PHARMACOMETRIC 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.
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TABLE OF CONTENTS

1 INTRODUCTION 2
2 AIM OF THE ANALYSIS 2
3 QUESTION BASED REVIEW 3
4 CONCLUSION 10

1 INTRODUCTION

Samska (Tolvaptan) is a small-molecule vasopressin antagonist designed to increase water removal from patients with fluid-overload and reduced serum sodium concentrations. This submission is a New Drug Application for the treatment of hyponatremia and worsening heart failure.

2 AIMS OF THE ANALYSIS

There are four main objectives of the following review:

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?

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

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

4. 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?

5. Does Tolvaptan prolong the QT-interval?

3 QUESTION BASED REVIEW

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 1 to Table 3). The effect of disease status is listed in Table 1.

Table 1. 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 2. 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 3. 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.

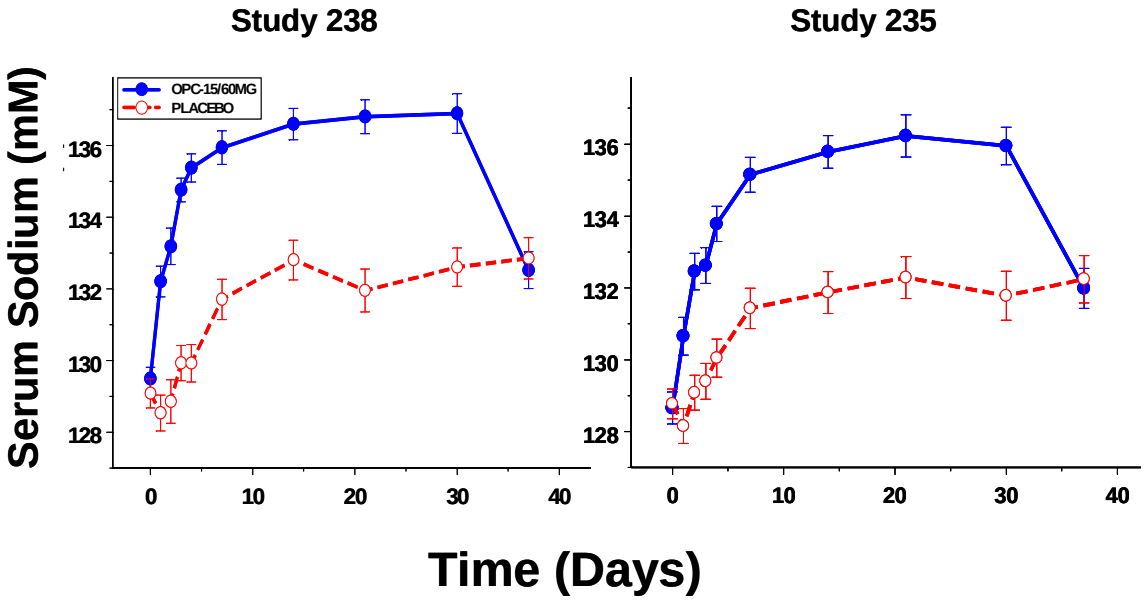
2. Is it necessary to adjust dose based on identified covariates?

Given the relatively small magnitude of covariate effect on apparent clearance (<30%, Table 1 to Table 3) 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?

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 1). 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 1. Time course of tolvaptan response in studies 238 and 235 (mean ± SE).



It is evident from Figure 1 that Tolvaptan effectively increases serum sodium concentrations to the normal range of health individuals (135-145 mM).

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

All longitudinal data from study 235 and 238 up to day 30 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:

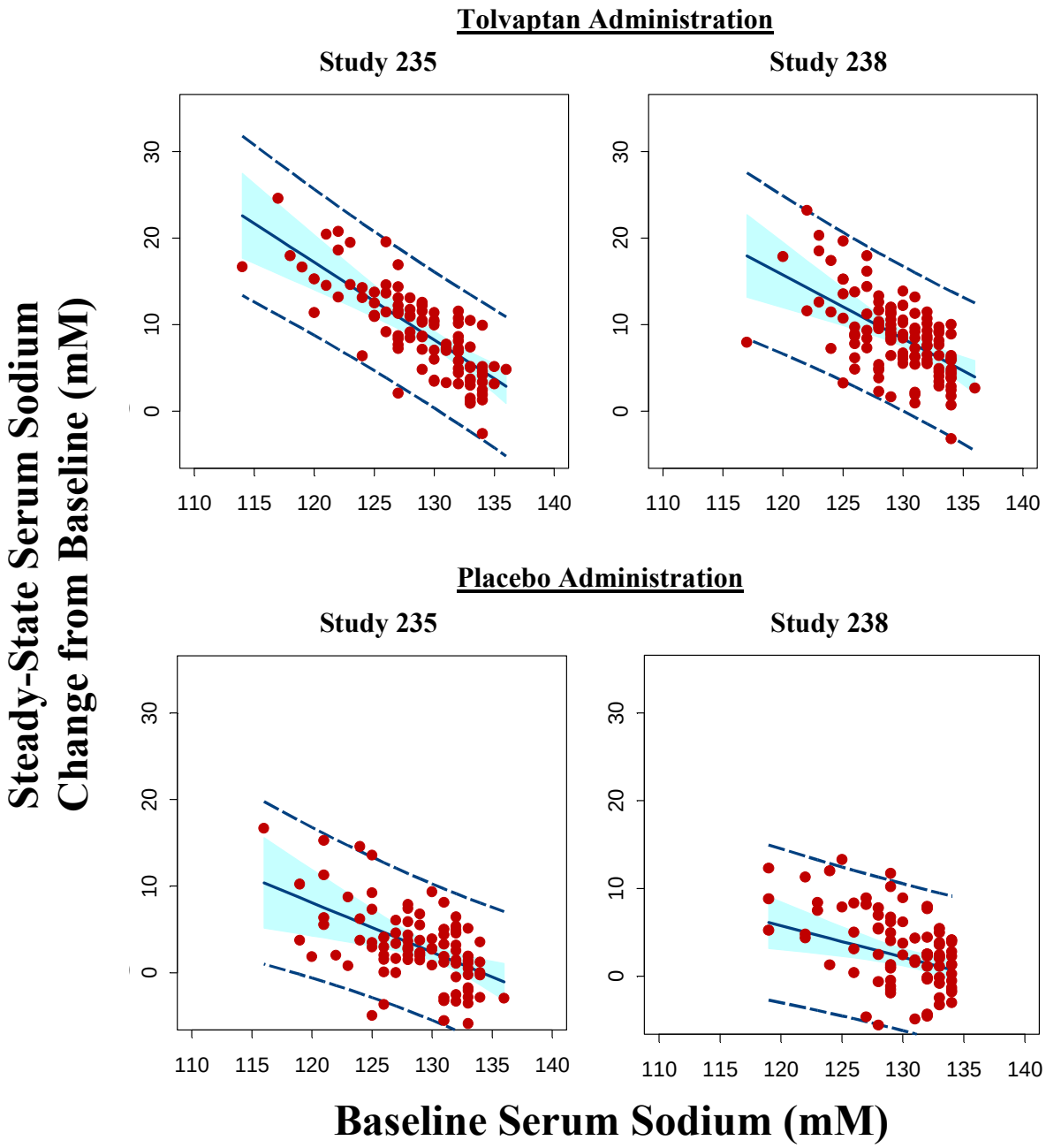
$$\text{Serum Sodium Change from Baseline} = \begin{cases} \dfrac{E_{max,placebo} \cdot \text{Time}}{ET_{50} + \text{Time}}, & \text{Placebo} \\ \dfrac{E_{max,treatment} \cdot \text{Time}}{ET_{50} + \text{Time}}, & \text{Treatment} \end{cases} \qquad \text{(Equation 1)}$$

where Time is the time after dosing in days and ET_{50} is the time at which half the maximal response for placebo ($E_{max,placebo}$) or for treatment ($E_{max,treatment}$) 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).

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

The intercept is defined by INT and slope by SL. The median of the baseline values is indicated by $BSLN_{median}$ and was 130 mM and fixed during the model fitting. 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 Emax and BSLN is shown in Figure 2. The final model parameters are presented in Table 4.

Figure 2. 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 2). 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.

Table 4. Parameter Estimates for Studies 235 and 238.

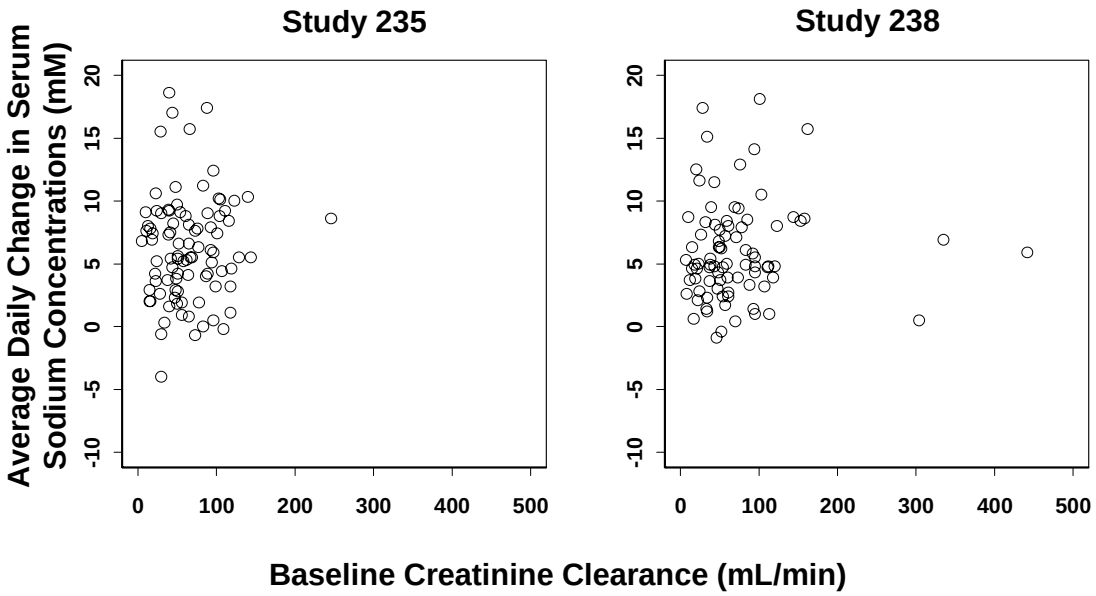
Study	**235**		**238**	
Number of Subjects	198		240	
Number of Observations	1341		1555	
Parameter	**Estimate**	**(%RSE)**	**Estimate**	**(%RSE)**
$INT_{placebo}$ (mM)	2.37	24.3	2.37	21.4
$INT_{tolvaptan}$ (mM)	8.22	6.3	8.37	5.4
$SL_{placebo}$	0.57	31.3	0.39	30.3
$SL_{tolvaptan}$	0.90	16.7	0.74	23.3
BSV 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

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 3). Figure 3 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 3: Serum Sodium Response – Baseline Creatinine Clearance Relationship

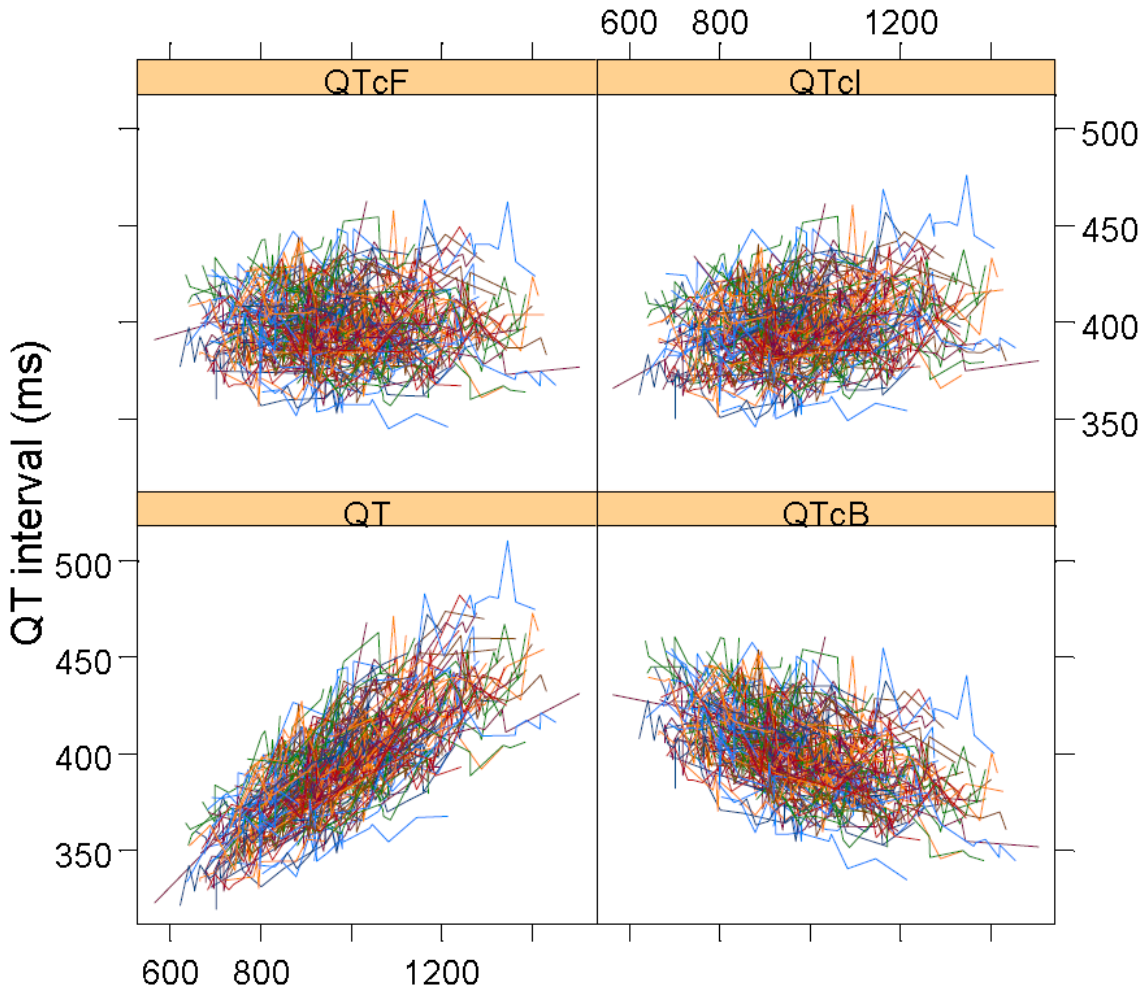


Does Tolvaptan prolong the QT interval?

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

The relationship between QT (raw and different correction methods) and RR interval at baseline is illustrated in the Figure 4**.** The Federicia's and Individual correction seem to be reasonable.

Figure 4: QT (Raw QT measurements, Bazett's, Fridericia's and Individual corrected QT)-RR interval relationship



The comparative time course for mean ΔΔQTcF on Day 1 and 5 are illustrated in Figure 5. It appears that tolvaptan does not prolong the QT interval at both the studied doses.

Figure 5: Time course of mean ΔΔQTcF

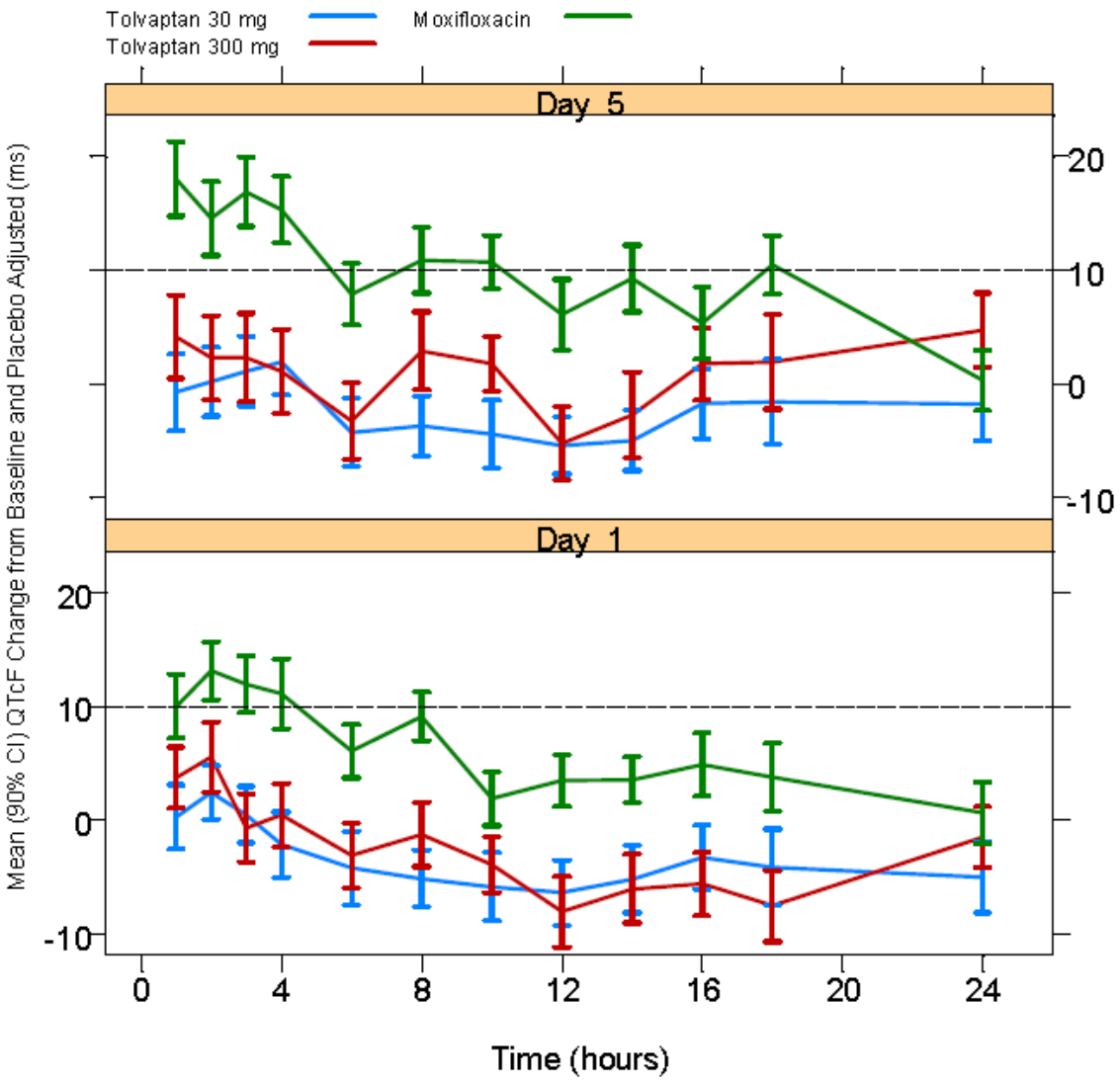
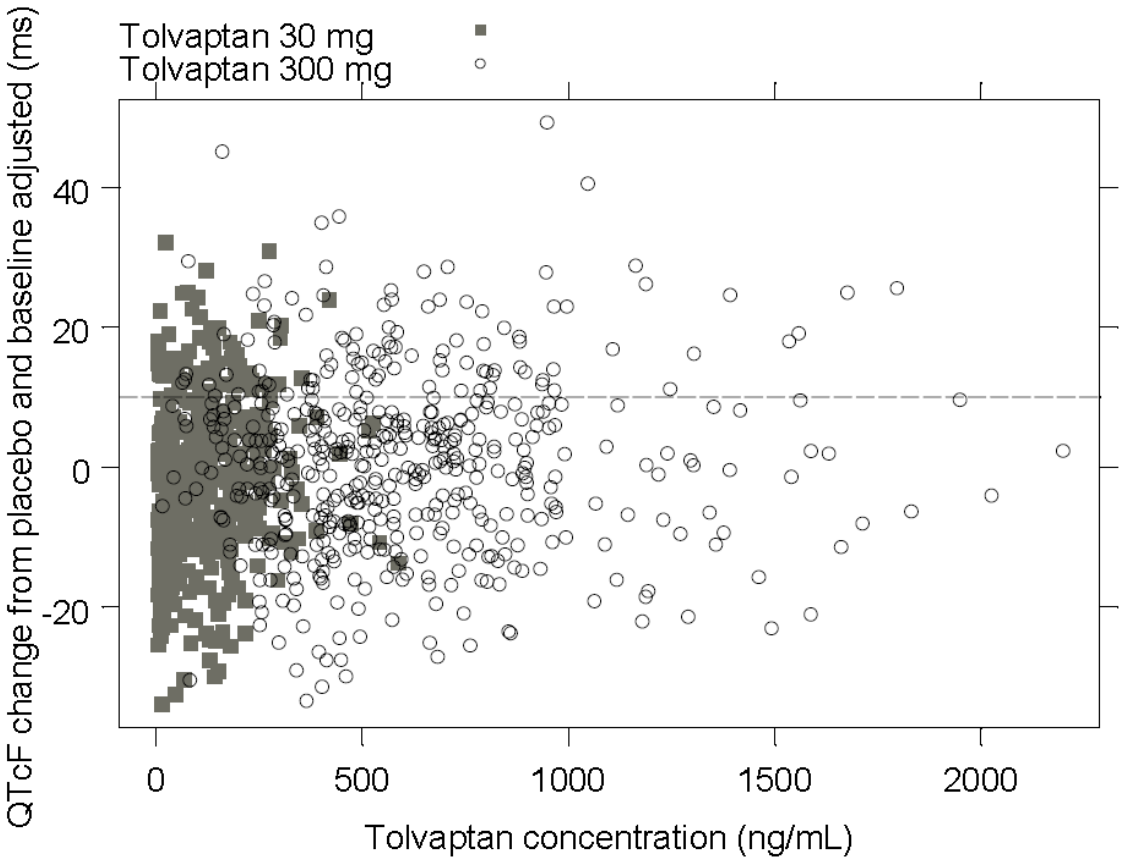


Figure 6 illustrates no relationship between Tolvaptan concentrations and ΔΔQTcF. The mean (upper CI) effect at mean Cmax (982.5 ng/mL) after supratherapeutic dose is 3.1 (5.6) ms.

Figure 6: Concentration-ΔΔQTcF relationship



Moxifloxacin increased the ΔΔQTcI 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 ΔΔQTcI 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.

4 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 tolvapatan 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).

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/s/

Yaning Wang
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BIOPHARMACEUTICS

Justin C Earp
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