FDA Advisory Committee Meeting

Dapagliflozin

July 19, 2011

Ilan Irony, M.D.

DMEP / CDER / FDA

AC for Dapagliflozin

- Introduction
- Agenda
- Topics for Discussion
- Questions

First in class Antidiabetic Drug

- Dapagliflozin: an inhibitor of the sodium glucose cotransporter-2
- Familial renal glycosuria: gene mutation
- Effect on glycemia independent of insulin secretion or sensitivity
- Effect dependent on plasma glucose concentration and glomerular filtration rate

AC meeting for Dapagliflozin

- Applicant and FDA presentations in the morning
- Oral Public Hearing Session: after lunch
- Panel discussion of selected issues and questions for the rest of the day

Topics for discussion - Efficacy

- Effect depends on GFR; as GFR declines, so does the efficacy of dapagliflozin
- 252 diabetics with moderate renal impairment enrolled (eGFR 30 - 59 mL/min/1.73 m^2)
- Placebo-adjusted Change from Baseline in HbA1c at 24 weeks
  - -0.1 % (-0.4, 0.2) for dapagliflozin 5 mg
  - -0.1 % (-0.4, 0.2) for dapagliflozin 10 mg

Topics for discussion - Efficacy

Discuss implications of this reduced efficacy in T2DM where renal impairment can impact a sizeable proportion of individuals with this disease.

Discuss whether additional studies should be conducted (e.g., in specific populations) to better characterize the efficacy of dapagliflozin in T2DM or whether monitoring for renal function should be performed prior to and/or during treatment with dapagliflozin.

Topics for discussion - Safety

Hepatic Safety

- 5 dapagliflozin-treated patients had ALT or AST > 3x ULN with total bilirubin > 2x ULN (biochemical Hy's law). Adequate explanation for biochemical abnormalities identified in all but one case: probable DILI.
- No overall imbalances in severe (> 5X ULN and > 10X ULN) hepatic aminotransferases in the dapagliflozin program, and no signal for hepatotoxicity in the nonclinical program.

Comment on the clinical relevance of the one case and whether sufficient evaluation has been conducted premarketing to determine if dapagliflozin is associated with a risk of hepatotoxicity.

Topics for discussion - Safety

Breast and Bladder Cancer

- Numeric imbalances in breast and bladder cancer observed in the clinical development program:
  - Females with breast cancer (9 [0.4%] vs. 1 [0.1%])
  - Males with bladder cancer (9 [0.3%] vs. 1 [0.05%])
- Cases among dapagliflozin-treated subjects exceed the expected in diabetics based on comparison to the Surveillance, Epidemiology and End Results (SEER) database and on literature.

Topics for discussion - Safety

Breast and Bladder Cancer

- For both types of cancer, discuss:
  - Whether these imbalances signify a risk of carcinogenic potential associated with dapagliflozin?
- For both types of cancer, comment whether the numeric imbalances were impacted by:
  - Any imbalances of baseline risk factors
  - Any detection bias.

Topics for discussion - Safety

Other Safety Findings:

- Please discuss the clinical significance of the following in the T2DM population:
  - increased genital-urinary infections with dapagliflozin
  - bone safety concerns
  - any other safety issues identified in the premarketing application

Voting Question

- Do the efficacy and safety data provide substantial evidence to support approval of dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM?
- Please vote Yes or No.

Voting Question

- If yes, do you recommend any further data be obtained post-marketing?
- If no, what further data should be obtained?

Overview of Efficacy for Dapagliflozin Advisory Committee NDA 202-293

Jonathan Norton, PhD
Office of Biostatistics
CDER

July 19, 2011

Overview

- Applicant submitted 11 Phase 3 studies of dapagliflozin (DAPA).
- In consultation with medical team, determined that my review would focus on 6 studies.
- Will present some results from other studies, as reported by Applicant.

Selected Studies

Study ID (Abbrev.)	Population	Test Tx	Background Tx	Comparator(s)
MB102013 (2013)	Drug-naïve	DAPA 2.5,5, 10 mg	None	Placebo
MB102014 (2014)	Failed on background	DAPA 2.5, 5, 10 mg	Metformin	Placebo
MB102030 (2030)	Failed on background	DAPA 5, 10 mg	Pioglitazone	Placebo
D1690C00006 (C00006)	Failed on background	DAPA 2.5, 5, 10 mg	Insulin and up to two oral anti-diabetics	Placebo
D1690C00004 (C00004)	Failed on background	DAPA 2.5/5/10 mg (titrated)	Metformin	Glipizide
MB102034 (2034)	Drug-naïve with higher HbA1c	DAPA 10 mg + metformin	None	DAPA 10 mg, metformin

Design Features

- Parallel-arm designs.
- All used change from baseline in HbA1c as primary endpoint.
- All but C00004 (glipizide-controlled) used test for superiority at Week 24.
- C00004 tested for non-inferiority at Week 52.
- All but C00004 included glycemic rescue therapy.

Primary Efficacy Analysis

- Analysis of covariance (ANCOVA) with adjustment for baseline HbA1c, other factors depending on study.
- Primary imputation was last-observation-carried-forward (LOCF), excluding observations after rescue. Raises issues that will be discussed later.

Change in HbA1c at Week 24

Placebo-controlled studies

Study		Dapagliflozin Dose			
		Placebo	**2.5 mg**	**5 mg**	**10 mg**
2013 (N=262)	**Adj. Mean (SE)**	-.23 (.10)	-.58 (.11)	-.77 (.11)	-.89 (.11)
	Diff. vs. Placebo	--	***-.35 (.15)****	***-.54 (.15)****	***-.66 (.15)****
2014 (N=534)	**Adj. Mean (SE)**	-.30 (.07)	-.67 (.07)	-.70 (.07)	-.84 (.07)
	Diff. vs. Placebo	--	***-.38 (.10)****	***-.41 (.10)****	***-.54 (.10)****
2030 (N=418)	**Adj. Mean (SE)**	-.42 (.08)	N.A.	-.82 (.08)	-.97 (.08)
	Diff. vs. Placebo	--	***N.A.***	***-.40 (.12)****	***-.55 (.12)****
C00006 (N=788)	**Adj. Mean (SE)**	-.30 (.05)	-.75 (.05)	-.82 (.05)	-.90 (.05)
	Diff. vs. Placebo	--	***-.45 (.07)****	***-.52 (.07)****	***-.60 (.07)****

*p < .05 vs. placebo **p < .001 vs. placebo. Note: LOCF imputation.

Change in HbA1c (cont.)

- Initial combination (2034) – Week 24

	Treatment Arm		
	DAPA 10 mg + MET (N=202)	**DAPA 10 mg (N=216)**	**MET (N=203)**
Adj. Mean (SE)	-1.98 (.08)	-1.45 (.07)	-1.44 (.08)
Diff. from DAPA	***-.53 (.11)*****	--	--
Diff from. MET	***-.54 (.11)*****	--	--

**p < .001 vs. monotherapy. Note: LOCF imputation.

- Secondary analysis showed DAPA alone to be non-inferior to MET alone.

Change in HbA1c (cont.)

- Glipizide-controlled (C00004)
  - Both DAPA and SU (glipizide) arms showed change of -.52% from baseline (N=801).
  - 95% interval for difference = (-.11%, .11%).
  - Planned NI margin was .35%. Consistent with FDA advice.

Subgroup Analysis: HbA1c

- Conducted subgroup analysis in the six studies that I closely reviewed.
- Focused on following: baseline HbA1c, age (under 65 vs. 65+), gender, race, and region (US + Canada vs. rest of world).
- In fixed-dose studies, pooled 5 and 10 mg doses and excluded 2.5 mg.
- In three studies (2013, 2030, C00006), DAPA had significantly stronger effect in patients with higher baseline HbA1c (p for interaction < .01 for each study).
- In study 2014, DAPA had stronger effect in patients under 65 years (p = .002). For older patients, placebo (MET alone) numerically better. However, this pattern did not hold for other studies.

Subgroup Analysis (cont.)

- For Study C00004 (glipizide-controlled), treatment effect interacted with race (p = .04).

Race		**Arm**	
		SU	**DAPA**
White (N=650)	**Adj. Mean (SE)**	-.63 (.04)	-.55 (.04)
	Diff. vs. SU	--	***.09 (.06)***
Black/ African-American (N=50)	Adj. Mean (SE)	.01 (.16)	*-.37 (.15)*
	Diff. vs. SU	--	***-.38 (.22)***
Asian (N=61)	Adj. Mean (SE)	.07 (.14)	*-.25 (.15)*
	Diff. vs. SU	--	***-.33 (.20)***
Other (N=40)	Adj. Mean (SE)	-.29 (.18)	*-.55 (.18)*
	Diff. vs. SU	--	***-.26 (.25)***

Issue: Imputation

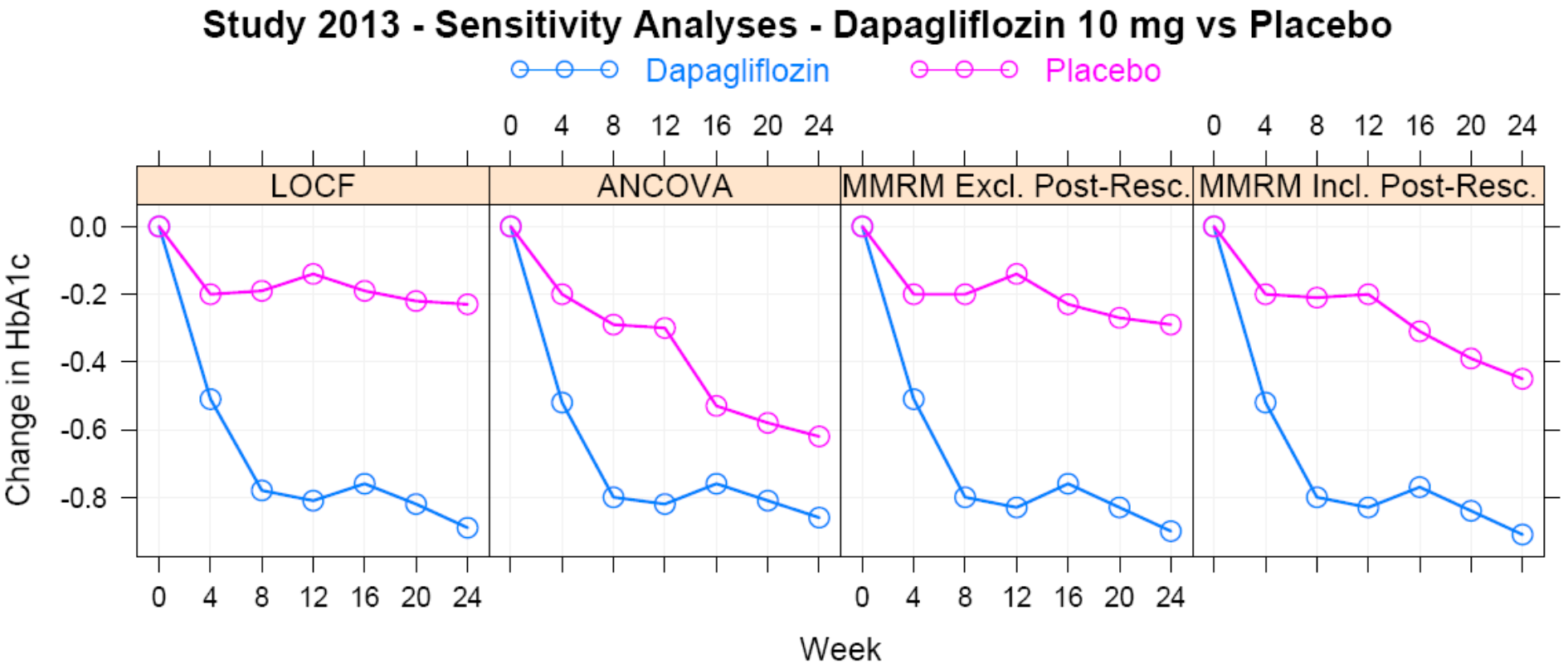
- As noted earlier, the primary imputation method was LOCF, excluding observations after rescue.
- In the past, FDA has implicitly endorsed this method.
- In July 2010, the National Academy of Sciences released a report, commissioned by FDA, which is critical of LOCF and other single-imputation methods.
- Studies show DAPA to be an effective drug, but appropriate estimate of efficacy is needed.

Sensitivity Analyses

- Applicant:
  - ANCOVA of observed cases, excluding observations after rescue
  - Mixed-effects model for repeated measures (MMRM), excluding observations after rescue
- Reviewer:
  - MMRM, ***including observations after rescue***

More on Rescue

- May seem counterintuitive to include observations after rescue treatment.
- However, intent-to-treat principle says that analysis should be based on the randomized treatment (e.g., DAPA 10 mg), not the actual treatment (e.g., DAPA 10 mg + rescue).
- If post-rescue observations are excluded, then we are no longer strictly basing the analysis on the randomized treatment, and the analysis is not guaranteed to be statistically valid.


Study 2013 - Sensitivity Analyses - Dapagliflozin 10 mg vs Placebo
Dapagliflozin
Placebo
LOCF
ANCOVA
MMRM Excl. Post-Resc.
MMRM Incl. Post-Resc.
Change in HbA1c
0.0
-0.2
-0.4
-0.6
-0.8
0 4 8 12 16 20 24
Week

Reviewer Sensitivity Analysis

Study		Dapagliflozin Dose			
		Placebo	2.5 mg	5 mg	10 mg
2013	Adj. Mean (SE)	-.45 (.09)	-.72 (.10)	-.81 (.10)	-.91 (.10)
	Diff. vs. Placebo	--	*-.27 (13)**	*-.36 (.14)**	*-.45 (.13)***
2014	Adj. Mean (SE)	-.43 (.07)	-.72 (.07)	-.70 (.07)	-.87 (.07)
	Diff. vs. Placebo	--	*-.29 (.10)**	*-.27 (.10)**	*-.44 (.10)***
2030	Adj. Mean (SE)	-.58 (.08)	N.A.	-.86 (.08)	-1.02 (.08)
	Diff. vs. Placebo	--	*N.A.*	*-.28 (.12)**	*-.44 (.12)***
C00006	Adj. Mean (SE)	-.39 (.06)	-.80 (.05)	-.89 (.05)	-.97 (.05)
	Diff. vs. Placebo	--	*-.40 (.08)***	*-.50 (.08)***	*-.57 (.08)***

*p < .05 vs. placebo **p < .001 vs. placebo. Imputation: MMRM, incl. post-rescue.

Reviewer Sensitivity (cont.)

- Initial combination (2034)

	Treatment Arm		
	DAPA 10 mg + MET	**DAPA 10 mg**	**MET**
Adj. Mean (SE)	-2.02 (.07)	-1.54 (.07)	-1.54 (.07)
Diff. from DAPA	***-.48 (.10)*****	--	--
Diff from. MET	***-.48 (.10)*****	--	--

**p < .001 vs. placebo. Imputation: MMRM, incl. post-rescue.

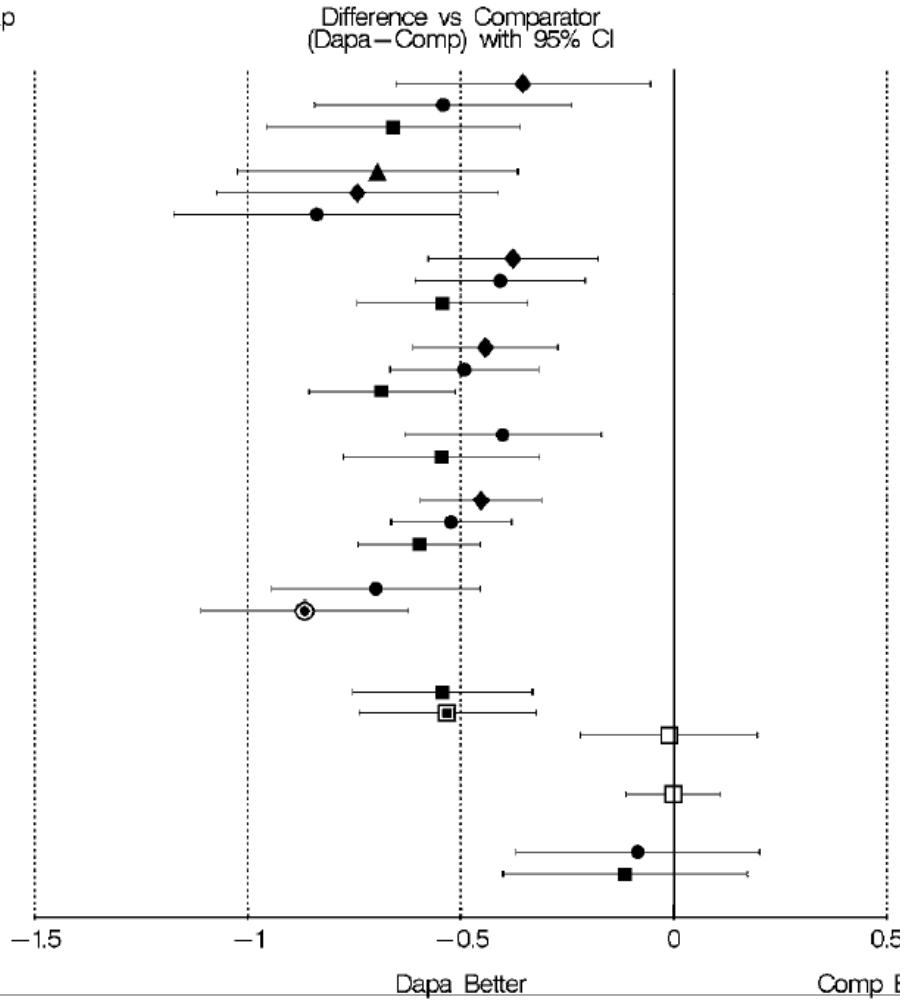
- SU-controlled (C00004) – no rescue.

Results for Other Studies

- Applicant submitted reports for four additional Phase 3 studies with change in HbA1c as the primary endpoint.
- Results were generally consistent with those from the studies that I closely reviewed, showing evidence of efficacy for the 5 and 10 mg doses.
- Results for all ten Phase 3 studies with HbA1c as the primary endpoint are shown on following slide.
- Only reported ***failed*** Phase 3 study was in subjects with moderate renal impairment. This study will be discussed later in the presentation.

Change in HbA1c, End of Short-Term Period

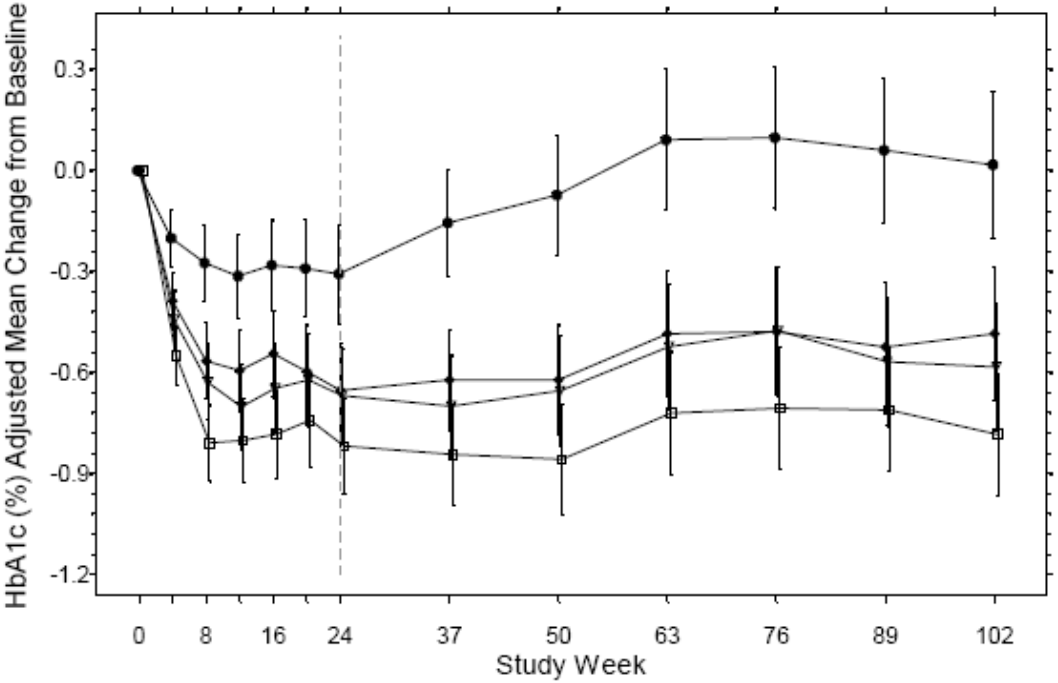
Study	Dapa vs Comparator	Dapa N	Comp N
MB102013 (Monotherapy)	2.5mg vs Pla	64	72
	5mg vs Pla	61	72
	10mg vs Pla	65	72
MB102032 (Monotherapy)	1mg vs Pla	72	68
	2.5mg vs Pla	72	68
	5mg vs Pla	66	68
MB102014 (Add–on to Met)	2.5mg vs Pla	135	134
	5mg vs Pla	133	134
	10mg vs Pla	132	134
D1690C00005 (Add–on to SU)	2.5mg vs Pla	154	143
	5mg vs Pla	142	143
	10mg vs Pla	150	143
MB102030 (Add–on to Pio)	5mg vs Pla	140	138
	10mg vs Pla	140	138
D1690C00006 (Add–on to Ins)	2.5mg vs Pla	198	188
	5mg vs Pla	210	188
	10mg vs Pla	192	188
MB102021 (Initial Combo)	5mg+ Met vs Met	185	195
	5mg+ Met vs 5mg	185	196
	5mg vs Met	196	195
MB102034 (Initial Combo)	10mg+ Met vs Met	202	203
	10mg+ Met vs 10mg	202	216
	10mg vs Met	216	203
D1690C00004 (SU Active Control)	10mg vs SU	400	401
MB102029 (Renal Impairment)	5mg vs Pla	83	82
	10mg vs Pla	82	82



Source: Figure 5, Bristol-Myers Squib/ AstraZeneca Background Document for Dapagliflozin AC Meeting, 7/19/2011.

Issue: Durability

Figure 15: **Adjusted Mean Change from Baseline in HbA1c (%), Up to Week 102, Add-on to Metformin**



Sample Size per Time Point

PLA + MET	133 128 127 120 115 102 100	96	74	60	46	38	28
DAPA 2.5 MG + MET	135 133 133 128 127 118 117	115	96	82	65	57	36
DAPA 5MG + MET	133 131 131 128 127 122 118	116	94	84	64	59	47
DAPA 10MG + MET	132 130 130 126 128 114 117	113	102	96	80	75	57

Treatment Group

(N= 137) PLA + MET
(N= 137) DAPA 2.5 MG + MET
(N= 137) DAPA 5MG + MET
(N= 135) DAPA 10MG + MET

Source: Bristol-Myers Squib / AstraZeneca Background Document for Dapagliflozin AC Meeting, 7/19/2011.

Durability (cont.)

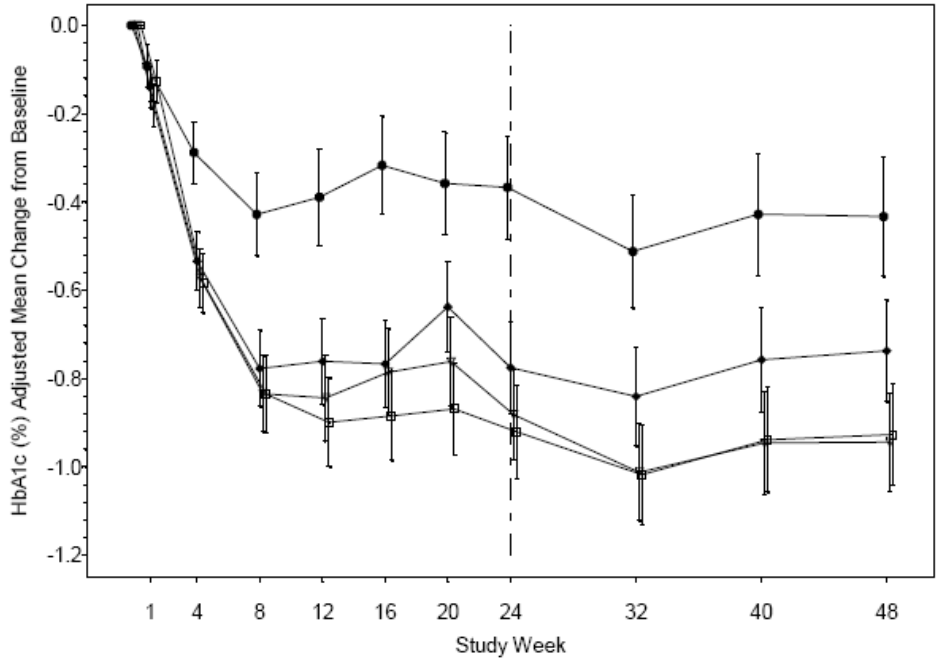
- Previous figure purports to show evidence of durability.
- However, sample size drastically reduced over time, due to dropout or rescue:

	Placebo	2.5 mg	5 mg	10 mg
N – Wk. 0	133	135	133	132
N – Wk. 102	28 (21%)	36 (27%)	47 (35%)	57 (43%)

- Considering limited, selective sample remaining at end of extension period, this figure should be interpreted with caution.

Durability (cont.)

Figure 17: **Adjusted Mean Change from Baseline HbA1c (%) up to Week 48, Add-on to Insulin**



Sample Size per Time Point

PLA + INS	184	168	142	135	128	120	122	111	100	89
DAPA 2.5MG + INS	199	195	183	176	172	168	162	151	145	135
DAPA 5MG + INS	209	197	182	178	175	171	165	163	153	147
DAPA 10MG + INS	188	185	176	171	166	160	158	153	148	139

Treatment Group
(N= 193) PLA + INS
(N= 202) DAPA 2.5MG + INS
(N= 211) DAPA 5MG + INS
(N= 194) DAPA 10MG + INS

Source: Bristol-Myers Squib / AstraZeneca Background Document for Dapagliflozin AC Meeting, 7/19/2011.

Durability (cont.)

- Similarly, Figure 17 shows the results for the insulin add-on study (C00006) to Week 48. N is greatly reduced in placebo arm, from 184 to 89 (48%).

Summary: HbA1c

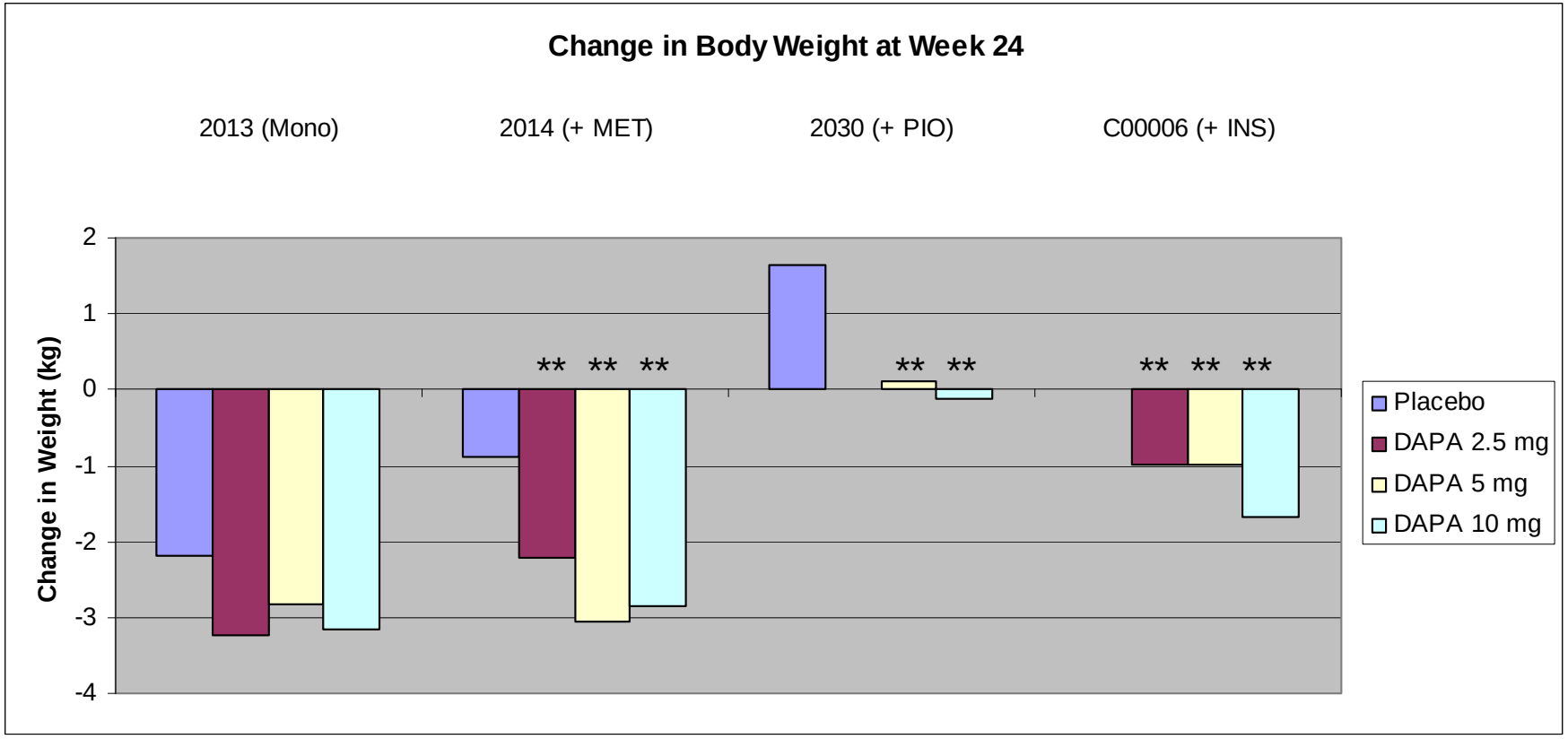
- Results from the six studies that I focused on showed dapagliflozin to be effective as monotherapy and in combination with other drugs. Results for other four studies, as reported by Applicant, also support this finding.
- With LOCF, 10 mg dose shown to have an effect of -.5% to -.6% on HbA1c.
- Sensitivity analyses suggest effect may be smaller.
- Figures in Applicant briefing package do not provide convincing evidence of durability.

Results: FPG

- Fasting plasma glucose (FPG)
- In the four placebo-controlled studies, both 5 and 10 mg doses superior to control at Week 24 ($p < .001$). Est. effect of 10 mg dose ranged from -17.5 to -25.0 mg/dL. Effect of 5 mg dose range from -15.5 to -22.1 mg/dL.
- In combination study (2034), DAPA + MET superior to each component ($p < .001$). Effect of DAPA + MET vs. MET was -25.5 mg/dL.

Results: Weight Loss

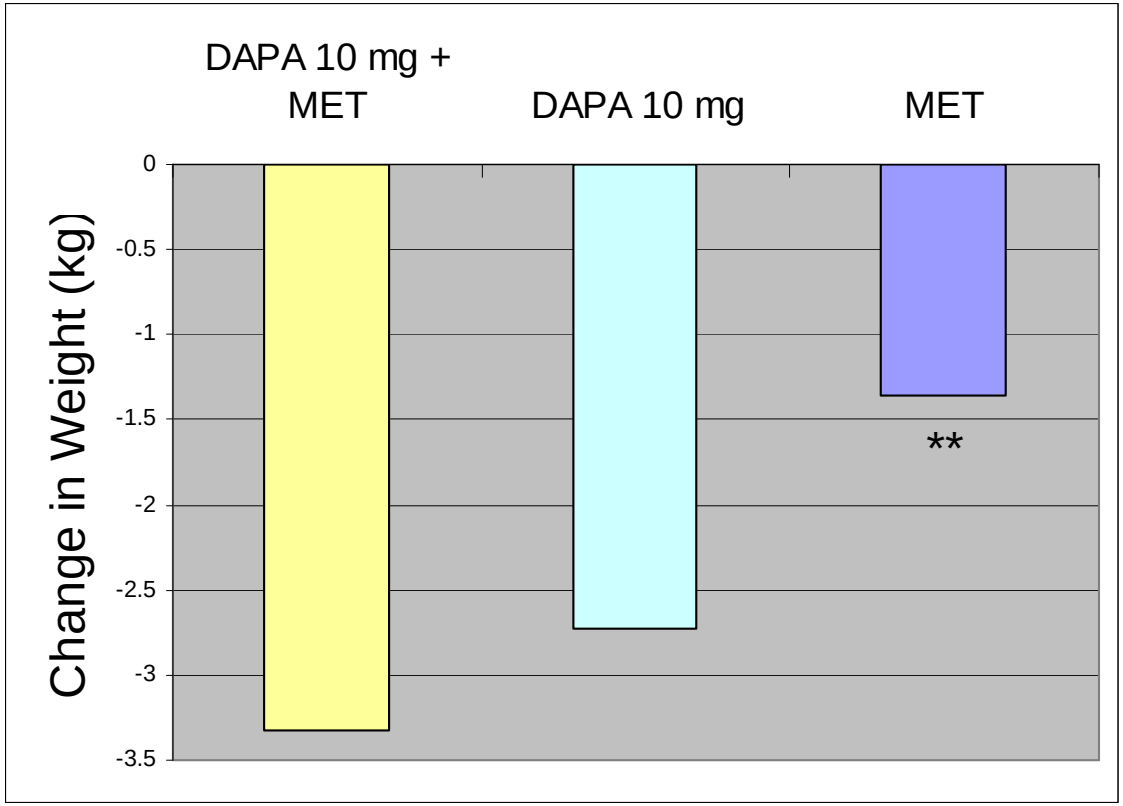
Results from placebo-controlled studies



**p < .001 vs. placebo. Note: LOCF imputation.

Results: Weight Loss (cont.)

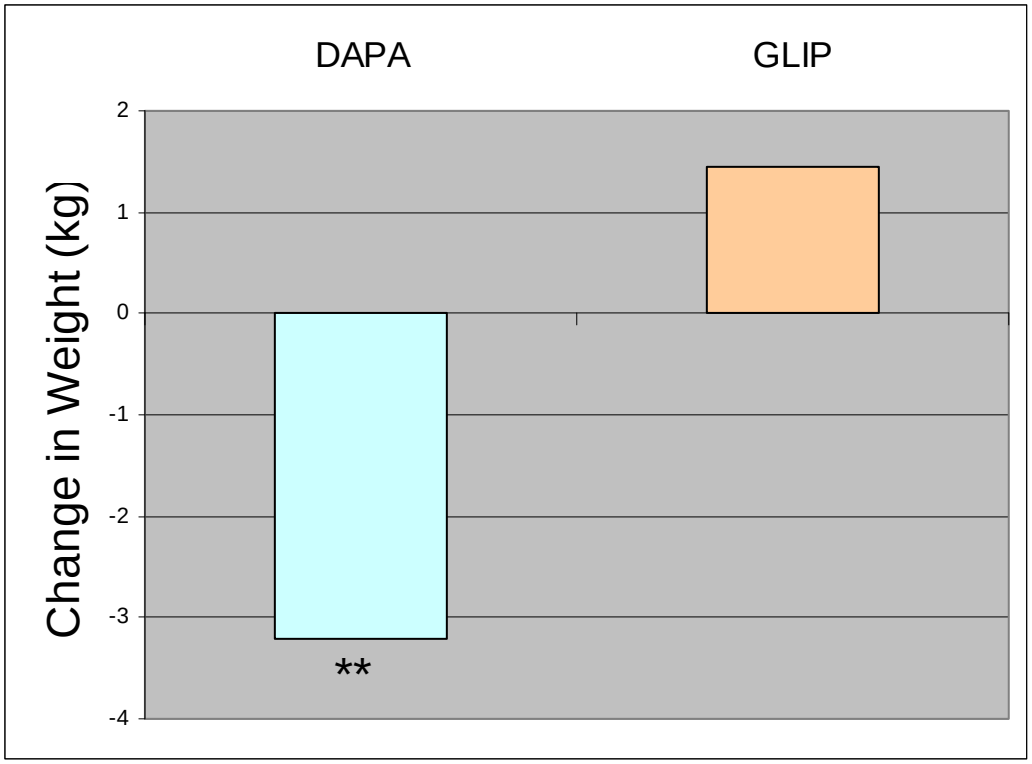
Initial combination (2034), Week 24



**p < .001 for combination vs. comparator. Note: LOCF imputation.

Results: Weight Loss (cont.)

SU-controlled (C00004), Week 52

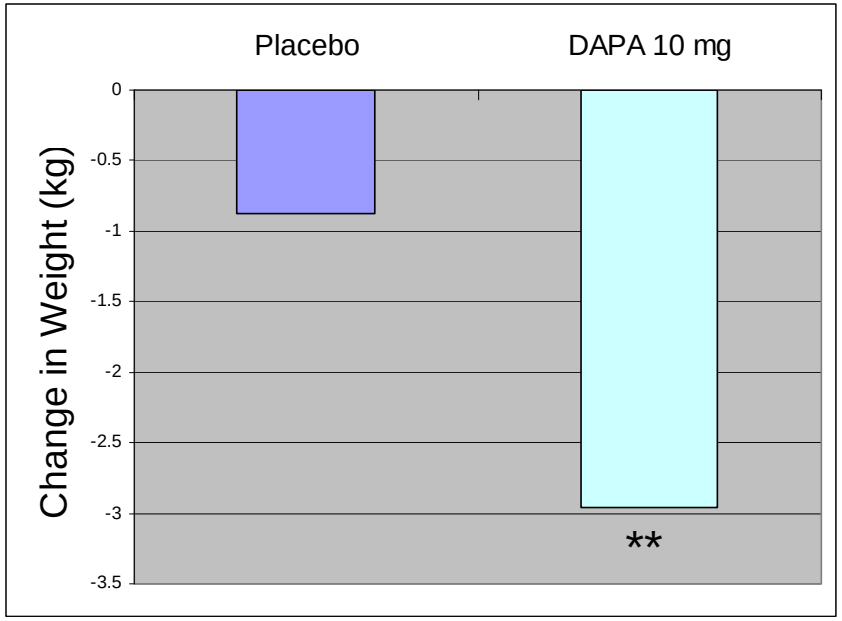


**p < .001 vs. glipizide. Note: LOCF imputation.

Weight Loss Study

- Study D1690C00012 tested DAPA 10 mg as an add-on to MET (placebo-controlled). N=180.
- Primary endpoint was change in total body weight at Week 24.

- Applicant reports that subjects on DAPA arm lost 2.96 kg (SE = .27), compared to .88 kg (.28) lost on placebo arm. Difference of -2.08 kg ($p < .0001$).



Weight Loss by Gender

- For weight-loss study (C00012), Applicant reports differential effect by gender (p for interaction = .048) in kg lost at Wk 24.

Gender		Arm	
		Placebo + Metf.	Dapa. 10 mg + Metf.
Male (N=100)	Adj. Mean (SE)	-.80 (.37)	-3.56 (.39)
	Diff.	**--**	***-2.76 (.52)***
Female (N=80)	Adj. Mean (SE)	-1.06 (.42)	-2.28 (.42)
	Diff.	**--**	***-1.22 (.58)***

Renal Impairment Study

- Study MB102029 was in subjects with moderate renal impairment, defined as an eGFR of 30-59 mL/min/1.73m^2.
- DAPA was not statistically better than placebo for change in HbA1c at Week 24 for either 5 or 10 mg dose.
- Moreover, an “ad-hoc” subgroup analysis in ***stage 3A*** patients with eGFR of 45-59 also failed to show statistical significance for either dose.

Renal Impairment (cont.)

Study 2029 – Change in HbA1c at Week 24

Patient Population		Dapagliflozin Dose		
		Placebo	5 mg	10 mg
Moderate Renal Impairment (N=247)	Adj. Mean (SE)	-.32 (.17)	-.41 (.17)	-.44 (.17)
	Diff. vs. Placebo	--	-.08 (.14)	-.11 (.15)
Stage 3A Subgroup (N=107)	Adj. Mean (SE)	-.11 (.23)	-.47 (.25)	-.44 (.25)
	Diff. vs. Placebo	--	-.37 (.23)	-.33 (.24)

No treatment comparisons were statistically significant. Note: LOCF imputation.

Renal Impairment (cont.)

- In background package (p.181-182), Applicant states:

  [W]hen the stage 3A sub-group population… from the special study [2029] was analyzed for HbA1c effects of dapagliflozin 10 mg, the mean change from baseline and placebo-corrected mean change from baseline at Week 24 were –0.44% and –0.33%, respectively (n = 32). These mean changes are consistent with changes evident in the larger pooled analysis… ***Dapagliflozin was modestly effective in patients with stage 3A moderate renal impairment.*** [emphasis added]

- Dedicated renal study (2029) does not support this conclusion, because treatment effect was ***not statistically significant*** in this subgroup.

Renal Impairment (cont.)

- Applicant briefing package (p. 180) also refers to results for patients with moderate renal impairment (87% stage 3A) in a ***pooled analysis*** of nine studies. The Applicant reports that this analysis showed significant effect on the DAPA 10 mg dose on HbA1c at 24 weeks.
- We did not review this analysis because there was a dedicated study of moderate renal impairment of the same duration.

Summary

- Studies with HbA1c as primary endpoint show that dapagliflozin is effective in subjects with normal renal function or mild impairment.
- Due to study discontinuations and rescue, estimates of the magnitude of the treatment effect vary. LOCF may overstate effect.
- Secondary endpoints supportive.
- Durability claims in Applicant briefing package questionable.
- Dedicated study in patients with moderate renal impairment did not show efficacy.

Safety Issues: Dapagliflozin

Somya V. Dunn, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
July 19, 2011

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - Breast Cancer
  - Hepatic Events
  - Genital Infections
  - Urinary Tract Infections
  - Bone Health
  - Cardiovascular Safety

Dapagliflozin

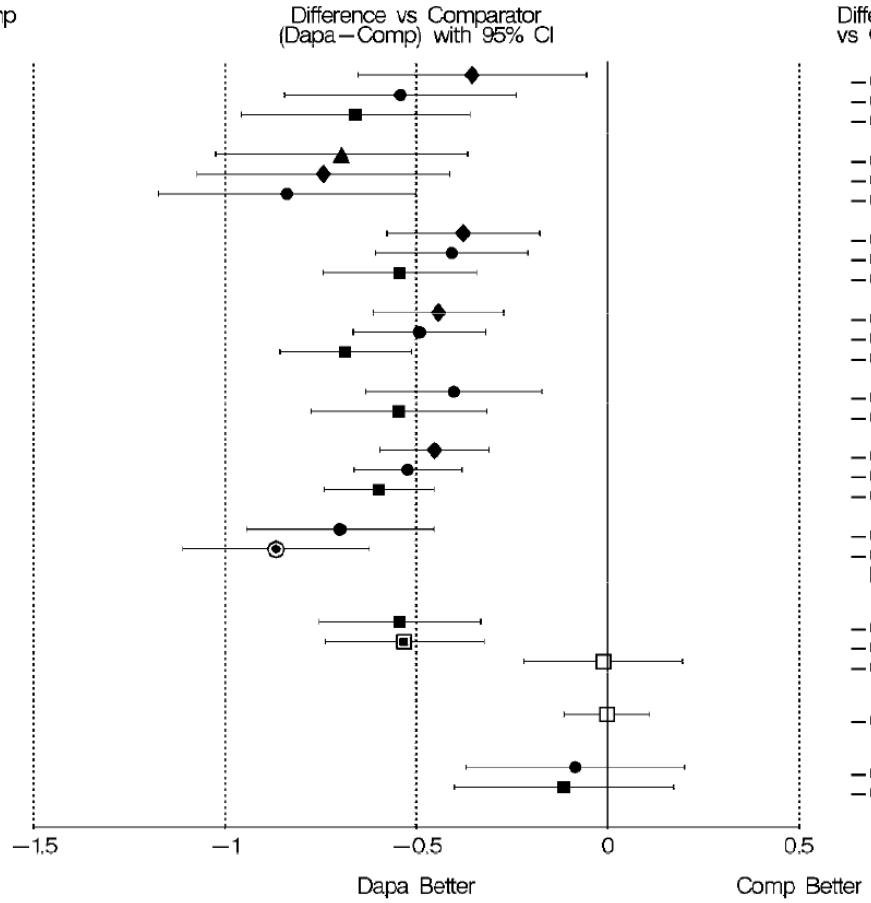
- SGLT2: Major transporter for renal glucose reabsorption
- Dapagliflozin is an SGLT2 inhibitor
- Insulin-independent, renal elimination of glucose
- Proposed indication: Adjunct to diet and exercise to improve glycemic control in adults with T2DM
- Proposed dose is 10 mg, once daily
- Patients at risk for volume depletion 5 mg
- If approved, dapagliflozin will be a first-in-class therapy

Dapagliflozin Clinical Program

- 26 Pharmacology trials
- 3 Phase 2b trials
- 11 Phase 3 trials
- Cumulative exposure in the Phase 2b and 3 clinical trials
  - 4009 patient-years in dapagliflozin treated subjects
  - 1682 patient-years in controls
- 2.2 times more subjects exposed to dapagliflozin (N=4287) than to control (N=1941)

Efficacy of Dapagliflozin—HbA1c

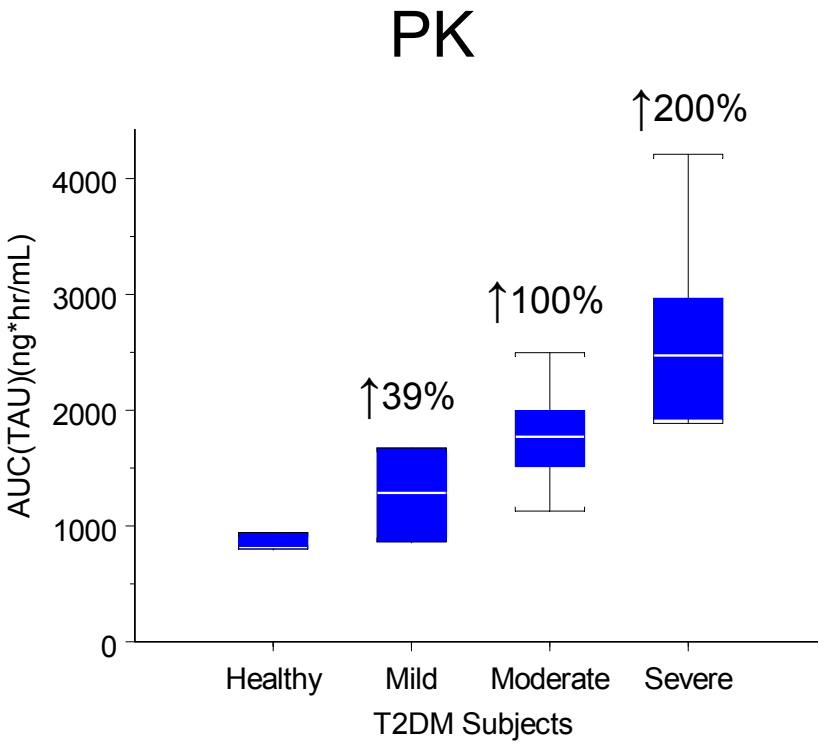
Study	Dapa vs Comparator	Dapa N	Comp N	Difference vs Comp	95% Conf. Interval
MB102013 (Monotherapy)	2.5mg vs Pla	64	72	−0.35	[−0.65 , −0.05]
	5mg vs Pla	61	72	−0.54	[−0.84 , −0.24]*
	10mg vs Pla	65	72	−0.66	[−0.96 , −0.36]*
MB102032 (Monotherapy)	1mg vs Pla	72	68	−0.69	[−1.02 , −0.37]*
	2.5mg vs Pla	72	68	−0.74	[−1.07 , −0.41]*
	5mg vs Pla	66	68	−0.84	[−1.17 , −0.50]*
MB102014 (Add−on to Met)	2.5mg vs Pla	135	134	−0.38	[−0.58 , −0.18]*
	5mg vs Pla	133	134	−0.41	[−0.61 , −0.21]*
	10mg vs Pla	132	134	−0.54	[−0.74 , −0.34]*
D1690C00005 (Add−on to SU)	2.5mg vs Pla	154	143	−0.44	[−0.61 , −0.27]*
	5mg vs Pla	142	143	−0.49	[−0.67 , −0.32]*
	10mg vs Pla	150	143	−0.68	[−0.86 , −0.51]*
MB102030 (Add−on to Pio)	5mg vs Pla	140	138	−0.40	[−0.63 , −0.17]*
	10mg vs Pla	140	138	−0.55	[−0.78 , −0.31]*
D1690C00006 (Add−on to Ins)	2.5mg vs Pla	198	188	−0.45	[−0.59 , −0.31]*
	5mg vs Pla	210	188	−0.52	[−0.66 , −0.38]*
	10mg vs Pla	192	188	−0.60	[−0.74 , −0.45]*
MB102021 (Initial Combo)	5mg+ Met vs Met	185	195	−0.70	[−0.94 , −0.45]*
	5mg+ Met vs 5mg	185	196	−0.86	[−1.11 , −0.62]*
	5mg vs Met	196	195	ND	
MB102034 (Initial Combo)	10mg+ Met vs Met	202	203	−0.54	[−0.75 , −0.33]*
	10mg+ Met vs 10mg	202	216	−0.53	[−0.74 , −0.32]*
	10mg vs Met	216	203	−0.01	[−0.22 , 0.20] ÷
D1690C00004 (SU Active Control)	10mg vs SU	400	401	−0.00	[−0.11 , 0.11] ÷
MB102029 (Renal Impairment)	5mg vs Pla	83	82	−0.08	[−0.37 , 0.20]
	10mg vs Pla	82	82	−0.11	[−0.40 , 0.17]



Applicant Response to Inquiry 5/18/11

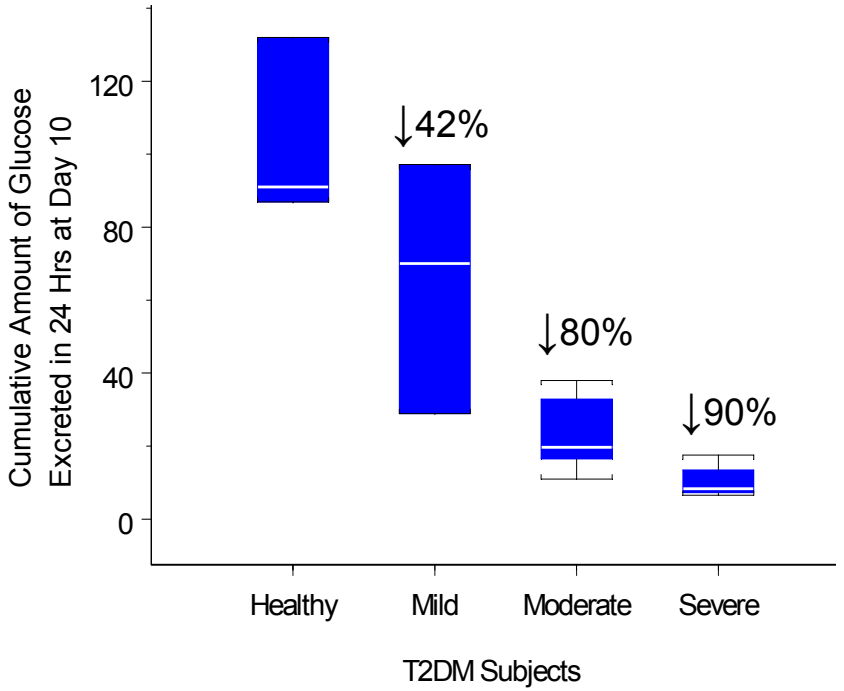
Effect of Renal Impairment on PK/PD of Dapagliflozin

- Dapagliflozin 20 mg once daily for 10 days in T2DM patients
- Higher systemic exposures in subjects with moderate and severe renal impairment



Effect of Renal Impairment on PK/PD of Dapagliflozin

- Despite higher exposure in renal impairment, there was a decrease in glucose excretion



Safety Pools

Safety Pool	**Treatment Period**	**Studies**
All Phase 2b and 3 Studies Pool	Short Term + Long Term	11 Phase 3 Studies 3 Phase 2b Studies
Placebo-controlled Pool	Short Term	9 Phase 3 Studies 3 Phase 2b Studies
Placebo-controlled Pool	Short + Long Term	5 Phase 3 Studies

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - **Bladder Cancer**
  - Breast Cancer
  - Hepatic Events
  - Genital Infections
  - Urinary Tract Infections
  - Bone Health
  - Cardiovascular Safety

Bladder Cancer
Dapagliflozin Clinical Program

- 7 cases in dapagliflozin treated male subjects in the phase 2b/3 pool reported at 4MSU
- Updated as 9 in dapagliflozin and 1 in placebo
- Estimated incidence rates with updated cases
  - Exposure of 3007 subject-years in males in the dapagliflozin arms
    - 299 per 100,000 subject-years (95% CI, 137 – 568)
  - Compared to 1 case during 1697 subject-years in male controls
    - 59 cases per 100,000 subject-years (95% CI, 0.8 – 328)

Bladder Cancer
Dapagliflozin Clinical Program

- Rate ratio comparing incidence of bladder cancer dapagliflozin vs. controls in males 5.08 (95% CI, 0.70 – 222.6); p=0.15
- Trials not powered to distinguish between incidence of bladder cancer in male dapagliflozin subjects versus controls

Bladder Cancer Risk Factors—Phase 2b/3 Pool

	DAPA TOTAL N=4310	All CONTROL N=1962
HEMATURIA AT BASELINE		
SUBJECTS WITH AT LEAST ONE URINE DIPSTICK PRIOR TO RECEIVING STUDY DRUG SHOWING 1+,2+,3+ OR GREATER BLOOD	387 (9.0)	176 (9.0)
SMOKING STATUS (%)		
NEVER	2589 (60.1)	1172 (59.7)
CURRENT	711 (16.5)	318 (16.2)
FORMER	1007 (23.4)	472 (24.1)
UNKNOWN	3 (0.1)	0 (0.0)
GENDER		
MALE	2192 (50.9)	1033 (52.7)
FEMALE	2118 (49.1)	929 (47.3)
RACE		
WHITE	3486 (80.9)	1591 (81.1)
BLACK/AFRICAN AMERICAN	158 (3.7)	73 (3.7)
ASIAN	558 (12.9)	242 (12.3)
HISTORY OF CHRONIC CYSTITIS	4 (0.1)	5 (0.3)
USE OF CYCLOPHOSPHAMIDE	0	0

Applicant Response to Inquiry 5/20/11

Bladder Cancer Epidemiology Review

- Bladder cancer incidence reviewed in the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute
- Rate adjusted with a literature-based factor
  - 40% increased risk for bladder cancer in a diabetic population, adjusted for smoking and other risk factors
- Standardized Incidence Ratio calculated
  - Compares observed incidence of bladder cancer in dapagliflozin treated patients with expected incidence in an age- and sex-matched background population

Bladder Cancer Epidemiology Study

Bladder Cancer Observed vs. Expected

Treatment	Observed in Clinical Trials	Expected Based on SEER Data
Dapagliflozin Treated	9	3
Controls	1	2

- Standardized Incidence Ratio of observed versus expected cases in males exposed to dapagliflozin was 2.98 (95% CI, 1.36 – 5.65), p=0.008

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - **Breast Cancer**
  - Hepatic Events
  - Genital Infections
  - Urinary Tract Infections
  - Bone Health
  - Cardiovascular Safety

Breast Cancer
Dapagliflozin Clinical Program

- Nine cases observed in the female dapagliflozin-treated patients versus none in controls in Phase 2b/3 Pool
- Updated data from sponsor: 1 case in controls
- Estimated incidence rates with the updated 1 case in controls included
  - Exposure of 2416 subject-years in female patients in dapagliflozin arms
    - 372 per 100,000 subject-years (95% CI, 170-707)
  - Exposure of 1085 subject-years in female controls
    - 92 per 100,000 subject-years in the control arms (95% CI, 23-5138)

Breast Cancer
Dapagliflozin Clinical Program

- Rate ratio of breast cancer among female dapagliflozin-treated patients vs. control

  4.04 (95% CI, 0.56 – 177.1); p=0.27

- Clinical trials not powered to distinguish the incidence of breast cancer in female dapagliflozin subjects vs. controls

Breast Cancer Risk Factors—Females Phase 2b/3 Pool

	DAPA TOTAL N=2110	ALL CONTROL N=922
BODY MASS INDEX (KG/M2)		
N	2110	922
MEAN	32.24	32.17
MEDIAN	32.00	31.90
MIN , MAX	16.90 , 48.40	17.50 , 45.20
Q1 , Q3	28.10 , 36.20	28.00 , 36.20
STANDARD DEVIATION	5.643	5.794
BODY MASS INDEX CATEGORIZATION (%)		
< 30 KG/M2	768 (36.4)	351 (38.1)
>= 30 KG/M2	1342 (63.6)	571 (61.9)
NOT REPORTED	0	0
AGE CATEGORIZATION (%)		
<=50 YEARS	576 (27.3)	256 (27.8)
>50 YEARS	1534 (72.7)	666 (72.2)
< 45	271 (12.8)	128 (13.9)
>= 45 - < 55	589 (27.9)	248 (26.9)
>= 55 - < 65	823 (39.0)	320 (34.7)
>= 65 - < 75	376 (17.8)	194 (21.0)
>= 75	51 (2.4)	32 (3.5)
NOT REPORTED	0	0

Applicant Response to Inquiry 5/4/11

Breast Cancer Risk Factors Continued

	DAPA TOTAL N=2110		ALL CONTROL N=922	
BODY MASS INDEX AND AGE CATEGORIZATION (%)				
>=30 KG/M2 AND >50 YEARS	940	(44.5)	409	(44.4)
ALCOHOL CONSUMPTION AT BASELINE (%)				
YES	654	(31.0)	273	(29.6)
NO	1456	(69.0)	649	(70.4)
NOT REPORTED	0		0	
TOBACO USE AT BASELINE (%)				
NEVER	1608	(76.2)	713	(77.3)
CURRENT	235	(11.1)	88	(9.5)
FORMER	267	(12.7)	121	(13.1)
UNKNOWN	0		0	
PRE-RANDOMIZATION USE OF OESTROGEN MEDICATION				
YES	79	(3.7)	45	(4.9)
NO	2031	(96.3)	877	(95.1)
NOT REPORTED	0		0	

Age-specific Incidence Rates of Female Breast Cancer Observed in Dapagliflozin-treated Arms vs. Reported in Literature — Literature Review

Age	Study	Incidence rate of breast cancer per 1,000 person-years	
		Literature	Dapagliflozin clinical trials*
55-64	Lipscombe (Canada)	2.90	5.73
65-79		3.02	7.15
40-69	Inoue (Japan)	0.62	3.87
50-75	Michels (U.S)	3.41	4.98
45-64	Mink (U.S)	4.04	4.11

* Data from female patients in the dapagliflozin-treatment arms in the phase 2b/3 pool

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - Breast Cancer
  - **Hepatic Events**
  - Genital Infections
  - Urinary Tract Infections
  - Bone Health
  - Cardiovascular Safety

Hepatic Adjudication Report

- Submitted with Four Month Safety Update
- Blinded adjudication process for liver abnormalities—3 expert hepatologists
- Criteria for adjudication were:
  - AST and/or ALT > 3X ULN and TB > 1.5X ULN (within 14 days of the AST and/or ALT elevation)
  - AST and/or ALT > 5X ULN
  - Liver-related adverse event leading to discontinuation
  - Liver-related SAE or AE in any subjects who died

Hepatic Adjudication Report

Clinical Assessment of Causality Scale: Definitions

Causal Relationship	Likelihood	Description
Definite	> 95%	The evidence for the study drug causing the injury is beyond a reasonable doubt
Highly Likely	75% - 95%	The evidence for the study drug causing the injury is clear and convincing but not definite
Probably	50% - 74%	The preponderance of the evidence supports the link between the study drug and the liver injury
Possible	25% - 49%	The evidence for the study drug causing the injury is equivocal but present
Unlikely	< 25%	There is evidence that an etiological factor other than the study drug caused the injury is clear

Applicant's Hepatic Adjudication Report

- 2 "probable" cases—both in control
- 15 "possible" cases—9 in dapagliflozin, 5 control, 1 blinded

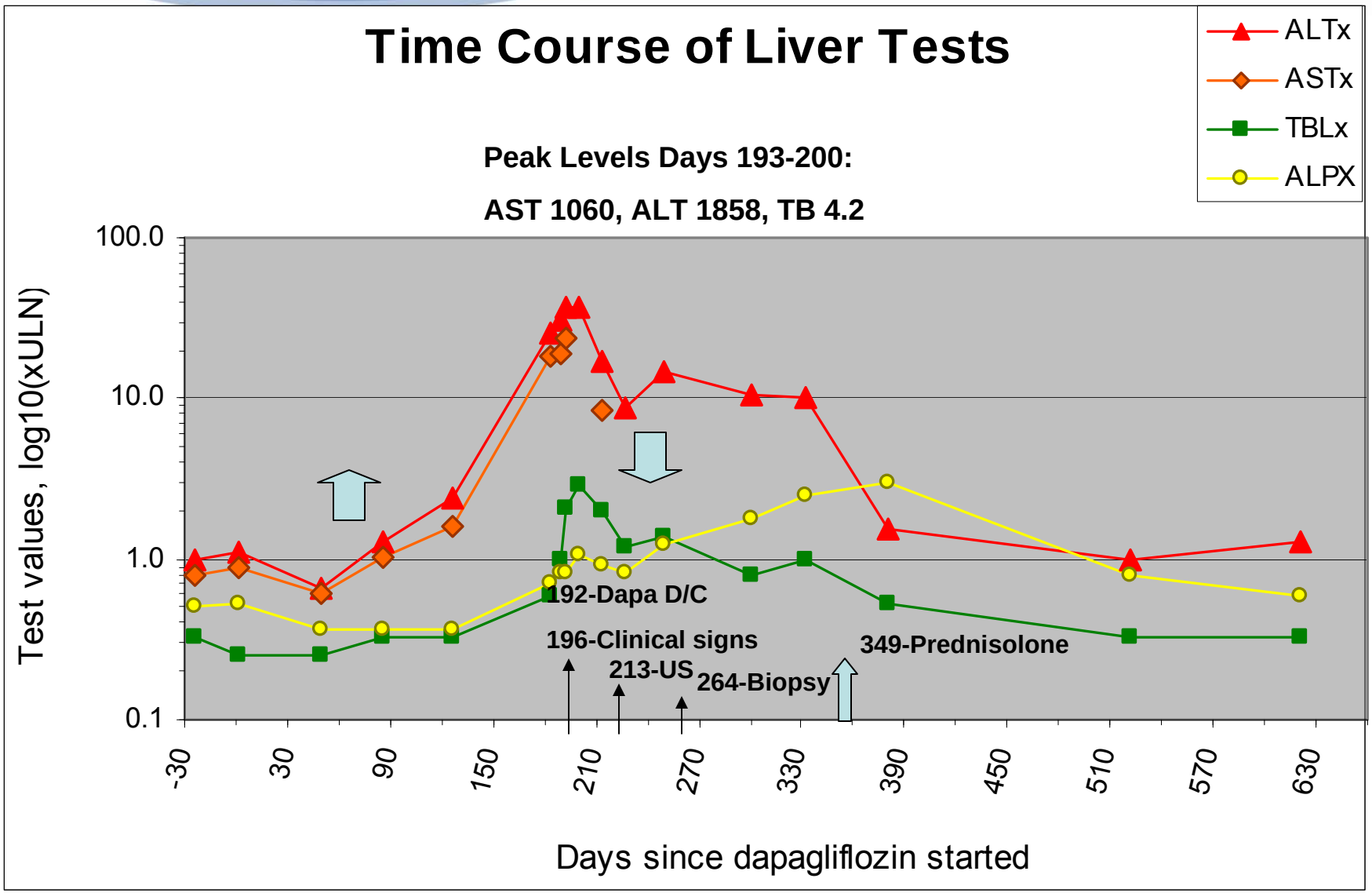
Drug Induced Liver Injury

- Hy's Law—Drug Induced Liver Injury
  - >3x ULN AST and/or ALT, >2x ULN bilirubin
  - No other clinical explanation
- In Phase 2b/3 pool, 5 dapagliflozin cases meet laboratory criteria for Hy's Law
  - 3 unlikely
  - 1 not DILI
  - 1 case probable

Probable Drug Induced Liver Injury Case

- 78 yo T2DM Indian male CAD, HTN, dyslipidemia, BPH
- On metformin, atorvastatin, cromolyn, lercanidipine, atenolol, parendopril, naproxen, aspirin, senna, ispaghula husk—all at least -90 days
- Enzyme elevations did not have alternative explanation
  - Diagnosed with hemochromatosis, not seen on biopsy (day 229)
  - Hep B, E, A negative, Hep C negative at enrollment
  - CMV and EBV IgG positive, IgM negative (day 365)
  - Elevated IgM, IgA and IgG (day 357)
  - Antiliver/kidney microsome type 1, anti-smooth muscle Ab, mitochodrial Ab, ANA all negative (day 365)

Time Course of Liver Tests



Marked Hepatic Enzyme Elevations Dapagliflozin Clinical Program

- Marked elevations 5x & 10x ULN display similar rates between dapagliflozin and controls Phase 2b/3 pool

Enzyme Elevation	**Dapagliflozin Total N=4287**	**Control Total N=1941**
AST >5x ULN	11/4258 (0.3)	8/1922 (0.4)
AST >10x ULN	5/4258 (0.1)	3/1922 (0.2)
ALT >5x ULN	17/4258 (0.4)	9/1922 (0.5)
ALT >10x ULN	4/4258 (<0.1)	3/1922 (0.1)

Applicant's SCS Table 84

Drug Induced Liver Injury

- Per FDA Guidance Document
  - One Hy's Law case in a clinical program is worrisome
  - Two are highly predictive that the drug has potential to cause serious DILI in a larger population
- It has been estimated that approximately 10% of Hy's law cases progress to serious DILI (i.e., death or liver transplant)
  - 1 case in 2489 patients exposed to dapagliflozin for at least 6 months
  - Estimate that approximately 1 in 25,000 patients exposed for at least 6 months would develop serious DILI

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - Breast Cancer
  - Hepatic Events
  - **Genital Infections**
  - Urinary Tract Infections
  - Bone Health
  - Cardiovascular Safety

Genital Infections
Dapagliflozin Clinical Program

Genital Infections—Short Term Placebo Controlled Pool

	Placebo N=1393	**Dapagliflozin 2.5 mg N=814**	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**	**Dapagliflozin Total N=3291**
Total Subjects with an Event	29 (2.3)	47 (5.8)	80 (7.0)	83 (7.0)	223 (6.8)

Applicant's SCS Table 49

- Appears dose related
- 2nd occurrence rate higher in placebo group (17.2% vs. 14.8%)
- Included in proposed labeling

Genital Infections
Dapagliflozin Clinical Trials

Genital Infections by Gender—Short Term Placebo Controlled Pool

Subjects with an Event	**Placebo N (%)**	**Dapagliflozin Total N (%)**
Females	23 (3.4)	165 (10.0)
Males	6 (0.8)	58 (3.5)

Applicant's SCS Tables 50 & 51

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - Breast Cancer
  - Hepatic Events
  - Genital Infections
  - **Urinary Tract Infections**
  - Bone Health
  - Cardiovascular Safety

Urinary Tract Infections Dapagliflozin Clinical Program

UTI—Short Term Placebo Controlled Pool

	Placebo N=1393	**Dapagliflozin 2.5 mg N=814**	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10 mg N=1193**	**Dapagliflozin Total N=3291**
Total Subjects with an Event	63 (4.5)	34 (4.2)	84 (7.3)	77 (6.5)	209 (6.4)

Applicant's SCS Table 57

- Not dose related
- Common AE
- 2nd occurrence rate higher in dapagliflozin treated patients (15.8% vs. 9.5%)
- The rate of pyelonephritis is equal—0.1% in both groups
- Included in proposed labeling

Urinary Tract Infections Dapagliflozin Clinical Program

UTI—Short Term Placebo Controlled Pool

Subjects with an Event	Placebo N (%)	Dapagliflozin Total N (%)
Females	52 (7.7)	165 (10.0)
Males	11 (1.5)	44 (2.7)

Applicant's SCS Tables 58 & 59

Dapagliflozin

- Introduction
- PK profile in renal impairment
- Safety issues
  - Bladder Cancer
  - Breast Cancer
  - Hepatic Events
  - Genital Infections
  - Urinary Tract Infections
  - **Bone Health**
  - Cardiovascular Safety

Bone Health

- Dapagliflozin increases trabecular bone in rats
  - Greater bone mass, density, and strength at high exposure multiples
- Fractures and markers of bone metabolism monitored
- No clinically significant changes in laboratory values (Ca, 25-OH D, Mg, Phos, PTH) in ST plus LT pool
- No pattern of changes with bone biomarkers in 5 studies

Bone Health: Fractures

- Placebo-controlled ST pool Normal Renal Function
  - 7 (0.6%) in dapagliflozin vs. 1 (0.2%) placebo
- Placebo-controlled ST pool
  - 14 (0.4%) in dapagliflozin vs. 10 (0.7%) placebo
- Placebo-controlled ST + LT pool
  - 30 (1.4%) vs. 10 (1.4%)
  - Fragility fracture rate in the dapagliflozin treated subjects vs. placebo (0.9% vs. 1%)

Bone Health: Fractures

- Renal Impairment Study 52 weeks
  - 7 (8.2%)—10 mg, 3 (3.6%)—5 mg, (0%)—placebo
  - Negligible lab value changes
- Placebo-controlled ST pool Moderate Renal Dysfunction
  - 0 in dapagliflozin vs. 2 (1.9%) in placebo

Bone Health

- Minimal effects on bone mineral density in Body Weight and Composition Study D1690C00012—50 week data
- Two year data pending
- No indication at this time of dapagliflozin effect on bone loss or fracture

Dapagliflozin

- Introduction
- PK profile in renal impairment
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  - Bladder Cancer
  - Breast Cancer
  - Hepatic Events
  - Genital Infections
  - Urinary Tract Infections
  - Bone Health
  - **Cardiovascular Safety**

Cardiovascular Safety Meta-analysis

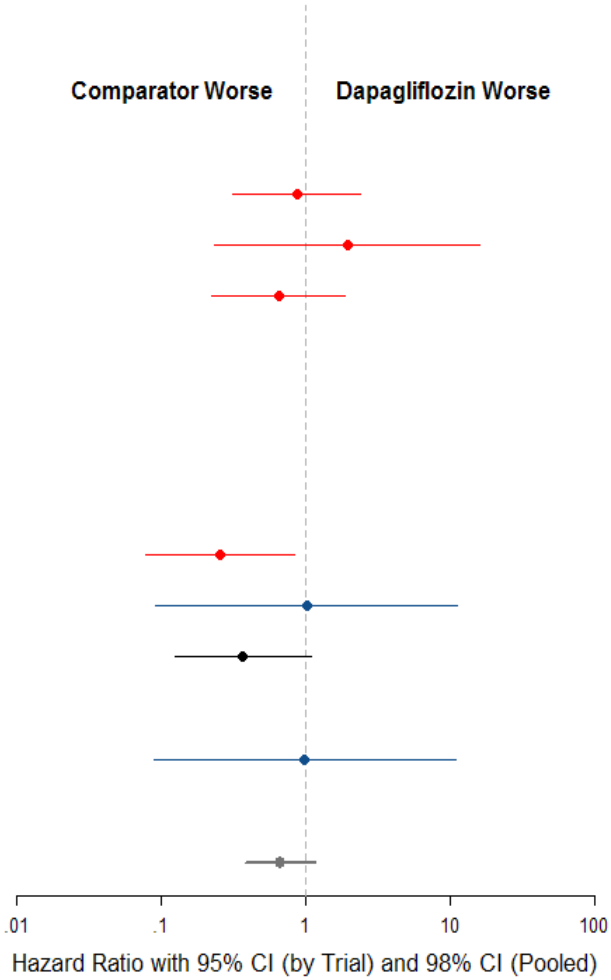
- Conducted by sponsor in 14 trials (Phase 2b/3 studies)
- Pre-specified primary composite endpoint consisted of adjudicated events: CV death, MI, stroke, and hospitalization for unstable angina
- 6228 subjects in the database, 78 subjects had a primary endpoint event (2 trials with zero events)
  - 48 of 4287 dapagliflozin subjects (1.1%)
  - 30 of 1941 comparator subjects (1.5%)

Cardiovascular Safety Meta-analysis

- Primary endpoint analysis — hazard ratio of dapagliflozin vs. comparator (stratified by study):
  - 0.67; 98% CI: (0.38, 1.18)
- Assessment of heterogeneity of studies:
  - Q-statistic p-value: 0.92; I^2 : 0% Heterogeneity
- No increased risk of cardiovascular events occurs with the use of dapagliflozin over control

CV Safety Meta-analysis: Forest Plot of Hazard Ratios †

Trial	Type of Therapy	Dapagliflozin CV events/N (%)	Comparator CV events/N (%)
D1690C00004	Add-on to Metformin (Glipizide)	7/406 (1.72)	8/408 (1.96)
D1690C00005	Add-on to SU	6/450 (1.33)	1/146 (0.68)
D1690C00006	Add-on to Insulin	11/610 (1.80)	5/197 (2.54)
D1690C00012*	Add-on to Metformin	0/91 (0.00)	1/91 (1.10)
D1692C00005*	Monotherapy	1/166 (0.60)	0/54 (0.00)
MB102008*	Monotherapy	1/279 (0.36)	0/110 (0.00)
MB102013*	Monotherapy	6/410 (1.46)	0/75 (0.00)
MB102014	Add-on to Metformin	5/409 (1.22)	6/137 (4.38)
MB102021	Combination with Metformin	2/397 (0.50)	1/201 (0.50)
MB102029	Monotherapy (renal impairment)	6/168 (3.57)	7/84 (8.33)
MB102030*	Add-on to TZD	1/281 (0.36)	0/139 (0.00)
MB102034	Combination with Metformin	2/430 (0.47)	1/208 (0.48)
	Pooled		



* estimate values are out of range.

† Zero event trials (MB102009 and MB102032) excluded from analysis

Safety Issues in Dapagliflozin

- Higher rates in Dapagliflozin treated patients
  - **Bladder Cancer**
  - **Breast Cancer**
  - Genital Infections
  - Urinary Tract Infections
- **One probable case of Hy's Law**
- Bone Health
  - Monitored in an ongoing study
- Cardiovascular Safety
  - No increased CV risk
  - Dedicated CV study proposed