

Note: Limit of quantification of the assay is 5.00 ng/mL.
Source: ST-8, ST-9 and ST-10

Figure 9.2.3.3-1 Mean Plasma Tolvaptan Concentrations Following a Single Oral Administration of 60 mg Tolvaptan Alone (Day 1), With Multiple Oral Administrations of 0.25 mg Doses of Digoxin QD (Day 12) or Multiple Oral Administrations of 60 mg Tolvaptan QD With Multiple Oral Administrations of 0.25 mg Digoxin QD (Day 16) in 14 Healthy Men and Women

The below table summarizes the parameters for tolvaptan:

Summary of Tolvaptan Pharmacokinetic Parameters Following a Single Oral Administration of 60 mg Tolvaptan Alone (Day 1) or With Multiple Oral Administrations of 0.25 mg Digoxin QD (Day 12) to Healthy Men and Women			
Parameters	Statistics	Day 1	Day 12
t_{max} (h)	N	14	14
	Median	2.00	2.00
	Range	1.00-4.00	1.00-1.00
C_{max} (ng/mL)	N	14	14
	Geo Mean	375	412
	Mean	401	441
	CV%	38.6	36.9
$t_{1/2}$ (h)	N	12	8
	Geo Mean	7.67	6.53
	Mean	7.88	6.66
	CV%	24.9	20.6
AUC_{0-24} (ng·h/mL)	N	14	14
	Geo Mean	3377	3630
	Mean	3714	3799
	CV%	52.0	31.9
AUC_{∞} (ng·h/mL)	N	12	8
	Geo Mean	4137	3737
	Mean	4547	3978
	CV%	51.2	38.6
V_z/F (L/kg)	N	12	8
	Geo Mean	2.10	1.89
	Mean	2.49	2.03
	CV%	61.5	39.1

Geometric means ratios and 90% confidence intervals for tolvaptan in the presence and absence of digoxin are presented in the below table:

Best Possible Copy

Comparison ^a		C _{max}	AUC ₀₋₂₄
		(N=14)	(N=14)
60 mg tolvaptan (T) + 0.25 mg digoxin vs 60 mg tolvaptan alone (R)	Ratio	1.111	1.075
	90% CI	0.969-1.274 ^b	0.917-1.261 ^b

^a T is test; R is Reference.
^b Not equivalent.

Thus, the sponsor's above geometric mean ratio based on AUC₀₋₂₄ should be considered only as a crude estimate for change in average exposure. The results suggest that peak and average exposure of tolvaptan in the presence of digoxin are both unchanged.

Pharmacodynamics

The results on the mean 24 h urine excretion rate corrected for baseline on Days 1, 12 and 16 are shown in the below table:

Mean Change from Baseline in 24 h Urine Excretion Rate

	Mean Change from Baseline in Urine Excretion Rate, mL/min		
	Day 1	Day 12	Day 16
n	14	14	14
Mean	3.8	3.7	2.9
CV%	25	35	52

The net excretion rates are similar on Day 1 (single dose administration of tolvaptan in the absence of digoxin) and Day 12 (single dose administration of tolvaptan and continuous treatment with digoxin 0.25 mg). The mean net excretion rate on Day 16 (after 4 days treatment with 60 mg tolvaptan and continuous treatment with digoxin 0.25 mg qd) is reduced compared to those on Days 1 and 12 suggestive of a rebound effect with increased fluid retention.

Conclusions

PK

Digoxin

Co-administration of multiple doses of 60 mg qd increases peak and average exposure to digoxin at steady-state (0.25 mg digoxin qd) 1.3 and 1.2 fold, respectively. The extent of this interaction appears not to be clinically relevant. The renal clearance of digoxin is statistically significantly reduced to 41% in the presence of tolvaptan. The findings suggest inhibition of digoxin's tubular renal clearance by tolvaptan. MDR1 inhibition by tolvaptan has been demonstrated *in vitro*.

The respective renal clearance values of 1.05 mL/min/kg (in the absence of tolvaptan) and 0.43 mL/min/kg (in the presence of tolvaptan) are low for healthy subjects with normal renal function and raise questions regarding the specificity of the assay used for digoxin.

Co-administration of multiple dose of 0.25 mg digoxin qd appears no to impact exposure to tolvaptan after single dose administration of 60 mg tolvaptan.

PD

The mean net 24 urine excretion rates are similar whether tolvaptan is administered alone or co-administered with digoxin.

Study Report 156-96-205: Single-Center, Randomized, Open-Label, Safety Study to Assess Potential Pharmacodynamic and Pharmacokinetic Interactions between OPC-41061 and the Diuretics Furosemide and Hydrochlorothiazide in Normal Male Volunteers

Investigator and Study Site



b(4)

Objectives

To assess the potential pharmacodynamic and pharmacokinetic interaction between OPC-41061 and furosemide and hydrochlorothiazide (HCT)

Investigational Drugs and Formulations

OPC-41061 15 mg tablets (Lot No. 5L70A015) 40 mg Furosemide (Lasix®) tablets (Lot No. 0600396) and HCT (HydroDiuril®) 50 mg tablets (Lot No. D6811)

Design

This was a single-center, randomized, open-label, crossover study conducted in normal healthy male volunteers. Twelve subjects were enrolled in the study with six subjects each assigned to two treatment arms. Within each treatment arm subjects were initially randomized to one of three treatment arms; they were then crossed-over (three-period, three way cross-over design) to the other two treatment regimens based on a randomization schedule. The arms and regimens were as follows:

Treatment Arm 1

- 30 mg (2 x 15-mg tablets) OPC-41061
- 80 mg (2 x 40-mg tablets) furosemide (Lasix)
- 30 mg (2 x 15-mg tablets) OPC-41061 and 80 mg (2 x 40-mg tablets) furosemide

Treatment Arm 2

- 30 mg (2 x 15-mg tablets) OPC-41061
- 100 mg (2 x 50-mg tablets) hydrochlorothiazide (HydroDiuril)
- 30 mg (2 x 15-mg tablets) OPC-41061 and 100 mg hydrochlorothiazide (2 x 50-mg tablets)

Each subject received all three treatments in an arm in which he was enrolled. A one day washout separated each treatment period. At scheduled time points during the 24 h after administration of the study drug, blood and urine samples were taken for the determination of the pharmacokinetic and pharmacodynamic parameters. Subjects were to abstain from alcohol within 72 h of enrollment and xanthine-containing products for 48 h before admission to the study. Subjects were also to abstain from grapefruit and tobacco products for the duration of the study. Subjects were to fast from food and beverages, other than water, from midnight on the evening before dosing until approximately 1 h before administration of each dose, at which time they received approximately 150 mL water. Study drug was administered together with 240 mL water at approximately 0800 h on each of three dosing days. The subjects were to sit upright for at least 4 h after dosing. Subjects received 100 mL water at 1, 2, 3, 4, 5, and 6 h after dosing.

The scheduled study activities are shown on the below charts:

TABLE 3.6-1: SCHEDULE OF ASSESSMENTS

Day	-21	-2	-1	1	0.5	1	1.5	2	3	4	5	6	7	8	12	16	21
Medical History	*																
Consent	*																
Inclusion/Exclusion	*																
Physical Examination	*																
Electrocardiogram	*																
Vital Signs	*																
Adverse Experiences																	
Serum Chemistry																	
Hematology																	
Urealytic																	
Alcohol and Drug Screen																	
Hepatitis and HIV Screen																	
Blood Collection - (CPC-4104)					*	*	*	*	*	*	*	*	*	*	*	*	*
Blood Collection - F and II					*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Vancomycin (AVT)					*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Electrolytes					*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Creatinine					*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Collection					*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Measurements*					*	*	*	*	*	*	*	*	*	*	*	*	*
Dispense Medication					*	*	*	*	*	*	*	*	*	*	*	*	*
EMR Assessment																	

Abbreviations: F, furosemide; II, hydrochlorothiazide. Source: Study Protocol, Appendix 1.1.
 * Urine measurements: volume voided, sodium and potassium concentrations, pH, osmolality, furosemide, hydrochlorothiazide, and CPC-4104 concentrations were determined from urine collected before dosing, at one-hour intervals for the first 8 hours after dosing, and from 8-12 and 12-24 hours after dosing on days 1, 3, and 5.
 * Urine was collected on day -1 beginning with the first void of the day, then hourly for the first 8 hours afterwards, and from 8-12 and 12-24 hours thereafter during on day 11 after the initial void.

TABLE 3.6-1: SCHEDULE OF ASSESSMENTS (Continued)

Day	1	0.5	0.5	1	1.5	2	3	4	5	6	7	8	12	16	21	0.5	0.5	1	1.5
Medical History																			
Consent																			
Inclusion/Exclusion																			
Physical Examination																			
Electrocardiogram																			
Vital Signs																			
Adverse Experiences																			
Serum Chemistry																			
Hematology																			
Urealytic																			
Alcohol and Drug Screen																			
Hepatitis and HIV Screen																			
Blood Collection - CPC-4104					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood Collection - F and II					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Vancomycin (AVT)					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Electrolytes					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Creatinine					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Collection					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Measurements*					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Dispense Medication					*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
EMR Assessment																			

Abbreviations: F, furosemide; II, hydrochlorothiazide. Source: Study Protocol, Appendix 1.1.
 * Urine measurements: volume voided, sodium and potassium concentrations, pH, osmolality, furosemide, hydrochlorothiazide, and CPC-4104 concentrations were determined from urine collected before dosing, at one-hour intervals for the first 8 hours after dosing, and from 8-12 and 12-24 hours after dosing on days 1, 3, and 5.
 * Urine was collected on day -1 beginning with the first void of the day, then hourly for the first 8 hours afterwards, and from 8-12 and 12-24 hours thereafter during on day 11 after the initial void.

Best Possible Copy

TABLE 3.5-1: SCHEDULE OF ASSESSMENTS (Continued)

Day	5											6	30 Day Follow-Up
Hours	0	1	2	3	4	5	6	7	8	12	16	(14)	
Medical History													
Consent													
Informed Consent													
Physical Examination	*											*	
Electrocardiogram	*											*	
Vital Signs	*	*	*	*	*	*	*	*	*	*	*	*	*
Adverse Experiences													
Serum Chemistry												*	*
Hematology												*	*
Creatinine												*	*
Alcohol and Drug Screen													
Hepatitis and HIV Screen													
Blood Collection - OPC-41061	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood Collection - F and H	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Furosemide (AVP)	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Electrolytes	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Osmolality	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma Renin	*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Collection	*	*	*	*	*	*	*	*	*	*	*	*	*
Urine Measurements*	*	*	*	*	*	*	*	*	*	*	*	*	*
Dispense Medication													
Risk Assessment													

Abbreviations: F, Furosemide; H, Hydrochlorothiazide; Source: Study Protocol, Appendix 1.1.
 * Urine measurements - volume, creatinine, sodium and potassium concentrations, pH, osmolality, furosemide, hydrochlorothiazide, and OPC-41061 concentrations were determined from urine collected before dosing, at one-hour intervals for the first 8 hours after dosing, and from 8-12 and 12-24 hours after dosing on days 1, 3, and 5.

Best Possible Copy

Pharmacokinetic Profiling:

Plasma

Furosemide and HCT

Blood samples for the determination of the plasma concentrations of furosemide and HCT (Treatments B and C) for both arms of the study were collected on the following times: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after dosing.

OPC-41061

Blood samples for the determination of the plasma concentrations of OPC-41061 were collected at the following times: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose.

Urine

OPC-41061, Furosemide, HCT

Urine was collected for the determination of the concentrations of OPC-41061, furosemide and HCT in urine at the following times on:

- Day-1: 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-12, and 12-24 h post-dose
- Days 1, 3, 5: pre-dose, and 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-12, and 12-24 h post-dose

Bioassay

OPC-41 061, furosemide and HCT in plasma and urine were determined by HPLC/UV assays. There was no interference between the analytes in plasma and urine.

The assay for OPC-41061 was performed by [REDACTED]

The assays for furosemide and HCT were performed by [REDACTED]

b(4)

OPC-41061

Plasma

The plasma concentrations of OPC-41061 were measured by a validated HPLC/UV method with an internal standard. The assay for OPC-41061 is linear in the range between 5 ng/mL and 1000 ng/mL. The mean correlation coefficient is 0.999. Using QC samples the accuracy of the assay ranges between 0.2% and 7.9% and the precision is $\leq 16.6\%$.

The stability of the analyte was tested by exposing the matrix to room temperature (4 h) and 3 freeze/thaw cycles. OPC-41061 and the internal standard were found to be stable after extraction from plasma and storage for 49 h in the autosampler. Long term freezer stability and stability during processing of the OPC-41061 in plasma is not reported.

Urine

The urine concentrations were measured by a HPLC/UV method with an internal standard. The assay for OPC-41061 in urine is linear in the range between 2.5 ng/mL and 500 ng/mL.

The mean correlation coefficient is 0.997. The accuracy of the assay ranges between 4.4 % and 7.9 % and the precision is $\leq 10.0\%$. Except for the results on exposure to freeze-thaw cycles data on the stability of the analyte in urine are not provided.

Furosemide

Plasma

The plasma concentrations of furosemide were measured by a HPLC/UV method with an internal standard. The assay is linear (1/y) in the range between 20 ng/mL and 2000 ng/mL (mean correlation coefficient is 0.9997). The accuracy of the assay ranges between - 6.5 % and 3.0 % and the precision is $\leq 7.7\%$.

The stability of the analyte was tested by exposing the matrix to room temperature (24 h) and 3 freeze/thaw cycles. Furosemide was found to be stable for 96 h at room temperature and after extraction from plasma and storage for 24 h in the autosampler. Long term freezer stability of furosemide in plasma is not reported.

Urine

The urine concentrations of furosemide were determined by a HPLC/UV method with an internal standard. The assay is linear in the range between 1 $\mu\text{g/mL}$ and 100 $\mu\text{g/mL}$ (mean correlation coefficient=0.9961). The accuracy ranges between -10.0 % and -1.3 % and the precision is $\leq 6.7\%$.

The stability of the analyte in the matrix was tested by exposing the matrix to room temperature (24 h) and 3 freeze/thaw cycles. Furosemide was found to be stable after extraction from plasma and reconstitution prior to analysis when stored for 48 h at room temperature. Furosemide and the internal standard in stock solutions were stable for 7 days. Long term, freezer stability of furosemide in urine is not reported.

HCT

Plasma

The plasma concentrations of HCT were measured by a HPLC/UV method using an internal standard. The assay is linear (1/y) in the range between 10 ng/mL and 500 ng/mL (mean correlation coefficient 0.9999). The accuracy ranges between 2.0 % and 7.0 % and the precision is $\leq 10.2\%$

The stability of the analyte in the matrix was tested by exposing the matrix to room temperature (24 h) and 3 freeze/thaw cycles. HCT after extraction from plasma and reconstitution prior to analysis was found to be stable for 48 h at room temperature. Long term freezer stability of HCT over 90 days was demonstrated. The stability of HCT and the internal standard in stock solutions was not reported.

Urine

The urine concentrations of HCT were determined by a HPLC/UV method with an internal standard. The assay is linear in the range between 1 µg/mL and 50 µg/mL (correlation coefficient=0.9996). The accuracy ranges between -2.5 % and 3.0 % and the precision is ≤ 5.7 %.

HCT was stable for 24 h at room temperature after extraction and reconstitution prior to analysis and when exposed to 3 freeze/thaw cycles. Long term freezer stability of HCT over 682 days was also demonstrated.

Pharmacokinetic Data Analysis

The following parameters were determined: C_{max} , t_{max} , λ_z , AUC_t , AUC_{∞} , CL/F , V_D/F and CL_R , and the fraction of the dose excreted over 24 h after administration. Standard non-compartmental methods were used. C_{max} and t_{max} were taken directly from the data. AUC_t was calculated using the linear trapezoidal rule. The λ_z was obtained from subjects having at least three quantifiable plasma concentrations of OPC-41061 in the terminal phase. Since AUC_{0-24} was not available from all subjects AUC_{∞} was calculated to obtain CL_R from Ae_{-024}/AUC_{∞} . CL/F , V_D/F and CL_R were body weight normalized.

Pharmacodynamic Profiling

Plasma AVP

Blood samples for the determination of AVP in plasma were collected at the following times on:

Day -1

Days 1, 3 and 5: pre-dose, 0, 2, and 4 h post-dose

Plasma Electrolytes

Blood samples for the determination of the plasma electrolytes Na^+ and K^+ were collected at the following times on:

Day-1

Days 1, 3 and 5: pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 h post-dose

PRA

Blood samples for the determination of PRA were collected at the following times on:

Day-1

Days 1, 3 and 5: pre-dose, 2, and 24 h post-dose

Plasma Osmolality

Blood samples for the determination of the plasma osmolality were collected at the following times on:

Day -1

Days 1, 3, and 5: pre-dose, 2, and 24 h

Urine Na^+ , K^+ , pH, and Osmolality

Total urine volumes were collected on the following times on:

Day-1

Days 1, 3 and 5: pre-dose and in the intervals 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, 8-12, and 12-24 h post-dose

Free Water Clearance

Free water clearance C_{H_2O} was calculated from $C_{H_2O} = V - \text{Cosm}$, where $\text{Cosm} = \text{osmolar clearance (Uosm} \bullet V/\text{Posm)}$, where Uosm is urine osmolality ($\text{mOsm/kg H}_2\text{O}$), V represents urine excretion rate (mL/min) and Posm corresponds to plasma osmolality ($\text{mOsm/kgH}_2\text{O}$).

Pharmacodynamic Data Analysis

The last value determined before administration of the first dose of study drug in each treatment period was used as the baseline for the analysis of the pharmacodynamic parameters in plasma. For any post-dosing urine collection interval, the corresponding interval on Day -1 was used as the baseline for the analysis of the pharmacodynamic parameters in urine.

Statistical Analysis

Tests of statistical significance for the pharmacokinetic parameters were done by pairwise comparison of treatment regimens (i.e., OPC-41061 alone versus OPC-41061 + furosemide, OPC-41061 alone versus OPC-41061 + hydrochlorothiazide, furosemide alone versus OPC-41061 + furosemide, and hydrochlorothiazide alone versus OPC-41061 + hydrochlorothiazide). An analysis of variance (ANOVA) was performed on natural logarithmic transformations of the pharmacokinetic parameters, with the model terms of sequence, subject within sequence, period, and treatment. Standard bioequivalence tests (i.e., contrast, least square means, and one-sided t-test) were used to compare the treatment pairs. All tests were conducted at the 0.05 significance level unless otherwise specified. The software used for the statistical analyses was WinNonlin Professional, Version 1.5. Test of statistical significance for the pharmacokinetic parameter T_{max} was also done by pairwise comparison of the above mentioned treatment regimens, using the non-parametric Wilcoxon-Mann-Whitney Test. The software used for this test was SAS (SAS Institute Inc., Cary, NC 27513) version 6.12 with Proc-Stat Xact (Cytel Software Corp., Cambridge, MA 02139).

No formal statistical evaluation of the pharmacodynamic data was performed.

RESULTS

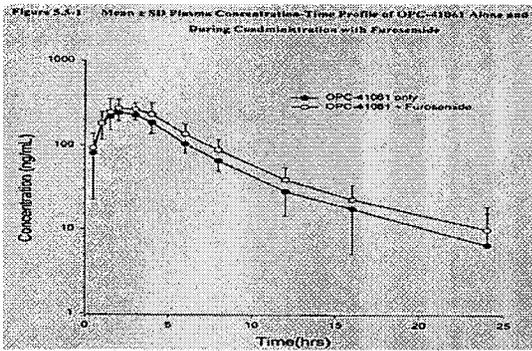
Demographics and Disposition of Subjects

Twelve subjects were enrolled in the study and 12 completed the study per protocol. The mean (SD) age of the subjects in Treatment Arm 1 was 23.3 (4.4) years and the body weight ranged between 140 to 186 pounds. For subjects in Treatment Arm 2 the mean (SD) age was 25.0 (2.3) years and the body weight ranged between 159 and 228 pounds.

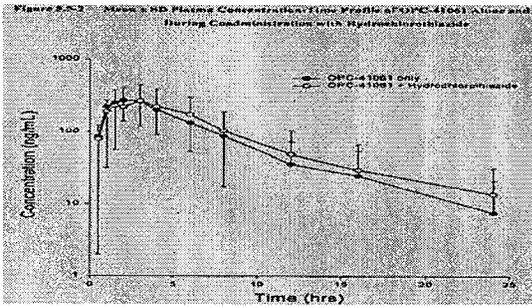
Pharmacokinetics

Four subjects had positive values of furosemide and four other subjects had positive HCT values in the pre-dose samples. The concentrations were small and replaced by a value of zero.

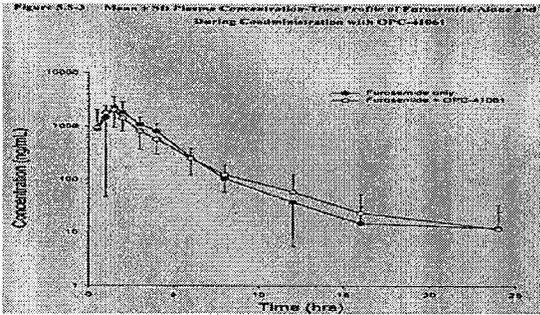
Semi-logarithmic plots of the mean plasma concentration profiles truncated to 24 h of OPC-41061 in the presence and absence of furosemide and HCT and of furosemide and HCT in the presence and absence of OPC-41061 are shown in the below figures:



Peak and average exposure to OPC-41061 after co-administration with furosemide appear to be slightly increased compared to alone administration of OPC-41061.

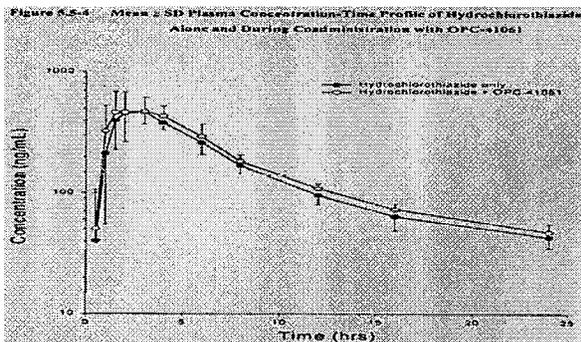


Peak exposure to OPC-41061 in the presence and absence of HCT appear to be similar. Average exposure to OPC-41061 after co-administration with HCT appear to be slightly increased compared to alone administration of OPC-41061.



Peak exposure of furosemide in the presence of OPC-41061 appears to slightly greater than in the absence of OPC-41061. Average exposure to furosemide appears to be similar after alone administration of furosemide and after co-administration with OPC-41061.

Best Possible Copy



Best Possible Copy

Peak exposure of HCT appears not to be affected by co-administration of OPC-41061. Average exposure to HCT appears to be slightly increased after co-administration of OPC-41061 compared to alone administration of HCT.

The geometric means of C_{max} and AUC for OPC-41061 in the presence and absence of furosemide or HCT, and furosemide or HCT in the presence and absence of OPC-41061 are summarized in the below table:

Geometric Means and Ratios for OPC-41061 in Presence and Absence of Furosemide and HCT and for Furosemide and HCT in the Presence and Absence of OPC-41061

Compound	Geometric Means						
	Administered alone		Co-Administered with			Ratio	
	C _{max} ng/mL	AUC ng • h/mL		C _{max} ng/mL	AUC ng • h/mL	C _{max}	AUC
OPC-41061	277	1558 ^a	Furosemide	318	1915 ^a	1.1	1.2
	310	1625 ^a	HCT	276 ^a	1760 ^a	0.89	1.1
Furosemide	2742	7017 ^b	OPC-41061	2303	6404 ^b	0.84	0.91
HCT	520	3653 ^a	OPC-41061	567	4069 ^a	1.1	1.1

^aAUC_t ^bAUC_∞

It should be noted that only the plasma concentrations of furosemide were measured long enough to reliably estimate AUC_∞. In contrast, OPC-41061 and HCT were not measured long enough to determine reliably AUC_∞. Therefore, the above comparisons for OPC-41061 and HCT are based on AUC_t and thus should be considered only as crude estimates. The results suggest that neither co-administered furosemide nor HCT affect the kinetics of OPC-41061 clinically relevantly. Also, co-administered OPC-41061 does not affect the kinetics of furosemide or HCT clinically relevantly.

The below table summarizes the the respective renal clearances of OPC-41061, furosemide and HCT in the absence and presence of each other:

Impact of Tolvaptan, Furosemide and Hydrochlorothiazide on their Respective Renal Clearance

Mean (SD) Renal Clearances, CL _r , mL/min/kg					
Drug	Dose mg	Impact on	Dose mg	CL _r , mL/min/kg	
				In absence	In presence
OPC-41061	30 mg	HCT	100 mg, SD	2.43 (0.47)	2.19 (0.32)
OPC-41061	30 mg, SD	Furosemide	80 mg, SD	1.12 (0.41)	1.09 (0.28)

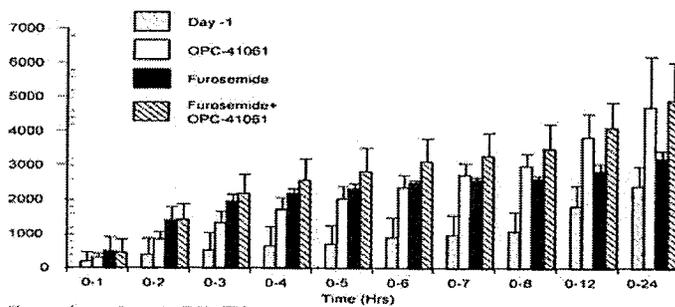
Furosemide	80 mg, SD	OPC-41061	30 mg, SD	0.006 (0.002)	0.005 (0.002)
HCT	100 mg, SD	OPC-41061	30 mg, SD	2.43 (0.47)	2.19 (0.32)

The data do not suggest a relevant impact of co-administered OPC-41061, furosemide or HCT on their respective renal clearances.

Pharmacodynamics

ARM 1: Interaction between Tolvaptan and Furosemide

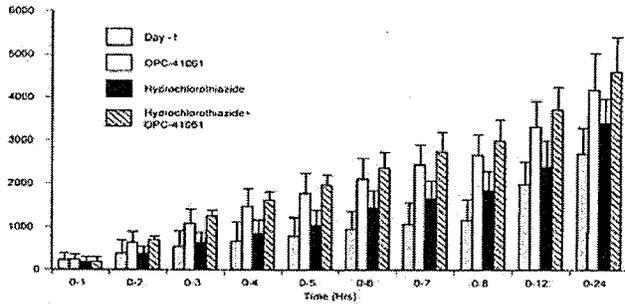
Mean ± SD Cumulative Urine Volume up to 24 Hours After Administration of OPC-41061 Alone, Furosemide Alone, and OPC-41061 and Furosemide Combined



The mean cumulative urine volumes excreted up to 24 h after administration of OPC-41061 alone, furosemide alone and the combination treatment are all greater than the baseline values on Day-1. The aquaretic effect of furosemide initially is greater than that of OPC-41061. However, at later times OPC-41061 is more effective and the cumulative 24 h urine volume excreted with the OPC-41061 alone treatment exceeds that of furosemide alone. The combination treatment results in a not relevantly greater 24 h urine volume than the OPC-41061 alone treatment. The aquaretic effect of the combination treatment compared to that of the alone treatments is clearly infra-additive compared to the respective alone treatments.

Arm 2: Interaction between Tolvaptan and Hydrochlorothiazide

Mean \pm SD Cumulative Urine Volume up to 24 Hours After Administration of OPC-41061 Alone, Hydrochlorothiazide Alone, and OPC-41061 and Hydrochlorothiazide Combined



The mean cumulative urine volumes excreted up to 24 h after administration of OPC-41061 alone, HCT alone and the combination treatment are all greater than those by the subjects during Day-1 (baseline). The aquaretic effect of OPC-41061 on the cumulatively excreted 24 h urine volume exceeds that of the HCT alone treatment throughout the collection period. The aquaretic effect of co-administered HCT and OPC-41061 is not relevantly greater than that of OPC-41061 alone. However, the aquaretic effect of the combination treatment is greater than with the HCT alone treatment. It can be concluded that co-administering HCT and OPC-41061 results in a clearly infra-additive aquaretic effect compared to the respective alone treatments..

Free Water Clearance, Plasma and Urine Osmolality

The below table shows the results of the effect of the test treatments on mean free water clearance measured over 4 h post-dose:

Mean (SD) Free Water Clearance after Alone and Combination Treatments with OPC-41061, Furosemide and HCT in 6 Healthy Male Subjects

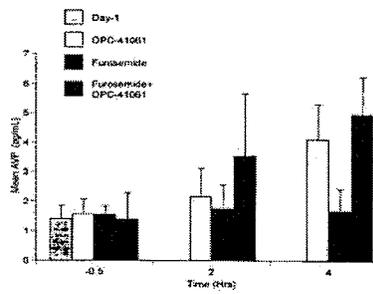
Treatment	Free Water Clearance, mL/min			
	1 h	2 h	3 h	4 h
Arm 1				
OPC-41 061 30 mg alone	1.39	7.03	3.62	3.67
Furosemide 80 mg alone	-0.03	1.05	0.21	0.69
OPC-41061/Furosemide	0.90	3.17	4.74	2.26
Arm 2				
OPC-41061 30 mg alone	-0.01	4.79	4.17	3.80
HCT 100 mg alone	-2.18	-1.41	1.00	-0.80
OPC-41061/HCT	-0.15	4.80	4.82	2.75

The results indicate a marked increase in the free water clearance occurs only with OPC-41061 alone or combination treatments, but not with either furosemide or HCT alone indicating that significant aquaresis occurs only with OPC-41061.

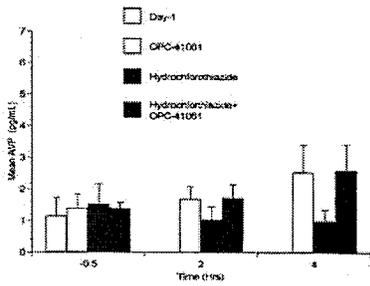
Plasma AVP

The below figures show the impact of the test treatments in Arms 1 and 2 on mean AVP plasma concentrations:

Arm 1: OPC-41061-Furosemide Interaction



Arm 2 OPC-41061- Hydrochlorothiazide Interaction

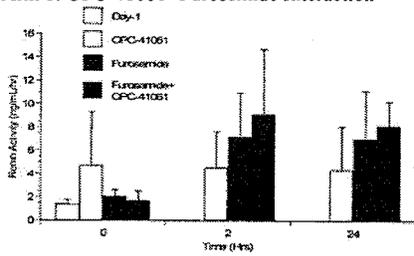


The mean baseline concentrations of AVP are similar. The 2 h and 4 h post-dose measurements show a trend for an increase in plasma AVP after all treatments with OPC-41061. In contrast, furosemide or HCT treatments appear not to impact AVP in the subjects.

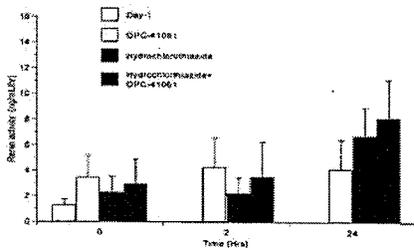
Mean PRA

The below 2 figures show the impact of the test treatments in Arms 1 and 2 on PRA:

Arm 1: OPC-41061- Furosemide Interaction



Arm 2: OPC-41061-Hydrochlorothiazide Interaction

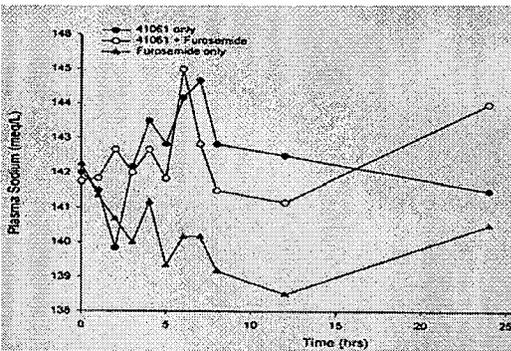
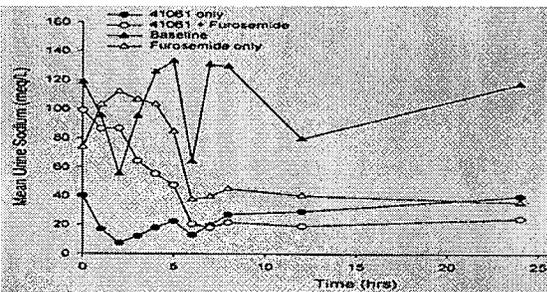


The data suggest a trend for an increase in mean PRA for furosemide- and HCT alone- and combination treatments.

Plasma Na⁺ Concentrations

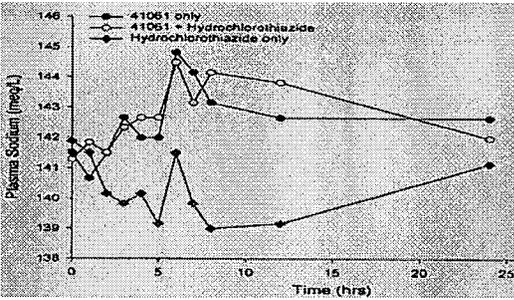
The below plots show the mean plasma Na⁺ concentrations over a period of 24 h post-dose following the different treatments in Arms 1 and 2:

Arm 1: OPC-41061-Furosemide Interaction



Best Possible Copy

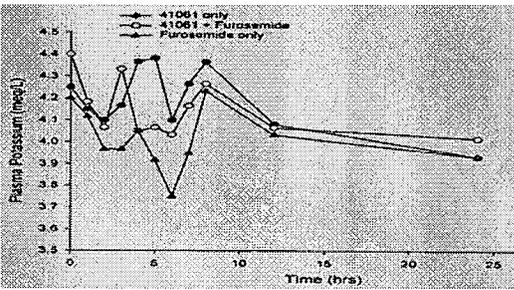
Arm 2: OPC-41061-Hydrochlorothiazide Interaction



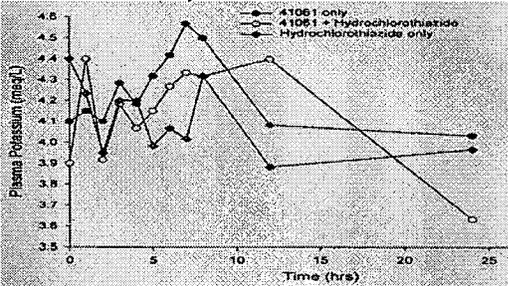
The pre-dose values during the different treatments in each arm are close. The mean Na⁺ concentrations appear to be greater with the OPC-41061 alone or combination treatments than with either furosemide or HCT alone.

The below two figures show the impact of the test treatments on the plasma K⁺ concentrations in Arms 1 and 2:

Arm 1: OPC-41061-Furosemide Interaction



Arm 2: OPC-41061-Hydrochlorothiazide Interaction

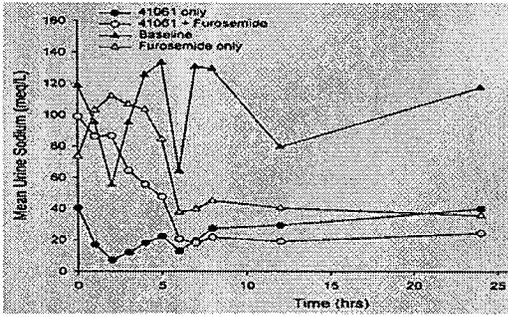


The pre-dose values for the different treatments in Arms 1 and 2 vary. The plots appear to show a trend for a greater increase in the mean K⁺ concentration with the OPC-41061 containing treatments than with furosemide or HCT alone treatments.

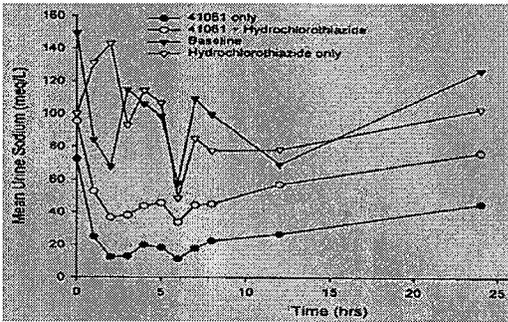
The next two plots show the urine Na⁺ excretion during the different treatments in Arms 1 and 2:

Arm 1: OPC-41061-Furosemide

Best Possible Copy



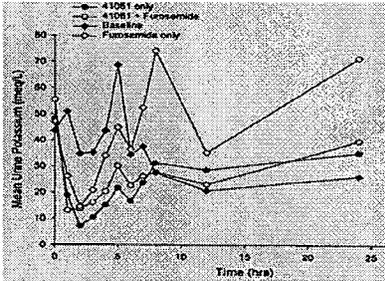
Arm 2: OPC-41061- Hydrochlorothiazide



The pre-dose values vary significantly among the different treatments. The data appear to indicate that the mean urine Na^+ concentration relative to the baseline is greater with the furosemide or hydrochlorothiazide alone treatments than with the OPC-41061 alone or combination treatments.

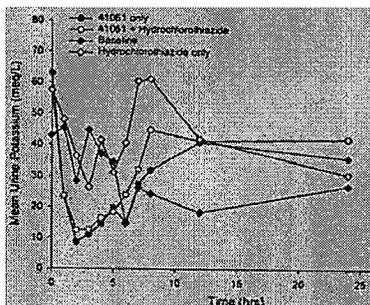
The impact of the test treatments on the urine K^+ excretion is shown in the final 2 figures:

Arm 1: OPC-41061-Furosemide Interaction



Best Possible Copy

Arm 2: OPC-41061-Hydrochlorothiazide Interaction



Best Possible Copy

Compared to baseline the furosemide or hydrochlorothiazide alone treatments appear to increase the mean urine K^+ concentration more than the OPC-41061 alone or combination treatments.

Conclusions

PK

Single doses of co-administered furosemide (80 mg) or HCT (100 mg) do not affect the kinetics of OPC-41061 (30 mg) clinically relevantly. Also, co-administered OPC-41061 does not affect the kinetics of furosemide or HCT clinically relevantly.

PD

OPC-41061-Furosemide Interaction

The cumulative 24 h urine volume excreted in the OPC-41061 alone treatment exceeds that observed in the furosemide alone treatment. The combination treatment results in a not relevantly greater 24 h urine volume than that observed with the OPC-41061 alone treatment. However, the combination treatment produces an aquaresis that is greater than with furosemide alone. The aquaretic effect of the combination treatment compared to that of the respective alone treatments is clearly infra-additive.

OPC-41061- Hydrochlorothiazide Interaction

The aquaretic effect of OPC-41061 on the cumulatively excreted 24 h urine volume exceeds that of HCT throughout the 24 h collection period. The co-administration of HCT and OPC-41061 produces a not importantly greater 24 h urine volume than the alone treatment with OPC-41061. However, the aquaresis produced by the combination treatment is greater than with the HCT alone treatment. It can be concluded that the aquaretic effect of co-administered HCT and OPC-41061 is clearly infra-additive compared to respective alone treatments.

Comments

1. It would have been more appropriate to measure the amounts excreted of sodium and potassium than the urine concentrations of the electrolytes.
2. It is questionable whether the one day washout phase between the treatments observed in this study is sufficient to avoid carry-over effects.
3. A dose of 60 mg tolvaptan should have been tested.

5. BIOPHARMACEUTICS

Drug Substance

The water solubility of tolvaptan is low (0.00005% w/v) and pH independent. Tolvaptan's permeability/absolute bioavailability has not been determined.

Drug Product

The below 2 tables show the composition of the 15, 30 and 60 mg clinical service formulations and 15 and 30 mg to be marketed formulations of tolvaptan:

Table 2.7.1.5.1-3 Composition of Tolvaptan 15-, 30-, and 60-mg Tablets Used in Phase 2 and 3 Clinical Studies

Component	Composition (mg/Tablet)		
	15-mg Tablets	30-mg Tablets	60-mg Tablets
Tolvaptan	15.0	30.0	60.0
Hydroxypropyl cellulose ^a	[REDACTED]	[REDACTED]	[REDACTED]
Lactose monohydrate	[REDACTED]	[REDACTED]	[REDACTED]
Corn starch	[REDACTED]	[REDACTED]	[REDACTED]
Microcrystalline cellulose	[REDACTED]	[REDACTED]	[REDACTED]
Hydroxypropyl cellulose ^c	[REDACTED]	[REDACTED]	[REDACTED]
Low-substituted hydroxypropyl cellulose	[REDACTED]	[REDACTED]	[REDACTED]
Magnesium stearate	[REDACTED]	[REDACTED]	[REDACTED]
Total weight	100.0	114.0	[REDACTED]
Tablet shape and color	White, round, 8 mm diameter, flat-face, beveled edge		

b(4)

2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods Tolvaptan NDA

Table 2.7.1.5.1-4 Composition of Proposed Marketing Tolvaptan 15-, 30-, and 60-mg Tablets

Component	Function	15-mg Tablets	30-mg Tablets	60-mg Tablets
		mg	mg	mg
Tolvaptan	Active Ingredient	15,000	30,000	60,000
Hydroxypropyl cellulose ¹				
Lactose monohydrate				
Corn starch				
Microcrystalline cellulose				
Hydroxypropyl cellulose ²				
Low-substituted hydroxypropyl cellulose				
FD&C Blue No.2				
Aluminum Lake				
Total weight		87,000	174,000	

b(4)

The proposed marketing formulations of tolvaptan are blue uncoated tablets containing tolvaptan

b(4)

The clinical service formulations were used in the pivotal Phase 3 trials. An in vivo study showed that the clinical service formulations of 15 and 30 mg strength are bioequivalent. An in vivo study demonstrating the bioequivalence of the service formulations and to be marketed formulations was not performed. As shown in the below table the clinical service formulations and to be marketed formulations of strength 30 mg are compositionally identical, whereas the clinical service formulation and to be marketed formulation of strength 15 mg are compositionally different:

	Tablets Phase 2/3 Studies			Commercial Tablets		
	15 mg	30 mg	60 mg	15 mg	30 mg	60 mg
Tolvaptan						
Total Weight mg	180	174		87	174	
Filler Lactose Monohydrate						
Filler/ Total Ratio						
Inactive /Total Ratio						

b(4)

The sponsor seeks granting of a biowaiver based on in vitro dissolution data. However, the submitted data do not demonstrate the discriminatory ability of the dissolution method, because the amounts of the surfactant laurylsulfate (0.22%) are relatively high. Until such data are provided, an in vivo biowaiver cannot be granted until the sponsor justifies the choice of the dissolution method and medium used.

Food was shown not to impact the bioavailability of tolvaptan with the clinical service formulations.

6. PHARMACOMETRICS REVIEW

NDA:	22275
Drug name:	Tolvaptan
Indication:	Treatment of Hyponatremia and Worsening Heart Failure
Proposed Regimen (Sponsor):	15 mg QD with titration up to 60 mg QD
Applicant:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Clinical Pharmacology Reviewer	Peter Hinderling, M.D.
Clinical Pharmacology Team Leader	Patrick J Marroum, Ph.D.
Pharmacometrics Reviewer:	Justin C. Earp, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Type of Submission:	NDA
Submission Date:	October 22, 2007
PDUFA Date:	August 22, 2008

EXECUTIVE SUMMARY

This document addresses the following five questions.

- 1. The sponsors constructed three population pharmacokinetic models depending on disease status. What are the major covariates affecting pharmacokinetic parameters based on population pharmacokinetic analysis?***

Body weight and liver impairment were the major covariates affecting clearance and volume of distribution of tolvaptan in all hyponatremia populations. Renal impairment had no significant influence on the clearance of tolvaptan.

- 2. Is it necessary to adjust dose based on the identified pharmacokinetic covariates?***

Given the relatively small magnitude of covariate effect on apparent clearance (<30%) and efficacy (serum sodium level)-based dose titration, adjusting dose based on these PK covariates is not necessary.

- 3. Is the proposed dosing of Tolvaptan effective for Hyponatremia?***

Following dosing of Tolvaptan there is a noticeable increase in sodium concentrations that reaches a maximum effect significantly greater than the placebo response and above the lower limit of the normal serum sodium concentration range (135 mEq). Upon termination of therapy serum sodium concentrations fall to concentrations equivalent to patients treated with placebo.

- 4. Is tolvaptan effective for hyponatremia patients and hyponatremia patients with lower baseline serum sodium concentrations?***

The patients' change from baseline in steady-state serum sodium concentrations increased with a decrease in baseline concentrations. Tolvaptan was able to return patients with the lowest starting sodium concentrations to normal serum sodium levels. While tolvaptan is effective for a full range of baseline values, dose titration may be required to achieve the desired serum sodium concentration range.

- 5. Tolvaptan acts by increasing free water clearance, indirectly causing an increase in serum sodium concentrations. Do patients with impaired renal function yield less responsiveness to Tolvaptan and require dose-adjustment?***

Comparison of average daily change in serum sodium concentrations with renal function as indicated by creatinine clearance from two phase III efficacy trials in patients with hyponatremia did not evidence any correlation between renal function and response to tolvaptan.

- 6. Does Tolvaptan prolong the QT-interval?***

The IRT-QT review analysis indicates that tolvaptan does not prolong the QT interval at the therapeutic doses.

RECOMMENDATION

The Pharmacometrics group in Office of Clinical Pharmacology has reviewed the submitted information and has found the application acceptable

Signatures:

Justin C. Earp, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

Yaning Wang, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology

**Appears This Way
On Original**

TABLE OF CONTENTS

PHARMACOMETRIC REVIEW.....	350
EXECUTIVE SUMMARY.....	351
RECOMMENDATION.....	352
TABLE OF CONTENTS.....	353
LIST OF TABLES.....	354
LIST OF FIGURES.....	354
INTRODUCTION.....	355
1 SPONSOR'S ANALYSIS.....	356
1.1 POPULATION PHARMACOKINETICS.....	356
1.1.1 Datasets.....	356
1.1.2 Summary of Trials.....	359
1.1.3 Methods.....	363
1.1.4 Results.....	366
1.1.5 Sponsor's Conclusions:.....	369
1.1.6 Reviewers Comments.....	370
1.2 HYPONATREMIA EFFICACY TRIALS.....	371
1.2.1 Summary of Trials.....	371
1.2.2 Sponsor's Results.....	374
2 REVIEWER'S ANALYSIS: QUESTION BASED REVIEW.....	375
2.1 POPULATION PHARMACOKINETICS.....	375
2.1.1 What are the major covariates affecting pharmacokinetic parameters?.....	375
2.1.2 Is it necessary to adjust dose based on identified covariates?.....	375
2.2 HYPONATREMIA EFFICACY TRIALS.....	377
2.2.1 Is the proposed dosing of Tolvaptan effective for Hyponatremia?.....	377
2.2.2 Is tolvaptan effective for patients with lower baseline serum sodium concentrations?.....	378
2.2.3 Is dose-adjustment required for patients with impaired renal function?.....	381
2.3 DOES TOLVAPTAN PROLONG THE QT INTERVAL?.....	382
CONCLUSION.....	385

LIST OF TABLES

Table 1. Sponsors Data Set Overview	357
Table 2. Sponsor’s Data Set Summary	358
Table 3. Sponsor’s Clinical Trial Designs	362
Table 4. Summary of Categorical Covariates for Hyponatremia (PKT-6) and Hyponatremia and CHF trials (PKT-21)	364
Table 5. Summary of Continuous Covariates for Hyponatremia Trials	365
Table 6. Summary of Continuous Covariates for Hyponatremia and CHF Trials.....	365
Table 7. Sponsor’s Hyponatremia Population PK Model Parameters.....	367
Table 8. Sponsor’s Hyponatremia of Any Origin Population PK Model Parameters	368
Table 9. Sponsor’s Congestive Heart Failure Population PK Model Parameters.....	369
Table 12. Typical values for apparent clearance, volume of distribution, and half-life as reported from the final population PK model parameter estimates.	375
Table 13. Values for apparent clearance, volume of distribution, and half-life after correction for the influence of body weight in patients with hyponatremia of any origin.	375
Table 14. Values for apparent clearance, volume of distribution, and half-life after correction for the influence of hepatic impairment (Child-Pugh scores B=moderate or C=severe) in patients with hyponatremia of any origin.....	375
Table 15. Parameter Estimates for Studies 235 and 238.	380

LIST OF FIGURES

Figure 1: Clinical Trial Design for Studies 156-02-235 and 156-03-238.....	373
Figure 2: Dose Titration Schematic for Studies 156-02-235 and 156-03-238	374
Figure 3: Time course of tolvaptan response in studies 238 and 235 (mean ± SE).....	377
Figure 4: Final model fitting of E_{max} dependent on baseline serum sodium for studies 235 and 238, with Tolvaptan (top row) and with placebo (bottom row).....	379
Figure 5: Serum Sodium Response – Baseline Creatinine Clearance Relationship	381
Figure 6: QT (Raw QT measurements, Bazett’s, Fridericia’s and Individual corrected QT)-RR interval relationship	382
Figure 7: Time course of mean $\Delta\Delta QTcF$	383
Figure 8: Concentration- $\Delta\Delta QTcF$ relationship.....	384

INTRODUCTION

Samska (Tolvaptan) is a selective arginine vasopressin 2 receptor antagonist designed to increase water removal from patients with fluid-overload and reduced serum sodium concentrations. Tolvaptan acts by inhibiting the expression of aquaporin-2 water channels and re-absorption of water in the distal tubules. Water is removed without increasing the excretion of electrolytes.

The compound has been developed for the short-term improvement of signs and symptoms of worsening heart failure beyond that achieved with standard of care and for the treatment of hypervolemic and euvolemic hyponatremia (including patients with heart failure, cirrhosis, SIADH, etc.) and for the prevention of worsening hyponatremia. (Source: Sponsor's CTD Introduction Document)

Trials in healthy subjects showed that tolvaptan pharmacokinetics (PK) were linear for single oral doses ranging from 5 to 480 mg, although the maximum concentration of each dosing interval (C_{max}) showed less than a proportional increases with increasing dose and plateaued at doses ≥ 300 mg. The mean (standard deviation [SD]) of the elimination half-life ($t_{1/2,z}$) is 7.8 (4.9) hours. The median time to reach maximum concentration (t_{max}) was 2 hours. Mean oral clearance (CL/F) ranged from 4.0 to 7.7 mL/min/kg (16.8 to 32.3 L/h) for single doses and from 3.2 to 5.4 mL/min/kg (13.4 to 22.7 L/h) following multiple oral doses. Tolvaptan PK was dose proportional for multiple oral doses of 30 mg and 60 mg given once daily (QD) for 28 days. There was no accumulation of tolvaptan after 28 days with 60 mg QD. (Source: Sponsor's Clinical Study Report 156-01-224)

**Appears This Way
On Original**

1 SPONSOR'S ANALYSIS

1.1 POPULATION PHARMACOKINETICS

1.1.1 Datasets

Two core PK datasets were created, one including subjects with hyponatremia of any origin enrolled in the hyponatremia trials and one including subjects with heart failure with or without hyponatremia enrolled in the heart failure trials. The core PK data file for the hyponatremia analysis contained 1,486 plasma samples from 213 subjects enrolled in the 3 hyponatremia trials listed below and the heart failure analysis contained 10,020 plasma samples of 2,392 subjects from the 5 heart failure trials listed below. A second hyponatremia analysis included subjects with hyponatremia at baseline enrolled in all eight of the trials below, the dataset contained 2,716 plasma samples from 490 subjects:

156-97-251: Multicenter, randomized, double-blind, placebo-controlled, oral, dose-ranging, efficacy, safety, and PK study of tolvaptan tablets in patients with congestive heart failure (CHF) with extracellular volume expansion

156-97-252: Multicenter, randomized, double-blind, placebo-controlled, oral, dose-defining, efficacy and safety study of tolvaptan in patients with extracellular volume expansion secondary to CHF

156-98-213: Multicenter, randomized, double-blind, placebo-controlled study of OPC-41061 to evaluate the effects of tolvaptan on the acute and chronic outcomes of hospitalized patients with worsening CHF

156-01-232: Multicenter, randomized, double-blind, placebo-controlled efficacy study of OPC-41061 on the effect of left ventricular dilatation and function in patients with CHF and left ventricular (LV) systolic dysfunction

156-03-236 Multicenter, randomized, double-blind, placebo-controlled study to evaluate the long term efficacy and safety of oral tolvaptan tablets in subjects hospitalized with worsening CHF

156-96-203: multicenter, randomized, doubleblind, placebo-controlled, dose-ranging, efficacy, safety, and PK study of tolvaptan in Hospitalized Patients with hyponatremia secondary to liver disease

156-02-235: International, multicenter, randomized, double-blind, placebocontrolled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia

156-03-238: International, multicenter, randomized, double-blind, placebocontrolled, efficacy and safety study of the effects of titrated oral tolvaptan tablets in patients with hyponatremia

Covariates investigated in both heart failure and hyponatremia analysis included demographics (age, race sex), size metrics (eg, body weight, lean body weight, body mass index), liver function (Child-Pugh Classification), renal function (creatinine clearance calculated from the Cockcroft-Gault equation), and concomitant medications (loop, potassium sparing, and thiazide diuretics, CYP3A4 inhibitors and CYP3A4 inducers, and drugs that interact with Pglycoprotein [P-gp]). The hyponatremia analysis included disease etiology (CHF, cirrhosis, or SIADH/other), hyponatremic severity (mild or severe) and volume status (euvolemic or hypervolemic). The

heart failure analysis included NYHA class and drug classes associated with this population (ACE inhibitors, beta-blockers, vasodilators, angiotensin receptor antagonists [ARBs], inotropes, and antacids).

Table 1. Sponsors Data Set Overview

Table 3.1-1 Data Sets					
Subject Population	Trial Indication	# of Subjects		# of Samples	
		dense	sparse	dense	sparse
hyponatremia	hyponatremia	30	183	672	814
hyponatremia	hyponatremia and heart failure	97	393	1099	1617
heart failure with and without hyponatremia	heart failure	430	1962	2174	7846

Source: Sponsor's Clinical Study Report 156-01-224
 (\\Cdsesub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

**Appears This Way
 On Original**

Table 2. Sponsor's Data Set Summary

PKT- 3 Dataset Summary							
Study	Indication	Dose	D ^a	Sampling	#P ^b	#S ^c	Assay
hyponatremia, hyponatremia studies							
96203	hyponatremia - liver disease	5, 10, 15, or 30 mg QD	13 days	dense, Day1 and optionally Day13	30	310	HPLC/UV
02235	hyponatremia - liver disease, CHF, SIADH/ other	titration 15, 30, 45 mg QD	30 days	sparse, Weeks 1, 2, 3, Day 30; predose and 2-4 hrs post-dose	88	2384	LC/MS /MS
03235	hyponatremia - liver disease, CHF, SIADH/ other	titration 15, 30, 45 mg QD	30 days	sparse, Weeks 1, 2, 3, Day 30; predose and 2-4 hrs post-dose	95	2764	LC/MS /MS
hyponatremia, hyponatremia and CHF studies							
97251	hospitalized CHF (NYHA I-III)	10, 15, 30, or 60 mg QD	13 days	dense on Day1 and optionally on Day13, sparse on Days 2-4,5,7,9	10	211	HPLC/UV
97252	hospitalized CHF (NYHA I-III)	10, 15, 30, or 60 mg QD	24 days	sparse, 2 hr post-dose Days 3, 7, 14	19	53	HPLC/UV
98213	hospitalized worsening CHF (NYHA III-IV)	30, 60, or 90 mg QD	59 days	semi-dense on Day 1 and sparse on Discharge and Week7	38	163	LCMS
01232	hospitalized CHF (NYHA I-III)	30 mg QD	1 year	sparse, 1 hr post-dose on Day1 and Weeks 1,12,20,28,36,44,54	2	9	LC/MS /MS
03236	hospitalized worsening CHF (NYHA III-IV)	30 mg QD	60 days to > 1 year	sparse, Day 0, Day 7, Weeks 1, 4, 8	208	794	LC/MS /MS
CHF, CHF studies							
97251	hospitalized CHF (NYHA I-III)	10, 15, 30, or 60 mg QD	13 days	dense on Day1 and optionally on Day13, sparse on Days 2-4,5,7,9	36	767	HPLC/UV
97252	hospitalized CHF (NYHA I-III)	10, 15, 30, or 60 mg QD	24 days	sparse, 2 hr post-dose Days 3, 7, 14	174	485	HPLC/UV
98213	hospitalized worsening CHF (NYHA III-IV)	30, 60, or 90 mg QD	59 days	semi-dense on Day 1 and sparse on Discharge and Week7	220	922	LCMS
01232	hospitalized CHF (NYHA I-III)	30 mg QD	1 year	sparse, 1 hr post-dose on Day1 and Weeks 1,12,20,28,36,44,54	104	669	LC/MS /MS
03236	hospitalized worsening CHF (NYHA III-IV)	30 mg QD	60 days to > 1 year	sparse, Day 0, Day 7, Weeks 1, 4, 8	1858	7177	LC/MS /MS

a Duration

b # of Subjects

c # of Samples

Source: Sponsor's Clinical Study Report 156-01-224

(\\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

1.1.2 Summary of Trials

Protocol 156-97-251, Phase 2, Safety and Efficacy of Tolvaptan in Subjects with CHF with Extracellular Volume Expansion

Trial 156-97-251 was a phase 2, multicenter, double-blind, randomized, placebocontrolled, dose-ranging trial of the efficacy, safety, and PK of tolvaptan tablets in subjects with CHF with extracellular volume expansion. Subjects were enrolled in 10 centers in the US. The trial consisted of a one-day baseline period (Study Day 0), a 13-day treatment period with study drug, a termination visit, and one follow-up evaluation on Study Day 20 to 23. Six groups of subjects were randomized on Day 1 in the following order: 10 mg, 15 mg, 30 mg, 60 mg, 90 mg, and 120 mg. In each treatment group, 6 subjects received tolvaptan and 3 subjects received placebo with exception of the 10 mg dose group (5 tolvaptan subjects and 4 placebo subjects). The subjects were hospitalized during the first three days of treatment. The subjects were required to return to the clinic on study days 7, 10, 13 and 14. On study day 13, the final day of dosing, the subjects could volunteer for an extra day of hospitalization after the final dose of study drug so that additional blood and urine samples could be obtained for assessing the PK of tolvaptan. A follow-up visit was to be done on study day 20 to 23. Dose escalation was evaluated at the completion of each dose group. PK data from 10 subjects with hyponatremia who received at least one tolvaptan dose was used for the hyponatremia PK analysis and 36 subjects for the heart failure analysis.

Protocol 156-97-252, Phase 2, Safety and Efficacy of Tolvaptan in Subjects with Extracellular Volume Expansion Secondary to CHF

Trial 156-97-252 was a phase 2, multicenter, double-blind, randomized, placebocontrolled, oral, dose-defining, trial of the efficacy and safety of tolvaptan in subjects with extracellular volume expansion secondary to CHF. Subjects were enrolled in 35 centers in the US. The trial consisted of a screening evaluation, a 3-day baseline run-in period, a treatment period with study drug, and two follow-up evaluations. Four groups of 60 subjects were to be randomly assigned to receive 30, 45, or 60 mg of tolvaptan or placebo daily for 25 days in an outpatient setting. The subjects also received a baseline dose of furosemide (40 to 240 mg daily). They were to return to the clinic on Study Days 3, 4, 7, 10, 14, 21 and 28 during the treatment period. Follow-up visits were to be done on Days 35 and 58 of the study. Plasma tolvaptan samples were to be obtained at 8 AM on Day 0 and two hours postdose on Days 3, 7, and 14. PK data from 19 subjects with hyponatremia who received at least one tolvaptan dose was used for the hyponatremia PK analysis and 174 subjects for the heart failure analysis.

Protocol 156-98-213, Phase 2b, Dose-Ranging Trial of Tolvaptan in Hospitalized Subjects with Worsening CHF

Trial 156-97-251 was a phase 2, multicenter, double-blind, randomized, placebocontrolled, dose-ranging trial to evaluate the effects of tolvaptan on the acute and chronic outcomes of hospitalized subjects with worsening CHF. The trial consisted of a screening day, up to a 10-day inpatient period, followed by a 7-week outpatient period. Subjects were randomized on day 1 to

either receive 30, 60 or 90 mg of tolvaptan or placebo. Study drug administration began on inpatient Day 1. Subjects were to be discharged no later than 10 days after the first dose of study drug. Subjects who, in the investigator's opinion, could not be discharged from the hospital by inpatient Day 10 were considered treatment failures and withdrawn from the study. Study drug dosing continued in the outpatient setting for 49 to 51 days, with office visits scheduled for Outpatient Weeks 1, 3, 5 and 7. A follow-up telephone contact was to be done 7 days after the last dose of study drug. PK data from 38 subjects with hyponatremia who received at least one tolvaptan dose was used for the hyponatremia PK analysis and 220 subjects were used for the heart failure analysis. b(4)

Protocol 156-01-232, Phase 2 Efficacy Trial of Tolvaptan on the Effect of Left Ventricular Dilatation and Function in Subjects with CHF and Left Ventricular Systolic Dysfunction

Trial 156-01-232 was a phase 2 multicenter, randomized, double-blind, placebocontrolled trial to assess the effects of oral tolvaptan, in addition to standard therapy, on left ventricular (LV) dilatation and function in 240 subjects with heart failure and LV systolic dysfunction. Subjects who met inclusion and exclusion criteria returned on Day 1 for randomization to either placebo or 30 mg of tolvaptan once daily (QD). Subjects participated in an outpatient setting and returned to the study center for study visits on Weeks 4, 12, 20, 28, 36, 44, 54, and 55. PK data from 2 subjects with hyponatremia who received at least one tolvaptan dose was used for the hyponatremia PK analysis and 104 subjects for the heart failure analysis. b(4)

Protocol 156-03-236, Phase 3 Trial to Evaluate the Long Term Efficacy and Safety of Oral Tolvaptan Tablets in Subjects Hospitalized with Worsening CHF

Trial 156-03-236 was a phase 3, multicenter, randomized, double-blind, placebocontrolled trial to evaluate the long term efficacy and safety of oral tolvaptan tablets in subjects hospitalized with worsening heart failure. The screening period could last up to 48 hours after initial hospitalization. The qualifying subjects were randomized to treatment with 30 mg tolvaptan tablets or matching placebo. After randomization, treatment with the study drug was continued until the termination of the trial, which occurred after the 1065th death and all subjects currently enrolled had received a minimum of 60 days of study drug. Any subject terminating study drug during the trial was contacted every three months until the Study Termination Date to collect safety information. A follow-up visit occurred 7 days after the last dose of study drug for all subjects to allow for adjustments in concomitant diuretic therapy. A follow-up telephone call was made 14 days after the last dose of study drug for all subjects to collect safety information. PK data from 208 subjects with hyponatremia who received at least one tolvaptan dose was used for the hyponatremia PK analysis and 1858 from the heart failure analysis. b(4)

Protocol 156-96-203, Phase 2 Trial, Safety and Efficacy of Tolvaptan in Hospitalized Subjects with Hyponatremia

Trial 156-96-203 was a phase 2, multicenter, double-blind, randomized, placebocontrolled, dose-ranging trial of the efficacy, safety, and PK of tolvaptan in subjects with hyponatremia secondary to liver disease¹. Subjects were enrolled in seven centers in the US. The trial consisted of a two-day baseline period (study days -1 and 0), a 13-day treatment period with study drug, a termination visit, and one follow-up evaluation 6 to 9 days after the termination visit. Five groups of 9 subjects were randomized on day 1 in the following order: 5 mg, 10 mg, 15 mg, 30 mg, and 60 mg. In each treatment group, 6 subjects received tolvaptan and 3 subjects received placebo. The subjects were hospitalized during the first four days of treatment. They were

allowed to be discharged from the hospital after completing study day 5 assessments. The subjects were required to return to the clinic on study days 7, 9, 11, 13 and 14. On study day 13, the final day of dosing, the subjects could volunteer for an extra day of hospitalization after the final dose of study drug so that additional blood samples could be obtained for assessing the plasma sodium and potassium levels and PK of tolvaptan. A follow-up visit was to be done on study day 20 to 23. Dose escalation was evaluated at the completion of each dose group. PK data from all 30 subjects who received at least one tolvaptan dose was used for the hyponatremia PK analysis.

Protocol 156-02-235, Phase 3, Safety and Efficacy of Titrated Oral Tolvaptan Tablets in Subjects with Hyponatremia

Trial 156-02-235 was a phase 3, multicenter, double-blind, randomized, placebocontrolled, efficacy and safety trial oral tolvaptan as adjunct to standard therapy in subjects with nonacute hyponatremia in euvolemic or hypervolemic states². In this trial, 205 subjects from 42 active US trial sites were randomized to receive either placebo or 15 mg of oral tolvaptan. During the study treatment period, subjects continued their current medications and may have been offered standard therapies for hyponatremia as clinically indicated. Subjects entering the trial with a serum sodium value of < 130 mEq/L may have been fluid restricted, if necessary, at the discretion of the investigator. For those subjects randomized during a hospitalization, the subjects were to remain in the hospital or inpatient observational unit after Day 1, until the investigator determined that the subject may be discharged. Once discharged the subject was to return for outpatient visits on a weekly basis until a total of 30 days of treatment was completed. The total dosing duration was up to 30 days. The subject was not required to be hospitalized in order to be randomized into the trial. Subjects were to stay over night in an observational unit or hospital for at least 24 hours on Day 1. For subjects randomized to receive 15 mg tolvaptan, dose titration to 30 mg and then 60 mg of study drug occurred depending on the subject's serum sodium concentrations. PK data from 88 subjects was used for the hyponatremia PK analysis.

Protocol 156-03-238 Phase 3, Safety and Efficacy of Titrated Oral Tolvaptan Tablets in Subjects with Hyponatremia

Trial 156-03-238 was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety trial of the effects of oral tolvaptan in subjects with non-acute hyponatremia in euvolemic or hypervolemic states.³ This trial was conducted in 72 centers in the US, Canada, and Europe. A total of 243 subjects were randomized to either placebo or 15 mg tolvaptan. During the trial treatment period, subjects continued their current medications and may have been offered standard therapies for hyponatremia as clinically indicated. Subjects who met inclusion and exclusion criteria were randomized to either placebo or 15 mg tolvaptan. Subjects who entered the trial with a serum sodium value of <130 mEq/L could have been fluid restricted, if necessary, at the discretion of the investigator. Subjects who were randomized during a hospitalization remained in the hospital or inpatient observational unit after Day 1 until the investigator determined that the subject could be discharged. Once discharged, the subject returned for outpatient visits on a weekly basis until a total of 30 days of treatment was completed. Outsubjects also could have been randomized into the trial if they were willing to be admitted for the first dosing day. Subjects were required to stay over night in an observational unit or hospital for at least 23 hours on Day 1. For subjects randomized to receive 15 mg tolvaptan, dose titration to 30 mg and then 60 mg of study drug occurred depending on subject's

serum sodium concentrations. PK data from 95 subjects was used for the hyponatremia PK analysis.

Table 3. Sponsor's Clinical Trial Designs

PKT- 1 Summary of Study Designs				
Study	Population	Number of Subjects	Treatment Group(s)	Dosing Duration
Clinical trials that enrolled patients with hyponatremia				
156-96-203	Hospitalized patients with hyponatremia secondary to liver disease	N = 36 (6 active/3 placebo per dose group)	5, 10, 15, and 30 mg tolvaptan or placebo	QD for 13 Days
156-02-235	Non-acute hyponatremia associated with euvolemic or hypervolemic states with no single etiology (CHF, cirrhosis, SIADH/other)	N=205 (102 active/103 placebo per group)	15 mg tolvaptan or placebo with upwards titration to 30 mg and to 60 mg based on serum sodium levels	QD for 30 days
156-03-238	Non-acute hyponatremia associated with euvolemic or hypervolemic states with no single etiology (CHF, cirrhosis, SIADH/other)	N=243 (123 active/120 placebo per group)	15 mg tolvaptan or placebo with upwards titration to 30 mg and to 60 mg based on serum sodium levels	QD for 30 days
Clinical trials that enrolled patients with CHF				
156-97-251	Hospitalized patients with CHF (NYHA Class I-III)	N = 36 (6 active, 3 placebo per group)	(1) 10 mg tolvaptan or placebo (2) 15 mg tolvaptan or placebo (3) 30 mg tolvaptan or placebo (4) 60 mg tolvaptan or placebo	QD for 13 Days
156-97-252	Hospitalized patients with CHF (NYHA Class I-III)	N = 240 (60/group)	Days 1-2: placebo; Days 3-27: (1) 30 mg tolvaptan (2) 45 mg tolvaptan (3) 60 mg tolvaptan (4) placebo	QD for 24 Days
156-98-213	Hospitalized patients with worsening CHF (NYHA Class III-IV)	N = 320 (80/group)	(1) Placebo (2) 30 mg tolvaptan (3) 60 mg tolvaptan (4) 90 mg tolvaptan	QD for 59 Days
156-01-232	Hospitalized patients with CHF (NYHA Class I-III) and left ventricular systolic dysfunction	N = 240 (120/group)	(1) 30 mg tolvaptan (2) placebo	QD for 1 Year
156-03-236	Patients hospitalized with worsening CHF (NYHA III-IV, LVEF ≤ 40%, and extracellular volume expansion)	N=4,133 2,072 active/ 2,061 placebo	(1) 30 mg tolvaptan (2) placebo	QD for a minimum of 60 days

Source: Sponsor's Clinical Study Report 156-01-224

(\\Cdsesub1\levsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

1.1.3 Methods

Model building was performed in several steps:

Step 1: Base model without covariates.

In this step, a compartmental model was chosen. The objective function value, diagnostic goodness-of-fit plots, and distributions of random effects guided model selection. Diagnostic goodness-of-fit plots included plots of population and individual predicted concentrations versus observed concentrations, time after the first dose, and time after the most recent dose (PRED and IPRED versus DV, TAFD, and TAD), WRES versus time after the most recent dose (WRES versus TAD), CWRES versus time after the most recent dose (CWRES versus TAD), distributions and a scatter-plot matrix of individual Bayes estimates of inter-subject random effects.

Also, dependencies of model parameters on weight were selected. Three types of dependencies were investigated: weight-independent apparent clearance and volume; allometric scaling, and power dependencies with estimated powers. Merits of inclusion of time-dependent body size measures were investigated.

Step 2: Construction of the full covariate model.

In this step, a full covariate model was chosen. The full model included covariates prospectively pre-defined in the modeling and simulation plan. Various combinations of covariates were tested, and the best way of accounting for the liver disease stage was identified.

Step 3: Refinement of the full covariate model

At this step, diagnostic plots of the full model were investigated to screen for additional dependencies not included into the prospective modeling and simulation plan. If warranted by the data, scientific rationale and/or prior information, additional dependencies can be included into the full model to account for observed trends.

Step 4: Selection of the parsimonious covariate model

At this step, covariate effects with both point estimates and 95% confidence intervals within 25% of the typical value were excluded from the full covariate model to arrive at parsimonious model.

Step 5: Univariate Screening of covariates¹ (Hyponatremia dataset, Hyponatremia and heart failure trials)

In this step, screening of all covariates was performed. The base model 001 was used as the base for comparison. First, all covariates were included (one at a time) on clearance or volume parameters. For ordinal categorical covariates with multiple levels (Child- Pugh Class and NYHA), multiple models were considered to arrive at a parsimonious model that fully reflects the covariate effect.

¹The univariate covariate screen was conducted only for the combined hyponatremia and CHF study dataset.

Step 6: Construction of the alternative covariate model.

At this step, covariates clearing a 10-point drop in objective function were to be combined into alternative covariate model. No additional models were to be investigated if covariates not already included in the Full Model approach failed to clear the threshold.

Table 4. Summary of Categorical Covariates for Hyponatremia (PKT-6) and Hyponatremia and CHF trials (PKT-21)

PKT- 6 Summary of Categorical Covariates for the Population PK Database		
Covariate	Level	Number (Percent)
SERM	1: < 130 mEq/L	N=108 (50.7%)
Baseline Serum Sodium	2: ≥ 130 mEq/L	N=105 (49.3%)
DTYP	1: Cirrhosis	N=84 (39.4%)
Disease etiology	2: CHF	N=55 (25.8%)
	3: SIADH/Other	N=74 (34.7%)
HGRP	1: mild	N=103 (48.4%)
Hyponatremia stage	2: severe	N=110 (51.6%)
HST	missing	N=2 (0.9%)
Hyponatremia type	1: euvolemic	N=101 (47.4%)
	2: hypervolemic	N=110 (51.6%)
	missing	N=7 (3.3%)
PUGH	1: Normal	N=89 (41.8%)
Child-Pugh Grade	2: A (5-6)	N=35 (16.4%)
	3: B(7-9)	N=53 (24.9%)
	4: C (10-15)	N=29 (13.6%)
SEX	1: males	N=124 (58.2%)
Gender	2: females	N=89 (41.8%)
RACE	1: Caucasian	N=177 (83.1%)
	2: Black	N=12 (5.6%)
	3: Hispanic	N=19 (8.9%)
	4: Asian	N=3 (1.4%)
	5: Other	N=2 (0.9%)
STUD	2235	N=88 (41.3%)
Study	3238	N=95 (44.6%)
	96203	N=30 (14.1%)
PGP	0: not administered	N=60 (28.2%)
PGP-interaction	1: administered	N=153 (71.8%)
CINH	0: not administered	N=177 (83.1%)
CYP3A4 inhibitors	1: administered	N=36 (16.9%)
CIND	0: not administered	N=207 (97.2%)
CYP3A4 inducers	1: administered	N=6 (2.8%)
DIU1	0: not administered	N=89 (41.8%)
Type 1 Diuretics (loop)	1: administered	N=124 (58.2%)
DIU2	0: not administered	N=206 (96.7%)
Type 2 Diuretics (potassium sparing)	1: administered	N=7 (3.3%)
DIU3	0: not administered	N=183 (85.9%)
Type 3 Diuretics (HCTZ)	1: administered	N=30 (14.1%)
DIU4	0: not administered	N=110 (51.6%)
Type 4 Diuretics (spironolactone)	1: administered	N=103 (48.4%)
DIU5	0: not administered	N=208 (97.7%)
Type 5 Diuretics (other)	1: administered	N=5 (2.3%)

Source: CatCovSummaryAll.csv

PKT- 21 Summary of Categorical Covariates for the Population PK Database		
Covariate	Level	Number (Percent)
SEX	1: males	N=347 (70.8%)
Gender	2: females	N=143 (29.2%)
RACE	1: Caucasian	N=399 (81.4%)
	2: Black	N=37 (7.6%)
	3: Hispanic	N=44 (9%)
	4: Asian	N=3 (0.6%)
	5: Other	N=7 (1.4%)
STUD	1232	N=2 (0.4%)
Study	2235	N=88 (18%)
	3236	N=208 (42.4%)
	3238	N=95 (19.4%)
	96203	N=30 (6.1%)
	97251	N=10 (2%)
	97252	N=9 (3.9%)
	98213	N=38 (7.8%)
HGRP	1: mild	N=338 (69%)
Hyponatremia stage	2: severe	N=152 (31%)
PUGH	-1: missing	N=7 (1.4%)
Child-Pugh Grade	1: Normal or A (5-6)	N=59 (6%)
	2: B(7-9)	N=149 (30.4%)
	3: C(10-15)	N=42 (8.6%)
CHF	-1: missing	N=2 (0.4%)
CHF Diagnosis	0: no CHF	N=154 (31.4%)
	1: CHF	N=334 (68.2%)
CIRR	-1: missing	N=2 (0.4%)
Cirrhosis Diagnosis	0: no cirrhosis	N=404 (82.4%)
	1: Cirrhosis	N=84 (17.1%)
SIAD	-1: missing	N=2 (0.4%)
SIADH	0: no SIAD	N=449 (91.6%)
	1: SIAD	N=39 (8%)
NYHA	-1: missing	N=7 (1.4%)
NYHA Class	1: Class 1 (mild)	N=146 (29.8%)
	2: Class 3 (mild)	N=42 (8.6%)
	3: Class 4 (moderate)	N=159 (32.4%)
	4: Class 5 (severe)	N=136 (27.8%)
OLD	0: CHF studies	N=277 (56.5%)
CHF or Hyponatremia Study	1: Hyponatremia Studies	N=213 (43.5%)

CatCovSummaryAll.csv

Source: Sponsor's Clinical Study Report 156-01-224
 (\\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

Table 5. Summary of Continuous Covariates for Hyponatremia Trials

PKT- 7 Summary of Continuous Covariates for the Population PK Database					
Covariate	Units	Mean	SD	Median (Range)	Missing Number (%)
BNA	mEq/L	129.03	3.97	129 (11	-
WT	kg	75.22	21.45	72.6 (39.7	-
HT	cm	168.08	10.36	168 (14	-
IBW	kg	62.67	10.35	63.2 (45	-
BMI	kg/m ²	26.41	6.46	25.03 (15.	1 (0.5)%
BSA	m ²	1.87	0.29	1.85 (1.	1 (0.5)%
AGE	years	60.85	14	59 (2	-
CR0 (CrCl)	mL/min	64.61	35.85	57 (10	74 (34.7)%
CR1 (CrCl Cockcroft Gault)	mL/min	85.53	35.45	82.18 (1:	12 (5.6)%
CR2 (CrCl Salazar Corcoran)	mL/min	72.99	33.46	69.16 (1	11 (5.2)%
ALT	U/L	32.22	33.47	24 (:	14 (6.6)%
AST	U/L	44.94	37.58	30 (1	16 (7.5)%
ALB	G/dL	3.32	0.83	3.4 (1	11 (5.2)%
BILI	mg/dL	2.02	4.25	0.7 (0	16 (7.5)%
PROT	g/dL	6.85	0.98	6.8 (4	10 (4.7)%
CRE	mg/dL	1.05	0.51	0.9 (:	11 (5.2)%
CR0N normalized CR0	mL/min/(1.73 m ²)	61.17	34.89	52.69 (:	75 (35.2)%
CR1N normalized CR1	mL/min/(1.73 m ²)	80.1	32.97	76.17 (1	12 (5.6)%
CR2N normalized CR2	mL/min/(1.73 m ²)	68.65	32.04	64.05 (:	12 (5.6)%

Source: ContCovSummaryAll.csv

Table 6. Summary of Continuous Covariates for Hyponatremia and CHF Trials

PKT- 24		Summary of Continuous Covariates for the Population PK Database		
Covariate	Units	Mean	SD	Median (Range)
WT	kg	78.55	20.66	75.3 ()
BSA	m ²	1.89	0.25	1.88 ()
BMI	kg/m ²	27.1	6.15	26.45 ()
AGE	years	62.59	14	63 (2)
IBW	kg	64.64	9.92	65.9 ()
BNA (serum sodium)	mEq/L	130.56	3.69	132 ()
CRE	mg/dL	1.23	0.55	1.1 (0)
CRCL (Cockroft Gault)	mL/min	75.14	34.8	69.45
CRCLN (normalized CRCL)	mL/min/(1.73 m ²)	69.4	31.26	63.8 ()
CRIBWN (Cockroft Gault with IBW)	mL/min	67.25	29.66	62.05 ()
CRIBW (normalized CRIBW)	mL/min	63.61	29.74	59.45 ()

Source: ContCovSummaryAll.csv

Source: Sponsor's Clinical Study Report 156-01-224
 (\\Cdsesub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

1.1.4 Results

Hyponatremia Population, Hyponatremia Trials:

The population PK of tolvaptan in subjects with hyponatremia associated with cirrhosis, CHF, or syndrome of inappropriate antidiuretic hormone secretion (SIADH)/other was described by a one-compartment model with first-order absorption. Typical oral clearance (95% CI) given the reference covariates (70 kg, Child-Pugh Class Normal or A) was estimated at 10.7 (8.85; 13.0) L/h. Oral clearance mildly increased with weight in the power 0.423 (0.074; 0.791). Subjects with Child-Pugh Class B and C were estimated to have oral clearance reduced by 19% (2%; 32%) and 24% (5; 40%), respectively. Concomitant administration of CYP3A4 inhibitors was estimated to have negligible effect on tolvaptan clearance. Co-administration of CYP3A4 inducers resulted in 45% (7%; 84 %) increase in tolvaptan clearance, this estimate was based on data from only 5 subjects.

Typical apparent volume of distribution (95% CI) given the reference covariates (70 kg, no SIADH/other, euvoletic hyponatremia, Child-Pugh Class Normal, A or B) was estimated at 176 (126; 247) L. Apparent volume increased proportionally to weight in the power 0.981 (0.503; 1.44). Subjects with Child- Pugh Class C were estimated to have apparent volume increased by

b(4)

50% (17%; 109%). Hyponatremia severity and concomitant administration of diuretics was shown to have no clinically important influence on the tolvaptan volume of distribution. Estimates of the effects of SIADH/other diagnosis and hypervolemic (vs. euvoletic) hyponatremia were inconclusive with the effects (95%CI) estimated at 27% (9%; 43%) and 25% (4%; 42%) reduction in volume, respectively.

Subjects with CHF were estimated to have bioavailability increased by about 28%, but the effect was poorly defined with the estimate ranging from a 3% decrease to a 71% increase of relative bioavailability (F1/F). Co-administration of P-gp-interacting drugs was shown to have negligible effect on F1/F. The absorption rate constant (KA) was estimated at 1.24 (0.773; 3.82) h⁻¹. Final estimates of unexplained variability in CL/F, V/F, and KA were 64%, 48 %, and 124% coefficient of variation (CV), respectively. Residual error was described by an exponential model with CV=51% (46%; 56%).

Table 7. Sponsor's Hyponatremia Population PK Model Parameters

PKT- 15		Parameter Estimates of the Parsimonious PK Model 132					
Parameter	Notation	Units	Value	SEa	RSE (%)	95% CI	Variability
θ_1	CL/F	L/hr	10.6	0.779	7.35	9.07 - 12.1	
θ_2	V/F	L	166	20.7	12.4	126 - 207	
θ_3	KA	1/hr	1.24	0.296	23.8	0.663 - 1.82	
θ_4	η -ratio		-1.56	0.471	30.2	-2.48 - (-0.636)	
θ_5	CL _{WT}		0.412	0.157	38.1	0.104 - 0.721	
θ_6	V _{WT}		0.953	0.212	22.3	0.537 - 1.37	
θ_7	CL _{CHPU3}		0.813	0.074	9.1	0.668 - 0.958	
θ_8	CL _{CHPU4}		0.745	0.0825	11.1	0.584 - 0.907	
θ_9	V _{HST}		0.744	0.0792	10.6	0.589 - 0.899	
θ_{10}	V _{SIADH}		0.746	0.0816	10.9	0.586 - 0.906	
θ_{11}	V _{CHPU4}		1.49	0.208	13.9	1.08 - 1.9	
θ_{12}	F _{1,CHF}		1.28	0.178	13.9	0.931 - 1.63	
Ω_{11}	$\Omega_{CL,CL}$		0.41	0.0725	17.7	0.268 - 0.553	CV=64.1%
Ω_{21}	$\Omega_{CL,V}$		0.229	0.0637	27.8	0.104 - 0.353	R=0.739
Ω_{22}	$\Omega_{V,V}$		0.233	0.07	30	0.0961 - 0.37	CV=48.3%
Ω_{33}	$\Omega_{KA,KA}$		1	0.642	64	-0.255 - 2.26	CV=100%
σ_2			0.26	0.0263	10.1	0.209 - 0.312	CV=51.0%

Population parameter point-estimates, standard errors (SE), percent standard errors (%SE), 95% CI are presented for the full population PK model (Run 132, 132cov.lst).

Source: 132covParEst.csv

Source: Sponsor's Clinical Study Report 156-01-224

(\\Cdsesub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

Hyponatremia Population, Hyponatremia and Heart Failure Trials:

The population PK of tolvaptan in subjects with hyponatremia enrolled in hyponatremia or heart failure trials was described by a one-compartment model with first-order absorption.

Typical oral clearance (95% CI) given the reference covariates (70 kg, Child-Pugh Class Normal or A) was estimated at 9.60 (8.4; 11.0) L/h. Oral clearance mildly increased with weight in the power 0.276 (0.060; 0.512). Subjects with Child-Pugh Class B and C were estimated to have oral clearance reduced by 17% (7%; 27%). Concomitant administration of CYP3A4 inducers increased tolvaptan clearance by 74%; a plausible mechanism exists, since tolvaptan is a CYP3A4 substrate. Renal impairment (as estimated by the normalized creatinine clearance calculated from the Cockcroft-Gault equation) had no effect on tolvaptan clearance.

Typical V/F (95% CI) given the reference covariates (70 kg, Child-Pugh Class Normal, A or B) was estimated to be 112 (94; 133) L. Apparent volume increased proportionally to weight in the power 0.81 (0.56; 1.07). Subjects with Child-Pugh Class C were estimated to have V/F increased by 52% (23%; 88%). Hyponatremia severity and SIADH diagnosis was shown to have no or almost no clinically important influence on the tolvaptan volume of distribution. Subjects with CHF were estimated to have an increase in bioavailability by about 33% (17%; 54%). Co-administration of weak P-gp inhibitors was shown to have negligible effect on F1/F. Moderate and strong P-gp inhibitors differed in the direction of effect on F1/F, with uncertainty intervals that included values indicating no effect.

The absorption rate constant was estimated at 0.82 (0.672; 1.03) h⁻¹. Final estimates of unexplained variability in CL/F, V/F, and KA were 61%, 49 %, and 114% CV, respectively. Residual error was described by an exponential model with CV=62% (58% - 66%).

Table 8. Sponsor's Hyponatremia of Any Origin Population PK Model Parameters

PKT- 32		Final Parsimonius Model 117				
Parameter	Notation	Units	Value	RSE (%)	95% CI	Variability
θ_1	CL/F	L/hr	10.0	6.54	8.72 - 11.3	
θ_2	V/F	L	121	7.72	103 - 139	
θ_3	ka	1/hr	0.816	9.68	0.661 - 0.971	
θ_4	CL _{WT}		0.284	45.4	0.031 - 0.537	
θ_5	V _{WT}		0.792	18.9	0.498 - 1.09	
θ_6	CL _{CHPBC}		0.860	5.95	0.760 - 0.960	
θ_7	V _{CHPUC}		1.53	11.4	1.19 - 1.87	
θ_8	CL _{CIND}		1.71	12.1	1.30 - 2.12	
θ_9	F _{1,CHF}		1.39	6.99	1.20 - 1.58	
Ω_{11}	$\Omega_{CL,CL}$		0.383	10.5	0.306 - 0.464	CV=62.0%
Ω_{21}	$\Omega_{CL,V}$		0.224	17.4	0.154 - 0.314	R=0.754
Ω_{22}	$\Omega_{V,V}$		0.236	26.1	0.122 - 0.378	CV=50.0%
Ω_{33}	$\Omega_{KA,KA}$		1.33	22.3	0.721 - 1.84	CV=113%
Σ_{11}	σ^2		0.389	7.58	0.331 - 0.447	CV=62.4%

Source: Sponsor's Clinical Study Report 156-01-224

(\\Cdsesub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

Heart Failure Population, Heart Failure Trials:

Tolvaptan pharmacokinetics is described as a one-compartment model with typical values of 7.09 (6.84; 7.34) L/h, 83.8 (80; 87) L, and 0.823 (0.757; .889) h⁻¹ for CL/F, V/L, and KA

respectively. CL/F mildly increased with body weight by a factor of 0.031(0.020; 0.040) multiplied by (body weight-70) and V/F increased with body weight by a factor of 0.716 (0.560; 0.872) multiplied by (body weight-70). The between-subject variability was 66%, 42%, and 124% for CL/F, V/F, and K_A, and the random residual error was 52%. Plots of random effects versus covariates revealed CYP3A4 inducer effects, no other meaningful trends were observed.

Table 9. Sponsor's Congestive Heart Failure Population PK Model Parameters

PKT- 35 Parameter Estimates of the Final CHF PK Model						
Final PK Model Population Pharmacokinetic Parameter Estimates						
Parameter	Notation	Units	Value	RSE (%)	95% CI	Variability estimate
θ1	CL/F	L/hr	7.1	1.82	7.21 - 8.37	
θ2	V/F	L	83.8	2.11	93.3 - 114.9	
θ3	K _A	1/hr	0.823	4.12	0.715 - 1.03	
θ4	CL _{WT}		0.031	11.1	-0.137 - 0.372	
θ5	V _{WT}		0.716	18.7	0.377 - 1.02	
Ω11	Ω _{CL,CL}		0.358	4.0	0.336 - 0.502	CV=65.6%
Ω21	Ω _{CL,V2}		0.13	7.4	0.184 - 0.344	R=0.543
Ω22	Ω _{V2,V2}		0.16	7.4	0.197 - 0.451	CV=41.7%
Ω33	Ω _{K_A,K_A}		0.936	7.2	0.683 - 1.82	CV=124
Σ11	σ ²		0.27	1.7	0.330 - 0.447	CV=52.0%
K	CL/V	1/hr	0.085			
t _{1/2}	ln(2)/K	hr	8.18			
t _{1/2}	ln(2)/K _A	hr	0.778			

Source: Sponsor's Clinical Study Report 156-01-224

(\\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224)

Other model details and equations may be found in the sponsor's population pharmacokinetic report: (\\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-156-01-224).

1.1.5 Sponsor's Conclusions:

- The population pharmacokinetics of tolvaptan in both the hyponatremia and heart failure populations evaluated were best described by a one-compartment model with first-order absorption, random effects on CL/F, V/F, and K_A, and exponential residual error. Between subject variability and residual error were high with % CVs of 61-66 for CL/F, 42-49 for V/F, 114-124 for K_A and 51-62 for the random residual error.
- Tolvaptan oral clearance mildly increased with weight while apparent volume was proportional to weight.
- Child-Pugh Class was identified as a predictor of oral clearance (19 and 24% increase for Class B and C, respectively) and volume (50% increase for Class C) in the core hyponatremia dataset. The expanded hyponatremia dataset showed a mild increase in oral clearance for Class B and C and a 50% increase in volume for Class C. The heart failure

dataset analysis showed no strong trend for Class B (25% of the subjects in the database with Class B) and mild trends for Class C V/F and CL/F (1.2% of the database).

- Renal function (as estimated by the normalized creatinine clearance calculated from the Cockcroft-Gault equation) had no effect on tolvaptan clearance in the hyponatremia analysis. Plots of random effects versus creatinine clearance from the heart failure database showed a very small, but consistent linear relationship with clearance, the metric is correlated with body weight.
- Co-administration of CYP3A4 inducers resulted in a 45% increase in tolvaptan oral clearance, based on data from only five subjects in the core hyponatremia analysis and a 75% increase based on data from 11 subjects in the expanded hyponatremia analysis (hyponatremia trials and subjects with hyponatremia enrolled in heart failure trials). The heart failure database included a very small number of subjects reporting concomitant administration with CYP3A4 inducers; however, plots of random effects versus concomitant CYP3A4 inducer showed an effect.
- Hyponatremia severity, concomitant administration of diuretics, CYP3A4 inhibitors, heart failure concomitant medications, and P-gp inhibitors did not have a meaningful influence on tolvaptan pharmacokinetics for the patient populations investigated.

1.1.6 Reviewers Comments

The sponsor provided a very comprehensive population pharmacokinetic analysis on 3 disease populations from 8 different clinical trial data sets. It was good that this much data was used for the analysis and that the covariates employed were mechanistically relevant to the disease states for the patient populations. While this analysis provides a comprehensive report of the kinetics per population, an improvement might have been to develop one population pharmacokinetic model where disease state presence or disease status are covariates and would account for the differences in the kinetics of Tolvaptan between populations.

**Appears This Way
On Original**

1.2 HYPONATREMIA EFFICACY TRIALS

1.2.1 Summary of Trials

Study 156-02-235:

This study was a multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of the effects of oral tolvaptan as adjunct to standard therapy in subjects with nonacute hyponatremia in euvolemic or hypervolemic states. A total of 205 subjects were randomized from 42 active study sites.

Subjects were consented and screened 1 to 2 days prior to potential randomization or on the same day as randomization (Day 1). If the subject was screened and randomized on the same day, the screening procedures were considered baseline. Subjects who met inclusion and exclusion criteria were randomized to either placebo or 15 mg tolvaptan. Randomization was stratified by baseline serum sodium level (< 130 mEq/L or ≥ 130 mEq/L) with a target of 50% of subjects having a serum sodium level of < 130 mEq/L; and underlying disease state (CHF or non-CHF) with no single etiology (CHF, cirrhosis, SIADH/other) representing more than 50% of the subjects. Subjects who entered the study with a serum sodium level value < 130 mEq/L could have been fluid restricted if necessary, at the discretion of the investigator. Subjects who were randomized during a hospitalization remained in the hospital or inpatient observational unit after Day 1 until the investigator determined that the subject could be discharged. Once discharged, the subject returned for outpatient visits on a weekly basis until a total of 30 days of treatment was completed. Outpatients could also have been randomized into the trial, if they were willing to be admitted for the first dosing day. Subjects were required to stay over night in an observational unit or hospital for at least 24 hours on Day 1.

Study drug was administered orally at approximately 0900 hours (dosing was acceptable between 0700 and 1100 hours) for 30 days. During the study treatment period, subjects continued their current medications.

Study drug could be titrated, depending on the subject's serum sodium levels. For subjects randomized to receive 15 mg tolvaptan, dose titration to 30 mg and then 60 mg of study drug occurred if the subject's change in serum sodium level was < 5 mEq/L from the previous day's measurement and was ≤ 135 mEq/L. Titration to the next dose did not occur if the subject's serum sodium level was > 135 mEq/L or the change in serum sodium level was ≥ 5 mEq/L from the previous day's measurement. If the serum sodium increased at too great a rate (either > 12 mEq/L/24 hours or > 8 mEq/L/8 hours on the first day, or if it exceeded the normal range of 145 mEq/L, the investigator was to confirm the results with a stat repeat test and if confirmed, the investigator was to contact the medical monitor for guidance. The investigator could decrease the dosage during the 30-day treatment at his/her discretion. A study drug titration scheme is provided in Figure 2.

Study 156-03-238:

This study was an international, multicenter, randomized, double-blind, placebocontrolled, efficacy and safety study of the effects of oral tolvaptan in subjects with non-acute hyponatremia in euvolemic or hypervolemic states. A total of 243 subjects were randomized from 50 active study sites.

Subjects were consented and screened 1 to 2 days prior to potential randomization or on the same day as randomization (Day 1). If the subject was screened and randomized on the same day, the screening procedures were considered baseline. Subjects who met inclusion and exclusion criteria were randomized to either placebo or 15 mg tolvaptan. Subjects who entered the study with a serum sodium value < 130 mEq/L (mmol/L) could have been fluid restricted if necessary, at the discretion of the investigator. Subjects who were randomized during a hospitalization remained in the hospital or inpatient observational unit after Day 1 until the investigator determined that the subject could be discharged. Once discharged, the subject returned for outpatient visits on a weekly basis until a total of 30 days of treatment was completed. Outpatients could also have been randomized into the trial, if they were willing to be admitted for the first dosing day. Subjects were required to stay over night in an observational unit or hospital for at least 23 hours on Day 1.

Study drug was administered orally at approximately 0900 hours (dosing was acceptable between 0700 and 1100 hours) for 30 days. During the study treatment period, subjects continued their current medications, and may have been offered standard therapies for hyponatremia as clinically indicated.

Study drug could be titrated, depending on the subject's serum sodium levels. For subjects randomized to receive 15 mg tolvaptan, dose titration to 30 mg and then 60 mg of study drug occurred if the subject's change in serum sodium level was < 5 mEq/L (mmol/L) from the previous measurement (ie, from 22-24 hours) and was \leq 135 mEq/L (mmol/L). Titration to the next dose did not occur if the subject's serum sodium level was > 135 mEq/L (mmol/L) or the change in serum sodium level was \geq 5 mEq/L (mmol/L) from the previous measurement (ie, from 22-24 hours). If the serum sodium level increased at too great a rate (either > 12 mEq/L/24 hours [mmol/L/24 hours] or > 8 mEq/L/8 hours [mmol/L/8 hours] on the first day, or if it exceeded the normal range of 145 mEq/L (mmol/L), the investigator was to take appropriate actions to ensure the safety of the subject (ie, either hold the next dose, decrease study drug or diuretic dosage, and/or contact the medical monitor for guidance on withdrawal of the subject from the study). The investigator could decrease the dosage during the 30-day treatment period at his/her discretion; however, for subjects taking diuretics, the investigator was to first consider a reduction in diuretic dose. A study drug titration scheme is provided in Figure 2.

Both Studies 156-02-235 & 156-03-238:

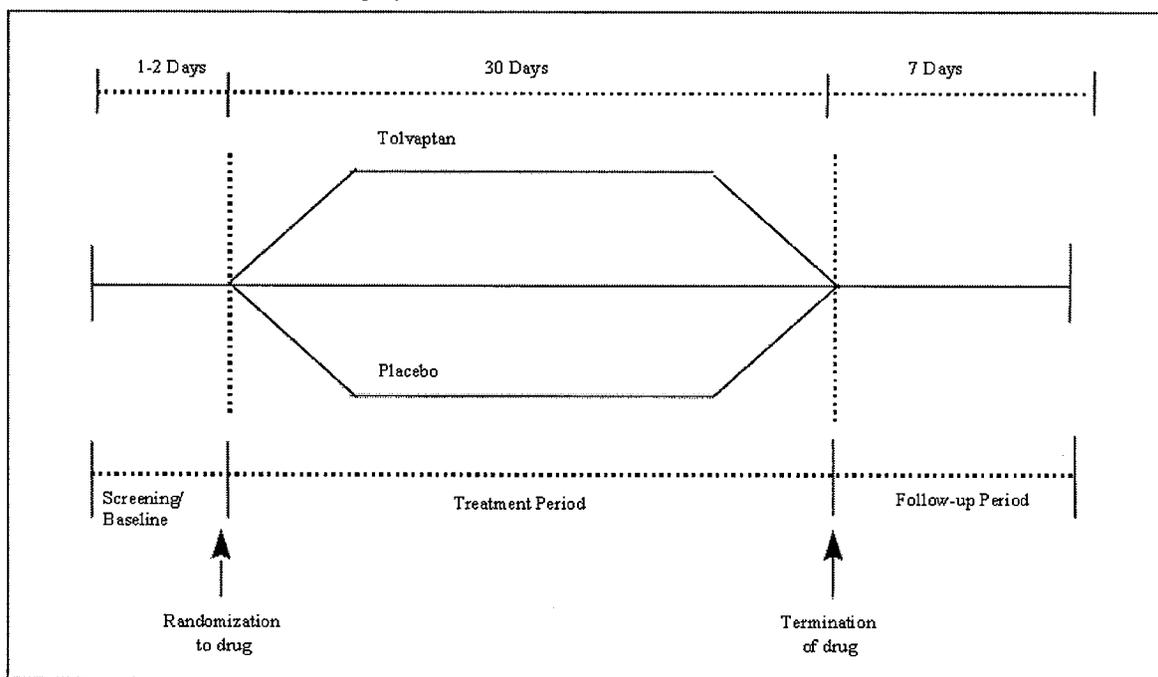
Depending on the subjects' clinical condition, the option of initiating fluid restriction (all fluids) for subjects with serum sodium level < 130 mEq/L (mmol/L) to 1 L/day was available at the investigator's discretion. If possible, fluid restriction should have been withheld for at least the first 24 hours in order to determine the rate and magnitude of serum sodium level change.

Subjects who discontinued from the study early were to complete all of the Day 30 assessments on or near the date of early termination. A safety follow-up visit was performed at least 7 days after the last dose of study medication. Figure 1 presents the study design.

An SOC composed of 2 independent clinicians, an independent subject advocate, and a biostatistician was utilized for this study and for the other studies in the phase 3 hyponatremia program (studies 156-02-235 and 156-03-244). Collectively, the members of the SOC had experience in the management of patients with hyponatremia and in the conduct and monitoring of randomized clinical trials. The SOC was responsible for safeguarding the interests of study subjects, assessing safety of the interventions during the trial, and for monitoring the overall

conduct of the study. The SOC could also make recommendations relating to the ongoing selection, recruitment, management, and retention of subjects, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. The SOC was scheduled to meet annually as deemed necessary and appropriate by the SOC Chair.

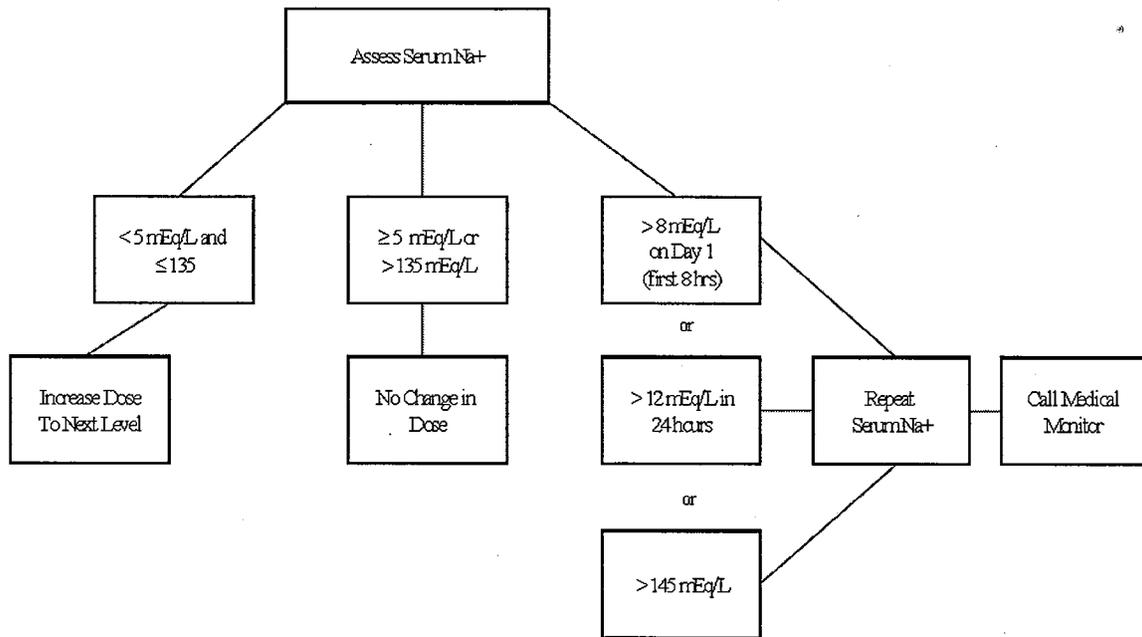
Figure 1: Clinical Trial Design for Studies 156-02-235 and 156-03-238



(Source: Sponsor's Clinical Study Report 156-02-235
 \\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-
 stud\hyponatremia\5351-stud-rep-contr\study-156-02-235)

**Appears This Way
 On Original**

Figure 2: Dose Titration Schematic for Studies 156-02-235 and 156-03-238



(Source: Sponsor's Clinical Study Report 156-02-235
 \\Cdsub1\evsprod\NDA022275\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\hyponatremia\5351-stud-rep-contr\study-156-02-235)

1.2.2 Sponsor's Results

The sponsor did not explore the relationship between baseline serum sodium concentrations and the individuals responsiveness to tolvaptan. This question is addressed further under "Reviewer's Analysis".

Appears This Way
 On Original

2 REVIEWER'S ANALYSIS: QUESTION BASED REVIEW

2.1 POPULATION PHARMACOKINETICS

2.1.1 What are the major covariates affecting pharmacokinetic parameters?

Population pharmacokinetic (PK) models were developed for three different disease scenarios: hyponatremia of any origin, hyponatremia with CHF, and CHF. The sponsor's population pharmacokinetic models identified several covariates affecting clearance and volume of distribution (*Table 10 to Table 12*). The effect of disease status is listed in *Table 10*.

Table 10. Typical values for apparent clearance, volume of distribution, and half-life as reported from the final population PK model parameter estimates.

	Hyponatremia	CHF
CL/F (L/hr)	10	7
V/F (L)	143	84
T1/2 (hr)	10	8

Table 11. Values for apparent clearance, volume of distribution, and half-life after correction for the influence of body weight in patients with hyponatremia of any origin.

	35 kg	70 kg	150kg
CL/F (L/hr)	8	10	13
V/F (L)	74	143	276
T1/2 (hr)	7	10	14

Table 12. Values for apparent clearance, volume of distribution, and half-life after correction for the influence of hepatic impairment (Child-Pugh scores B=moderate or C=severe) in patients with hyponatremia of any origin.

	Normal	Moderate/Severe
CL/F (L/hr)	10	8
V/F (L)	143	213
T1/2 (hr)	10	18

Creatinine clearance had no significant impact on clearance of Tolvaptan. The range of creatinine clearance values from patients with hyponatremia or hyponatremia and CHF were between 9.5 and 150 ml/min. There were 198 patients with normal, 169 with mild, 100 with moderate, and 33 with severe renal impairment. For the CHF data set there were 345 patients with severe, 957 with moderate, 961 with mild renal impairment and 363 individuals with normal renal function.

2.1.2 Is it necessary to adjust dose based on identified covariates?

Given the relatively small magnitude of covariate effect on apparent clearance (<30%, *Table 10* to *Table 12*) and efficacy (serum sodium level)-based dose titration, adjusting dose based on these PK covariates is not necessary.

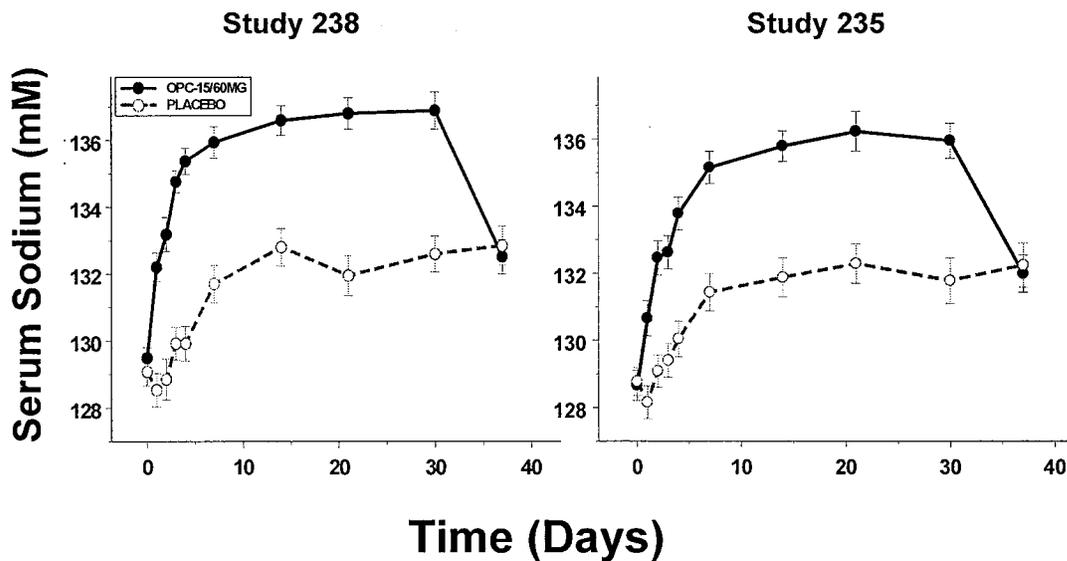
Appears This Way
On Original

2.2 HYPONATREMIA EFFICACY TRIALS

2.2.1 Is the proposed dosing of Tolvaptan effective for Hyponatremia?

There appears to be a clear increase in serum sodium concentrations following 15-60 mg Tolvaptan QD, when compared to placebo response in phase 3 studies 238 and 235 (*Figure 3*). Treatment is once daily for 30 days with dose titration increasing dose if the change in serum sodium from baseline was less than 5 mM and the serum sodium concentrations were below 135 mM. After day 30 when treatment stops, the effect is confirmed by a drop in serum sodium concentration to a level that is similar to what was observed in placebo group. The rise in placebo is attributed to restricted fluid intake to no more than one liter per day. This restriction was not done for the first study day to prevent too rapid a rise in serum sodium concentrations.

Figure 3: Time course of tolvaptan response in studies 238 and 235 (mean \pm SE).



It is evident from *Figure 3* that Tolvaptan effectively increases serum sodium concentrations to the normal range of health individuals (135-145 mM).

2.2.2 Is tolvaptan effective for patients with lower baseline serum sodium concentrations?

Data from phase three studies 2-235 and 3-238 were analyzed separately for this analysis. All longitudinal data from study day 0 up to day 30 for both placebo and treatment data were fitted with sigmoid E_{\max} model (Equation 1). Response was the change from baseline of serum sodium concentrations. The base structural model independent of error was parameterized as:

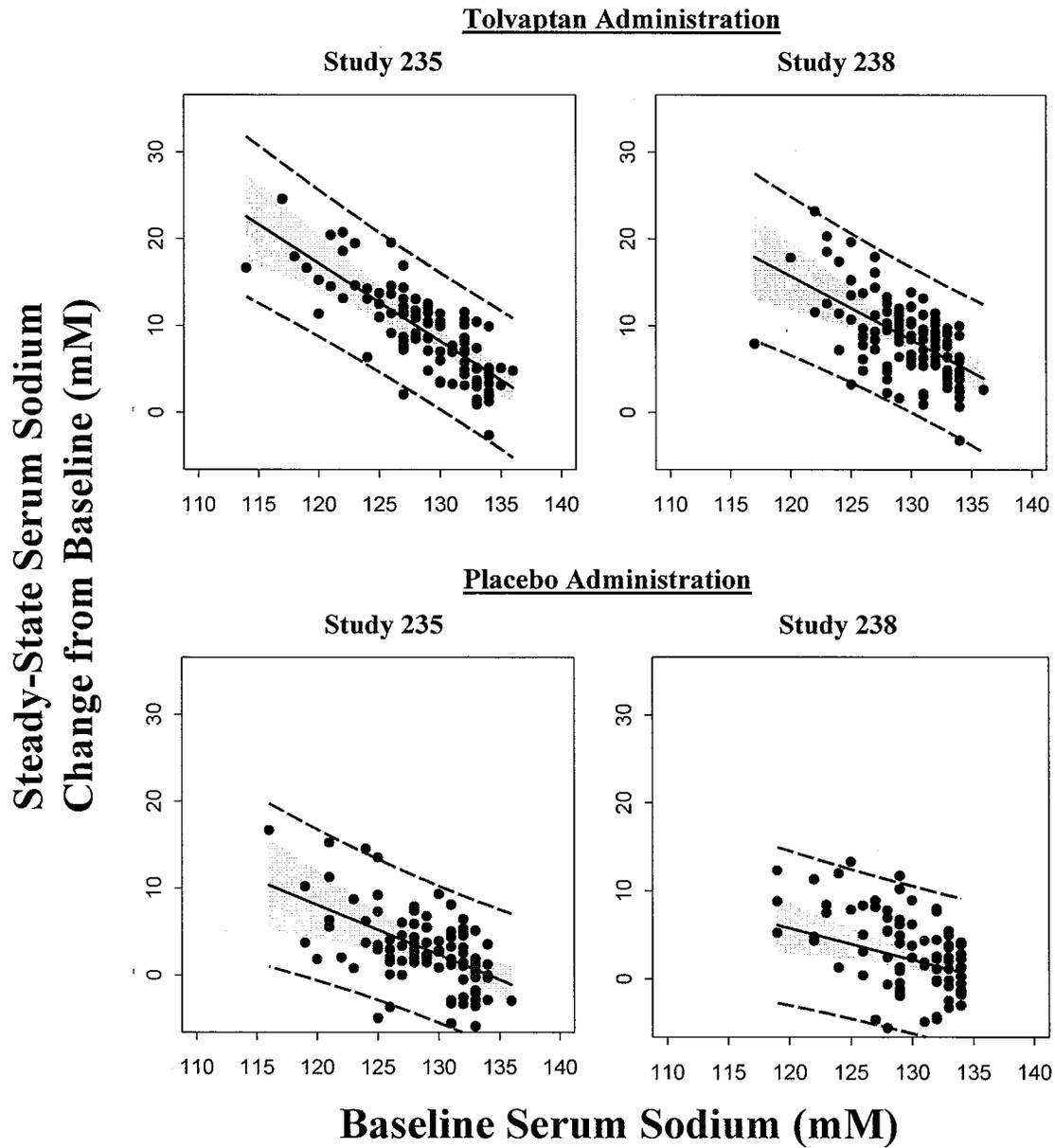
$$\text{Serum Sodium Change from Baseline} = \begin{cases} \frac{E_{\max, \text{placebo}} \cdot \text{Time}}{ET_{50} + \text{Time}}, & \text{Placebo} \\ \frac{E_{\max, \text{treatment}} \cdot \text{Time}}{ET_{50} + \text{Time}}, & \text{Treatment} \end{cases} \quad (\text{Equation 1})$$

where Time is the time after dosing in days and ET_{50} is the time at which half the maximal response for placebo ($E_{\max, \text{placebo}}$) or for treatment ($E_{\max, \text{treatment}}$) is reached. Since the doses were adjusted to achieve a target level of serum sodium concentration (between 135 and 145 mM), the maximum response corresponds to a steady state response. The objective of this analysis was to determine whether a larger change in serum sodium concentration can be achieved for a patient with lower baseline serum sodium concentration in order to reach the target. Exploratory analysis indicates a greater responsiveness in individuals with a lower baseline, which is consistent with the experimental design. The model parameter E_{\max} was used as the individuals measure of responsiveness to tolvaptan and was modeled as a function of baseline serum sodium (BSLN, Equation 2).

$$E_{\max} = \text{INT} + \text{SL} \cdot (\text{BSLN} - \text{BSLN}_{\text{median}}) \quad (\text{Equation 2})$$

The intercept is defined by INT and slope by SL. The median of the baseline values is indicated by $\text{BSLN}_{\text{median}}$ and was 130 mM and fixed during the model fitting. The covariate BSLN was centered about this median in Eq. 2. Model fitting was performed using the FOCE algorithm of NONMEM VI (Globomax, San Francisco, CA). Inter-individual variation was modeled on ET_{50} and E_{\max} parameters by an exponential relationship. Residual error was modeled using an additive relationship. The final model fitting relationship for E_{\max} and BSLN is shown in *Figure 4*. The final model parameters are presented in *Table 13*.

Figure 4: Final model fitting of E_{max} dependent on baseline serum sodium for studies 235 and 238, with Tolvaptan (top row) and with placebo (bottom row).



In the final model, both $E_{max, placebo}$ and $E_{max, treatment}$ were modeled as a linear function of baseline serum sodium concentration (

Figure 4). Figure 2 shows that for individuals with lower baselines a greater response is observed. The modeling results indicate that, by average, a patient with lower baseline serum sodium will have a larger response. For example, a patient with a baseline of 120 mM is expected to have a response of 16 mM, reaching a steady state serum sodium concentration of 136 mM. This trend in the data and model parameter estimates were similar across both phase three studies. While individuals with lower baselines may be expected to have a greater response, this is largely due to the need to treat the patient further to a target normal serum sodium concentration. Patients who are closer to this normal level to begin with would conversely need less therapy to achieve the target response. It is clear, however, that tolvaptan is effective for returning serum sodium concentrations to between 135 and 145 mM in patients with hyponatremia regardless of their baseline serum sodium concentrations.

Table 13. Parameter Estimates for Studies 235 and 238.

Study	235		238	
Number of Subjects	198		240	
Number of Observations	1341		1555	
Parameter	Estimate (%RSE)		Estimate (%RSE)	
INT _{placebo} (mM)	2.37	24.3	2.37	21.4
INT _{tolvaptan} (mM)	8.22	6.3	8.37	5.4
SL _{placebo}	0.57	31.3	0.39	30.3
SL _{tolvaptan}	0.90	16.7	0.74	23.3
BSV E _{max} (CV%)	3.99	2.8	4.24	4.0
ET ₅₀ (hr)	4.17	16.3	2.70	14.9
BSV ET ₅₀ (CV%)	0.76	1.98	0.73	1.6
Residual Variability (mM)	8.34	6.70	8.22	7.0

BSV: Between Subject Variability

RSE: Relative Standard Error

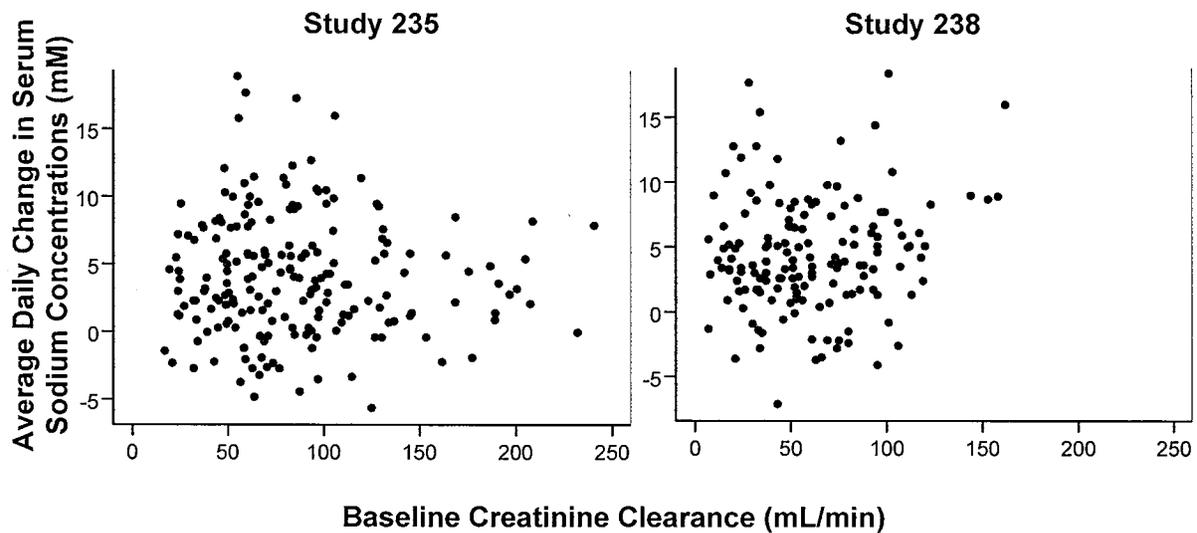
INT: Intercept

SL: Slope

2.2.3 Is dose-adjustment required for patients with impaired renal function?

It was hypothesized that reduced renal function as indicated by creatinine clearance might mean less aquaretic effect and less water removal, which may lead to less effect on serum sodium. The average change of serum sodium concentration at day 30 from baseline was plotted against baseline creatinine clearance for each individual (*Figure 5*). *Figure 5* did not indicate any apparent relationship between serum sodium response following treatment and baseline creatinine clearance. Therefore dose-adjustment is not required for patients with renal impairment.

Figure 5: Serum Sodium Response – Baseline Creatinine Clearance Relationship



Appears This Way
On Original

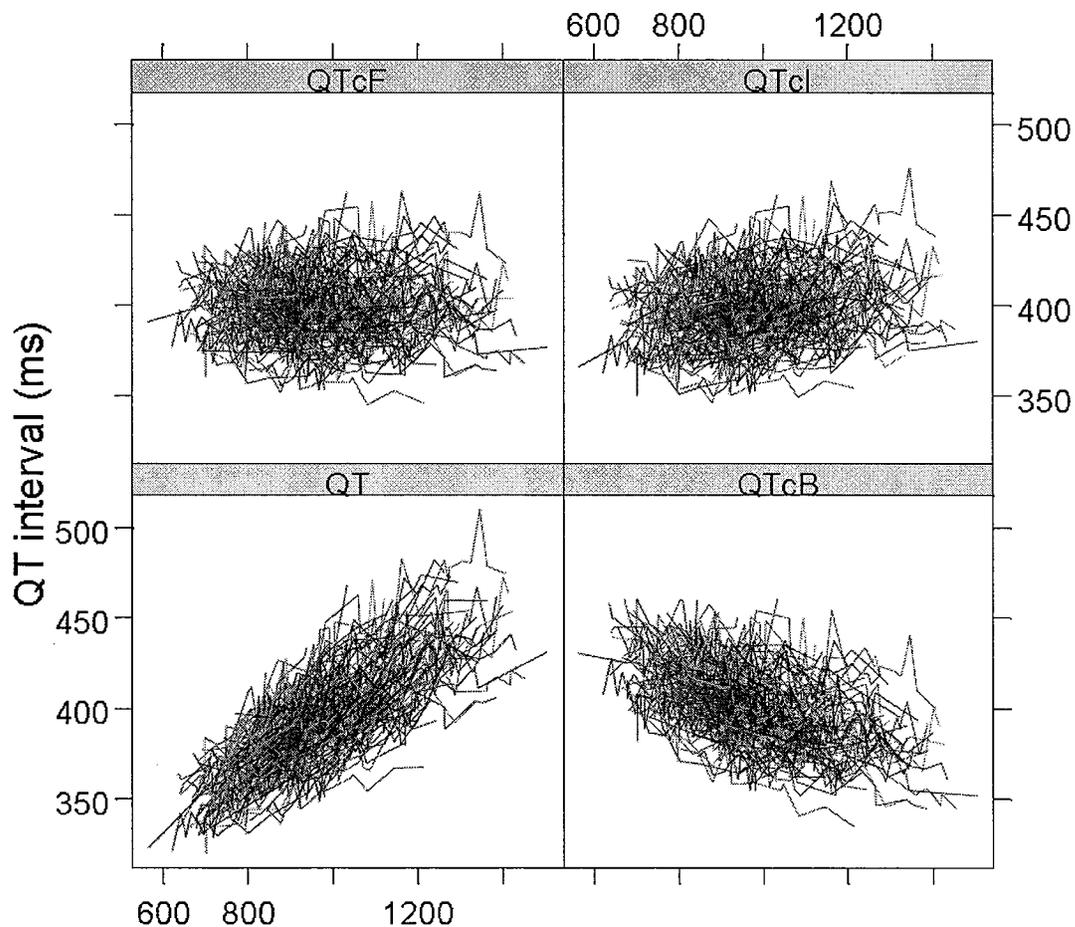
2.3 DOES TOLVAPTAN PROLONG THE QT INTERVAL?

The text and figures relevant to question 1 are taken from the IRT-QT group's assessment of Tolvaptan

(http://eroom.fda.gov/eRoom/CDER1/CDERnterdisciplinaryReviewTeamQTGroup/0_ef7c).

The relationship between QT (raw and different correction methods) and RR interval at baseline is illustrated in the Figure 6. The Federicia's and Individual correction seem to be reasonable.

Figure 6: QT (Raw QT measurements, Bazett's, Fridericia's and Individual corrected QT)-RR interval relationship



The comparative time course for mean $\Delta\Delta\text{QTcF}$ on Day 1 and 5 are illustrated in Figure 7. It appears that tolvaptan does not prolong the QT interval at both the studied doses.

Figure 7: Time course of mean $\Delta\Delta QTcF$

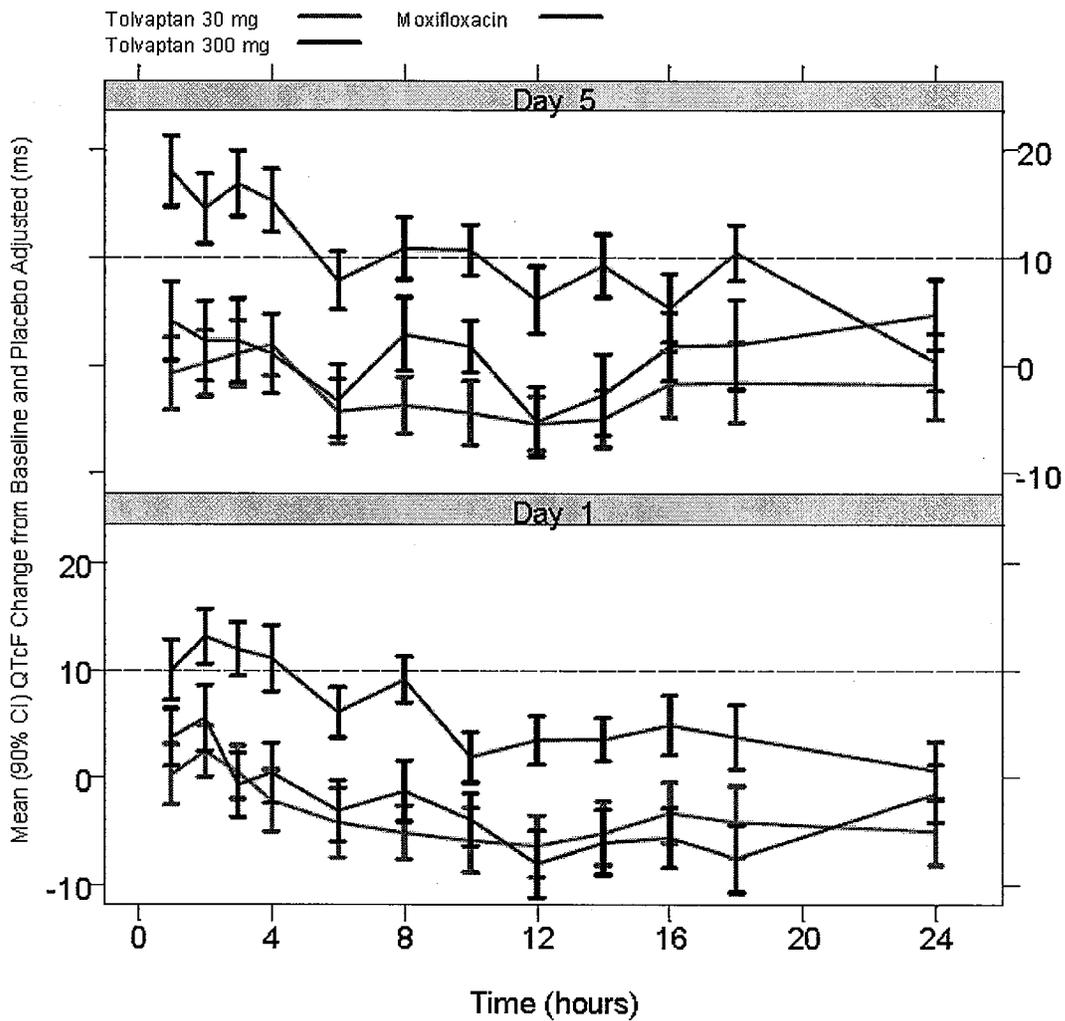
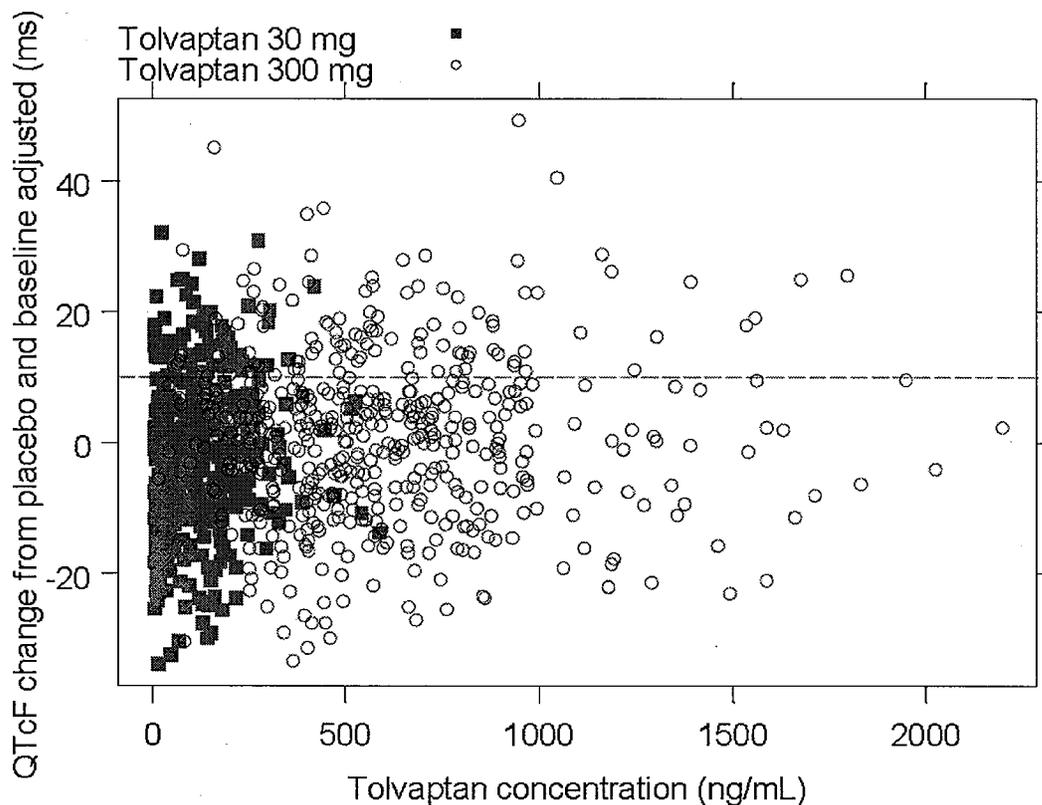


Figure 8 illustrates no relationship between Tolvaptan concentrations and $\Delta\Delta QTcF$. The mean (upper CI) effect at mean C_{max} (982.5 ng/mL) after suprathreshold dose is 3.1 (5.6) ms.

Figure 8: Concentration- $\Delta\Delta$ QTcF relationship

Moxifloxacin increased the $\Delta\Delta$ QTcI interval by 12.3 ms with lower bound of 95% CI of 6.1 ms at 2 hours after dosing on Day 1. At steady-state on Day 5 moxifloxacin increased the $\Delta\Delta$ QTcI interval by 16.7 ms with lower bound of 95% CI of 9.4 ms at 1 hour after dosing on Day 5. These results are consistent for moxifloxacin following a single dose as well as at steady-state indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

**Appears This Way
On Original**

CONCLUSION

1. A clear increase is observed on serum sodium concentrations after treatment with tolvaptan when compared to placebo.
2. Major covariates affecting pharmacokinetics are body weight, liver function (indicated by the Child-Pugh score) and disease status. Typical values of clearance were higher at 10 L/hr for individuals with hyponatremia when compared to patients with CHF (CL = 7 L/hr). Values for the volume of distribution were primarily dependent on liver impairment (1.5-fold increase) and proportional to body weight.
3. The individual responsiveness to tolvaptan was correlated with baseline serum sodium concentrations. At lower concentrations a greater response was observed and sufficient to return the patient to normal serum sodium concentrations within the studied patient population. For all baseline serum sodium levels observed in the studies, tolvaptan is generally effective in returning the serum sodium to between 135 and 145 mM.
4. No clear relationship between baseline renal function as indicated by creatinine clearance and effect on serum sodium concentrations was observed. Dose adjustment based on renal-impairment is not necessary.
5. There does not appear to be an increase in prolongation of the QT interval after tolvaptan administration at 5 times the maximum recommended therapeutic dose (60 mg).

Appears This Way
On Original

**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information
NDA Number	22275	Brand Name	Samska
OCPB Division (I, II, III)	I	Generic Name	Tolvaptan
Medical Division	DCRP	Drug Class	Vasopressin Receptor Antagonist
OCPB Reviewer	Peter Hinderling	Indication(s)	CHF/ Hyponatremia
OCPB Team Leader	Patrick Marroum	Dosage Form	15 mg and 30 mg tablets
		Dosing Regimen	30 mg qd/ 15-60 mg qd
Date of Submission	October 22, 2007	Route of Administration	Oral
Estimated Due Date of OCPB Review	June 28, 2007	Sponsor	Otsuka
PDUFA Due Date	August 22, 2007	Priority Classification	S
Division Due Date	July 8, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	13		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	4		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	x	2		
Patients-				
single dose:				
multiple dose:	x	2		
Dose proportionality -				
fasting / non-fasting single dose:	x	2		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	7		
In-vivo effects of primary drug:	x	7		
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1		
gender:	x	1		
pediatrics:				

geriatrics:	x	1		
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	x	2		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	9		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	2		
II. Biopharmaceutics				
Absolute bioavailability:	x	1		
Relative bioavailability -	x	1		
solution as reference:				
alternate formulation as reference:	x	4		
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	7		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	Thorough Q1c Study			
Genotype/phenotype studies:	0			
Chronopharmacokinetics	0			
Pediatric development plan	None			
Literature References				
Total Number of Studies		66		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Peter Hinderling, 11-21-07			

Secondary reviewer Signature and Date	Patrick Marroum, 11-21-07
---------------------------------------	---------------------------

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peter Hinderling
6/6/2008 12:29:08 PM
BIOPHARMACEUTICS

Justin C Earp
6/6/2008 12:32:35 PM
BIOPHARMACEUTICS

Yaning Wang
6/6/2008 02:45:08 PM
BIOPHARMACEUTICS

Patrick Marroum
6/9/2008 09:43:30 AM
BIOPHARMACEUTICS