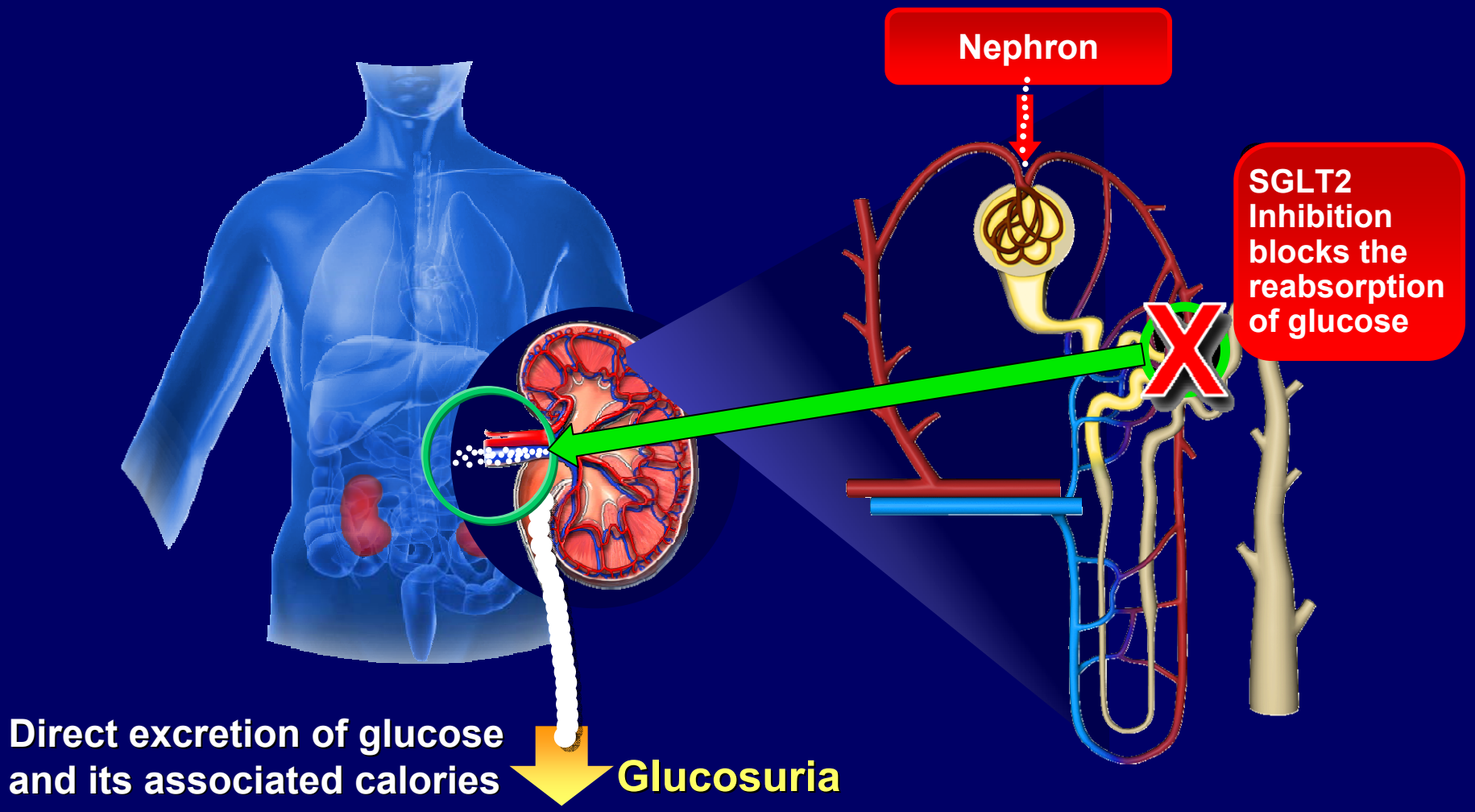
SGLT2 is the Major Transporter for Renal Glucose Reabsorption

Site of Action of Current Therapies

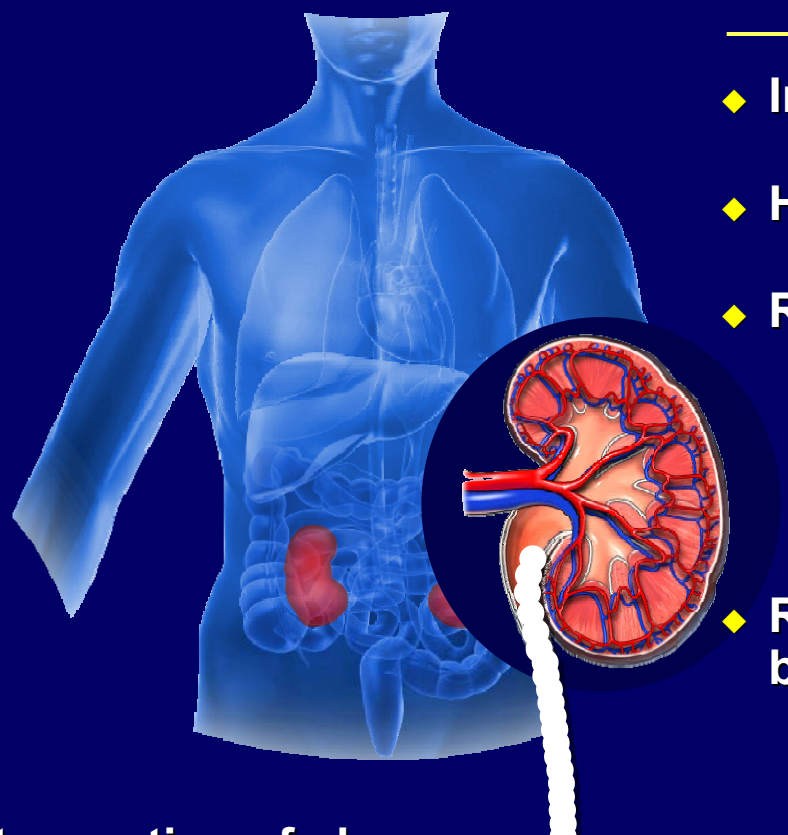
- Pancreas
- Liver
- GI System
- Muscle



SGLT2 Inhibition Lowers Blood Glucose Levels by Acting on the Kidney Where Glucose is Reabsorbed



Effects of SGLT2 Inhibition (Mode of Action)



Direct excretion of glucose and its associated calories

Glucosuria

Benefits

- Insulin-independent
- HbA1c lowering
- Reduction in
  - FPG
  - PPG
  - Weight
- Reduction in blood pressure

Risks

- Hypoglycemia
- Renal function
- Diuretic effect
  - Hypovolemia
  - Hypotension
  - Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis

SGLT2 Inhibition: Botanical and Genetic Precursors

- **Phlorizin: derived from apple bark, stimulated urinary glucose excretion[1]; non-selective inhibitor of SGLT**
- **Familial renal glucosuria (FRG): benign syndrome associated with mutations in SGLT2**
- **Dapagliflozin: Potent, competitive inhibitor of SGLT2, >1400 fold more selective for SGLT2 versus other glucose transporters**

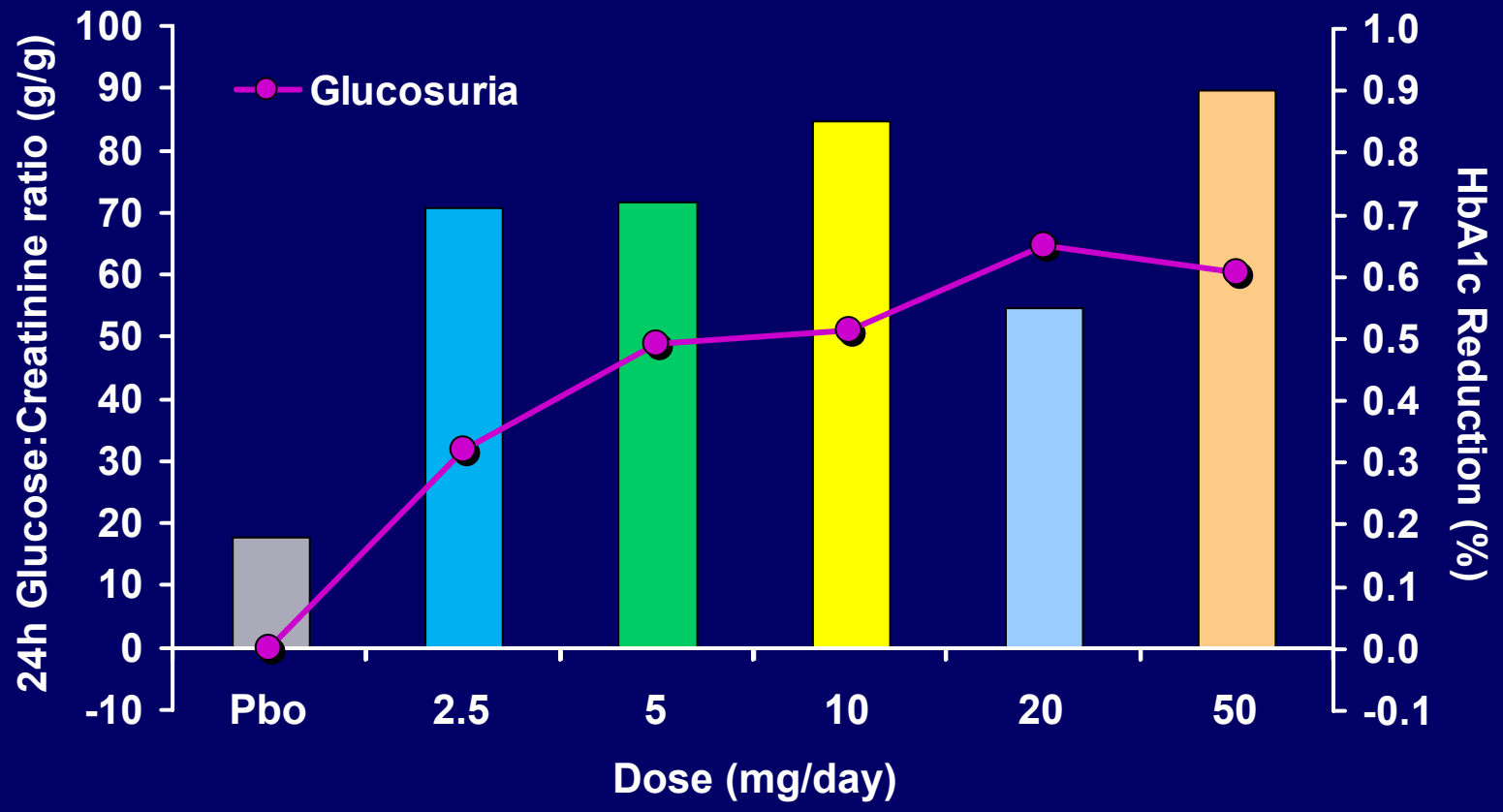
[1] von Mering, *J. Ueber kunstlichen Diabetes*. Centralbl Med Wiss 1886; xxii: 531.

Key Clinical Pharmacology Findings

- Dapagliflozin was generally safe and well-tolerated up to single doses of 500 mg and 100 mg once-daily for 2 weeks
- PK/PD was characterized over a wide range of doses (1 microgram to 500 mg)
  - The proposed dose of 10 mg is near the upper end of the dose response curve
- No signal for QTc prolongation or heart rate changes in a thorough QTc study
- Clinical pharmacology characteristics:
  - amenable to once-daily dosing
  - may be taken without regard to meals
  - no dose adjustment based on pharmacokinetics
  - no meaningful drug-drug interactions

Dose Selection for Phase 3

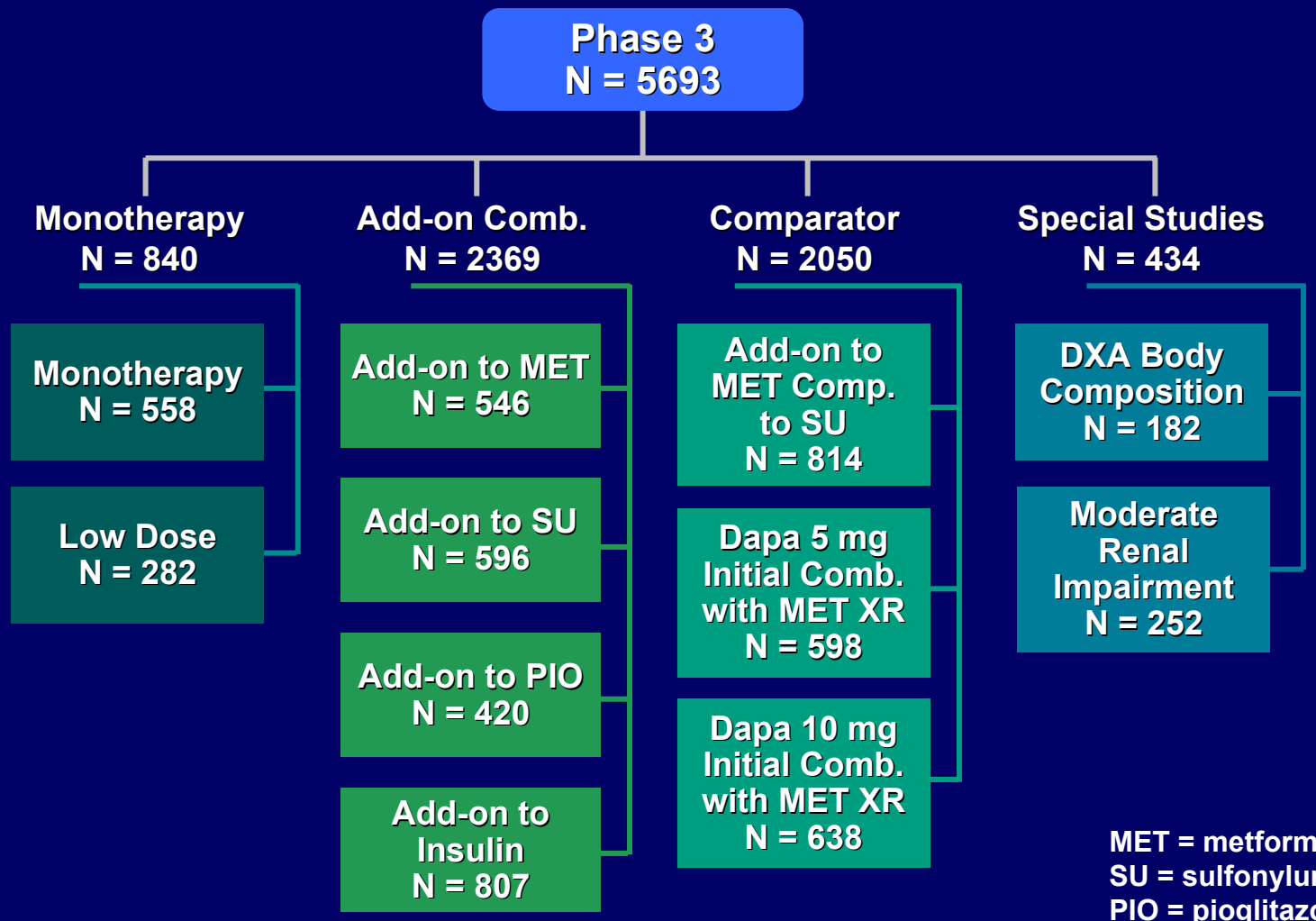
- Dose range of 2.5 to 50 mg once daily studied over 12 weeks in treatment-naïve patients with T2DM



Doses 2.5, 5 and 10 mg were progressed to phase 3

SCE Table 10

Dapagliflozin Phase 3 Clinical Development Program



MET = metformin
SU = sulfonylurea
PIO = pioglitazone
XR = extended release

SCE Table 5

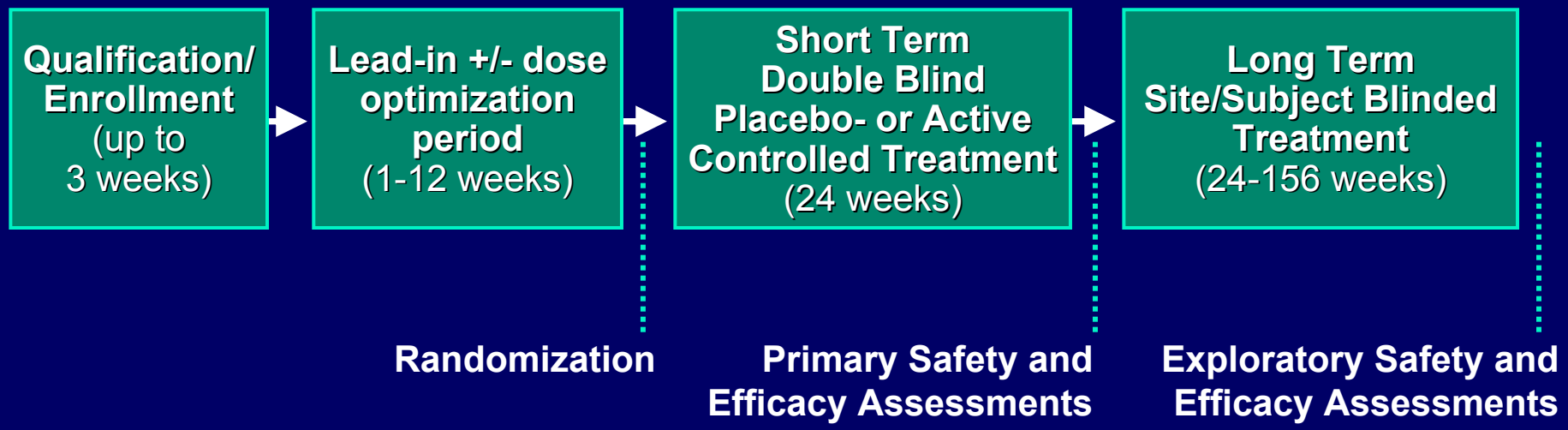
Dapagliflozin

Clinical Efficacy

Shamik Parikh, MD

AstraZeneca

Phase 3 Trial Design



Populations Studied

- HbA1c 6.5 – 12.0%
- Renal function criteria defined by metformin use
- Allowed patients with previous urinary tract and/or genital infections
- Excluded patients 'at risk' for dehydration per Investigator judgment

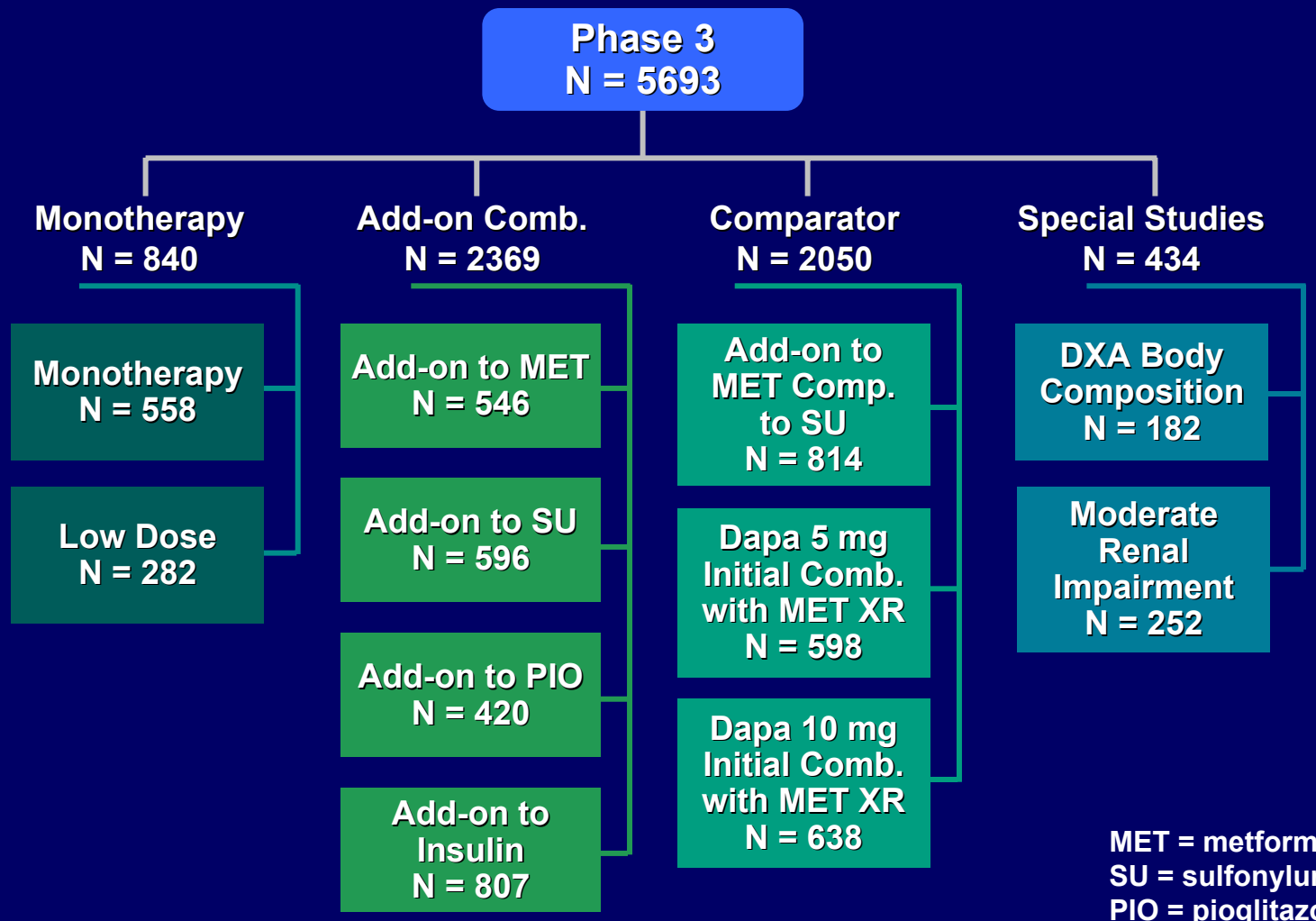
Analyses Conducted

- Primary efficacy analysis was by LOCF
- Sensitivity analyses conducted
- ST + LT analyses by longitudinal model

Dapagliflozin Efficacy Topics

- Short-term data (24 Weeks)
  - HbA1c, FPG, PPG
  - Weight
- Active comparison data
- Efficacy in subgroups
- Long-term extension data

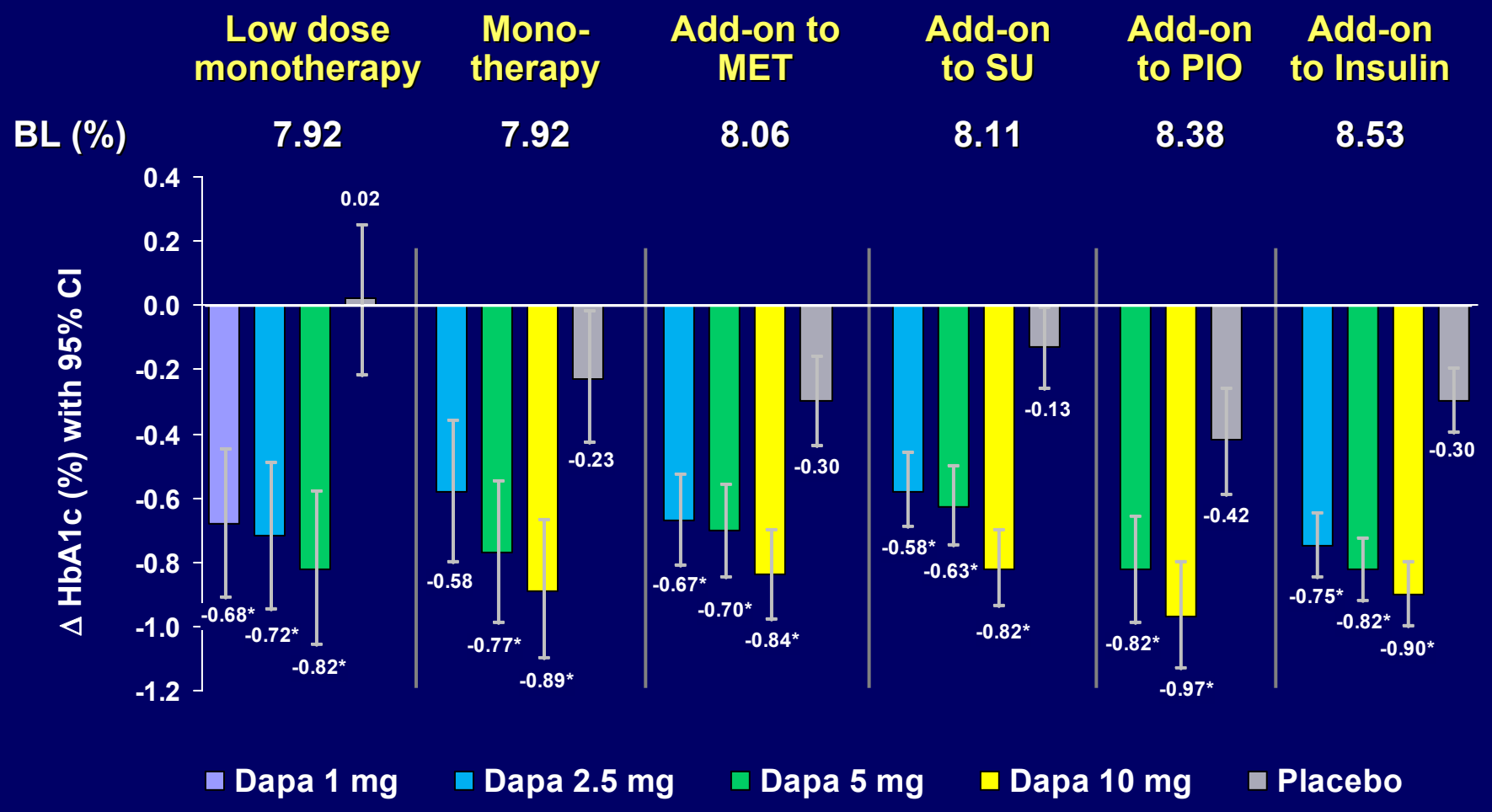
Dapagliflozin Phase 3 Clinical Development Program



MET = metformin
SU = sulfonylurea
PIO = pioglitazone
XR = extended release

SCE Table 5

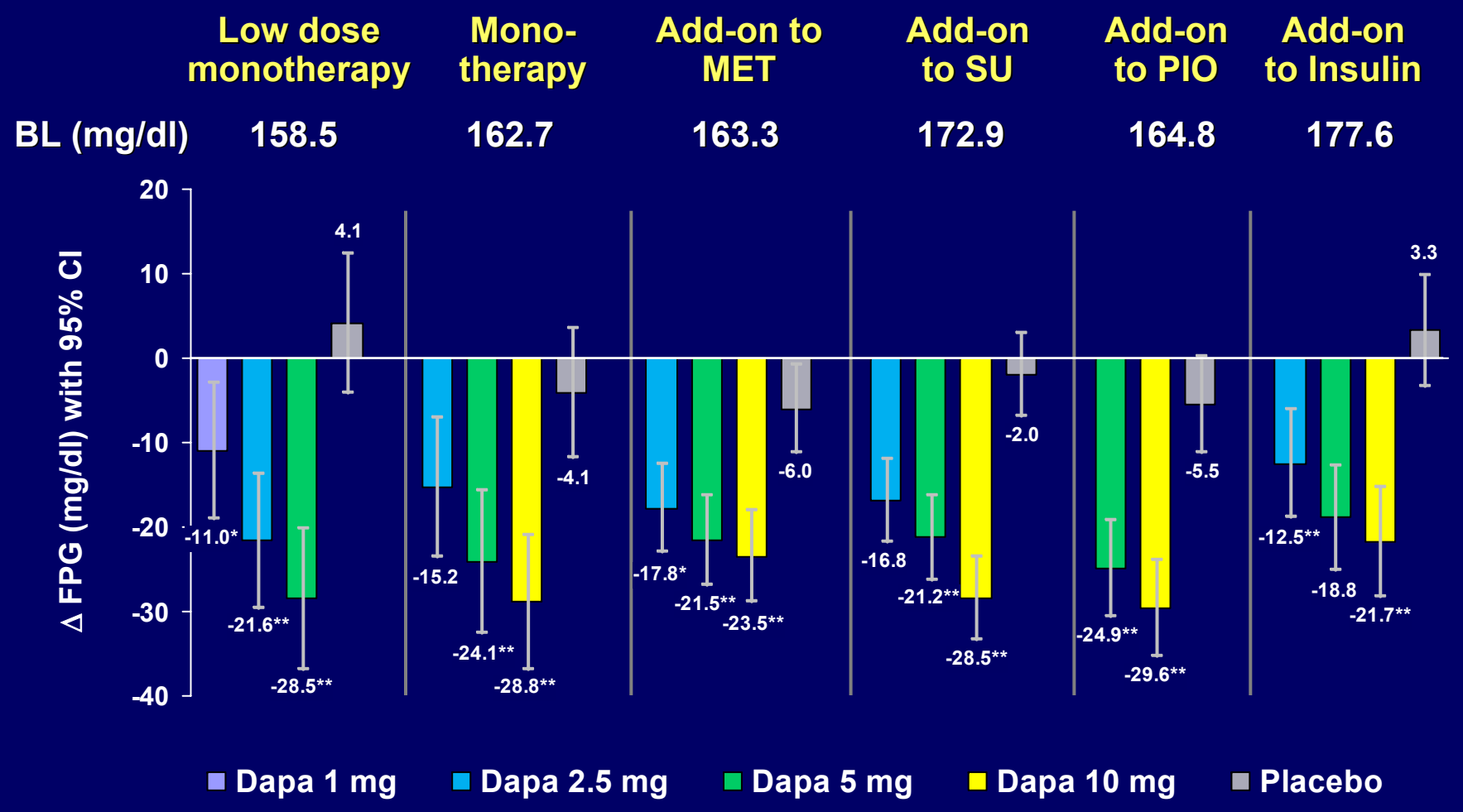
Consistent and Dose-dependent Reduction in HbA1c at Week 24 Across Studies



* Statistically significant vs. placebo using Dunnett's correction

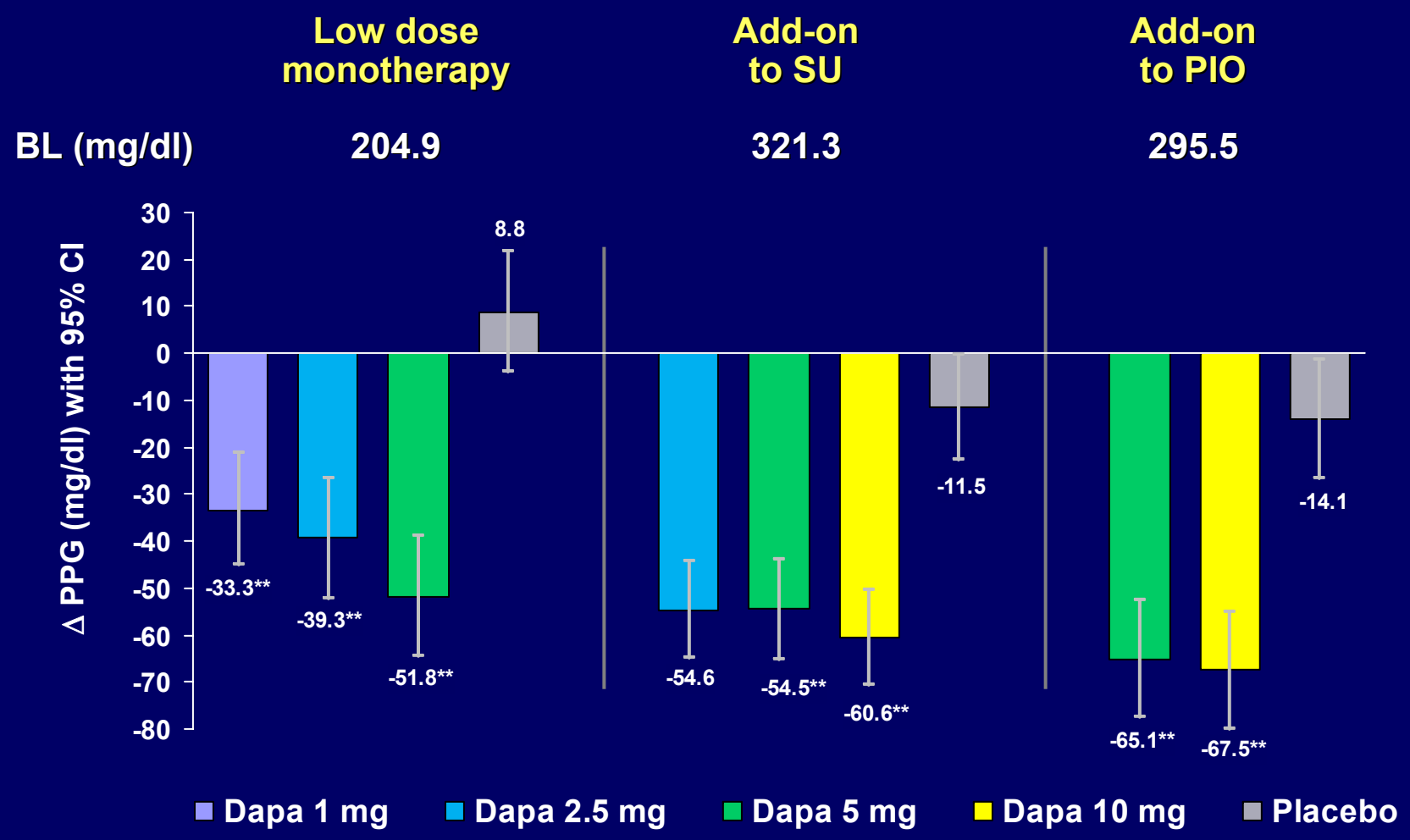
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Consistent and Dose-dependent Reduction in FPG at Week 24 Across Studies



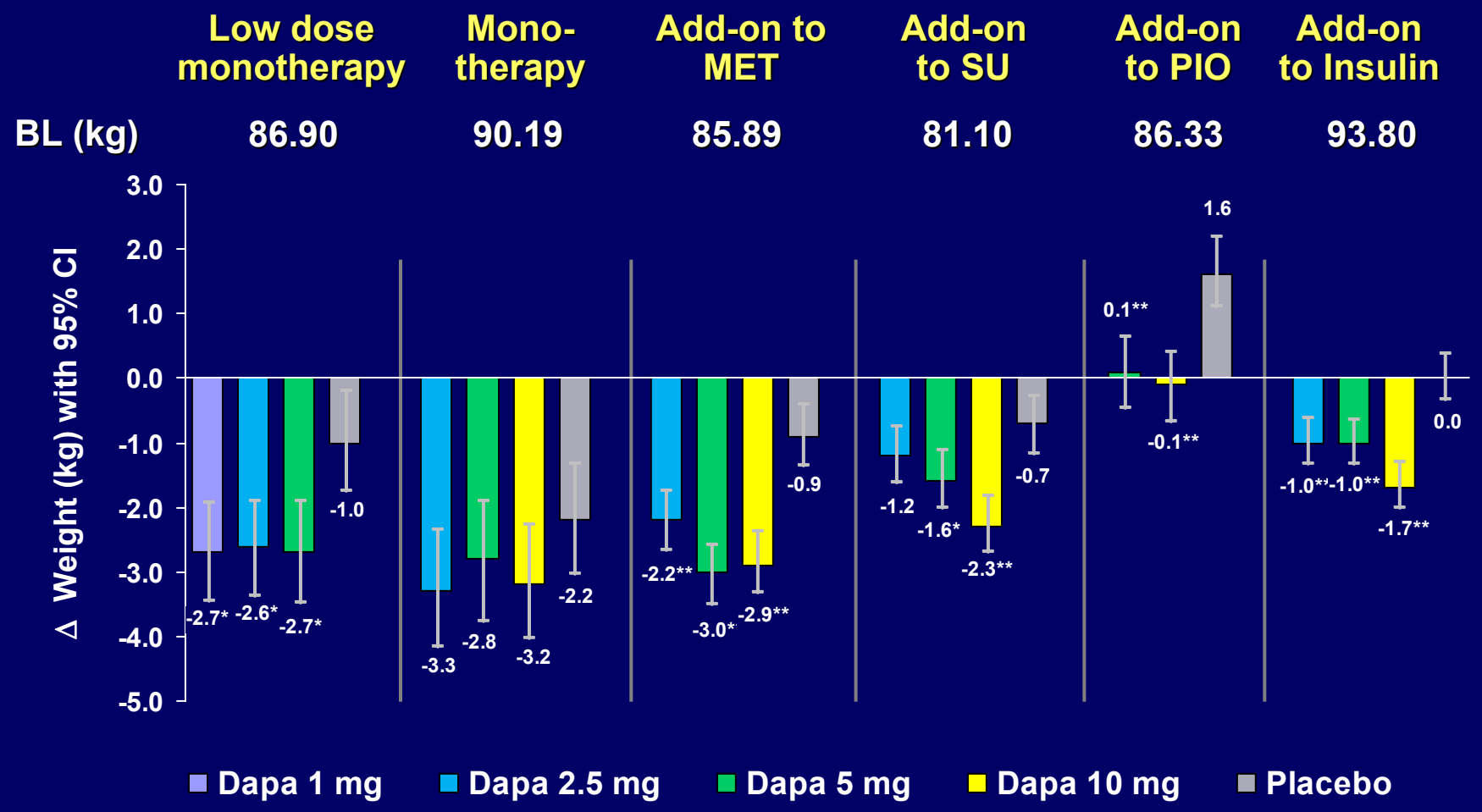
Statistically significant vs. placebo by hierarchical testing rule: * = p<0.05; ** = p<0.001
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Reduction in Post-Prandial Glucose at Week 24



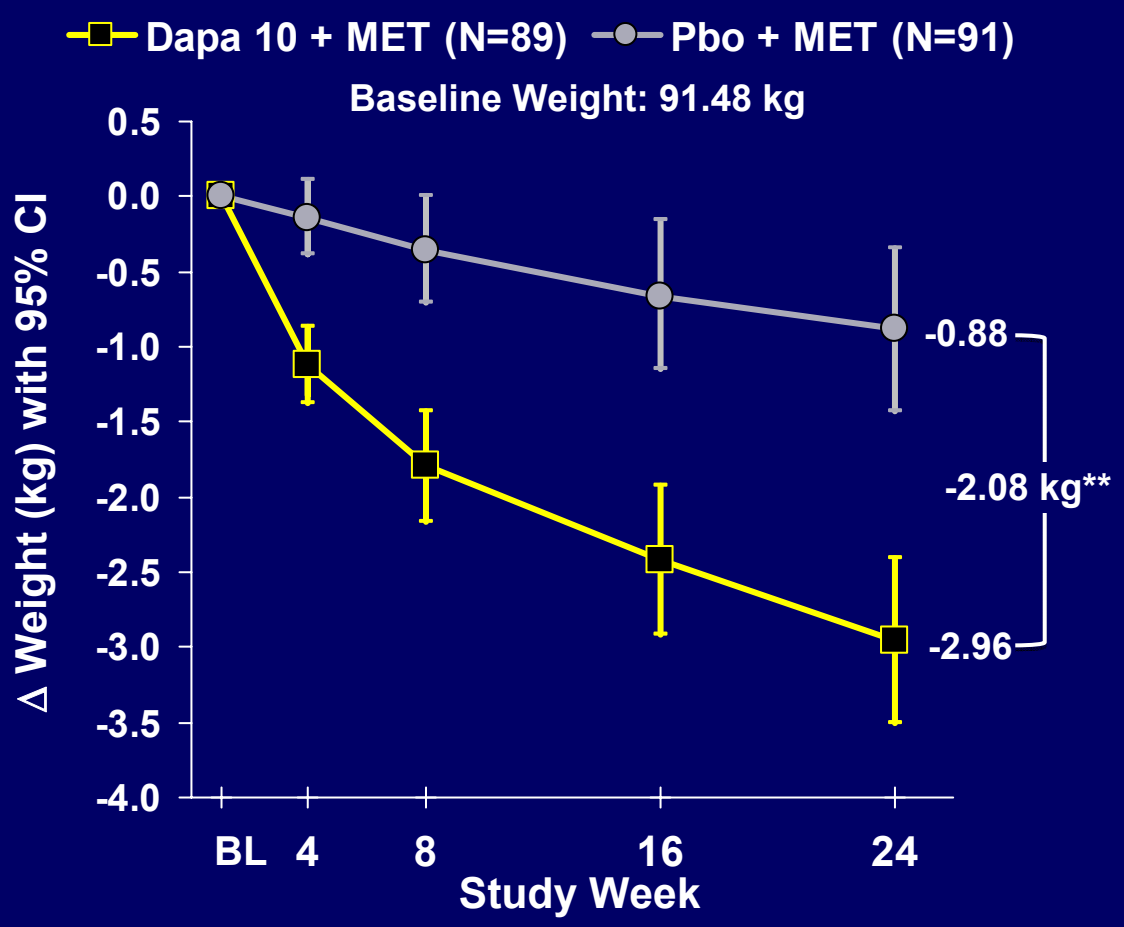
Statistically significant vs. placebo by hierarchical testing rule: ** = p<0.001
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Change in Body Weight at Week 24

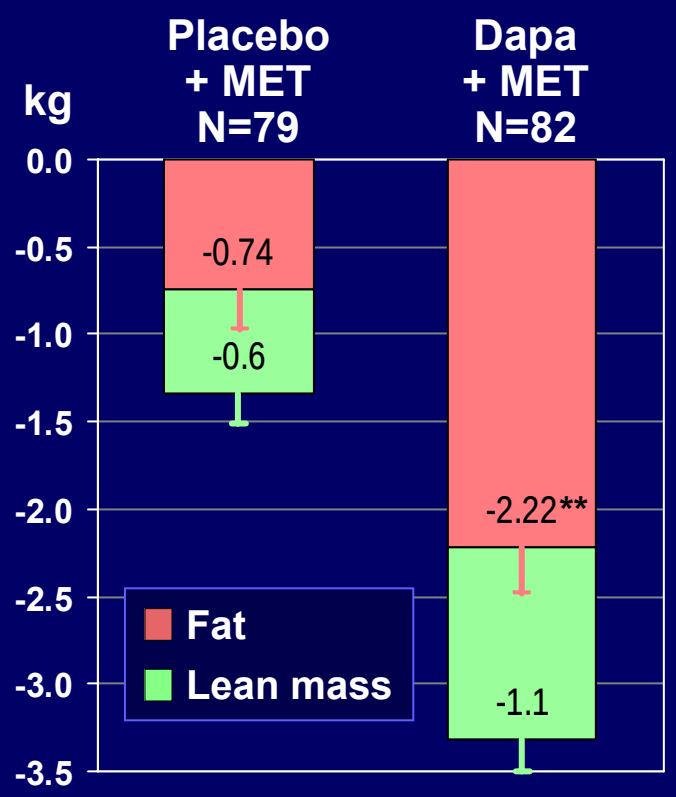


Statistically significant vs. placebo by hierarchical testing rule: * = p<0.05; ** = p<0.001
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Reduction in Body Weight and Body Fat Mass at Week 24



** Statistically significant vs. placebo (p<0.0001)



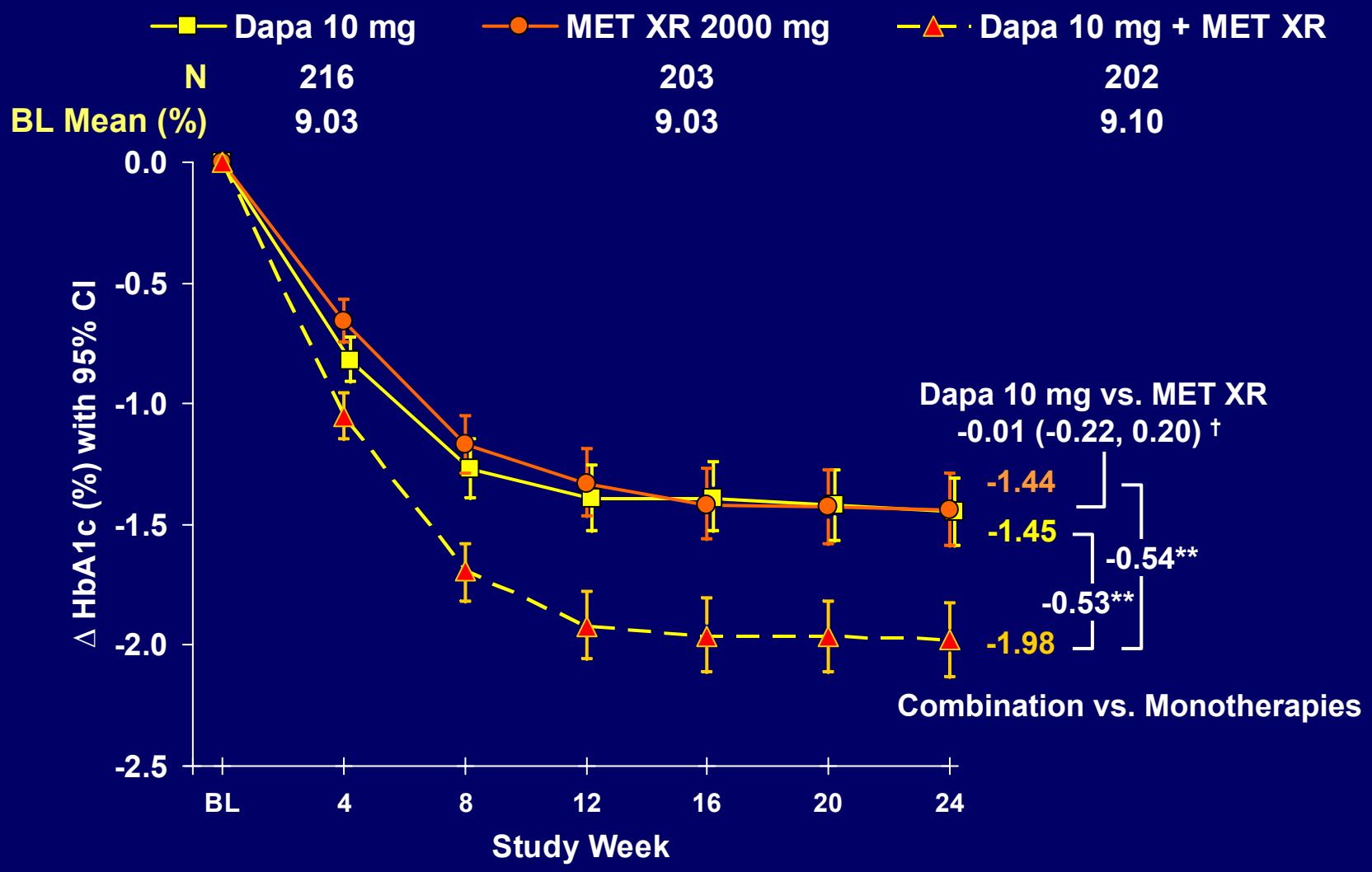
** Statistically significant vs. placebo by Hochberg's method (p<0.001)

DXA = dual X-ray absorptiometry.
Adjusted mean change from baseline using ANCOVA, including data after rescue (LOCF)

Dapagliflozin Efficacy Topics

- Short-term data (24 Weeks)
  - HbA1c, FPG, PPG
  - Weight
- Active comparison data
- Efficacy in subgroups
- Long-term extension data

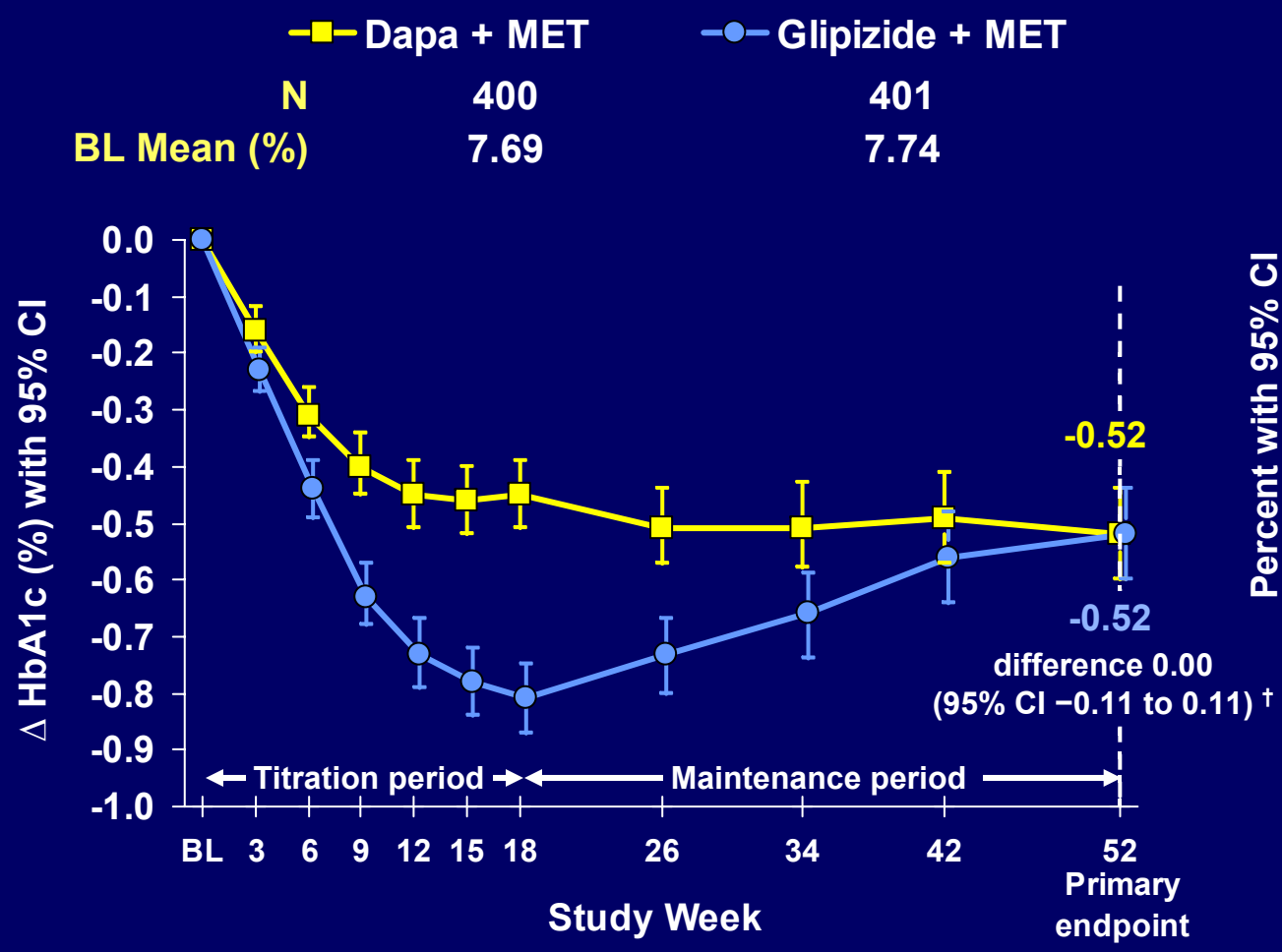
HbA1c Comparison at Week 24

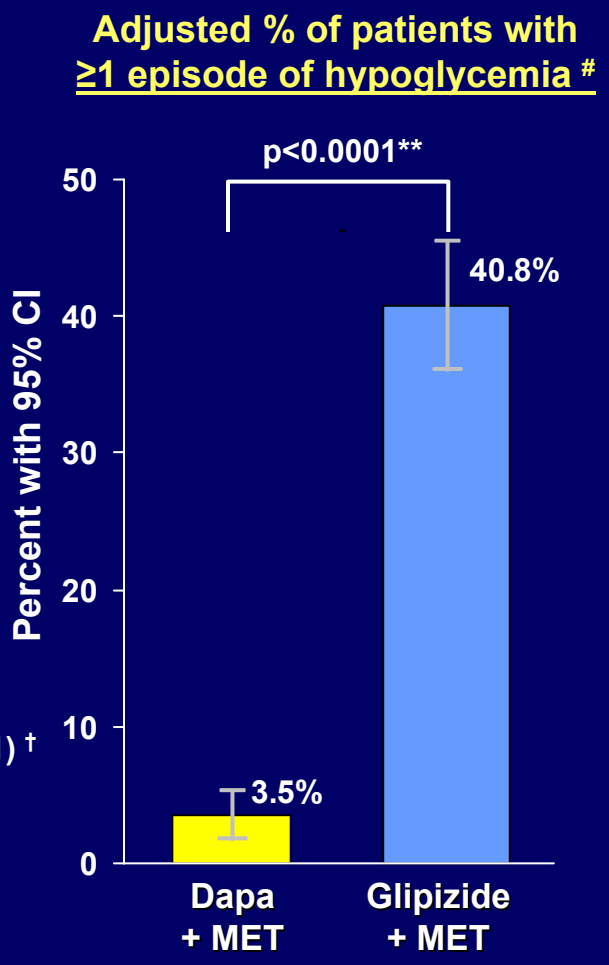


** Significantly superior to monotherapy (p<0.0001)
† Non-inferior compared to limit of 0.35%
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Source: CSR 034, Table S.5.1

Dapagliflozin vs. SU: Similar HbA1c Reductions at Week 52 with Significantly Fewer Hypoglycemic Episodes

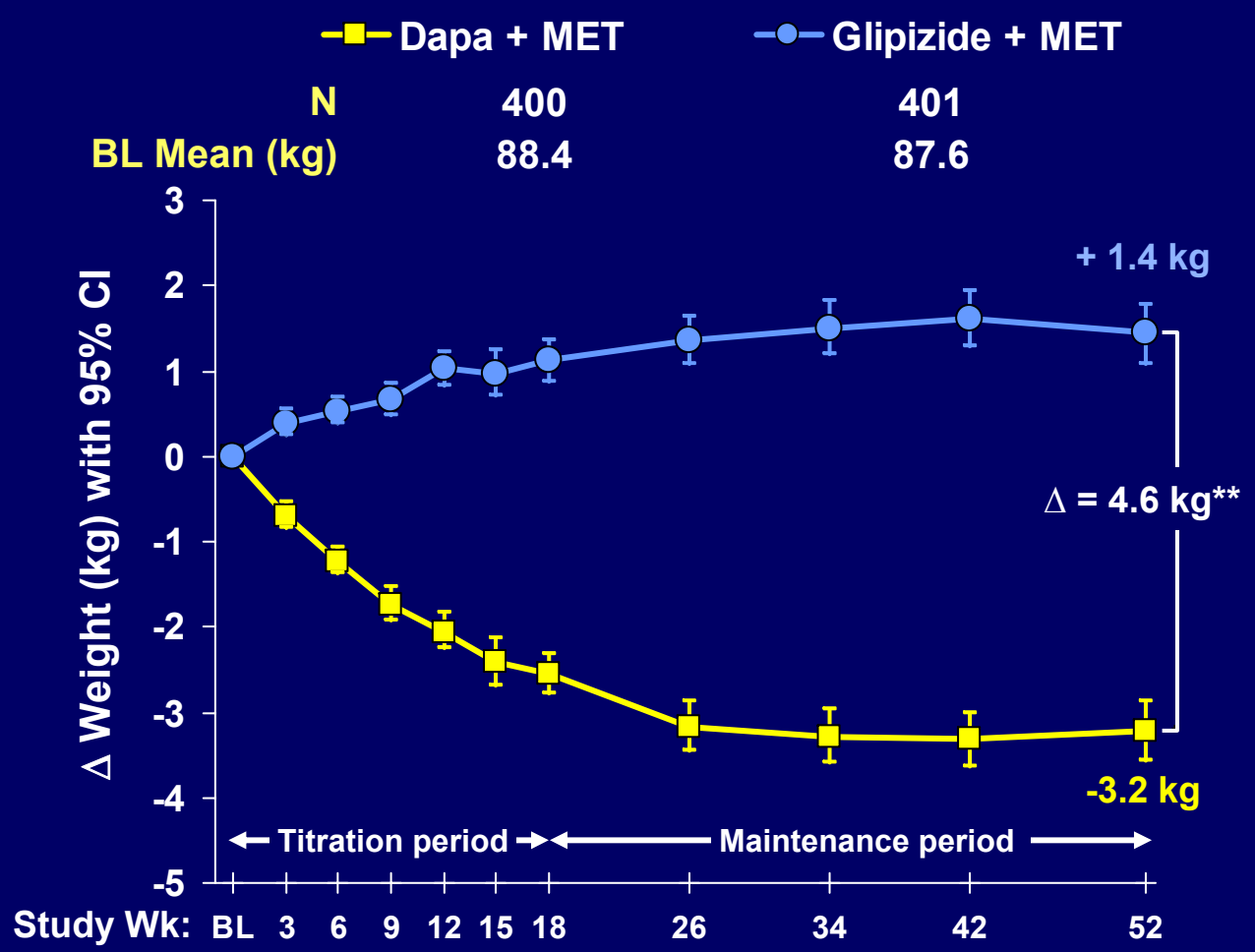




Adjusted mean change from baseline using ANCOVA (LOCF)
N's at Week 52 equal N's at baseline
† Non-inferior compared to limit of 0.35%

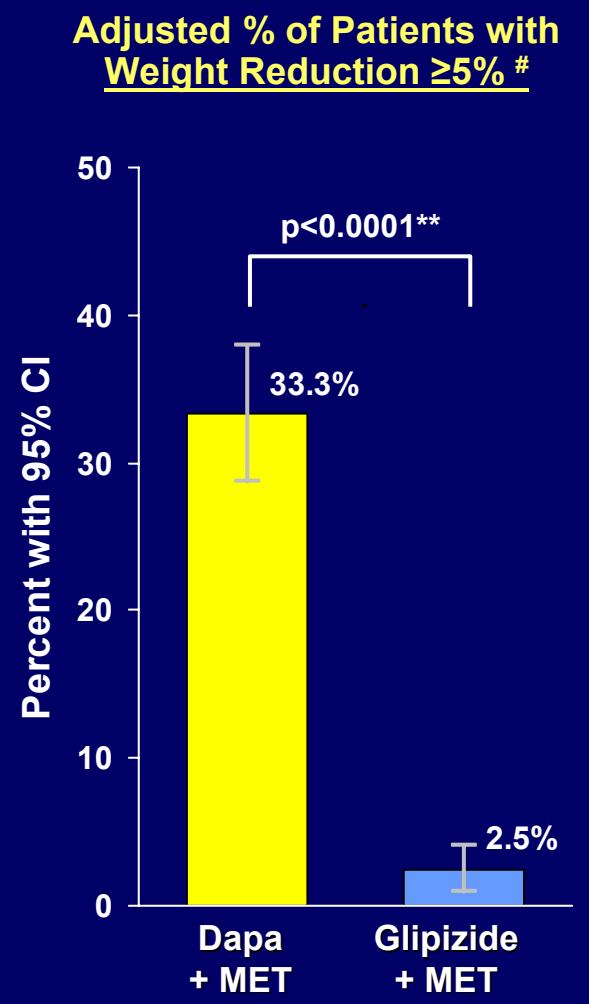
Adjusted percent using modified logistic regression analysis
** Statistically significant by heirarchical testing rule.

Dapagliflozin vs. SU: Significant Reduction in Body Weight at Week 52



Statistically significant vs. glipizide by heirarchical testing rule: ** p<0.0001

Adjusted mean change from baseline using ANCOVA (LOCF)
N's at Week 52 equal N's at baseline



Adjusted percent using modified logistic regression analysis
** Statistically significant by heirarchical testing rule.

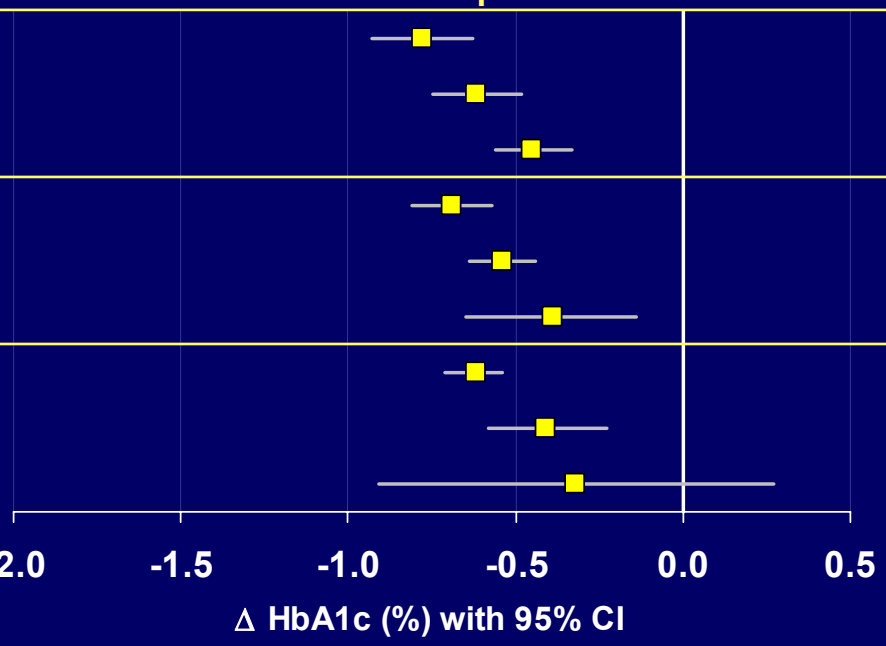
Dapagliflozin Efficacy Topics

- Short-term data (24 Weeks)
  - HbA1c, FPG, PPG
  - Weight
- Active comparison data
- Efficacy in subgroups
- Long-term extension data

Subgroup Analyses – Change in HbA1c at Week 24

- No differential efficacy detected with gender, race, ethnicity, region, baseline BMI, or duration of T2DM
- Interactions were detected with 3 subgroup variables in overall population

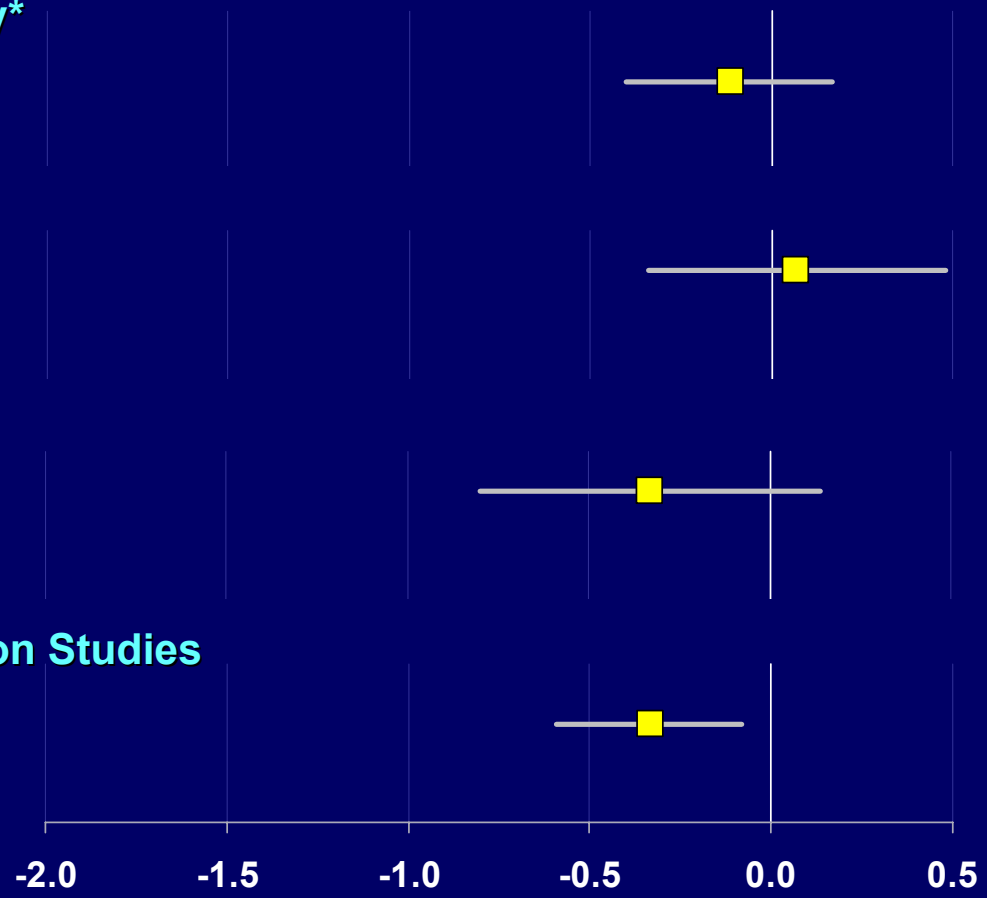
	Baseline Category	Dapa 10 mg N	Pbo N	Δ
HbA1c (%)	≥ 9%	265	347	-0.78
	≥ 8% - < 9%	320	372	-0.62
	< 8%	457	513	-0.45
eGFR (mL/min/1.73m^2)	≥ 90	395	443	-0.69
	≥ 60 - < 90	562	688	-0.54
	≥ 30 - < 60	85	101	-0.39
Age (yrs)	< 65	866	988	-0.62
	≥ 65	176	244	-0.41
	≥ 75	16	20	-0.32



Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

HbA1c Lowering in Moderate Renal Impairment

eGFR Category	Tx Group	N	BL eGFR	Difference from Placebo (Dapa better ←→ Pbo better) Δ
Moderate Renal Impairment Study*				
	Dapa 10 mg	82	43.9	-0.11
	Placebo	82	45.6	
≥30 – <45 (3B)	Dapa 10 mg	45	37.3	+0.07
	Placebo	33	38.3	
≥45 – <60 (3A)	Dapa 10 mg	32	51.9	-0.33
	Placebo	40	50.4	
Pooled Monotherapy / Combination Studies				
≥45 – <60 (3A)	Dapa 10 mg	70	54.6	-0.33
	Placebo	92	55.4	



Mean adjusted Δ HbA1c (%) with 95% CI

* Study target eGFR ≥30 – <60 ml/min/1.73m^2; analysis includes all randomized and treated subjects with baseline and ≥1 post-baseline value.

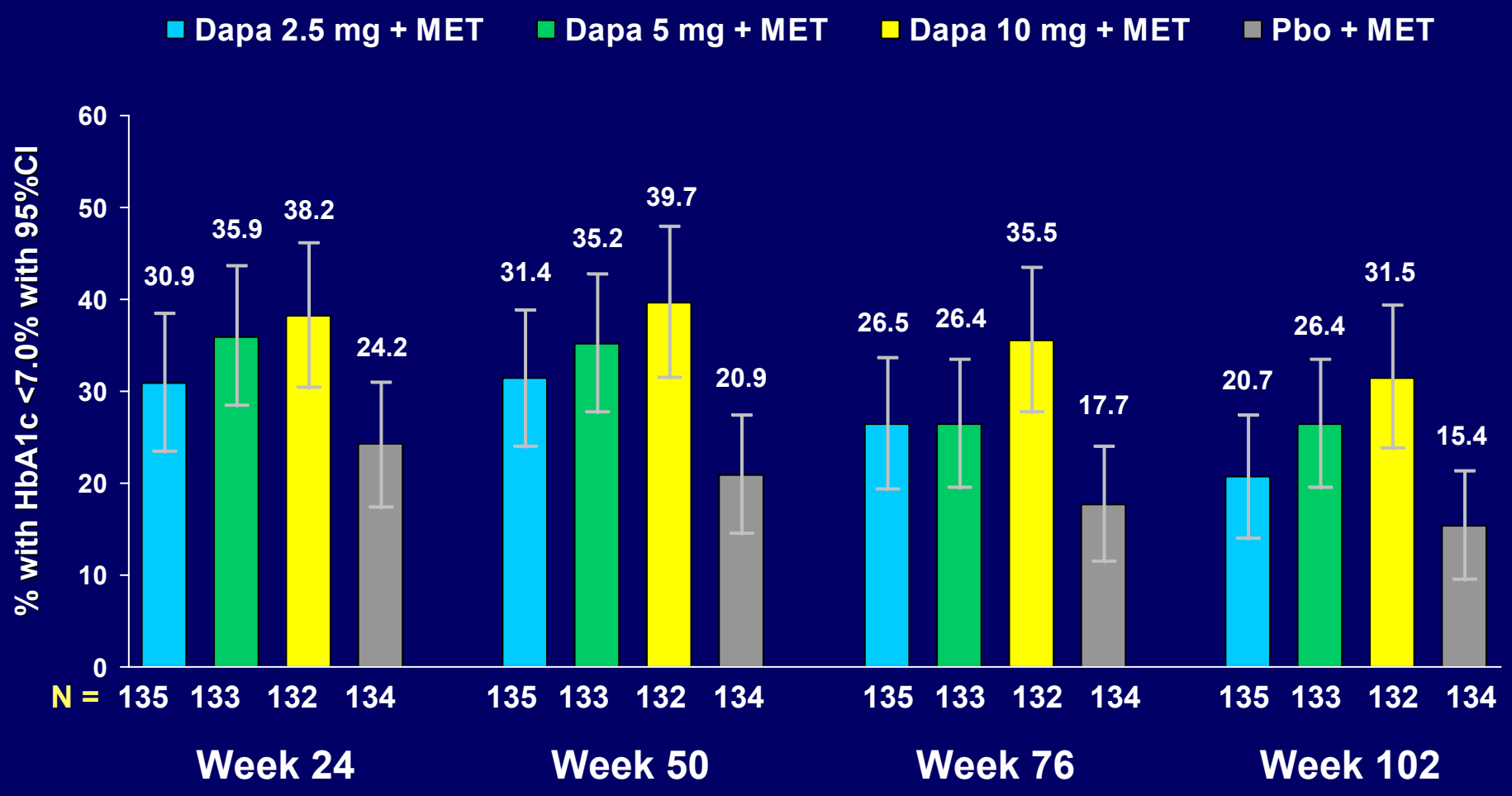
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

Source: CSR 029 Table 7.1...

Dapagliflozin Efficacy Topics

- Short-term data (24 Weeks)
  - HbA1c, FPG, PPG
  - Weight
- Active comparison data
- Efficacy in subgroups
- Long-term extension data

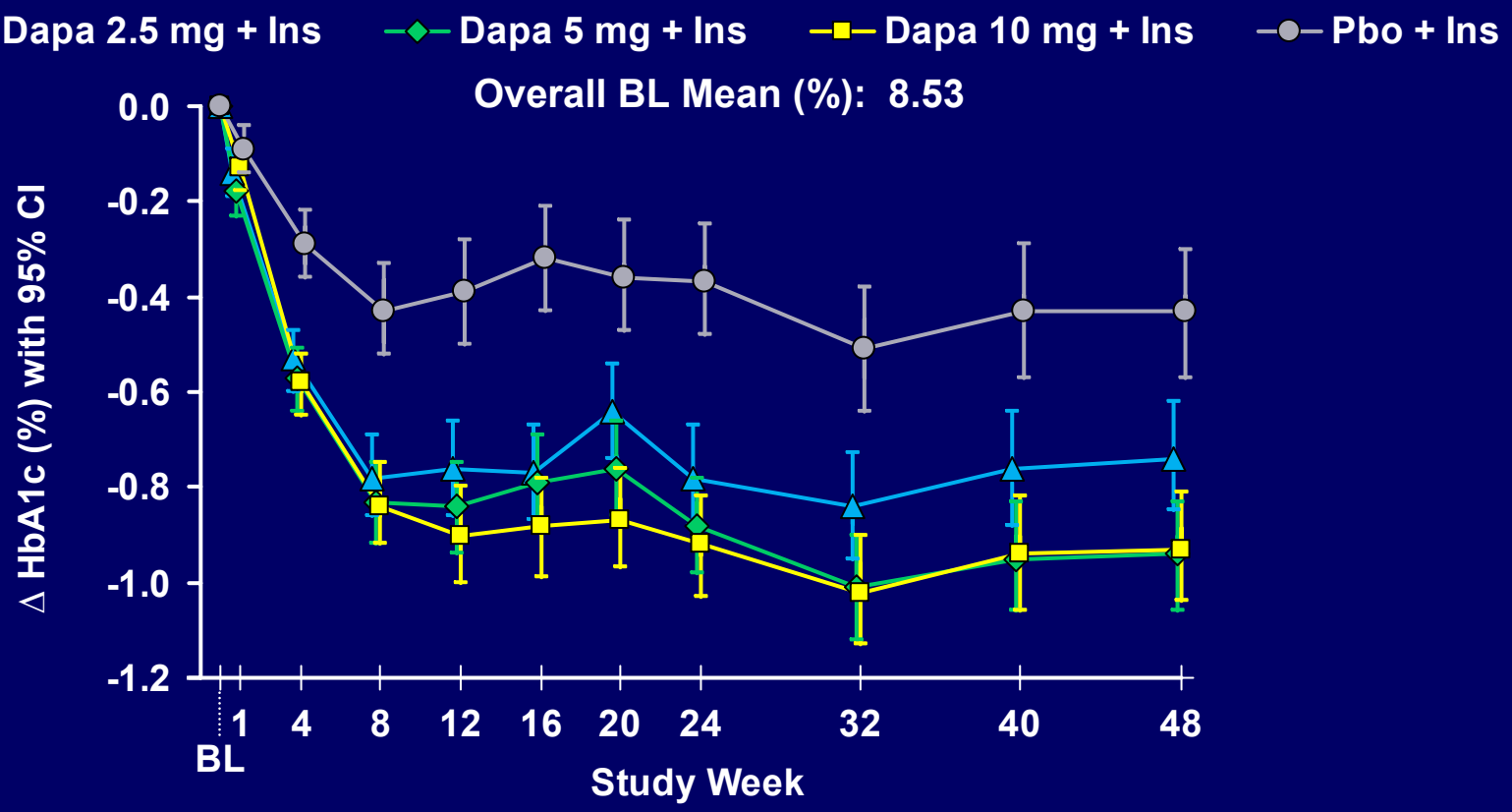
Proportion Achieving HbA1c <7.0% Over Time



Source: Study 014, Table S.5.9

Adjusted percent using modified logistic regression analysis
Patients rescued, discontinued, or missing at visit are considered treatment failures

Sustained HbA1c Reduction over 48 Weeks

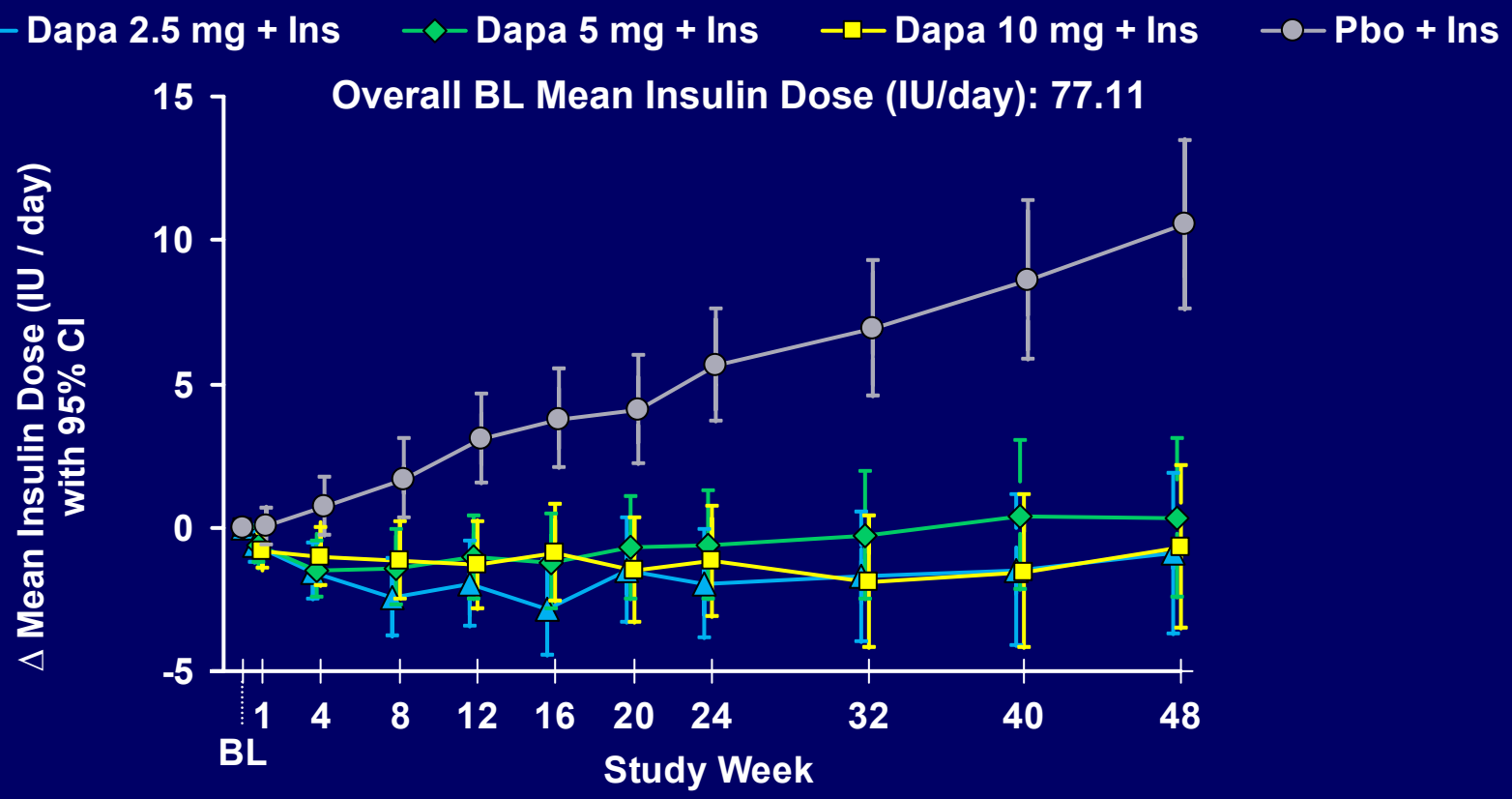


Number of Patients							
Dapa 2.5mg + Ins	199	183	172	162	151	145	135
Dapa 5mg + Ins	210	182	175	165	163	153	147
Dapa 10mg + Ins	192	176	166	158	153	148	139
Pbo + Ins	188	142	128	122	111	100	89

Adjusted mean change from baseline using a longitudinal repeated measures mixed model, excluding data after insulin up-titration (observed values)

Source: Study 006 Table 11.2.1.1.1, 11.2.1.1.3

Dapagliflozin Mitigates Need for Increased Insulin Requirements over 48 Weeks



Number of Patients							
Dapa 2.5mg + Ins	200	189	186	180	174	176	173
Dapa 5mg + Ins	209	194	190	187	183	181	171
Dapa 10mg + Ins	194	185	180	177	175	173	166
Pbo + Ins	191	176	170	168	164	158	157

Adjusted mean change from baseline using a longitudinal repeated measures mixed model, including data after insulin up-titration (observed values)

Source: Study 006 Figure 11.2.5; Table 11.2.6.1.1, Table 11.2.6.1.3

Dapagliflozin – Efficacy Summary

- Consistent improvement in glycemic parameters across studies
- Overall, 10 mg is the most effective dose
  - Greater mean reductions in HbA1c, FPG than lower doses
  - Comparable to commonly prescribed OAD agents
- Modest weight loss, primarily fat loss
- Mitigates the need for increased insulin requirements
- Consistent glycemic efficacy across subgroups
  - Dependent on baseline HbA1c and renal function
- Sustained efficacy over duration of the studies

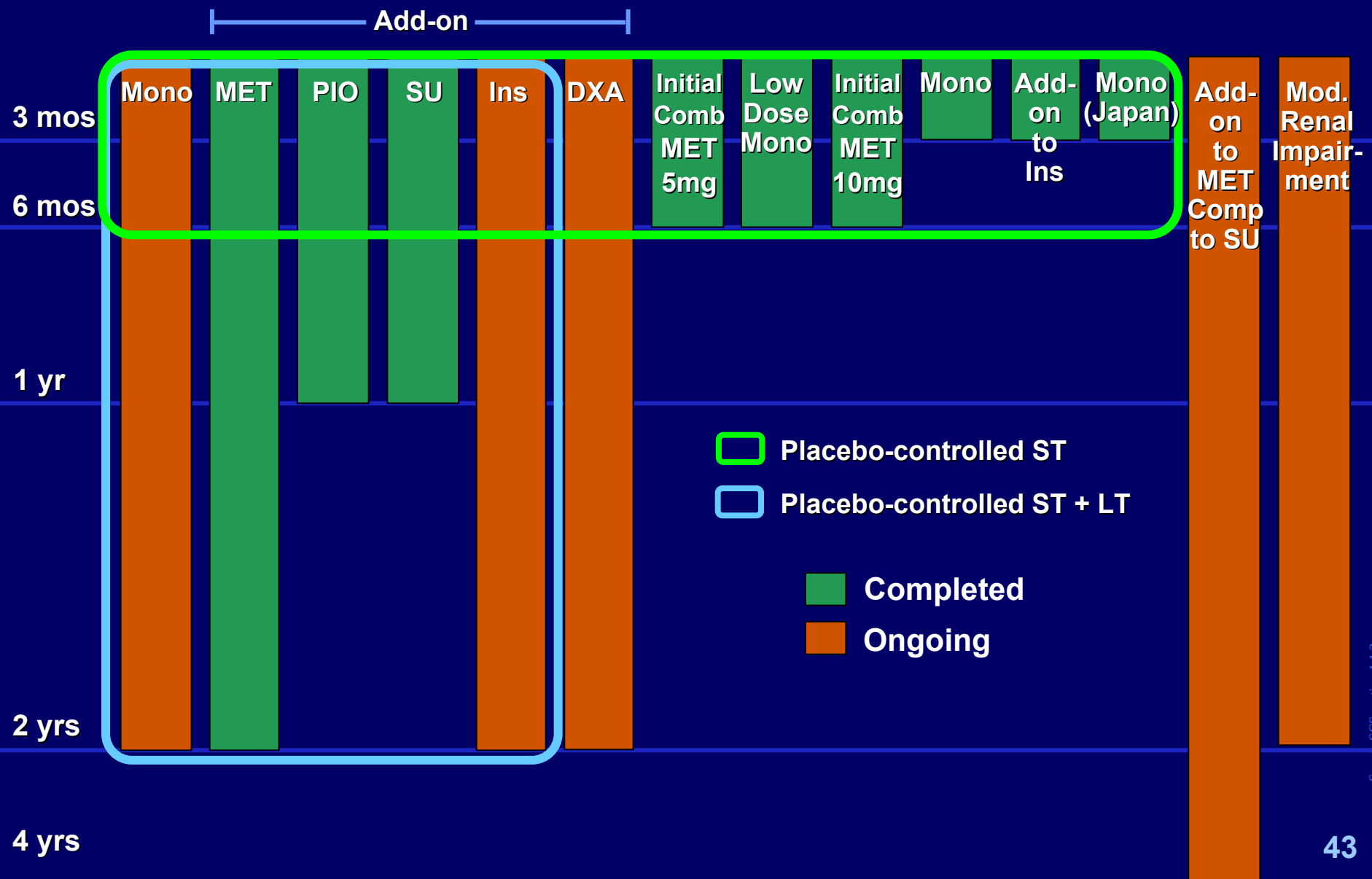
Dapagliflozin

Safety

James List, MD, PhD

Bristol-Myers Squibb

Safety Data Pooling Strategy (NDA)



Source SCS section 1.1.2

Dapagliflozin Exposure

Exposure	Dapagliflozin NDA	Dapagliflozin 4 Month Safety Update
Total	4287	4310
≥ 1 Year	2232	2302
≥ 18 Months	1317	1424
≥ 2 Years	441	956

Source SCS table 7, 4MSU Table 4

Demographic and Baseline Characteristics

		All Dapa N = 4287	All Control N = 1941
Age	Mean, years	55.9	56.5
Race	White, %	81.0	81.2
Gender	Female, %	49.2	47.5
Geography	N. America (US, Canada), %	31.6	27.0
BP	Mean SBP, mmHg	130.4	130.9
	Mean DBP, mmHg	79.3	79.7
Weight	Mean, kg	87.46	87.55
BMI	Mean, kg/m^2	31.54	31.53
HbA1c	Mean, %	8.29	8.24
Duration of T2DM	Mean, years	6.09	5.92

Source: SCS Tables 18-20 and 23; rt-dm-sumlt23a0010.lst

Summary of Adverse Events

Placebo-controlled Pool
ST Period

	Percent of Patients			
	Dapa 2.5 mg N = 814	Dapa 5 mg N = 1145	Dapa 10 mg N = 1193	Pbo N = 1393
At least one AE	60.6	61.9	61.5	56.9
At least one SAE	4.5	3.5	3.5	3.3
Discontinuations due to AEs	2.2	2.8	3.2	2.5

All Phase 2b and 3 Pool
ST + LT period

	All Dapa N = 4287	Control N = 1941
Deaths	0.5	0.5

Source: SCS Tables 27 and 34

Dapagliflozin Safety Topics

- Topics explored because of the mechanism
  - Hypoglycemia
  - Urinary tract infections and vulvovaginitis / balanitis
  - Blood pressure and hypovolemia
  - Renal function
  - Laboratory data (electrolytes, uric acid, hematocrit)
  - Bone health
- Other safety topics
  - Malignancy data
  - Hepatic data
- Cardiovascular safety
  - Cardiovascular meta-analysis

Hypoglycemia

Low Intrinsic Propensity to Cause Hypoglycemia

	% of Patients			
	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Pbo
Placebo-controlled Pool	n=814 15.5	n=1145 10.9	n=1193 10.2	n=1393 7.0
Monotherapy Pool	n=321 2.5	n=316 2.2	n=245 2.9	n=251 2.0
Add-on Combination + MET (pool)	—	—	n=226 3.1	n=228 3.1
+ PIO	—	n=141 2.1	n=140 0	n=139 0.7
+ SU	n=154 7.1	n=145 6.9	n=151 7.3	n=146 4.8
+ Insulin	n=202 51.5	n=212 45.3	n=196 42.3	n=197 35.0

Urinary Tract Infections and Vulvovaginitis / Balanitis

Urinary Tract Infections

	Percent of Patients			
	Dapa 2.5 mg N=814	Dapa 5 mg N=1145	Dapa 10 mg N=1193	Pbo N=1393
Total	3.6	5.7	4.3	3.7
Female	n=400	n=581	n=598	n=677
	5.8	9.6	7.7	6.6
Male	n=414	n=564	n=595	n=716
	1.4	1.6	0.8	1.0

Source SCS Appendix 4F tables 1-3

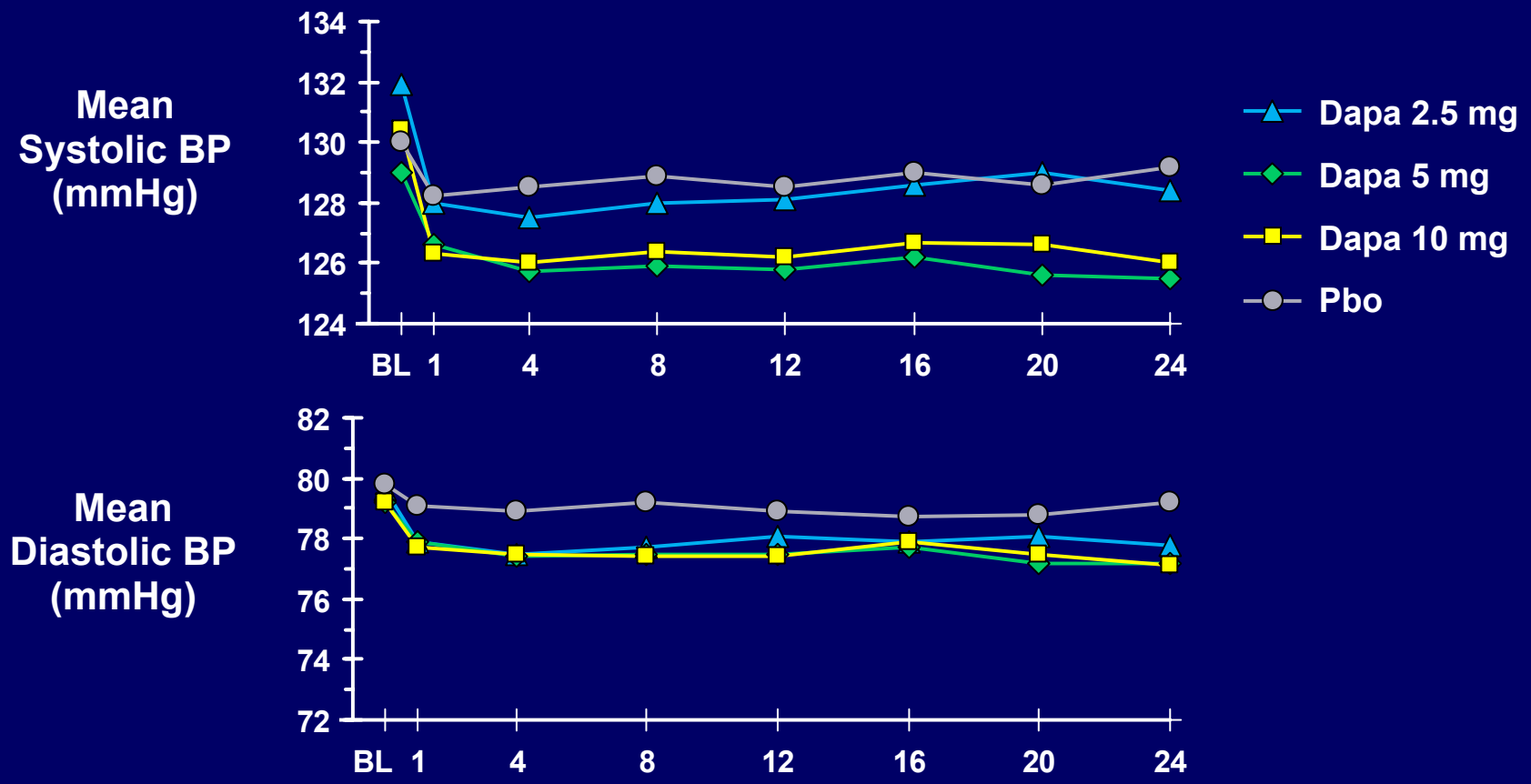
Vulvovaginitis, Balanitis and Related Infections

	Percent of Patients			
	Dapa 2.5 mg N=814	Dapa 5 mg N=1145	Dapa 10 mg N=1193	Pbo N=1393
Total	4.1	5.7	4.8	0.9
Female	n=400	n=581	n=598	n=677
	5.8	8.4	6.9	1.5
Male	n=414	n=564	n=595	n=716
	2.4	2.8	2.7	0.3

Source SCS Appendix 4E tables 1-3

Osmotic Diuresis – Hemodynamic, Renal and Laboratory Effects

Blood Pressure Lowering



Number of Patients

Dapa 2.5mg	754	740	720	707	641	631	621
Dapa 5mg	1087	1052	1022	1007	941	925	908
Dapa 10mg	1127	1086	1070	963	975	871	949
Placebo	1320	1281	1247	1116	1137	1021	1096

Source: SCS Appendix 160B, 158B

Events of Hypotension / Hypovolemia / Dehydration

	Number (%) of Patients			
	Dapa 2.5 mg N = 814	Dapa 5 mg N = 1145	Dapa 10 mg N = 1193	Pbo N = 1393
Total Subjects with an Event	10 (1.2)	7 (0.6)	9 (0.8)	5 (0.4)
Hypotension	6 (0.7)	5 (0.4)	5 (0.4)	2 (0.1)
Syncope	0	0	2 (0.2)	1 (<0.1)
Dehydration	3 (0.4)	0	1 (<0.1)	0
Urine Flow Decreased	0	0	1 (<0.1)	0
Blood Pressure Decreased	0	0	0	1 (<0.1)
Orthostatic Hypotension	1 (0.1)	2 (0.2)	0	0
Urine Output Decreased	1 (0.1)	0	0	1 (<0.1)

Source: rt-ae-hytndhydhyvlsta0024.doc

Renal Function Remains Stable During Dapa

- Glomerular filtration rate
  - Overall population and Stage 3A CKD
    - Week 1 small decrease in estimated GFR
    - Subsequent return to baseline
    - Stable for up to 2 years of follow-up
  - Dedicated Study in Moderate Renal Impairment (Stages 3A + 3B CKD)
    - Week 1 small decrease in estimated GFR
    - Stability for up to 1 year (without return to baseline)
- Serum creatinine outliers: proportion similar to control
- Renal adverse events and serious adverse events: proportion similar to control

Electrolytes and Related Laboratory Findings

		Dapa 10 mg	
	Dapagliflozin	Change at Week 24 (SE)	Baseline
S-Sodium	No effect		
S-Potassium	No effect		
S-Chloride	No effect		
S-Bicarbonate	No effect		
S-Uric Acid (mg/dL)	↓	-0.57 (0.03)	5.28
Hematocrit (%)	↑	2.15 (0.08)	42.51

N range 911 to 938 for dapagliflozin 10 mg dose

Bone Health

Calcium and Related Laboratory Findings

		Dapa 10 mg	
	Dapagliflozin	Change at Week 24 (SE)	Baseline
U-Calcium*	No effect		
S-Calcium	No effect		
S-Magnesium (mEq/L)	↑	0.07 (0.01)	1.71
S-Phosphorus (mg/dL)	↑	0.17 (0.02)	3.58
S-PTH (pg/mL)	↑	1.8 (0.58)	37.7
S-25-OH Vitamin D	No effect		
S-1,25-OH Vitamin D *	No effect		

N range 812 to 936 for dapagliflozin 10 mg dose

* From 12 week Phase 2b study (dapa 10 mg, n=47).

Bone Data: No Increase in Fracture Risk

- Nonclinical: No fracture risk seen
  - No dapagliflozin–related bone resorption
  - No bone effects in mice or dogs at any dose or exposure tested
  - Species-specific effect in rats (6-month toxicology studies):
    - No bone changes at up to 675-fold exposure multiple of the human 10 mg dose
    - Increased mineralized trabecular bone at >2000-fold exposure multiple of the human 10 mg dose
- DXA Body Composition Study
  - No effect on bone mineral density at 1 year
- Bone fractures in phase 2b/3 program:
  - Balanced with control: 1.3% dapagliflozin; 1.3% control
  - More fractures on dapagliflozin in dedicated study in Moderate Renal Impairment (Stage 3)
  - Fractures balanced with placebo in pooled data in patients with moderate renal impairment (Stage 3A)

Malignancy Data

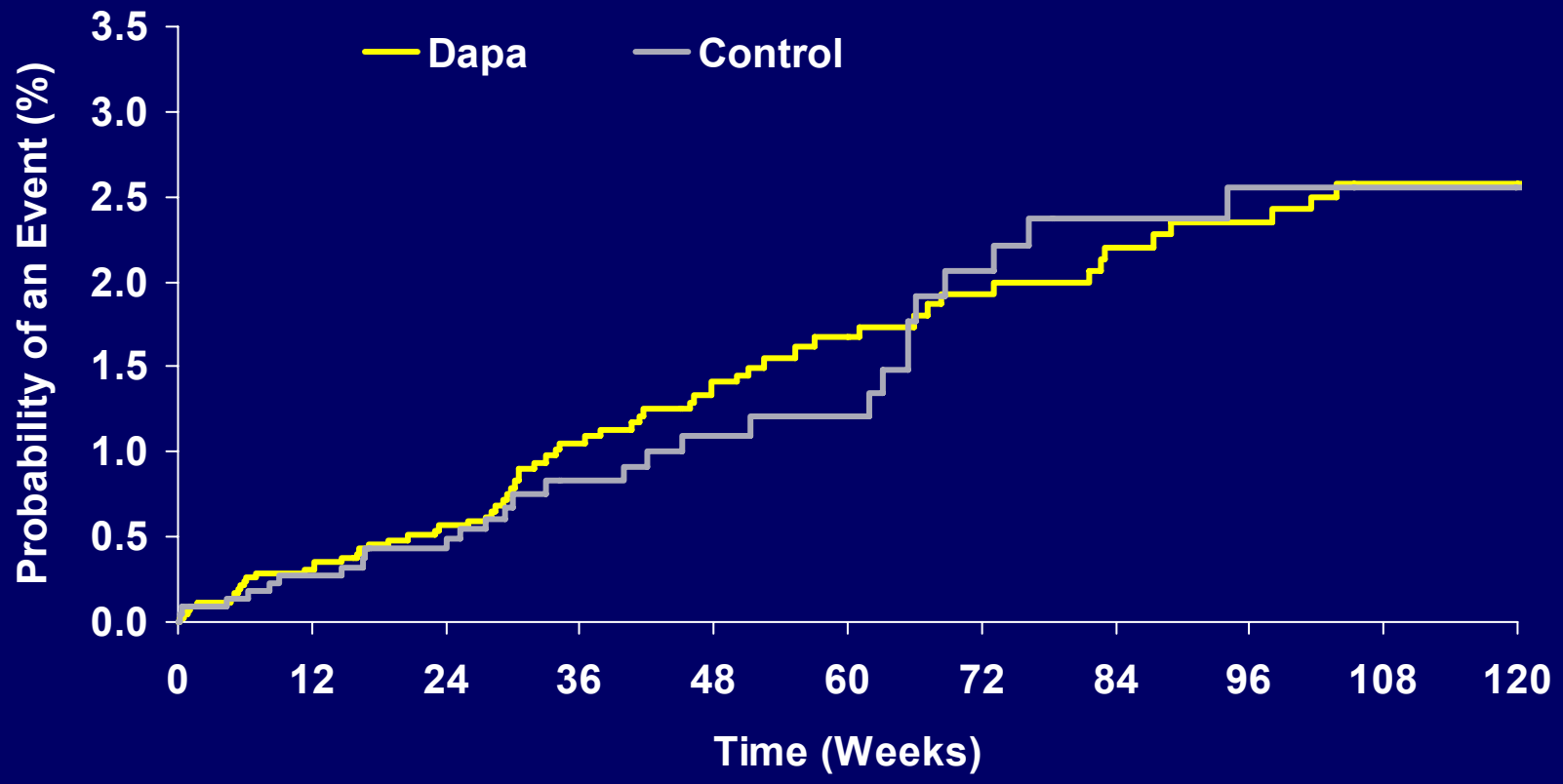
No Nonclinical Risk for Carcinogenicity

- Highly selective
  - >1400-fold selective for SGLT2 versus other family member
  - No significant off-target liabilities (>300 assays)
- Predictive computational structure activity models show no alerts
- No reactive metabolites
  - Predominant metabolite is a stable phase II ether glucuronide
- Not genotoxic
- No known linkage between mechanism of action and tumor risk
  - SGLT2 selectively expressed in kidney; not in bladder or breast

Two-Year Rodent Carcinogenicity Studies Negative

- No increase in tumors in 2-year rodent carcinogenicity studies
  - Exposure multiples of the human 10 mg dose of up to 105-fold in mice and 186-fold in rats
  - These rodent models detect known bladder and breast carcinogens
- No hyperplastic changes seen in bladder or breast tissue with dapagliflozin
  - No evidence for tumor promotion

Time to First Event of Malignant or Unspecified Tumor

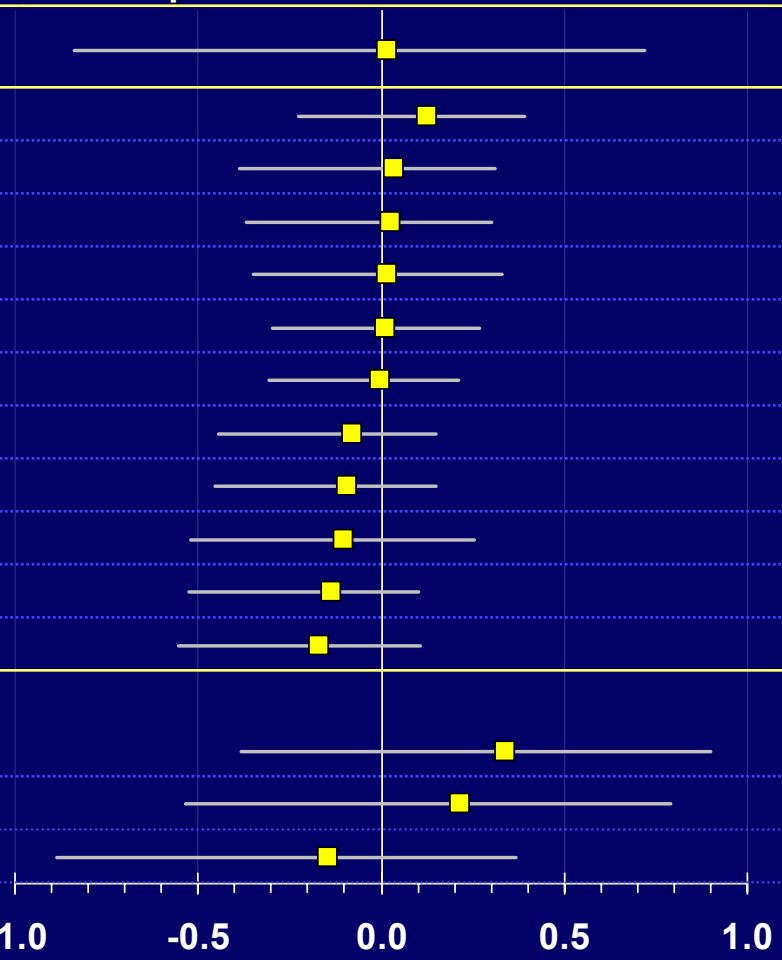


# of Patients	BL	12	24	36	48	60	72	84	96	108	120
Dapa	4559	4325	3607	2568	2417	1567	1481	1396	1298	343	195
Control	2239	2098	1744	1199	1075	702	642	564	514	247	180

Source: rgaetmmalsmqlt235a042.csv

Malignant and Unspecified Tumors by Tumor Origin

Tumor Origin	N =	Events: All Dapa 4559	Events: Control 2239	Δ
Overall Malignancies and Unspecified Tumors		65	29	0.018
Bladder		7	0	0.125
Thyroid and Endocrine		7	3	0.034
Gastrointestinal		6	2	0.028
Pancreatic		4	1	0.015
Hepatobiliary		2	0	0.014
Musculoskeletal and Soft Tissue		1	0	-0.003
Metastases and Site Unspecified		1	2	-0.080
Blood and Lymphatic		2	2	-0.091
Skin		12	8	-0.103
Renal Tract		0	2	-0.135
Respiratory and Mediastinal		5	5	-0.168
Gender-specific tumor types:				
Breast (Female)		9	1	0.339
Prostate (Male)		8	2	0.218
Female Reproductive (Female)		1	1	-0.146



Source: rgmalorgandifflt235a056.csv

Urothelial (Bladder) Cancer Cases by Study Day of Diagnosis

Age/Sex	Dapa Dose (mg)	Invasive	Grade	TNM	Diagnosis Study Day	Smoking	Baseline Hematuria
75/M	Dapa 2.5	+	Grade 2	T4 N0 M1 (lung mets)	43	Former	2+
48/M[1]	Dapa 10	–	Low Grade	Not avail.	74	Former	Negative
67/M	Dapa 5 + Pio	+	High Grade	T2	144	Never	Trace
55/M	Dapa 10	–	Low Grade	M0	169	Current	Trace
63/M	Dapa 5 + Ins	–	Grade 2	Ta	393 (tumor 358)	Current	Negative
67/M	Dapa 10 + Ins	Not avail.	Grade 2	Not avail.	399	Never	3+
60/M	Dapa 5 + Met	–	Low Grade	Ta N0 M0	512	Former	2+
66/M	Dapa 10 + Ins	–	Low Grade	Not avail.	581	Former	Negative
76/M	Dapa 2.5-10 + Met	+	High Grade	T1 M0	727	Former	Negative
67/M	Placebo	+	High grade	M0	136	Current	3+

All tumors were urothelial cancer (considered synonymous with transitional cell carcinoma). One tumor (in the 76 year old male) was noted to have partial squamous differentiation.

* Includes 3 cases from 2 recently unblinded studies (D1690C00018, D1690C00019)

[1] This subject had a history of hematuria since 2008.

Breast Cancer Cases by Study Day of Diagnosis

Age	Dapa Dose (mg)	Tumor Type	Grade	TNM	Estrogen Receptor Status	Diagnosis Study Day
63	Dapa 2.5 + Ins	Invasive ductal carcinoma	2	T1c N0 M0	(+)	6
53	Dapa 5	Invasive ductal carcinoma	3	T2 N1 M0	Tests not performed	39 (mass d16)
60	Dapa 2.5-10 + Met	Invasive ductal carcinoma	1	T1 N0 M0	(+)	193
61	Dapa 10 + Ins	Invasive lobular carcinoma	2	T2 N3a M0	(+)	204
64	Dapa 10 + Met	Invasive ductal carcinoma,	2-3	T1c N1 M0	(+)	211
64	Dapa 10 + Met	Invasive carcinoma	High grade	T2 N2a MX	(–)	285 (mass d246)
58	Dapa 2.5 + Ins	Not avail.	2	T2 N0 M0	(+)	292
74	Dapa 2.5	Invasive ductal carcinoma	2	T1b N0 M0	(+)	321 (mass d264)
69	Dapa 10 + Gli	Not avail*	Not Avail.	Not Avail.	Not Avail.	334
73	Placebo	Invasive lobular carcinoma	2	T3 N3a M0	(+)	57

* One subject withdrew consent, no further info available.

Cancer: Overall Summary

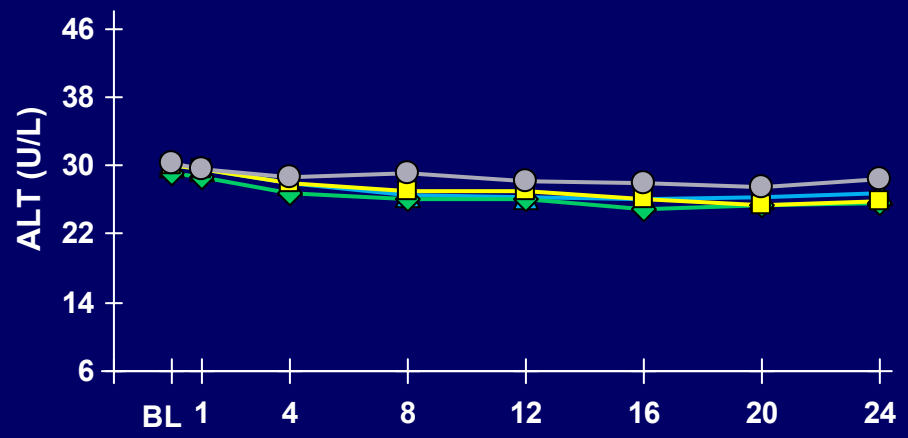
- Biological plausibility: dapagliflozin is not a carcinogen
  - No detected off-target pharmacology
  - No reactive metabolites
  - Not genotoxic
  - No SGLT2 target expression in bladder or breast tissue
  - No signal for bladder or breast tumors or hyperplasia in rodent carcinogenicity studies
- Statistical considerations:
  - Overall malignancies are balanced with control
  - Small numbers of bladder and breast cancers limit inference of causality
- Human cancer biology:
  - Clinical characteristics of cases are reflective of cancers seen in the general population
  - Events occur in relatively short time frame for human carcinogenesis

Hepatic Observations

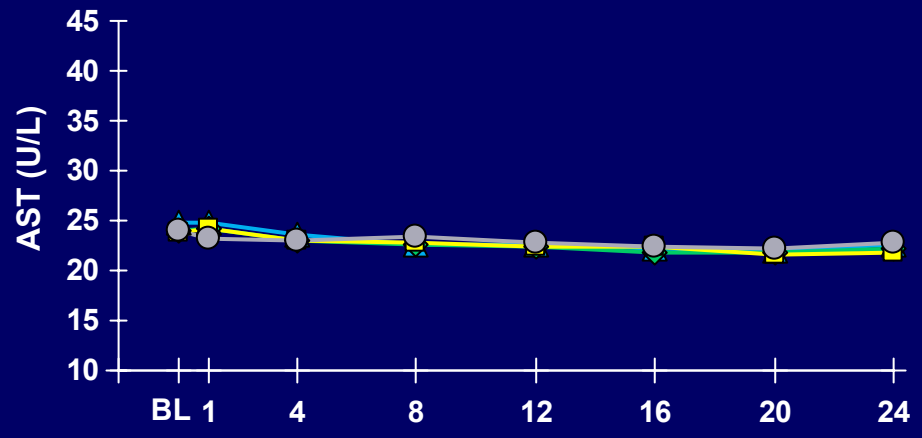
Mean Liver Test Values

	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Pbo
N range =	614 to 618	894 to 898	930 to 935	1083 to 1088

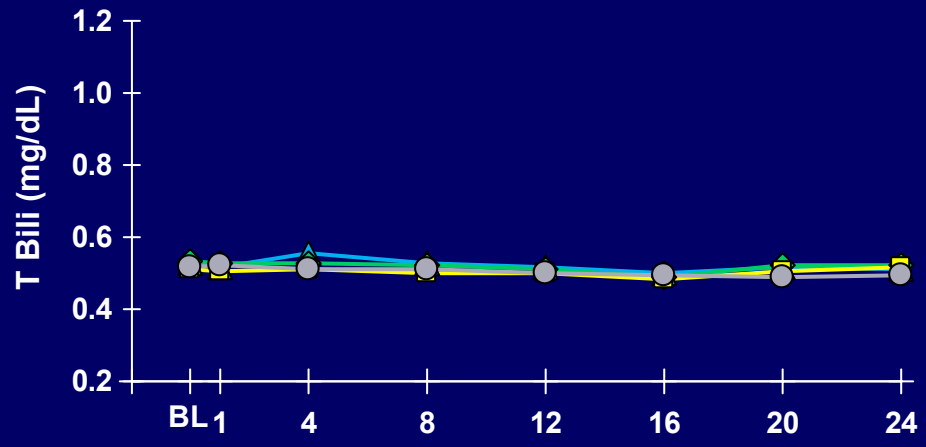
Alanine Aminotransferase (U/L)



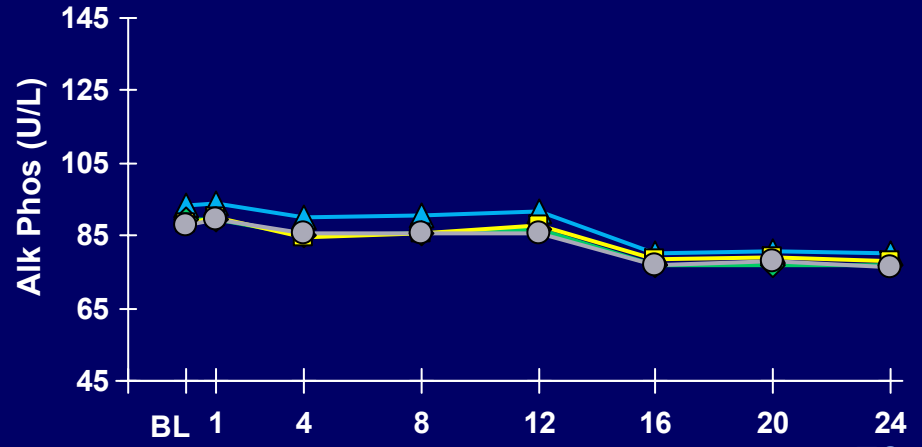
Aspartate Aminotransferase (U/L)



Total Bilirubin (mg/dL)



Alkaline Phosphatase (U/L)



Proportion of Patients with Elevated Liver Tests

	n/N# (% of Patients)	
	All Dapa N = 4310	All Control N = 1962
ALT Elevation		
>3x ULN	62 / 4281 (1.4)	31 / 1943 (1.6)
>5x ULN	17 / 4281 (0.4)	11 / 1943 (0.6)
>10x ULN	4 / 4281 (0.1)	3 / 1943 (0.2)
>20x ULN	2 / 4281 (<0.1)	1 / 1943 (0.1)
Total Bilirubin Elevation		
>2x ULN	18 / 4281 (0.4)	5 / 1942 (0.3)
Combined Elevations		
AST or ALT >3x ULN and Bilirubin >2x ULN within 14 days	5 / 4281 (0.1)	3 / 1942 (0.2)
AST or ALT >3x ULN and Bilirubin >1.5x ULN within 14 days	8 / 4281 (0.2)	4 / 1942 (0.2)

Source: 4MSU – pg. 2108 – Table 69A-Draft

Hepatic Adjudication Results

	All Dapa N=4310	All Control N=1962
Total Adjudicated	**35 (0.8)[1]**	**17 (0.9)**
Definite (>95%)	0	0
Highly Likely (75-94%)	0	0
Probable (50-74%)	0	2 (0.1)
Possible (25-49%)	9 (0.2)	5 (0.3)
Unlikely (<25%)	13 (0.3)	5 (0.3)
Excluded	13 (0.3)	5 (0.3)

[1] Includes the 8 cases of combined elevations of ALT/AST and bilirubin

Hepatic Case History: 78 year-old Indian Male (UK)

PMH: T2DM, CAD, HTN, dyslipidemia, BPH

Con Meds: ASA, atenolol, atorvastatin, lercanidipine, naproxen, perindopril

Study Meds: metformin, dapagliflozin 2.5-5 mg

Course by Study Day:

127 ALT rising above baseline

192 Last dose dapagliflozin

196–200 Mildly symptomatic;
ALT (1858 U/L) & Bili (4.2 mg/dL) peak

263–264 Liver U/S and biopsy

349 Prednisolone started

382 Prednisolone tapered; Azathioprine started

621 Last visit before patient withdraws consent;
ALT slightly elevated (baseline)

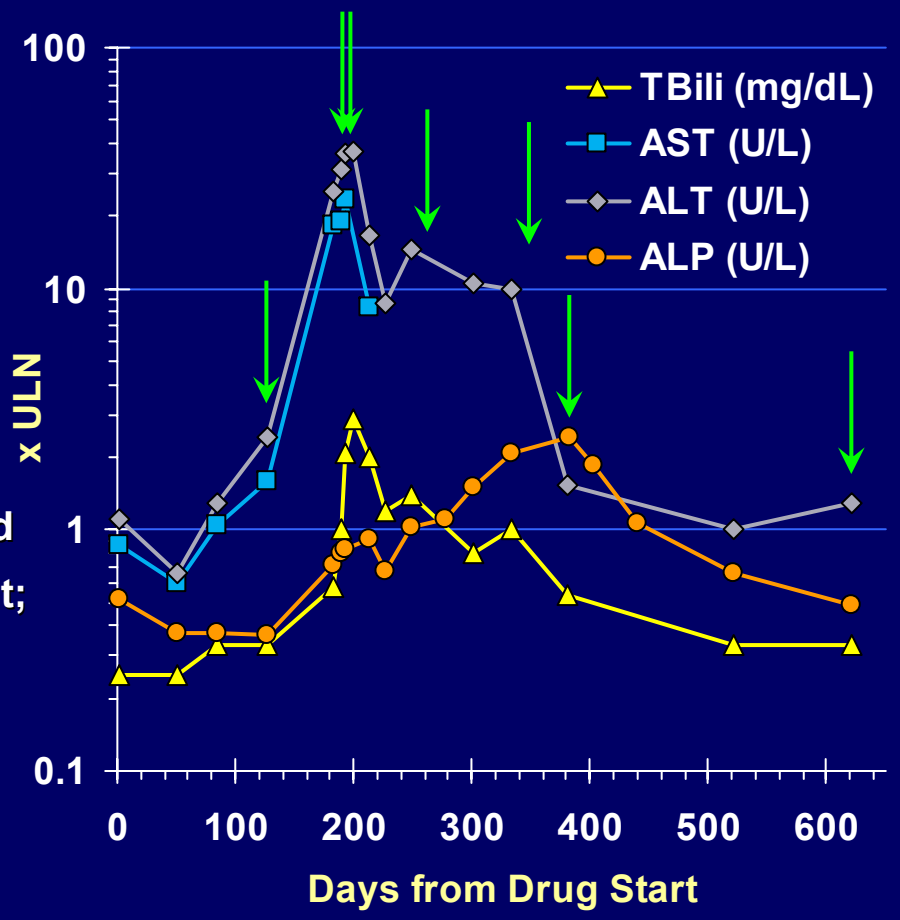
Data:

Viral and autoimmune serologies negative

Immunoglobulins elevated

Compound heterozygote for hemochromatosis

Pathology Ddx: viral, drugs, autoimmune

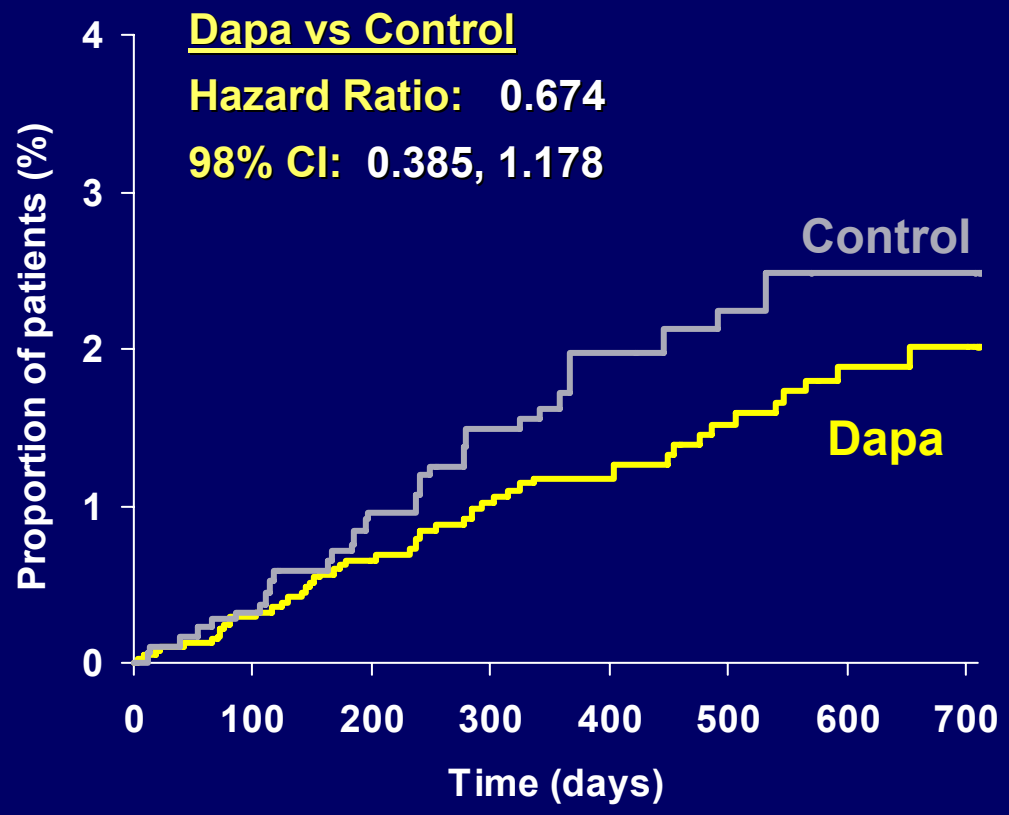


Hepatic Observations: Overall Summary

- No nonclinical evidence of liver injury indicative of clinical risk
- Clinical program shows no imbalance in hepatic enzyme elevations
- No cases of severe liver injury leading to death or transplantation
- One case of concern for possible drug-induced liver injury (versus autoimmune hepatitis)

Cardiovascular Meta-analysis

Summary of Events Contributing to the Primary CV Composite Endpoint During ST + LT Periods



Number of Patients								
Dapa	4097	3826	2767	2350	1532	1368	1062	585
Control	1850	1696	1197	1004	622	538	415	233

	Dapa		Control	
	No. of 1st Event	Event Rate	No. of 1st Event	Event Rate
Patient w/ Events	48	1.11%	30	1.64%
CV death	8	0.19%	4	0.22%
MI	18	0.42%	18	1.00%
Stroke	11	0.26%	5	0.28%
Unstable angina	11	0.26%	3	0.17%

Source: CV Report Figure 1, Table 6, Table 38; rt-pri-endpt-v01.sas

Cox proportional hazards model and composite event rates are stratified by study

Safety Summary

Topics explored because of the mechanism

- Low propensity to cause hypoglycemia
- Increase in urinary tract infections and genital infections
  - No increase in serious infections such as pyelonephritis
- Blood pressure lowering
  - No increase in orthostatic hypotension
- Renal function stable
- Laboratory findings
  - No change in electrolytes
  - Decrease in uric acid
  - Increase in hematocrit
- Bone Health
  - Increase in phosphorus, magnesium, PTH
  - No overall impact on bone density or fractures

Safety Summary

Other topics

- Malignancy data
  - Imbalances in bladder and breast cancers
  - Limited plausibility for causal role
- Hepatic Data
  - No overall signal of liver toxicity
  - One case of concern for possible drug-induced liver injury (versus autoimmune hepatitis)

Cardiovascular meta-analysis

- Excludes an unacceptable increase in cardiovascular risk

Dapagliflozin

Benefit-Risk

James Gavin, MD, PhD

Healing Our Village, Inc.

Dapagliflozin

Proposed Label and Post-Approval Benefit / Risk Assessment

Brian Daniels, MD

Bristol-Myers Squibb

Assessment of Benefit and Risk

BENEFITS	**Identified (NNT)** Glycemic Target (7) 5% Weight Loss (8) Blood Pressure Reduction	**Expected Reduction in:** Microvascular (Retinopathy, Renal Disease) Macrovascular (MACE)
RISKS	**Identified (NNH)** Genital Tract Infection (24) Urinary Tract Infection (125) Volume Depletion (400)	**Precautionary** Imbalances in Fracture (Moderate Renal Impairment) Imbalances in Breast & Bladder Malignancies Single Potential Hepatic Injury Case

NNT: Number needed to treat, NNH: Number needed to harm

Proposed Product Labeling to Ensure Safe Use

- **Patients with Renal Impairment**
  - **Exclusion for patients with estimated GFR of less than 45 mL/min/1.73m²**
  - **Renal function monitoring**
- **Volume Depletion**
  - **5 mg starting dose in patients at risk for volume depletion such as loop diuretics**
  - **Temporary interruption in patients who develop volume depletion**
- **Hypoglycemia**
  - **Lower dose of insulin or insulin secretagogue in combination with dapagliflozin to reduce hypoglycemia risk**
- **Urinary Tract Infections / Genital Infections**
  - **Temporary interruption in patients with pyelonephritis / urosepsis**

Complementary Nature of Various Safety Data by Event Frequency

	Uncommon	Rare	Very Rare
Spontaneous Reporting	-	+/-	+
Pharmacoepidemiology (Observational) Studies	+	+	+/-
Large, Randomized, Clinical Outcomes Study	+	+	+/-

- Data sources from PV system will complement each other in the detection of signals depending on nature of safety outcome

  Integration of these data sources will provide proactive coverage of safety signals from uncommon to very rare events

Assessment of Dapagliflozin Post-Approval: Pharmacovigilance

- Monthly review of spontaneous reports and clinical trial data
- Analyses of the FDA AERS database
- Targeted questionnaires for selected events
  - Serious events of UTI / genital infection
  - Hepatic
  - Renal
  - Breast and bladder cancer
- Blinded adjudication committees for CV and hepatic events and malignancy in clinical tests

Assessment of Dapagliflozin Post-Approval: Observational Studies

Pharmacoepidemiology Studies

- Comparing dapagliflozin with anti-diabetic agents
- Utilizing large US and EU databases with data collected under real-world settings
- Examining:
  - Severe complications of urinary tract infections
  - Liver / kidney injury
  - Bone fractures
  - Cancer

Assessment of Dapagliflozin Post-Approval: Randomized Clinical Trial Data

Clinical Outcomes Study – a large, randomized, controlled trial

- **Establishing dapagliflozin's improvement in long-term CV events using prospective adjudication and analyses**
- **Enabling a complementary mechanism to evaluate the long-term safety profile of dapagliflozin under a controlled setting for evaluation of**
  - **Fracture**
  - **Cancer**
  - **Liver Injury**