Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

SYNOPSIS

Final Clinical Study Report for Study MB102057

TITLE OF STUDY: A Randomized, Open-Label, Parallel Group, Multiple-Dose Study to Evaluate the Potential Pharmacokinetic Interaction and Pharmacodynamic Effects on Renal Parameters of Bumetanide (1mg) and Dapagliflozin (10 mg) when Co-administered in Healthy Subjects

INVESTIGATORS/STUDY CENTERS: [redacted]

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 24-Jul-2009 **CLINICAL PHASE:** 1

Study Completion Date: 02-Sep-2009

OBJECTIVES:

Primary Objective: To assess the potential pharmacokinetic (PK) interactions of bumetanide and dapagliflozin following multiple doses of 1-mg bumetanide and 10-mg dapagliflozin in healthy subjects.

Secondary Objective: To assess the safety and tolerability of bumetanide and dapagliflozin following multiple oral doses of 1-mg bumetanide and 10-mg dapagliflozin, administered together, either simultaneously or after adaptation to either agent alone, in healthy subjects.

To explore the potential pharmacodynamic (PD; serum and urine electrolytes) effects of bumetanide and dapagliflozin following multiple doses of 1-mg bumetanide and 10-mg dapagliflozin, administered together, either simultaneously or after adaptation to either agent alone, in healthy subjects

METHODOLOGY:

This was a randomized, open-label, parallel-group, multiple-dose PK and PD study in 42 healthy subjects. Subjects were randomized to one of 3 treatment groups: 1-mg dose of bumetanide (Trt A), 10-mg dose of dapagliflozin (Trt B) and combination of 1-mg bumetanide and 10-mg dapagliflozin (Trt C). Each subject received the assigned treatment once-a-day for 7 days. On Day 8, every subject received the combination of 1-mg bumetanide and 10-mg dapagliflozin once-a-day for an additional 7 days. Subjects were admitted to the clinical facility on Day -2 and were confined to the clinical facility for the duration of the study through study discharge on Day 15.

The subjects ate a controlled diet (not a high protein "Atkins" diet) with a focus on ≤ 20-mg sodium, 1-g calcium and 1-g phosphorus from admission to study discharge. A total of 6-g of salt tablets were provided

daily to be taken with meals, to ensure each subject had a fixed amount of sodium every day during the study. One hour after a standardized breakfast, subjects received the assigned treatment for 14 days.

Blood samples were collected for PK analyses for 24 h relative to dosing on Days 7 and 14. Blood samples were collected for PD (extended electrolyte panel) analysis predose daily from Days -1 to 14, and prior to discharge on Day 15. Urine was collected daily from Day -1 through to discharge and pooled over specified intervals for PD analyses. Figure 1 shows the study schematic.

Figure 1: Study Schematic

<table>
<tr><td rowspan="3">S/E</td><td rowspan="3">A</td><td rowspan="3">R</td><td>Group 1
(n=14)</td><td><u>Treatment A</u>
bumetanide 1 mg QD</td><td><u>Treatment C</u>
bumetanide 1mg QD +
dapagliflozin 10 mg QD</td><td rowspan="3">D</td></tr>
<tr><td>Group 2
(n=14)</td><td><u>Treatment B</u>
dapagliflozin 10 mg QD</td><td><u>Treatment C</u>
bumetanide 1mg QD +
dapagliflozin 10 mg QD</td></tr>
<tr><td>Group 3
(n=14)</td><td><u>Treatment C</u>
bumetanide 1mg QD +
dapagliflozin 10 mg QD</td><td><u>Treatment C</u>
bumetanide 1mg QD +
dapagliflozin 10 mg QD</td></tr>
<tr><td>Days
-21 to -3</td><td>Day
-2</td><td colspan="2">Day
1</td><td>Days
1-7</td><td>Days
8-14</td><td>Day
15</td></tr>
<tr><td colspan="7">S = Screening, E=Enrollment, A=Admission, R=Randomization, D=Discharge</td></tr>
</table>

NUMBER OF SUBJECTS (Planned and Analyzed): Forty two (42) subjects were planned and enrolled, 41 subjects completed the study. One subject was discontinued for non-compliance after receiving 1 mg of protocol-specific bumetanide on Days 1 and 2.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy male or female subjects (18-45 years of age) as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations were eligible to participate in the study.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dapagliflozin was provided by Bristol-Myers Squibb (BMS) as 10-mg film coated tablets ([redacted]). Bumetanide was provided by the Investigator. Subjects were randomized to one of the following 3 treatment groups according to the randomization schedule.

- Group 1 (AC): Received 1-mg bumetanide (Trt A) Days 1 to 7 and 1-mg bumetanide and 10-mg dapagliflozin (Trt C) on Days 8 to 14.
- Group 2 (BC): Received 10-mg dapagliflozin (Trt B) Days 1 to 7 and 1-mg bumetanide and 10-mg dapagliflozin (Trt C) on Days 8 to 14.
- Group 3 (CC): Received 1-mg bumetanide and 10-mg dapagliflozin (Trt C) on Days 1 to 14.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable.

CRITERIA FOR EVALUATION:

Pharmacokinetics: On Day 7 and 14, PK parameters (Cmax, Tmax, AUC(TAU), Cmin) were derived from plasma concentration versus time data for both dapagliflozin and bumetanide.

Safety: Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, ambulatory blood pressure measurements (ABPM), ECGs, physical examinations, and clinical laboratory tests. Seated blood pressure (BP) was monitored daily, predose, on Days 1 through 14 and at a corresponding time on Day 15. Clinical laboratory tests included serum chemistry, hematology, and urinalysis. The incidence of observed AEs were tabulated and reviewed for potential significance and clinical importance.

Pharmacodynamics: Urine was collected and pooled in 30 minute intervals on Days 1 and 8 for measurement of urine volume, sodium and bumetanide concentration. Urine was collected and pooled in 6 hour intervals on Days -1, 1, 2, 7, 8, and 9 for measurement of urine volume osmolality and sodium. Urine was collected and pooled over 24 hours, starting on Day -1 through to Discharge (15 samples per subject), to measure urine volume, total amounts of sodium, potassium, chloride, calcium, magnesium, phosphorus, glucose, creatinine, uric acid and osmolality. Blood for a serum electrolyte panel that included sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate, glucose, creatinine, uric acid, blood urea nitrogen (BUN) and osmolality was collected daily, predose, from Days 1 through 14 and at a corresponding time on Day 15. Blood for plasma renin activity (PRA) determination was collected predose on Days 1, 2, 8, 9 and prior to discharge on Day 15.

Pharmacokinetics/Pharmacodynamics

The relationship between bumetanide concentration and sodium excretion in urine for the first 6 h following bumetanide dosing on Days 1 and 8 was explored graphically.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The sample size was not based on statistical power considerations. However, data from 12 completed subjects provided at least 90% confidence that the estimated ratios of the geometric means for bumetanide Cmax and AUC(TAU), with or without dapagliflozin, were within 14% and 13%, respectively, of the true population ratios. Data from 12 completed subjects provided at least 90% confidence that the estimated ratios of the geometric means for dapagliflozin Cmax and AUC(TAU), with or without bumetanide, were within 18% and 10%, respectively, of the true population ratios.

In addition, data from at least 12 subjects in each group provided 80% probability of observing at least one occurrence of any AE which would occur with 13% incidence in the population from which the sample was drawn.

To allow for possible dropouts, 42 subjects (14 subjects per group) were dosed on Day 1.

Statistical Analysis:

Pharmacokinetics: To assess the effect of co-administration of dapagliflozin on the PK of bumetanide, point estimates and 90% confidence intervals were calculated for the Treatment C to Treatment A ratios of the geometric means for Cmax and AUC(TAU) of bumetanide. These estimates were constructed from the results of fitting general linear models for log-transformed data (using available bumetanide PK data from all subjects, including data collected on both Day 7 and Day 14 for treatment Group 3 [CC]) with

treatment, period (i.e., Day 7 or Day 14) and group as fixed effects, and subject within group as random effects. Point estimates of the differences and their 90% confidence intervals in the log scale were exponentiated to obtain estimates and confidence intervals for ratios of geometric means in the original scale. If the effect of period was not statistically significant at the 5% level, then the estimates of treatment differences were based on within-group paired t-statistics (on Group 1 data). Similar analysis was performed to assess the effect of co-administration of bumetanide on the PK (Cmax, AUC(TAU) and Cmin)) of dapagliflozin with the exception being if the effect of period was not statistically significant at the 5% level, then the estimates of treatment differences were based on within-group paired t-statistics (on Group 2 data).

Summary statistics were tabulated for all PK parameters by group and study day, for each analyte.

Safety: All recorded AEs were listed and tabulated by system organ class (SOC), preferred term and group. Vital signs and clinical laboratory test results were listed and summarized by group and study day. Any significant physical examination findings and clinical laboratory results were listed. Electrocardiogram readings were evaluated by the Investigator and abnormalities were listed.

For ambulatory blood pressure (ABP) parameters and the corresponding changes from baseline, summary statistics were tabulated by group and study day. The means for changes from baseline in ABP were plotted versus time, for all groups and study days.

Pharmacodynamics:

Sodium, Urine Volume and Osmolality Excretion: Summary statistics were tabulated for the amounts of sodium excreted in each 6-hour collection interval, and for the corresponding changes from baseline, by treatment group and study day. In addition, summary statistics were tabulated for the total amounts of sodium excreted in urine over 24 h, and for the corresponding changes from baseline, by treatment group and study day. The mean for the total amounts of sodium excreted in urine over 24 h was plotted versus study day, for all treatment groups. Similar analyses were performed for urine volume and osmolality.

Other Urinary PD Parameters: For each PD marker (potassium, chloride, calcium, magnesium, phosphorus, glucose and creatinine) in urine, summary statistics were tabulated for the total amounts excreted in urine over 24 h, and for the corresponding changes from baseline, by treatment group and study day. The mean total amounts of each PD marker excreted in urine in 24 h were plotted versus study day, for all treatment groups.

Serum Electrolyte Panel: For each PD marker in serum (the standard extended serum electrolyte panel including sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate, glucose, creatinine, uric acid, BUN and osmolality), summary statistics were tabulated for the serum concentration values and for the corresponding changes from baseline, by treatment group and study day. The means for the serum concentration of each PD marker in serum were plotted versus study day, for all treatment groups.

Plasma Renin Activity (PRA): Summary statistics were tabulated for PRA and for the corresponding changes from baseline, by treatment group and study day.

Bumetanide Pharmacokinetic/Pharmacodynamic Assessment: The relationship between bumetanide concentration and sodium excretion in urine for the first 6 hours following bumetanide dosing on Days 1 and 8 was explored graphically.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

A total of 42 subjects were randomized and administered study drug. One (1) subject was discontinued on Day 2 of the study for non-compliance; 41 subjects completed the study as designed. Demographic characteristics and baseline physical measurements (PM) were similar across treatment groups as presented in Tables 1 and 2, respectively.

Table 1: Demographic Characteristics Summary

	Treatment Group 1 (TRT A + C1) N=14	Treatment Group 2 (TRT B + C2) N=14	Treatment Group 3 (TRT C3 + C4) N=14	All Subjects N=42
Age (yrs)				
N	14	14	14	42
Mean	30	30	31	30
Standard Deviation	7	7	7	7
Median	29	28	30	29
Min-Max	21-43	19-45	22-45	19-45
Q1-Q3	26-32	25-35	26-36	26-35
Age Category n(%)				
< 65 years	14(100)	14(100)	14(100)	42(100)
>= 65 years	0	0	0	0
Not Reported	0	0	0	0
Gender n(%)				
Male	11(79)	10(71)	11(79)	32(76)
Female	3(21)	4(29)	3(21)	10(24)
Not Reported	0	0	0	0
Race n(%)				
Caucasian	8(57)	9(64)	11(79)	28(67)
Black	6(43)	5(36)	3(21)	14(33)
Asian	0	0	0	0
Other	0	0	0	0
Not Reported	0	0	0	0
Ethnicity n(%)				
Hispanic/Latino	6(43)	7(50)	8(57)	21(50)
Not Hispanic/Latino	8(57)	7(50)	6(43)	21(50)
Not Reported	0	0	0	0

TREATMENT : TRT A = Bumetanide 1 mg QD, TRT B = Dapagliflozin 10 mg QD, TRT C = Bumetanide 1 mg QD + Dapa 10 mg QD.
TRT C1 = Bumetanide 1 mg + Dapa 10 mg(GROUP1, Days 1-7), TRT C2 = Bumetanide 1 mg + Dapa 10 mg(GROUP2, Days 1-7)
TRT C3 = Bumetanide 1 mg + Dapa 10 mg(GROUP3, Days 1-7), TRT C4 = Bumetanide 1 mg + Dapa 10 mg(GROUP3, Days 8-14)

Table 2: Physical Measurements Summary

	Treatment Group 1 (TRT A + C1) N=14	Treatment Group 2 (TRT B + C2) N=14	Treatment Group 3 (TRT C3 + C4) N=14	All Subjects N=42
Weight (kg)				
N	14	14	14	42
Mean	79.7	76.9	78.5	78.4
Standard Deviation	12.0	13.9	10.6	12.0
Median	81.7	76.9	79.5	80.3
Min-Max	59.1-96.7	58.0-107.8	55.6-92.8	55.6-107.8
Q1-Q3	69.9-88.0	64.2-82.6	73.5-86.9	71.8-87.6
Height (cm)				
N	14	14	14	42
Mean	171.8	170.6	172.7	171.7
Standard Deviation	6.5	8.5	11.4	8.8
Median	171.8	171.0	171.0	171.3
Min-Max	161.2-183.5	158.0-186.5	151.5-199.0	151.5-199.0
Q1-Q3	168.0-176.5	163.0-178.0	167.0-177.5	166.5-177.5
BMI (kg/m2)				
N	14	14	14	42
Mean	26.9	26.3	26.3	26.5
Standard Deviation	3.4	3.2	3.1	3.2
Median	28.0	26.8	26.1	27.0
Min-Max	20.1-30.8	20.0-31.0	22.1-31.2	20.0-31.2
Q1-Q3	25.6-29.7	24.5-29.2	23.4-29.0	24.2-29.2

TREATMENT: TRT A = Bumetanide 1 mg QD, TRT B = Dapagliflozin 10 mg QD, TRT C = Bumetanide 1 mg QD + Dapa 10 mg QD.
TRT C1 = Bumetanide 1 mg + Dapa 10 mg(GROUP1, Days 1-7), TRT C2 = Bumetanide 1 mg + Dapa 10 mg(GROUP2, Days 1-7)
TRT C3 = Bumetanide 1 mg + Dapa 10 mg(GROUP3, Days 1-7), TRT C4 = Bumetanide 1 mg + Dapa 10 mg(GROUP3, Days 8-14)

Safety Results:

Administration of 10-mg dapagliflozin, alone or in combination with 1-mg bumetanide, was safe and generally well-tolerated by the healthy subjects in this study.

There were no deaths, serious adverse events (SAEs) or AEs that led to discontinuation (Table 3). Eighty-one (81) AEs occurred in 29 subjects, of which abdominal pain (23.8%), nausea (23.8%), and asthenia (23.8%) were the most common. In addition, 8 AEs of dizziness (including 2 AEs of postural dizziness) occurred in 7 subjects and 1 subject experienced AEs of syncope and orthostatic hypotension. Forty-four (44) clinical laboratory marked abnormalities (MAs) occurred in 33 subjects, of which elevated urine glucose (69.0%), an expected PD effect of dapagliflozin, was the most common. One (1) laboratory MA of decreased serum potassium was considered an AE by the Investigator. With the exception of the one subject with an AE of orthostatic hypotension who had orthostatic changes in heart rate (HR) but not blood pressure (BP), potentially abnormal vital sign measurements were not associated with clinical symptoms and were generally normal upon repeat. There were no clinically-important ECG findings, or physical examination findings.

Table 3: Adverse Event Summary

	Number (%) of Subjects				
	TRT A N = 14	**TRT B N = 14**	**TRT C N = 41**	**Any BMS N = 41**	**All Subjects N = 42**
Adverse event(s)	6 (42.9)	7 (50.0)	22 (53.7)	26 (63.4)	29 (69.0)
Death	0	0	0	0	0
Serious adverse event	0	0	0	0	0
Discontinuation due to adverse event	0	0	0	0	0

Ambulatory Blood Pressure Monitoring Results:

Ambulatory blood pressure monitoring was performed for sixteen hours on Day -1, Day 1, Day 7, Day 8 and Day 14. Systolic BP, diastolic BP, HR and mean arterial pressure (MAP) varied significantly throughout the day for all groups. While mean systolic BP trended downward with all treatments, this was most notable when subjects received dapagliflozin in combination with bumetanide. The maximum change from baseline was a transient reduction of mean systolic BP of up to 12 mm Hg (+/- 12.6 mm Hg) that was observed in Group 3 (CC) on Day 14 approximately 3-6 hours after dosing. Mean HR did not change meaningfully with dapagliflozin treatment alone, but trended higher in the first 8 hours of the day with bumetanide, alone or in combination with dapagliflozin. The maximum increase in mean HR of 24 bpm (+/- 19.6 bpm) was observed on Day 8 in Group 1 (AC) 4 hours after dosing. Mean diastolic BP and mean MAP did not change meaningfully during the study.

Pharmacokinetic Results:

Pharmacokinetic parameters for dapagliflozin and bumetanide are summarized in Table 4, 5 and 6.

Table 4: Summary Statistics for Dapagliflozin and Bumetanide Pharmacokinetic Parameters

Treatment Group	Study Day	Dapagliflozin Pharmacokinetic Parameters				Bumetanide Pharmacokinetic Parameters		
		Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	Cmin (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)
AC	7 (n=13)	NA	NA	NA	NA	55.0 (43)	126 (31)	1.50 (0.50, 2.00)
	14 (n=13)	215 (30)	834 (41)	9.50 (71)	0.75 (0.50, 1.52)	62.3 (49)	161 (45)	1.53 (0.50, 2.00)
BC	7 (n=14)	192 (32)	701 (30)	5.76 (45)	0.78 (0.75, 1.50)	NA	NA	NA
	14 (n=14)	208 (30)	835 (38)	8.17 (55)	0.75 (0.50, 4.00)	49.5 (42)	144 (45)	1.50 (0.75, 4.00)
CC	7 (n=14)	194 (23)	665 (24)	6.28 (33)	0.75 (0.43, 1.50)	51.1 (37)	120 (47)	1.47 (0.50, 2.00)
	14 (n=14)	210 (29)	757 (26)	7.36 (22)	0.75 (0.48, 1.03)	51.4 (33)	135 (40)	1.50 (0.75, 4.00)
Pooled C	7 and/or 14 (n=55)	206 (28)	769(35)	7.71 (59)	0.75 (0.43,4.00)	53.2 (42)	139 (44)	1.50 (0.50, 4.00)

AC =bumetanide 1 mg QD (Days 1-7), bumetanide 1 mg QD + dapagliflozin 10 mg QD (Days 8-14)
BC =dapagliflozin 10 mg QD (Days 1-7), bumetanide 1 mg QD + dapagliflozin 10 mg QD (Days 8-14)
CC =bumetanide 1 mg QD + dapagliflozin 10 mg QD (Days 1-14)
Pooled C = all PK profiles collected from subjects receiving trt C (bumetanide 1 mg QD + dapagliflozin 10 mg QD) on Days 7 and/or 14.

Table 5: Results of Statistical Analyses on Bumetanide Pharmacokinetic Parameters

Bumetanide Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means Point Estimate (90% C.I)
	Trt A	Trt C	(Trt C / Trt A)
Cmax (ng/mL)[a]	55.0	62.3	1.132 (0.979, 1.310)
AUC(TAU) (ng·h/mL)	121	138	1.132 (0.985, 1.302)

Trt A=bumetanide 1 mg QD

Trt C=bumetanide 1 mg QD + dapagliflozin 10 mg QD

[a]Within-group comparison in Group 1.

Note: The adjusted geometric means here are geometric means obtained from the general linear models after accounting for all other effects in the model.

Table 6: Results of Statistical Analyses on Dapagliflozin Pharmacokinetic Parameters

Dapagliflozin Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (Trt C / Trt B)	
	Trt B	Trt C	Point Estimate	90% C.I
Cmax (ng/mL)[a]	192	208	1.080	(0.953, 1.222)
AUC(TAU) (ng·h/mL)	723	757	1.047	(0.991, 1.106)
Cmin (ng/mL)	6.33	7.67	1.211	(1.059, 1.385)

Trt B=dapagliflozin 10 mg QD

Trt C=bumetanide 1 mg QD + dapagliflozin 10 mg QD

[a]Within-group comparison in Group 2.

Note: The adjusted geometric means here are geometric means obtained from the general linear models after accounting for all other effects in the model.

The geometric means for Cmax and AUC(TAU) of bumetanide increased by 13%, when bumetanide 1 mg was co-administered with dapagliflozin 10 mg for 7 days relative to those observed following administration of bumetanide 1 mg alone for 7 days. The 90% confidence intervals for the ratios of geometric means, with and without dapagliflozin, minimally extended above the usual equivalence criteria (0.80, 1.25) for Cmax and AUC(TAU) of bumetanide.

The geometric means for Cmax, AUC(TAU) and Cmin of dapagliflozin increased by 8%, 5% and 21%, respectively, when dapagliflozin 10 mg was co-administered with bumetanide 1 mg for 7 days relative to those observed following administration of dapagliflozin 10 mg alone for 7 days. The 90% confidence intervals for the ratios of geometric means, with and without bumetanide, were within the (0.80, 1.25) for Cmax and AUC(TAU) of dapagliflozin. However, the 90% confidence interval for the ratio of geometric means, with and without bumetanide, extended above the usual (0.80, 1.25) no-effect interval for Cmin of dapagliflozin.

Pharmacodynamic Results:

Key PD results are summarized briefly here and summarized in Table 7, below.

Glucose: As expected from its mechanism of action, dapagliflozin resulted in significant 24-h urinary glucose excretion (approximately 25 - 35 g/24h at Day 7). Bumetanide alone did not promote glucose excretion and had, at most, a small effect to reduce glucosuria in response to dapagliflozin. None of the treatments had a meaningful effect on serum glucose in this healthy, non-diabetic population.

Urine Volume: Either dapagliflozin or bumetanide alone increased urine volume for approximately one day. Likewise, the addition of bumetanide following 7 days of administration of dapagliflozin or the addition of dapagliflozin following 7 days of administration of bumetanide increased 24-h urine volume for approximately one day. The simultaneous initiation of the combination of dapagliflozin and bumetanide also increased 24-h urine volumes on the first day, but the return to baseline was slower than either agent alone, taking approximately 9 days to completely return to baseline.

Sodium: The increase in 24-h urinary sodium excretion with dapagliflozin alone (increase of 22 mEq/24 h or 35%) is difficult to assess because it does not appear that subjects were in sodium balance at baseline and the increase in sodium excretion may, in part reflects a higher sodium intake than at baseline. However, 24-h urinary sodium clearly increased (increase of 64 mEq /24 h or 78%) when dapagliflozin was added after 7 days of treatment with bumetanide. Bumetanide also showed a greater absolute natriuretic effect when added after 7 days of treatment (increase of 101 mEq/24 h or 108%) with dapagliflozin than when given alone (increase of 74 mEq/24 h or 108%), although the responses were similar as a percent of baseline. As expected, mean serum sodium did not change with any treatment.

Uric Acid: Dapagliflozin demonstrated a pronounced effect on urinary uric acid secretion and markedly reduced serum uric acid levels whether administered alone or in combination with bumetanide. While bumetanide alone had little effect on serum uric acid, the combination of bumetanide with dapagliflozin appeared to slightly diminish the reduction in serum uric acid levels in response to dapagliflozin. Despite this, serum uric acid levels remained decreased at the end of the study, suggesting that dapagliflozin produces reductions in serum uric acid by promoting urinary uric acid excretion.

Plasma Renin Activity (PRA): While no changes in PRA were observed with dapagliflozin alone, small increases in PRA were observed with bumetanide alone or in combination, the clinical relevance of which are unknown.

Table 7: Mean Change from Pre-Dose Baseline in Select Pharmacodynamic Parameters.

	Study Day*											
	Day 1			Day 7			Day 8			Day 14		
	Treatment Group-Change from Baseline (SD)											
	AC	BC	CC	AC	BC	CC	AC	BC	CC	AC	BC	CC
24-h Urinary Glucose (g/24 h)	0.01 (0.05)	36.99 (10.77)	26.96 (8.81)	-0.05 (0.05)	29.41 (10.99)	21.66 (12.26)	31.25 (10.43)	26.98 (10.88)	21.65 (11.05)	19.84 (11.25)	19.36 (8.44)	21.05 (11.21)
24-h Urine Volume (mL/24 h)	903 (1111)	823 (1219)	1164 (1116)	-553 (1167)	230 (706)	539 (915)	186 (1083)	1225 (1166)	573 (1161)	-67 (1183)	500 (1846)	-110 (873)
24-h Urinary Sodium (mEq/24 h)	74.5 (24.0)	22.4 (24.2)	80.2 (18.7)	11.6 (30.0)	29.1 (23.1)	29.1 (34.0)	75.6 (36.2)	130.1 (27.3)	44.6 (31.5)	24.6 (31.6)	20.2 (27.4)	27.1 (40.5)
24-h Urinary Uric Acid (mg/24 h)	-65.9 (110.1)	210.9 (86.2)	86.5 (176.1)	-98.9 (109.7)	-11.1 (57.9)	-31.4 (92.9)	162.0 (146.2)	-18.1 (226.3)	-56.2 (66.4)	-59.8 (96.2)	-67.1 (80.6)	-64.6 (76.4)
Serum Uric Acid (mg/dL)	0.13 (0.18)	-1.16 (0.44)	-0.96 (0.66)	0.20 (0.25)	-1.94 (0.73)	-1.24 (1.46)	-0.91 (0.50)	-1.56 (0.96)	-1.14 (1.75)	-1.30 (0.90)	-0.93 (0.92)	-1.24 (1.33)

*For serum uric acid, the data are provided for the following Study Day (Days 2, 8, 9, 15) to reflect the next sample following dosing on the study day indicated.

Pharmacokinetic/Pharmacodynamic Assessment:

The relationship between bumetanide concentration and sodium excretion in urine for the first 6 hours following bumetanide dosing on Days 1 and 8 was explored. For 1.5 h post-dose on Day 1 in the bumetanide alone treatment (Trt A) the amount of sodium excreted into urine was dependent on bumetanide urinary concentrations. Between 1.5 and 6 hours post-dose, the amount of sodium excreted into urine was not dependent on bumetanide urinary concentrations. Between 1.5 and 6 hours post-dose, bumetanide urinary concentrations remained relatively constant, whereas the amount of sodium excreted into urine declined to baseline amounts by 3.5 to 4 hours post-dose and remained at these baseline amounts up to 6 h post dose. These findings were similar for the first dose in the combination treatment (Trt C) on Day 8 and also at steady-state on Day 8 for Group 3 (i.e., after 8 once-daily doses of dapagliflozin plus bumetanide).

CONCLUSIONS:

[redacted]

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