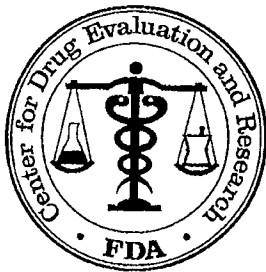


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-275

MEDICAL REVIEW(S)



Division of Cardio-Renal Products
Clinical Review

NDA: 22-275 (tolvaptan)

Sponsor: Otsuka

Clinical Reviewer: Aliza Thompson, M.D.

Document reviewed: Final Safety Update submitted May 7, 2009

Review Date: May 19, 2009

Background: NDA 22-275 was submitted on October 23, 2007 for tolvaptan for the treatment of hypervolemic and euvoletic hyponatremia. On August 22, 2008, a complete response letter was issued. The purpose of this memo is to document review of the sponsor's safety update submitted on May 7, 2009.

Safety Update: The sources of data for the final safety update are shown in Table 1 below; a table showing the design of these studies as well as the doses of tolvaptan administered in these studies is provided in the appendix. The safety update summarizes data available as of November 1, 2008 (September 12, 2008 for trials conducted exclusively in Japan or China) from 57 completed and 11 ongoing trials and provides data on 1575 additional exposed subjects. Of these 1575 subjects, 1463 subjects have completed or are participating in ongoing blinded trials. With respect to tolvaptan's development for hyponatremia, the update contains data from an ongoing uncontrolled trial of chronic administration in hyponatremic subjects (111 subjects exposed; 56 ongoing in the trial), and blinded data on 69 subjects participating in 2 ongoing placebo-controlled hyponatremia trials.

Table 1. Subjects exposed in original NDA and final safety update

Populations	Original NDA		Final Safety Update		
	Any Tolvaptan Dose	Placebo/other	Any Tolvaptan Dose	Placebo/other	Blinded
Hyponatremia Trial					
Subjects with hyponatremia from open-label phase 3 extension trial (156-03-244, ongoing)	111 [56]	--	111 [56]	--	--
Elderly subjects with hyponatremia from phase 3 pilot cognitive and neurological function trial (156-04-246, ongoing)	NA	NA	--	--	43
Subjects with nonhypovolemic, nonacute hyponatremia arising from various etiologies (156-07-892-01, ongoing)	NA	NA	--	--	22

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Table 1 continued

Populations	Original NDA		Final Safety Update		
	Any Tolvaptan Dose	Placebo/other	Any Tolvaptan Dose	Placebo/other	Blinded
Clinical Pharmacology Trials					
Healthy subjects (proposed marketing formulation): Trial 156-06-001-01 (completed)	64	--	64	--	--
Healthy subjects (proposed marketing formulation): 156-07-002 (completed)	NA	NA	20	--	--
Subjects with ADPKD (proposed marketing formulation): 156-06-260 (ongoing)	NA	NA	12	--	--
Healthy subjects (other formulations): 156-07-262 (completed)	NA	NA	18	--	--
156-07-263 (completed)	NA	NA	10	--	--
Other Indications (Proposed Marketing Formulation)					
Subjects with ADPKD:					
156-04-250 (ongoing)	46 [43]	--	46 [43]	--	--
156-04-251 (ongoing)	NA	NA	--	--	1160
156-05-002 (ongoing)	15 [15]	--	17 [17]	--	--
Subjects with edema:					
156-06-002 (ongoing)	NA	NA	--	--	110
156-06-005 (ongoing)	NA	NA	--	--	104
156-06-004 (ongoing)	NA	NA	--	--	20
156-06-006 (ongoing)	NA	NA	52	--	--
TOTAL, Safety Update trials	121	--	234	--	1463
TOTAL, Cumulative trials	4405	3099	4515	3099	1463

Includes all subjects who received at least one dose of trial medication as indicated on the dosing record. Subjects are counted once for any exposure(s) in tolvaptan group or placebo/other group.

[] indicates those subjects who received tolvaptan in more than one trial.

[Source: Tolvaptan Final Safety Update, Table 2-2, pages 75-76]

With respect to the safety findings contained in this update, 14 additional deaths (i.e., deaths not reported in the original NDA) are reported. Three of these deaths occurred in an uncontrolled long term study of tolvaptan (trial 156-03-244), 3 occurred in an uncontrolled study in subjects with heart failure and extracellular volume expansion despite conventional diuretic therapy (trial 156-06-006) and 8 occurred in subjects receiving blinded treatment in edema trials. These new deaths, shown in Table 2 below, do not alter the current understanding of tolvaptan's safety profile.

Trial	Population (N)	Number of Deaths	Treatment	Cause of death (Event term)
156-03-244	Hyponatremia (111)	3	Tolvaptan	cardiac arrest, urosepsis, and cerebral hemorrhage
156-06-002	Subjects with edema (110)	3	Blinded	ventricular tachycardia and 2 due to cardiac failure
156-06-005	Subjects with edema (104)	5	Blinded	chronic hepatitis, hepatorenal syndrome, hemorrhagic shock and 2 due to hepatic failure
156-06-006	Subjects with edema (52)	3	Tolvaptan	cerebral artery embolism, cardiac failure, and chronic renal failure

As previously noted, many of the subjects included in this update are participating in ongoing blinded trials, while others are participating in trials that lack a control group. For these reasons, interpretation of the data on serious adverse events and adverse events resulting in discontinuation is limited. As a whole,

the types of serious adverse events and adverse events resulting in discontinuation were not inconsistent with those reported in the original NDA. Notably, there were no reports of osmotic demyelination in the safety update. Following the cut-off date for this safety update, a serious adverse event of agranulocytosis was reported in a 60-year old male subject receiving tolvaptan in trial 156-07-802-1, an ongoing placebo-controlled hyponatremia trial being conducted in China. Based on review of the case as well as data contained within the original NDA application, the decision was made not to amend the proposed drug label to include this adverse event. For additional information on this event, see the clinical reviews filed to INDs [REDACTED] 54,200 on April 14, 2009 and May 16, 2009. b(4)

Common adverse events ($\geq 10\%$) in ongoing blinded hyponatremia trials were thirst and pollakiuria (protocol 156-04-246) and dry mouth (protocol 156-07-802-01). Common adverse events, and reported changes in laboratory and ECG data in protocol 156-03-244 were also, as a whole, similar to those observed in the original NDA and/or are represent events/changes that are not unexpected in the enrolled study population.

Reviewer's comments: The data contained in this safety update do not markedly alter the current understanding of tolvaptan's safety profile as based on the original NDA submission. Completion of the ongoing phase 3 extension study in subjects with hyponatremia (protocol 156-03-244) may provide further insight into the safety of chronic tolvaptan administration in hyponatremic subjects; however, given the lack of a control group in this trial, interpretation of these data may be limited. Completion of study 156-06-005, a double-blind trial in subjects with cirrhosis and ascites currently underway in Japan may also enable a better understanding of tolvaptan's safety profile in patients with cirrhosis. To date, there have been no known cases of osmotic demyelination; monitoring for this adverse event should continue in the ongoing clinical trials and post-marketing period.

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Appendix

Sponsor's summary of trials included in the safety update

Protocol Number (Trial Location) Phase Trial Initiation	Trial Design	Treatment Groups	No. Planned/ Enrolled/ Treated	Treatment Duration	Main Subject Selection Criteria	Trial Included in Original NDA?
Hyponatremia Trials						
156-04-245 ¹ (US) Phase 3 Sep 2007 (ongoing)	Randomized, double-blind, placebo- controlled, parallel arm, pilot	Toltraptan tablet PO 15 mg QD, 30 mg QD, or 60 mg QD (given as titrated dose) Placebo QD	50-60/47/47	21 days	Elderly subjects (≥ 50 years of age) with chronic, otherwise asymptomatic hyponatremia	No
156-07-S02-01 ² (China) Phase 2 Apr 2008 (ongoing)	Randomized, double-blind, placebo- controlled	Toltraptan tablet PO 15 mg, 30 mg, 60 mg Placebo	240/22/22	7 days	In-patient subjects with nonhypovolemic and nonacute hyponatremia arising from various etiologies	No
156-03-244 ³ (Multinational) Phase 3 May 2004 (ongoing)	Open-label, extension of 156-02-235 and 156-03-238	Toltraptan tablet PO 15 mg QD, 30 mg QD, or 60 mg QD (given as titrated dose)	up to 200/111/111	Up to 214 weeks	Completed a phase 3 double-blind hyponatremia trial (156-02-235 or 156-03-238)	Yes
Clinical Pharmacology Trials						
156-06-801-01 ⁴ (China) Phase 1 Oct 2006 (completed)	Stage 1: Open-label, sequential cohort, single ascending doses Stage 2: sequential cohort, multiple doses	Toltraptan tablets Single dose: 15 mg 30 mg 60 mg 120 mg Multiple dose (Day 1, Day 3-5): 30 mg 60 mg	10/10/10 10/10/10 10/10/10 10/10/10 12/12/12 12/12/12	Single dose 3 days	Healthy males	Yes

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Protocol Number (Trial Location) Phase Trial Initiation	Trial Design	Treatment Groups	No. Planned/ Enrolled/ Treated	Treatment Duration	Main Subject Selection Criteria	Trial Included in Original NDA?
156-06-260 ⁵ (US) Phase 1 Apr 2007 (ongoing)	Open-label, multiple dose	Tolvaptan Tablet PO 45/15 mg BID	12/12/12	8 days	• Adult subjects with ADPKD with GFR ≥ 60 mL/min	No
156-07-262 ⁶ (US) Phase 1 Jul 2007 (completed)	Open-label, 4-period, randomized, incomplete crossover	Tolvaptan Capsule PO 60 mg MR-1 Tolvaptan Capsule PO 60 mg MR-2 Tolvaptan Capsule PO 60 mg MR-3 Tolvaptan Tablet PO 3 x 15 mg AM - 1 x 15 mg PM	18/18/18	Single treatment x 4; 4-day washout between treatments	• Healthy subjects	No
156-07-263 ⁷ (US) Phase 1 Mar 2008 (completed)	Open-label, sequential, multiple dose	Tolvaptan Capsule PO 60 mg MR-3	10/10/10	7 days	• Healthy subjects	No
156-07-002 ⁸ (Japan) Phase 1 Jan 2008 (completed)	Randomized, open-label, crossover	Tolvaptan Tablet PO 15 mg	20/20/20	2 single doses; 2 to 6-day washout between doses	• Healthy male subjects	No
ADPKD Trials						
156-04-250 ⁹ (US) Phase 2 Dec 2005 (ongoing)	Open-label, split dose regimen with titration	Tolvaptan tablet PO 30/15 mg BID 45/15 mg BID 60/30 mg BID 90/30 mg BID	approx. 50/45/45	Dose titration for up to 2 months followed by up to 36 months long-term treatment	• Previously participated in Trials 156-04-248 or 156-04- 149	Yes
156-04-251 ¹⁰ (Multinational) Phase 3 Mar 2007 (ongoing)	Randomized, double-blind, placebo- controlled, parallel arm	Tolvaptan Tablet PO 45/15 mg BID 60/30 mg BID 90/30 mg BID Placebo	1200- 1500/1165/1 160	Up to 36 months	• Adult subjects with ADPKD	No
156-05-002 ¹¹ (Japan) Phase 2 May 2006 (ongoing)	Open-label, split- dose regimen, long-term safety; extension of 156- 04-001	Tolvaptan tablet 15/15 mg BID	up to 18/17/17	Up to 36 months	• Previously participated in Trial 156-04-001	Yes
Edema Trials						
156-06-002 ¹² (Japan) Phase 3 May 2007 (ongoing)	Randomized, double-blind, placebo- controlled, parallel group	Tolvaptan tablet PO 15 mg QD Placebo	110/110/110	7 days	• CHF subjects with extracellular volume expansion despite conventional diuretic therapy	No
156-06-003 ¹³ (Japan) Phase 2 Jun 2007 (ongoing)	Randomized, double-blind, placebo- controlled, parallel group	Tolvaptan tablet PO 7.5 mg QD 15 mg QD 30 mg QD Placebo QD	100/104/104	7 days	• Cirrhosis with ascites despite conventional diuretics	No
156-06-004 ¹⁴ (Japan) Phase 3 Jun 2007 (ongoing)	Randomized, double-blind, parallel group	Tolvaptan Tablet PO 7.5 mg QD 15 mg QD	20/20/20	7 days	• CHF subjects with extracellular volume expansion despite the use of furosemide	No

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Protocol Number (Trial Location) Phase Trial Initiation	Trial Design	Treatment Groups	No. Planned/ Enrolled/ Treated	Treatment Duration	Main Subject Selection Criteria	Trial Included in Original NDA?
156-06-006 ¹⁵ (Japan) Phase 3 Aug 2007 (ongoing)	Open-label, uncontrolled	Tolvaptan Tablet PO Period 1: 15 mg QD Period 2: 15 or 30 mg QD	50/52/52	7 days in each period (14 days total)	* CHF subjects with extracellular volume expansion despite conventional diuretic therapy	No

CHF = congestive heart failure; PO = oral.

[Source: Tolvaptan Final Safety Update, Table 2-1, pages 70-73]

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/s/

Aliza Thompson
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MEDICAL OFFICER

Memorandum

Date: August 22, 2008

From: Robert Temple, MD
Director, ODE-I

To: Memo to File

Subject: NDA 22-275 Samsca (tolvaptan tabs) – Hypervolemic and euvolemic hyponatremia

b(4)

I. Introduction and Background

Dr. Unger's CDTL review [redacted] considers all aspects of [redacted] applications and all available reviews thoroughly. We have concluded that the [redacted] use of tolvaptan to treat certain patients with hyponatremia is supported and that tolvaptan can be approved with labeling changes and a REMS (Medguide plus assurance that tolvaptan will be initiated in hospitals). There are no internal disagreements, except for the question of whether treatment of cirrhotics should be contraindicated or less absolutely limited. This will be discussed below.

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II. Effectiveness

Tolvaptan is a vasopressin V2 antagonist that should lead to decreased antidiuretic (water retaining) effect and, in patients with too much water retention and resulting hyponatremia, to increased serum Na. A 4100 patient event-driven (1065 deaths or CHF hospitalizations) outcome study in which NYHA Class III-IV patients with worsening heart failure and volume overload despite all standard treatments were randomized to 30mg tolvaptan or placebo showed no effect on mortality (the primary outcome), with 25.9% on tolvaptan and 26.4% on placebo. Hospitalization plus death was also similar, 42% on tolvaptan vs 40.2% on placebo. There were hints of other pertinent effects (decrease in weight, but only about 0.8kg), a minimal effect on edema, and very small improvement in dyspnea on day 1. [redacted]

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The effect on serum sodium in patients with hypervolemic and euvolemic hyponatremia was readily demonstrated in patients with serum sodium < 125mg/L to > 125-135mM, where the hyponatremia was caused primarily by heart failure (and presumably excess diuresis), cirrhosis, and SIADH (syndrome of inappropriate ADH secretion). To avoid too rapid increase in Na⁺, which can lead to "osmotic demyelination" (a dangerous, potentially fatal consequence) patients were titrated from 15 mg up to 60 mg/day and were closely followed. The placebo-controlled trials had 448 patients, 225 given tolvaptan; patients were about 25% SIADH, 33% CHF, 27% cirrhotic and 21% "other." The 2 main trials lasted 30 days. Longer term safety is supported by the heart failure study.

Serum sodium, on average, rose a highly statistically significant 4-5mg/L to over 135 in about 4 days and persisted to 30 days. It returned to placebo-level (well above baseline) rapidly (in less than 7 days), indicating that in many cases, longer term therapy will be desired and probably needed. Effects were somewhat larger in the more hyponatremic patients, but this probably reflects the "titration to goal" design rather than greater responsiveness. Effects were similar for all etiologies of hyponatremia.

The principal question was the clinical value of the demonstrated effect on the serum Na surrogate endpoint. Patients overtly ill with very low Na were not included in the trial; they received hypertonic saline and fluid restriction. The treated patients had median Na about 129-130 and most were not overtly symptomatic. An attempt to demonstrate symptomatic benefit on a standard PRO QOL scale (SF-12) was not persuasive statistically or, for a number of reasons, to our SEALD team (who, among other issues, did not consider the SF-12 an established instrument for assessing symptoms of hyponatremia). It is not really surprising that no effect was seen, however, as most patients did not have symptoms at outset to be relieved.

For whom, then, is this treatment for, and what is its intent? Tolvaptan was presented on June 25, 2008 to the Cardio-Renal Advisory Committee for consideration of the hyponatremia indication. The Committee did not believe clinical benefits had been persuasively shown in the population studied, although they did believe the SF-12 results deserved some attention. Probably more importantly, they clearly believed that some patients with serum sodiums that were very low did need treatment acutely (but not with tolvaptan if emergent) and needed to be kept from going very low again, which tolvaptan did. The Committee did not pick a threshold Na to be treated and the labeling we are suggesting targets patients with serum sodium below 125 mM (mostly excluded from the trials because they were thought to need treatment) and patients with less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. As Dr. Unger notes, implicit in all this is the idea that treatment can keep patients from falling (again) to worrisome levels. Perhaps labeling should be revised to make that explicit.

III. Safety

Dr. Unger has fully reviewed safety issues. He notes that although the hyponatremia database is small (n = 607), the extensive study of a fragile CHF population (over 3000 patients) is reassuring, although the very fragility could mask low rates of toxicity that might be detected in healthier people.

The principal observed drug-placebo differences were for dehydration/volume depletion (1.8% vs 0.5%), hardly surprising for a drug intended to induce water diuresis, and GI bleeding, notably variceal bleeding in cirrhotic patients (6/63 vs 1/57). The latter finding caused Dr. Thompson to ask whether cirrhotics should be excluded in labeling, noting also that the 63 total exposed cirrhotic patients is a small number. I do not believe a contraindication, a possibility suggested fairly strongly by Dr. Unger, is needed (the bleeds were not fatal), but the labeling we sent Otsuka says that because of the bleeding risk tolvaptan "should be used in cirrhosis patients only when the need to treat outweighs this risk." Our letter will also point out that further data and discussion could make this limitation stronger or less stringent. Labeling needs to emphasize who should not be treated (people with urgent need for rapid Na correction, people lacking access to water or who cannot sense thirst, and people who are hypovolemic).

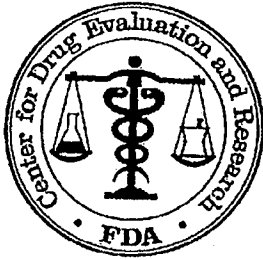
IV. Conclusion

Tolvaptan should be approved once the REMS provides a Medguide and a means of assuring that patients will be initially hospitalized for close observation to avoid too rapid Na correction. What to say about use in cirrhotics will need further discussion but at present I do not believe a Contraindication is warranted or would be in patients' interest.

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/s/

Robert Temple
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MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-275 (Samsca¹; tolvaptan for hyponatremia)
Sponsor: Otsuka
Review date: 21 August 2008

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-275
HFD-110/Brum/Unger

This memo conveys the Division's recommendation to approve tolvaptan for the treatment of moderately symptomatic hypervolemic or euvolemic hyponatremia in patients with SIADH or heart failure, and, if there is such a thing, asymptomatic hyponatremia <125 mM.

This application has been the subject of reviews of CMC (Mitra; 26 Jun 2008, 28 Jul 2008), pharmacology, toxicology, and carcinogenicity (Joseph and Rahman; 7 Feb 2008, 6 May 2008), QT (Zhang, Luan, Balakrishnan, Madabushi, and Garnett; 2 Apr 2008), biopharmaceutics (Hinderling and Earp; 9 May 2008, 9 Jun 2008), and clinical studies (Thompson, Targum, and Bai; 14 May 2008).

Most issues have been addressed in Dr. Unger's CDTL memo. I summarize very briefly.

Tolvaptan is a non-peptide V2 vasopressin receptor antagonist, more potent than native vasopressin. It is a racemate with stereospecific PK; the 2 isomers being about 3:1 in plasma at steady-state. Bioavailability is >40% with no food effect. It is highly protein-bound and so has a high apparent volume of distribution. It is metabolized by CYP 3A to inactive metabolites. Low-dose ketoconazole produces a 5-fold increase in exposure. Even orange juice produces a nearly 2-fold increase. CYP 3A inducer rifampin produces an 85% reduction in exposure. There are no other important covariates for exposure; in particular, renal clearance seems to be unimportant. Tolvaptan is also a substrate and inhibitor of the MDR1 transporter (which seems intimately associated with CYP 3A). Once-daily dosing produces 1.4-fold accumulation and peak-trough ratio of about 5. T_{max} is about 2 hours, but peak diuresis is at about 6 hours.

Use of tolvaptan in hypervolemic or euvolemic hyponatremia is mostly supported by two similarly designed studies using titrated doses of tolvaptan in patients with asymptomatic "non-acute" hyponatremia (Na <135 mM) attributable to SIADH, cirrhosis, or heart failure. There was a 30-day treatment period followed by a 7-day non-randomized withdrawal phase. Study 235 (SALT; n=205) and study 238 (SALT2; n=238), despite having 25-30% withdrawal rates, showed pretty compelling evidence of the ability to achieve normalization of sodium levels in treated subjects, with both groups being very similar upon withdrawal.

Both studies incorporated an SF-12 assessment among a set of secondary end points. The mental component score (MCS) of the SF-12 showed a nominally statistically significant difference in favor of tolvaptan in one study at one time point. The physical component score showed no statistically significant differences in either study at either

¹ Originally proposed name of Samsca appears in reviews

of two time points. No one on the review team regards the one favorable observation as an established finding of the development program.

The safety database overall includes over 3000 subjects treated with tolvaptan, but only about 607 (controlled studies) with hyponatremia, 410 with heart failure, 100 with cirrhosis, and 97 with SIADH. Only 189 subjects had baseline serum sodium <130 and only 52 had a sodium <125. Only 70 subjects were exposed to doses above 60 mg, and the only data at 6 months are from the heart failure study.

Despite having some subjects experience increases in serum sodium faster than is recommended, there were no cases of osmotic demyelination syndrome. The only identified safety issue is a 5-fold increased risk for GI hemorrhage in patients with cirrhosis. There is a plausible V2 receptor-mediated explanation for this and it is supported by analyses including less serious bleeding. I believe that this finding is sufficient to warrant contraindicating use in patients with cirrhosis, but a warning of the apparent risk in this population is acceptable.

Approval of tolvaptan for hyponatremia requires acceptance of serum sodium as a valid surrogate, because there is very little evidence of actual clinical benefit in the development program. A majority of the Advisory Committee seemed willing to accept this surrogate. The lack of evidence in favor of a clinical benefit (in hyponatremia) was perhaps attributable to design issues. Subjects were selected to be asymptomatic and there was no assessment specific to symptoms of hyponatremia.

The review team regards the overall safety database as inadequate, a position one can reach by giving little weight to the heart failure study. As Dr. Unger notes, finding no signal in a high-risk population is only provisionally reassuring. A vulnerable population may make some events more common, but if they were common anyway (sudden death, for example), then having a high background rate makes it harder to detect a given absolute increment in risk. There is also the issue that the heart failure study did not generate experience with the 60-mg dose. One may also be concerned about risks specific to the underlying disease (like the bleeding in cirrhotics); in that regard, there are few data in patients with SIADH. I am inclined to believe that the non-hyponatremic heart failure experience is generally of value, but its limitations cannot be dismissed.

Tolvaptan should not be used to treat hyponatremia requiring urgent intervention (to treat or prevent neurological sequelae) because its onset of action will take hours. This position was supported by the sponsor's own consultants. Nor does it make much sense to use tolvaptan in the setting of minimal asymptomatic hyponatremia because there is not even the theoretical possibility of clinical benefit. This leads to an oddity that ought to be reflected in labeling—tolvaptan should be used in patients with symptomatic hyponatremia, but it is not known to affect those symptoms.

I conclude that Samsca can be approved to treat patients with mildly or moderately symptomatic hypervolemic or euvolemic hyponatremia attributable to SIADH or heart failure.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2008.002.A.00073
APPLICATION NUMBER	NDA 22-275
LETTER DATE/SUBMISSION NUMBER	May 30, 2008
PDUFA GOAL DATE	August 23, 2008
REVIEW DIVISION	Division of Cardiovascular and Renal Products
MEDICAL REVIEWER	Aliza Thompson
REVIEW DIVISION PM	Dan Brum
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	July 17, 2008
ESTABLISHED NAME	Tolvaptan
TRADE NAME	Samska (proposed)
APPLICANT	Otsuka Pharmaceutical Development & Commercialization, Inc.
ENDPOINT(S) CONCEPT(S)	Functioning and Quality of Life in Patients with Hyponatremia
INSTRUMENT(S)	SF-12 Physical Component Summary (PCS); SF-12 Mental Component Summary (MCS); Hyponatremia Disease Specific Survey (HDS)
INDICATION	Treatment of Hypervolemic and Euvolemic Hyponatremia and for Prevention of Worsening Hyponatremia.

STUDY ENDPOINT REVIEW

A. EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Cardiovascular and Renal Products (DCRP) regarding NDA 22-275 and the proposed indication of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for prevention of worsening hyponatremia.

In this submission, the sponsor has provided a response to the FDA's information request (IR) concerning the patient reported outcome measures [SF-12 Physical Component Summary (PCS); SF-12 Mental Component Summary (MCS); and Hyponatremia Disease Specific Survey (HDS)] which were utilized in the pivotal trials submitted under NDA 22-275 in order to support the proposed indication of tolvaptan for the treatment of hyponatremia.

The SF-12 MCS and PCS were designed as measures of health status for the general population. Therefore, the items, scoring and interpretation do not result in a measure of hyponatremia symptoms or other health concerns that may be specific to the target population. In addition, the concepts measured by the SF-12 MCS and PCS are not clearly defined making it difficult to describe treatment effects in labeling. Data submitted by the sponsor that supports MCS and PCS score interpretation for the general population as well as with patients with other medical conditions are not useful for identifying a clinically meaningful response for the target population/indication.

Although the baseline MCS and PCS scores were low compared with the general population, this may not be a result of hyponatremia alone. The effects of underlying concomitant diseases in this population (e.g. symptoms associated with congestive heart failure or cirrhosis) may also be contributing to these scores. Also, since the instrument scoring is based upon norms for the general population and not patients with hyponatremia, a clinically meaningful change in score has not been established.

As a measure of health status in the general population the SF-12 is not a measure of the symptoms of hyponatremia or health related quality of life (HRQL), specifically for patients with hyponatremia. The domains of the SF-12 MCS are more consistent with a measurement of emotional state (e.g. anxiety and depression), rather than an extremely important manifestation of hyponatremia (change in cognitive state). Therefore, changes in MCS cannot be utilized to assess changes in cognition with treatment.

The information submitted by the sponsor, concerning the psychometric properties of the HDS do not address the content validity, and therefore do not support the use of the instrument as an adequate measurement of the signs and symptoms of hyponatremia. There is no evidence to suggest that the HDS represent a meaningful, comprehensive, appropriate, and interpretable measurement (evidence of content validity) of the symptoms of hyponatremia. At face value several important symptoms (e.g. headache, nausea, and dizziness) are not included. Although, unlike the SF-12 MCS, the HDS does include items related to cognition (e.g. concentrating and calculating), it is unclear how confused patients can identify or quantify their degree of mental functioning change.

STUDY ENDPOINT REVIEW

Finally, although statistically significant changes in SF-12 MCS scores and HDS item scores with treatment in the tolvaptan group compared with placebo suggests a clinical benefit, it is unclear how to define or adequately label this treatment benefit in order to support claims that are useful to prescribers and patients. Neither instrument represent meaningful, comprehensive, appropriate, and interpretable measurements (evidence of content validity) of the symptoms of hyponatremia or HRQL for the target population. Therefore, the instruments cannot be used as stand-alone measures of treatment benefit for efficacy claims.

See the review below for additional concerns and comments concerning the adequacy of SF-12 MCS and HDS scores to support claims in labeling.

B. STUDY ENDPOINT REVIEW

On April 25, 2008, FDA sent an information request (IR) to Otsuka requesting specific information concerning the development and implementation of the patient-reported outcome (PRO) instruments utilized in NDA 22-275 to support the efficacy of the proposed indication, tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for the prevention of worsening hyponatremia. _____

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The sponsor's response focuses on two PRO instruments utilized in their tolvaptan hyponatremia studies: the SF-12 PCS and MCS were used as secondary endpoints in both pivotal Studies 156-02-235 and 156-03-238; and the Hyponatremia Disease-Specific Survey (HDS) was used as an exploratory endpoint only in Study 156-03-238. A copy of both instruments is located in the Appendix.

1.1 Review of Specific IR Items

The following is a review of the pertinent information submitted by Otsuka. The sponsor's responses to FDA comments/questions are provided in **bold**, while SEALD's comments are provided in *italics*.

STUDY ENDPOINT REVIEW

FDA Comment: The content validity of the SF-12 has not been demonstrated for the purpose of measuring symptoms of hyponatremia in a clinical study setting to support labeling claims. At face value, the items included in the SF-12 do not appear to be representative of hyponatremia symptoms that are described in the published literature (e.g., altered mental status). The mental component summary (MCS) and physical component summary (PCS) of the SF-12 are composite scores, which include items that are not direct measurements of the concepts of mental and physical functioning, respectively.

Sponsor's Response: The sponsor notes that previously, FDA requested Otsuka provide evidence supporting the clinical relevance of serum sodium concentration correction in hyponatremia where the need for therapeutic intervention was not obvious (patients with serum sodium concentration ranges of 130-134 mEq/L). The SF-12 instrument was chosen because it included both physical and mental domains, the later being particularly sensitive to treatments aimed at correcting hyponatremia and its expected symptoms. Given that hyponatremia is found in a broad variety of diseases ranging from near-normal to near-mortal, this instrument was regarded as appropriate.

Later in the development program, the HDS was included in the hyponatremia clinical trials in order to incorporate a more disease specific questionnaire.

SEALD Comments: The SF-12 was developed as a generic health status instrument for the general population and not as a symptom-assessment tool or health related quality of life instrument in patients with hyponatremia. As such, the instrument is not effective as a primary or stand-alone assessment of treatment benefit in a clinical trial, because the clinical benefit measured by the SF-12 MCS and PCS is not clearly defined.

FDA Comment: Multiplicity not addressed:

Sponsor's Response: The planned MCS and PCS analyses were listed among other secondary endpoints in the Phase 3 study protocols. No procedures or adjustments for multiplicity were undertaken due to the supportive role of these endpoints.

SEALD Comment: Statistician comment suggested.

FDA Question: It would be helpful to evaluate whether there were baseline imbalances between treatment groups that may have influenced the findings, and whether any of the PRO findings are driven by a particular subgroup. For example, are findings on the MCS of the SF-12 influenced by baseline physical function, age, stage of disease, or some other variable that was measured?

Sponsor's Response: The summary of descriptive statistics of baseline MCS and PCS by subgroups and treatments is provided.

Evaluation of baseline imbalances between treatment groups that may have influenced PRO findings, such as physical function, age, stage of disease or other variable.

STUDY ENDPOINT REVIEW

Evaluation of baseline imbalance SF-12 scores between treatment groups and baseline variables were analyzed by an ANOVA table (Table 1) with each baseline variable (origin of disease, sex, age, sodium and US vs. non-US subjects), treatment and interaction for MCS and PCS scores.

Table 1. Baseline MCS and PCS Score Variability

Baseline MCS = Baseline Variable, Treatment and Interaction

The summary of ANOVA results are:

Baseline MCS

Baseline Var.	p-value		
	Baseline Var	Treatment	Interaction
Origin of Disease	0.66	0.24	0.20
Sex	0.42	0.32	0.80
Age (< vs > 65)	0.11	0.28	0.40
Sodium (< vs > 130)	0.40	0.32	0.39
US vs. Non-US	0.96	0.46	0.30

Baseline PCS

Baseline Var.	p-value		
	Baseline Var	Treatment	Interaction
Origin of Disease	<0.01	0.89	0.88
Sex	0.74	0.80	0.12
Age (< vs > 65)	0.78	0.74	0.07
Sodium (< vs > 130)	0.09	0.97	0.09
US vs. Non-US	0.99	0.74	0.16

SEALD Comments: As noted by the sponsor, none of the treatment groups and interactions of baseline variability and treatment group were statistically significant with respect to baseline MCS score differences. Some baseline differences were noted for PCS scores. Information pertaining to stage of disease is not noted. Statistician comment is suggested.

FDA Question. Please provide the following subgroup analyses (intergroup) comparisons of PRO data): (a) Cause for hospitalization for inpatients enrolled in the studies (b) Breakdown of inpatients and outpatients at enrollment (c) Underlying diagnosis (etiology or hyponatremia) (d) Demographics (e.g., age, gender) (e) U.S. versus non-U.S. (f) Baseline PRO data (SF-12, MCS, PCS) (g) Chronicity of hyponatremia (acute versus chronic) (h) Inpatient versus outpatient status at the time of PRO assessment (baseline and last observation)

Sponsor's Response: Although the sponsor notes that the majority of patients were not hospitalized prior to enrollment, the number of outpatients versus inpatients at enrollment is not provided. In addition, the duration of hyponatremia was not documented. Demographic data based on etiology of hyponatremia, age, and gender and baseline score is provided for both the SF-12 PCS and MCS.

SEALD Comments: Unfortunately, the sponsor has not provided a breakdown of the in-patient versus out-patient population or the chronicity of the hyponatremia population. This information would have been helpful in trying to understand how the differences in these subpopulation characteristics may have contributed to changes in SF-12 scores at both baseline and with treatment.

STUDY ENDPOINT REVIEW

FDA Question: To evaluate whether the composite score was driven by a particular component (or item); we need summary data including cumulative distribution function by treatment group and by study for the following:

- o Change from baseline of each item of the SF-12 and the MCS/PCS

Sponsor's Response:

In order to illustrate which items were most specifically affected by treatment to day 30, those with a difference of more than twice of the standard error are listed here (with scales of items of 1, 5, 6a and 6b converted so that positive change from baseline indicates improvement in these items):

SF-12 Question	Change from baseline	
	TLV	PLC
1. In general would you say your health is	0.21	0.03
4a Accomplished less – emotional problem	0.21	0.05
4b Didn't do activities as carefully as used	0.18	0.02
5 Pain interfered with normal work	0.33	0.04
6a Felt calm and peaceful	0.42	0.10
6b Have a lot of energy	0.39	0.08
7 Health interferes w/social activities	0.59	0.12

SEALD Comments: It is interesting to note that the items of the SF-12 which showed the greatest improvement in the tolvaptan group with treatment compared with placebo include: "Health interferes with social activities"; "Felt calm and peaceful"; and "Pain interfered with normal work". Based upon the background information submitted by the sponsor, pain and anxiety do not appear to be significant manifestations of hyponatremia, yet items referring to pain and calm and peaceful, appeared to show the greatest improvement with treatment.

FDA Question: Submit missing PRO data by treatment groups.

Sponsor's Response: Tables 2 and 3 provide the number of patients randomized as well as the missing data (i.e. number of patients without baseline, without post baseline, without both baseline and post baseline for the SF-12 MCS, PCS, and HDS, respectively.

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Table 2. SF-12 Health Survey Missing Score Summary

SF-12 ITEM	PROTOCOL	TREATMENT GROUP	PANE	MCS SCORE						PCS SCORE					
				MEAN EVALUATED		CHANGE EVALUATED		MEAN EXCLUDED		CHANGE EXCLUDED					
				N	NO POST	N	POST	N	NO DAY 30	N	DAY 30	N	NO	N	NO
MENTAL COMPONENT SCALE SCORE (MCS-12)	156-02-119	OPCA1061	87	87	19	68	3	7	4	74	23	51	23	3	
		PLACEBO	51	74	19	55	5	14	3	62	21	41	21	3	
	156-03-219	OPCA1061	113	104	19	101	0	13	3	98	19	79	19	3	
		PLACEBO	123	104	11	102	0	13	3	98	21	77	21	3	
	TOTAL	OPCA1061	212	251	25	184	5	20	7	165	42	123	42	6	
		PLACEBO	204	178	30	148	5	25	4	146	42	104	42	6	
PHYSICAL COMPONENT SCALE SCORE (PCS-12)	156-02-119	OPCA1061	87	87	16	71	3	7	4	74	23	51	23	3	
		PLACEBO	51	74	15	59	5	14	3	62	21	41	21	3	
	156-03-219	OPCA1061	113	104	15	101	1	13	3	98	19	79	19	3	
		PLACEBO	123	104	11	102	0	13	3	98	21	77	21	3	
	TOTAL	OPCA1061	212	251	25	184	5	20	7	165	42	123	42	6	
		PLACEBO	204	178	30	148	5	25	4	146	42	104	42	6	

STUDY ENDPOINT REVIEW

Table 3. Hyponatremia Disease Specific Survey Missing Score Summary (First 12 Items)

SF-12 ITEM	TREATMENT GROUP	RAND	LOSS SCORE								GC SCORE	
			MEAN EXCLUDED	CHANGE IN SCORE				MEAN EXCLUDING	CHANGE EXCLUDING			
				N	WT BEL	NO WHD	POST			DEL	N	DAY 10
IN GENERAL, HEALTH OVER THE PAST TWO DAYS	OPC41061 PLACEBO	119 115	40 44	76 71	41 42	63 65	7 6	2 2	32 31	87 84	32 31	87 84
CONCENTRATING ACTIVITIES (MCB-1)	OPC41061 PLACEBO	119 115	43 44	76 71	41 42	63 65	7 6	2 2	32 31	87 84	32 31	87 84
CALCULATING ACTIVITIES (MCB-2)	OPC41061 PLACEBO	119 115	43 44	76 71	41 42	63 65	7 6	2 2	32 31	87 84	32 31	87 84
LANGUAGE ACTIVITIES (MCB-3)	OPC41061 PLACEBO	119 115	43 44	76 71	41 42	63 65	7 6	2 2	32 31	87 84	32 31	87 84
MEMORY ACTIVITIES (MCB-4)	OPC41061 PLACEBO	119 115	42 43	77 72	40 41	63 65	8 7	2 2	32 30	87 85	32 30	87 85
ENDURANCE ACTIVITIES (PCS-1)	OPC41061 PLACEBO	119 115	42 44	77 71	40 43	63 65	8 6	2 2	32 31	87 84	32 31	87 84
STRENGTH ACTIVITIES (PCS-2)	OPC41061 PLACEBO	119 115	42 44	77 71	40 43	63 65	8 6	2 2	32 31	87 84	32 31	87 84
GROSS COORDINATION ACTIVITIES (PCS-3)	OPC41061 PLACEBO	119 115	42 43	77 71	40 43	63 65	8 7	2 2	32 30	87 84	32 30	87 84
FINE COORDINATION ACTIVITIES (PCS-4)	OPC41061 PLACEBO	119 115	42 43	77 72	40 41	63 65	8 7	2 2	32 30	87 85	32 30	87 85

SEALD's Comments: Both tables suggest that there was a significant amount of missing data associated with both instruments, especially the HDS. The missing data could jeopardize the validity and therefore the interpretability of the data.

1.2 Review of Additional Information

In addition to the IR responses, the sponsor submitted two briefing reports which were prepared with the assistance of [REDACTED]

- o *SF-12 Health as an Assessment of Functional Health Status and Psychological Well-Being for the Treatment of Hyponatremia*
- o *Technical Report on Psychometric Properties of the Hyponatremia Disease Survey (HDS)*

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The following is a review of the major principles discussed in both papers.

I. SF-12 Health as an Assessment of Functional Health Status and Psychological Well-Being for the Treatment of Hyponatremia

1. Symptoms of Hyponatremia

As noted by the sponsor, clinical symptoms of hyponatremia are primarily neurological and severe hyponatremia can result in life threatening symptoms such as cerebral edema, irreversible neurological damage, respiratory arrest, brainstem herniation and death. Chronic symptoms of hyponatremia can cause vague symptoms, which include headache, nausea, fatigue, dizziness, forgetfulness, vomiting, malaise, lethargy, confusion, mental dullness, or altered consciousness. These symptoms can eventually progress to seizure, coma, and death.

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STUDY ENDPOINT REVIEW

While there have been no studies systematically and directly assessing the association between cognitive deficits and patients psychological well-being in the hyponatremia, the sponsor contends that emotional state could influence or be influenced by cognitive functionality.

SEALD Comments: Signs and symptoms of acute hyponatremia may differ than those of chronic hyponatremia. Therefore, the selection of efficacy endpoints in the tolvaptan studies should have included assessments of the clinically important signs and symptoms associated with chronic hyponatremia. There is no evidence to suggest that the SF-12 PCS and MCS as well as the HDS represent meaningful, comprehensive, appropriate, and interpretable measurements (evidence of content validity) of the symptoms of hyponatremia. At face value several important symptoms (e.g. headache, nausea, and dizziness) are not included in any of the instruments.

In addition, it is unclear how confused patients can adequately identify or quantify their degree of mental functioning change. Although PRO instruments, such as the HDS which ask patients if they have difficulty with such tasks as concentrating or calculating can be helpful in understanding the patient's perspective, they cannot replace objective assessments, such as the mini mental status examination. Also, the concept of emotional state (e.g. anxiety and depression), as measured by the SF-12 MCS is not synonymous and cannot replace measures of cognitive state (e.g. confusion).

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STUDY ENDPOINT REVIEW

(4) Adding a constant (regression intercept), aggregate PCS-12 and MCS-12 scores are standardized to have the same mean as SF-36 versions in the general U.S. population. The fourth step involves transforming each summary scale score to the NBS, which is referred to as "50/10" scoring because means of 50 and SDs of 10 are achieved in the general U.S. population. For the PCS-12, this is accomplished by adding the respective constant (Table 4) to the sum of the 35 products (physical) from Step 2. Note that in Table 4 there are two options for standardizing both summary scales. The first option, "1990 constant", standardizes PCS-12 and MCS-12 to have a mean of 50 and SD of 10 in the 1990 general U.S. population. The second option, "1998 constant", standardizes PCS-12 and MCS-12 to have a mean of 50 and SD of 10 in the 1998 general U.S. population.

SEALD Comments: The scoring information provided by the sponsor shows that how each of the 12 items in the SF-12 contributes to the MCS and PCS score. In addition, the scoring is based upon norms for the general population and not specifically for hyponatremia patients.

3. Treatment Benefit

Table 5 presents the comparison of baseline SF-12 PCS and MCS scores for the hyponatremia trial sample with age and gender adjusted norms from the general U.S. population and several disease specific benchmarks from the Medical Outcomes Study, which was a 4-year observational study of chronically ill patients. As noted by the sponsor, the results of the burden analysis illustrate the extent of the physical and mental health burden experienced by hyponatremia patients enrolled in the pivotal hyponatremia trials.

Table 5. Health Status Burden of Hyponatremia, Comparison of Baseline Mean SF-12 Scores of Hyponatremia Patients vs. General and Disease Specific Norms

SF-12	Hyponatremia Patient Groups				Normative Groups ¹			Significance Testing		
	Total (n=392)	CHF (n=118)	Renal/ Liver (n=113)	SIADH (n=161)	Total (n=1,982)	CHF (n=216)	Renal/ Liver (n=90)	Total	CHF	Renal/ Liver
PCS	33.4 (10.7)	30.9 (9.1)	31.2 (9.9)	36.7 (11.4)	47.8 (10.3)	34.5 (12.1)	38.5 (11.6)	t=18.1, p<.001	t=2.8, p=.005	t=4.8, p<.001
MCS	44.1 (11.7)	43.9 (11.8)	43.2 (10.1)	44.8 (11.9)	52.3 (9.4)	50.4 (11.1)	47.5 (9.8)	t=10.1, p<.001	t=5.1, p<.001	t=3.1, p=.003

¹Normative data adjusted to the age and gender of the hyponatremia sample

SEALD Comments: The lower MCS and PCS values in patient with hyponatremia compared with the general population do not support the content validity of the instruments. In addition, as noted by the sponsor, the patients in the tolvaptan pivotal trials also had concomitant underlying illnesses, such as congestive heart failure, hepatic cirrhosis, and disease related SIAD. These conditions are also associated with symptoms (e.g. congestive heart failure symptoms of shortness of breath and decrease exercise tolerance), which would also contribute to overall lower health status as well.

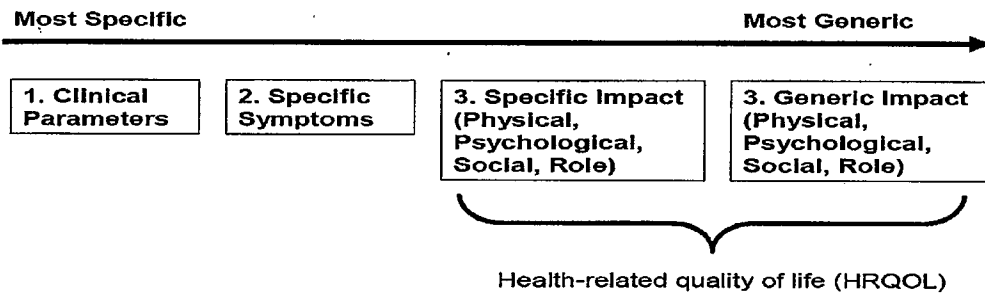
4. Endpoint Model

In developing an endpoint model, the sponsor has developed a conceptual model for describing the relationships between disease-specific and generic health status measures for clinical outcomes as noted in Figure 1. As noted by the sponsor, measures on the left (1 and 2) are the most specific and therefore, useful in diagnosis and determining the severity of a specific

STUDY ENDPOINT REVIEW

condition, while factors on the right (3 and 4) are useful in understanding the impact (functioning and well-being) of a disease and treatment as more generic instruments.

Figure 1. Sponsor's proposed conceptual model



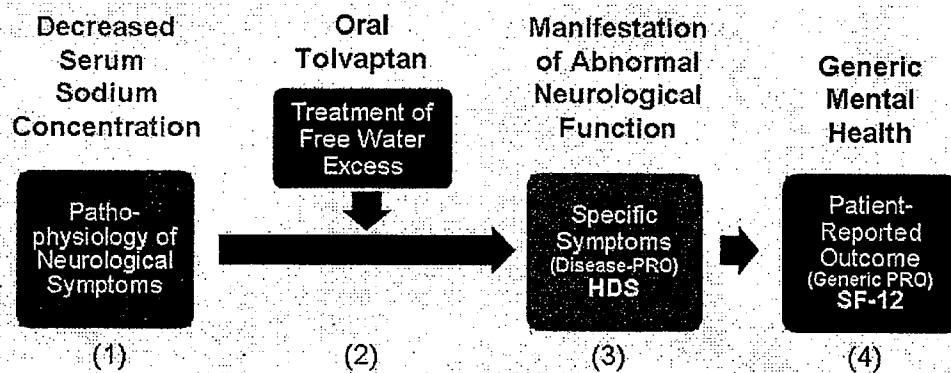
SEALD Comments:

As noted in the draft "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims", an endpoint model is the hierarchy of relationships among all endpoints, both PRO and non-PRO in a clinical trial. This hierarchical order is based upon clinical importance and not specificity of concept. Although HRQL is a multidimensional concept and therefore a broader concept, it still should be specific for the population. For example, physical functioning assessments in rheumatoid arthritis patients would involve items, such as opening doors and jars; while physical functioning assessments in a congestive heart failure population would involve items concerning walking distances or climbing stairs. A generic instrument would not adequately capture the clinically important subconcepts of each unique population. In addition, the proposed conceptual model has omitted the concept of clinical signs of hyponatremia (e.g. mental confusion) which is also extremely important in determining the severity of hyponatremia.

Based upon the principles of the generic conceptual model, the sponsor has created an endpoint model for both Studies 156-02-235 and 156-03-238, which is delineated in Figure 2. As noted by the sponsor, a lowered serum sodium concentration (i.e., hyponatremia or Step 1) is directly responsible for the neurological symptoms (Step 3) exhibited by patients. Hyponatremia's effects on a patient's neurological function can be detected as changes in cognitive abilities and fine and gross motor skills by the HDS instrument (Step 3). These same changes can adversely impact the general physical and mental health status of patients and this can be detected by SF-12 MCS (Step 4). In the current studies, and in accordance with the endpoint model, it was hypothesized that successful treatment with tolvaptan (Step 2) would increase serum sodium concentrations and favorably impact the patient's neurological status. Thus, normalizing serum sodium levels would correct the altered mental state of patients which would be associated with improvements in general.

STUDY ENDPOINT REVIEW

Figure 2. Studies 156-02-235 and 156-03-238 Endpoint Model.



SEALD Comments:

The sponsor's endpoint model does not delineate the clinically important hierarchy of all endpoints.

In addition, the specific concepts of interest are not accurate representations. Abnormal neurological functioning cannot be measured by a symptom questionnaire, but rather with specific well-defined neurological and cognitive testing. Symptoms (e.g. nausea) and signs (e.g. altered mental status) of hyponatremia, although both important concepts, are not synonymous and must be considered separately. "Mental health", is a subconcept of the larger multidimensional concept of health related quality of life (defined in the draft PRO Guidance as an overall perception of the impact of an illness that includes at minimum, physical, psychological, and social functioning). Therefore, mental health must be assessed in conjunction with the other subconcepts of health related quality of life and should be specific for the population. Mental health, which includes domains of anxiety and depression, is not a neurological measurement of cognition.

To provide empirical support for the endpoint model illustrated in Figure 2 analyses were conducted to investigate the associations between: 1) changes in serum sodium levels and HDS scales; 2) changes in serum sodium levels and SF-12 summary measures; and 3) changes in HDS scales and SF-12 summary measures.

For the first two analyses, patients were categorized in terms of clinically meaningful categories of change in serum sodium levels from baseline to Day 30. Patients whose serum sodium levels increased by 5 mEq/L or more were categorized as "better". Patients whose serum sodium levels decreased by 3 mEq/L or more were categorized as "worse". Patients whose serum sodium levels changes between +5 and -3 mEq/L were categorized as "same". Mean changes in HDS scales and SF-12 PCS and MCS scores from baseline to Day 30 were analyzed across these three categories of serum sodium level changes using ANOVA methods. It was hypothesized that HDS scale and SF-12 summary measure scores would show significantly greater improvement among those patients categorized as "better" on changes in serum sodium levels compared to patients categorized as the "same" or "worse" in serum sodium level changes.

STUDY ENDPOINT REVIEW

For the third set of analyses described above, changes in HDS scales from baseline to Day 30 were correlated with changes in SF-12 PCS and MCS scores from baseline to Day 30. This analysis was conducted to establish the link, or association, between the changes in the altered mental states associated with the treatment of hyponatremia and generic physical and mental health status as measured by the SF-12 Health Survey. It was hypothesized that there would be a significant correlation between the scales of the HDS and the SF-12 summary measures.

Table 6 shows the mean change in HDS scale scores and SF-12 PCS and MCS scores across three levels of change in serum sodium. In addition, categories of change in SF-12 PCS and MCS scores are presented across the three sodium categories of change. As shown changes in HDS cognitive ($F=3.21$, $p=0.05$) and motor coordination ($F=3.39$, $p=0.04$) scale scores showed significant differences across the three serum sodium categories of change in the hypothesized direction. Specifically, patients whose serum sodium levels improved showed improvement in the cognitive and motor coordination scale scores, while patients whose serum sodium levels worsened showed worsening in scores on both cognitive and motor coordination scales. No systematic relationship was found between changes in serum sodium and HDS physical function scale.

Mean and categorical changes in PCS-12 scores did not differ significantly across the three serum sodium categories of change. For MCS-12, significant differences in mean change scores were observed across the three serum sodium groups.

Table 6. Changes in HDS Scale and SF-12 PCS and MCS scores across clinically meaningful changes in serum sodium level

HDS*	Serum sodium level changes		N	Mean Change	SD	Better	Same	Worse
Cognitive	>5 ml improvement	Better	35	-2.31	0.3	-	-	-
	-2 to +4 ml change	Same	20	-0.04	0.5	-	-	-
	< 3 ml loss	Worse	8	2.00	0.7	-	-	-
Significance Test of Differences					$F=3.21$, $df=2$, $p=0.05$			
Motor Coordination	>5 ml improvement	Better	35	-1.13	0.2	-	-	-
	-2 to +4 ml change	Same	20	0.43	0.4	-	-	-
	< 3 ml loss	Worse	8	1.5	0.4	-	-	-
Significance Test of Differences					$F=3.39$, $df=2$, $p=0.04$			
Physical Function	>5 ml improvement	Better	35	-0.97	0.3	-	-	-
	-2 to +4 ml change	Same	20	0.22	0.4	-	-	-
	< 3 ml loss	Worse	8	-2.00	0.5	-	-	-
Significance Test of Differences					$F=1.51$, $df=2$, $p=0.21$			
SF-12	Serum sodium level changes		N	Mean Change	SD	Better	Same	Worse
PCS	>5 ml improvement	Better	160	1.9	40.0%	30.6%	29.4%	29.4%
	-2 to +4 ml change	Same	113	0.6	38.9%	25.7%	35.4%	35.4%
	< 3 ml loss	Worse	21	2.4	47.6%	23.8%	28.6%	28.6%
Significance Test of Differences					$F=0.72$, $df=2$, $p=0.49$		$\chi^2=1.9$, $p=0.76$	
MCS	>5 ml improvement	Better	160	5.3	12.0	53.8%	27.5%	18.7%
	-2 to +4 ml change	Same	113	2.0	12.3	43.4%	22.1%	34.5%
	< 3 ml loss	Worse	21	0.4	13.7	38.1%	9.5%	52.4%
Significance Test of Differences					$F=4.1$, $df=2$, $p=0.18$		$\chi^2=17.2$, $p=0.002$	

*Higher scores in HDS scales indicates worse functioning. HDS was administered in only in the SALT 2 trial.

STUDY ENDPOINT REVIEW

SEALD Comments: In reviewing the sponsor's conclusions, the following should also be considered:

- The sponsor's definition of "better" is based upon the change in the patient's serum sodium. Since a treatment effect is determined by how a patient feels, functions or survives as a result of treatment, "better" might best be determined by an improvement in one of these parameters (e.g. improved survival rates or improvement in cognition). A change in sodium from baseline does not necessarily equate with one of these parameters. This is supported by the fact that the physician's decision to treat a patient, especially patients such as those enrolled in the tolvaptan clinical trials with nonacute hyponatremia, is not based singularly on the patient's serum sodium, but also on the associated signs and symptoms of hyponatremia observed as well.*
- Since Studies 156-02-235 and 156-03-238 did not specifically enroll symptomatic hyponatremia patients, then a statistically significant change in function from baseline does not necessarily represent a clinically significant change.*
- The sponsor has not provided evidence that the HDS is an adequate measurement of the symptoms of hyponatremia. The domains of cognition, motor coordination and physical function were defined post-hoc and have not been shown to represent a complete list of the important symptoms of hyponatremia. Overall, the content validity of the instrument has not been established.*
- The HDS is not a measurement of the signs of hyponatremia, such as altered mental status as noted by the sponsor. The neurological abnormalities of hyponatremia, including abnormal mental status, must be determined by an objective, well-defined measurement. Patients who are confused cannot quantify their level of confusion.*
- The SF-12 MCS and PCS are not measurements of HRQL for the target population and are not measurements of mental and physical functioning in hyponatremia patients. The content validity of the instruments has not been demonstrated in the target population. At face value, some of the items may not be appropriate for the target population (i.e. assessment of pain).*
- The PCS and MCS are composite measures that combine weighted scores for all 8 SF-12 domains into a single score. Therefore, since the PCS and MCS contain items that are not directly associated with physical and mental functioning, respectively, they are not adequate measurements of the concepts proposed.*
- Correlation of changes in HDS from baseline to Day 30 with changes in SF-12 PCS and MCS from baseline to Day 30 will not establish the content validity of either instrument.*

Since the MCS-12 is a weighted linear sum of 8 domain scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) analyses were conducted to determine if changes on the domain scales that contributed the most to scoring of MCS-12 also show a similar relationship with changes in serum sodium. Analysis of variance was used to determine the significance of differences in mean changes in SF-12 domain scores (baseline to Day 30) across the three categories of change in serum sodium.

As noted by the sponsor, Table 7 shows several of the SF-12 domain scales that contribute most to scoring MCS-12 also showed significant relationships with categories of change in serum sodium in the hypothesized direction. Specifically, patients whose serum sodium got "better"

STUDY ENDPOINT REVIEW

showed a significantly greater improvement in the vitality, role emotional, and mental health scales, while the patients whose serum sodium got “worse” showed the least improvement or worsening in scores on these three scales. The only domain scale that contributes to scoring MCS-12 that did not show a significant relationship with the categories of change in serum sodium in the hypothesized direction was the social functioning scale. Of the SF-12 domain scales that contribute the most to scoring PCS-12, only the bodily pain scale showed a significant relationship with the categories of change in serum sodium however the relationship was not consistent with hypotheses. None of the other “physical health” scales showed a significant relationship with the categories of change in serum sodium.

Table 7. Changes in SF-12 Domain Scale Scores Across Categories of Change in Serum Sodium

SF-12 Domain Scales	Categories of Change in Serum Sodium			F	p-value
	Better	Same	Worse		
	Mean change (SE)	Mean change (SE)	Mean change (SE)		
Physical Functioning	0.92 (2.4)	-1.31 (2.9)	9.52 (6.8)	1.09	0.343
Role Physical	14.7 (3.6)	8.18 (4.3)	4.76 (10.2)	0.90	0.411
Bodily Pain	11.96 (2.8)	-1.71 (3.3)	5.95 (7.8)	4.99	0.007
General Health	6.42 (2.1)	4.23 (2.5)	-0.71 (5.9)	0.74	0.476
Vitality	9.63 (2.3)	1.88 (2.8)	-2.86 (6.5)	3.22	0.041
Social Functioning	10.67 (3.0)	6.62 (3.5)	17.85 (8.3)	0.90	0.406
Role Emotional	17.99 (3.9)	6.41 (4.6)	1.38 (9.1)	3.21	0.042
Mental Health	11.15 (1.9)	2.67 (2.3)	-1.43 (5.3)	5.43	0.005

SEALD's Comments: It is interesting to note that bodily pain, which is not one of the significant contributing domains of the MCS, and is also not a significant symptom of hyponatremia, based upon the information submitted by the sponsor, showed the greatest improvement with change in sodium, after mental health.

Table 8 depicts a matrix of correlations between the changes in HDS scale and SF-12 summary scores from baseline to Day 30 for patients. As noted by the sponsor, the correlations were statistically significant, except for the correlation between the HDS physical scale and MCS-12. As noted by the sponsor, given that link changes in serum sodium to changes in HDS cognitive and coordination scale scores and MCS-12 scores, and the significant association observed between HDS cognitive and coordination scales and MCS-12, it should follow that treatment of hyponatremia aimed at restoring a balance in serum sodium levels should have its greatest impact/effect on HDS cognitive and coordination scales and MCS-12.

STUDY ENDPOINT REVIEW

Table 8. Correlation between HDS and SF-12 PCS and MCS-Change Score

Spearman Correlation Coefficients Prob > r under HO: Rho=0 Number of Observations			
SF-12	HDS Scales		
	Cognitive	Physical	Coordination
PCS-12	-0.32719 0.0089 63	-0.49920 <.0001 63	-0.30270 0.0159 63
MCS-12	-0.41628 0.0032 63	-0.22213 0.0802 63	-0.37713 0.0023 63

SEALD's Comments:

In considering the sponsor's conclusions, the following should be noted:

- *Cognition cannot be quantitated by self-report*
- *The MCS is not a measure of cognition.*
- *The MCS and HDS scales measure different concepts (emotional state versus self-report cognition) and do not have coordinating scales.*
- *Correlation of instruments does not establish the content validity of either instrument or define a clinically meaningful response.*

5. Content Validity Documentation

As noted by the sponsor, the SF-12 MCS and PCS have proven to be useful in outcome trials. In support of the content validity of the SF-12 MCS and PCS instruments, the sponsor delineates several literature reviews and expert opinions that support the utility of these instruments as assessments of mental and physical health, respectively, in many different disease conditions. Additional evidence to support the content validity of SF-12 PCS and MCS as measures of physical and mental health can be derived from studies of their relationships with other measures of physical and mental health status. The SF-12 has been compared with at least other surveys, including generic health measures such as the Sickness Impact Profile, the Nottingham Health Profile, EuroQol and EQ-5D, the General Health Questionnaire, the Quality of Well-Being Scale, the Pain Disability Index, Behavioral Risk Factor Surveillance System (BRFSS) HRQoL modules, and the Health Assessment Questionnaire. As noted by the SF-12 summary measures have performed very well in most comparisons with other general measures, presenting high correlations of PCS-12 with measures of physical health and the MCS-12 with mental health measures, as hypothesized.

As noted by the sponsor, qualitative study protocols and interview guides are not available to support the content validity of the SF-12 PCS and MCS. Other measurement properties, including test-retest reliability, and internal consistency was evaluated by using data from the Studies 156-02-235 and 156-03-238. Construct validity with as measures of physical and mental status from the literature and association with other diseases are delineated. Factor analyses of the principle components of the instrument with Studies 156-02-235 and 156-03-238 data were also obtained.

STUDY ENDPOINT REVIEW

SEALD Comments: None of the information submitted justifies the content validity of the SF-12 PCS and MCS; based upon patient input the instrument represents a meaningful, comprehensive, interpretable, and appropriate measure of the concept of interest.

6. Interpretation of Scores

As noted by the sponsor, a responder definition for the SF-12 MCS and PCS was not determined a priori. The sponsor has provided two approaches were taken to derive MID's for PCS and MCS post hoc. The first approach was an anchor-based approach. Anchor-based approaches focus on the relationship between the measure in question, PCS and MCS, and some meaningful criteria that is conceptually related to the measure in question. Criterion measures used in the derivation of MID's for PCS included treadmill walking distance, being unable to work due to health reasons, risk of job loss in 6 months due to health reasons, risk of being hospitalized over night in the subsequent year, 2-year mortality rates, patient self-report of change in health status, unique burden of heart disease, lung disease, diabetes, osteoarthritis, chronic low back pain, ulcers, anemia, depression, and chronic allergies.

The second approach to deriving MID's for PCS and MCS was based on the distribution of scores themselves. Distribution-based methods of deriving MIDs interpret results in terms of the relation between the magnitude of difference and some measure, or measures, of variability. An early and often cited criterion for important group mean differences/changes is based on effect size: the mean difference/change divided by the standard deviation. In the context of comparing group differences, suggested that a small effect size is 0.2, a moderate effect size is 0.5, and a large effect size is 0.8.

Data used to derive MID's for PCS and MCS came from multiple sources. The first source of data was from the 1998 National Survey of Functional Health Status, a cross-sectional dataset used to norm the SF-12 and SF-36 Health Surveys. The second source of data was from the Medical Outcomes Study, a four-year, longitudinal, observational study of chronically ill patients. The third source of data was a public use file on the Medicare Health Outcomes Survey, a two year, longitudinal, U.S.

Based on the results of all the analyses conducted using both anchor-based and distribution based approaches to determining the MID for PCS and MCS, 3-point differences or changes in scores were recommended as MIDs for both PCS and MCS.

A responder analysis was not originally planned in the protocols written for the two tolvaptan pivotal trials of the treatment of hyponatremia. However, in post-hoc analyses, a responder analysis was conducted to identify the proportion of patients in both treatment and placebo groups who got "better", stayed the "same" or got "worse" on PCS and MCS from baseline to Day 30. Using the 3-point MID threshold established for PCS and MCS, patients were categorized as "better" if their Day 30 PCS/MCS score improved by 3 or more points from their baseline PCS/MCS score. Similarly, patients were categorized as "worse" if their PCS/MCS score at Day 30 was 3 or more points worse (lower) than their baseline PCS/MCS score. Patients were categorized as the "same" if score. The proportion of patients in the "better", "same", and "worse" categories were compared between treatment and placebo groups and chi-square tests

STUDY ENDPOINT REVIEW

were conducted to determine the significance of the difference in the proportion of patients in these change score categories between placebo and treatment groups.

SEALD Comments: The anchor-based method of establishing an MID correlated PCS and MCS scores with criteria that are not specific to the target population of patients with hyponatremia (e.g. patients with chronic low back pain and chronic allergies). The distribution based method, uses a statistical approach but also does not define a clinically important change for the patient.

7. Translation

The translation of the SF-12 involved both forward and backward translations by qualified translators. Translators placed an emphasis on conceptual rather than literal equivalence and the choice of wording and phraseology was to be compatible with a reading level of age 12.

SEALD Comments: The overall translation procedure appears adequate.

8. Protocol and Analysis Plan

In reference to the implementation of the SF-12 during Studies 156-02-235 and 156-03-238, the following was provided by the sponsor:

- In Study Studies 156-02-235 change from baseline in SF-12 PCS and MCS scales at Week 1 and Day 30 were secondary endpoints.
In Study Studies 156-03-238 change from baseline in SF-12 PCS and MCS scales at Week 2 and Day 30 were secondary endpoints.
- Plans for multiplicity comparisons were not implemented since the need to adjust for multiplicity with two outcome measures was considered unwarranted.
- For handling missing data:
 - At the level of the individual patient, persons missing any one question of the SF-12 Health Survey were ignored, i.e., their PCS-12 and MCS 12 scores were missing. For the comparison of outcomes, the intent-to-treat sample was used carrying the last observed case forward to account for missing data points.
 - For the early termination visit, if that visit fell to the protocol specified window of Week 1, the early termination visit was considered as Week 1. If the early termination visit fell to the protocol specified window for Day 30, the early termination visit was considered as a Day 30 visit. Early termination before Week 1 but out of its protocol specified window were considered LOCF to both Week 1 and Day 30 visits, and early termination visits before Day 30 but out of the protocol specified window for Day 30 were considered LOCF to Day 30 visit.

SEALD's Comments: Although a statistician's input is suggested, it is recommended that the sponsor's analysis plan should incorporate a plan for adjusting for multiplicity. In addition, excluding all items from a questionnaire for an efficacy analysis, due to one missing item, such as the SF-12, would most likely result in significant missing data and under-reporting of symptoms.

STUDY ENDPOINT REVIEW

II. Technical Report on Psychometric Properties of the Hyponatremia Disease Survey (HDS)

As noted by the sponsor, the Hyponatremia Disease Survey (HDS) was developed by the Otsuka Corporation in conjunction with clinical experts. The HDS consists of 13 items designed to assess the impact of hyponatremia on several aspects of the patient's life. These include overall health, cognitive functioning (including language, concentration, ability to calculate and memory); physical functioning (including strength, endurance, fine and gross motor coordination); sensation of thirst; self reported salt concentration level; and patient and physician assessment of treatment impact. The specific aims of this study are to evaluate the psychometric properties of the HDS, determine the optimal scaling of HDS items, and empirically test the validity of the HDS scales in relation to clinical criteria. In order to psychometrically validate the instrument, the sponsor used the data from Study 156-03-238 and provides descriptive statistics, factor analyses, multi-trait analyses, differential item functioning analyses, and validation analyses.

SEALD's Comments:

The sponsor has not provided any information to justify the conceptual framework or item generation of the HDS. No information is submitted to support the content validity. Since the content validity has not been established, the assessment of other measurement properties of the other psychometric properties is futile.

A summary of the patients who completed the HDS in Study 156-03-238 is delineated in Table 9. A total of 126/243 (51.9%) randomized subjects had mild hyponatremia and 117/243 (48.1%) had severe hyponatremia. In this study, mild hyponatremia was defined as a baseline serum sodium of ≥ 130 mEq/L; while severe hyponatremia was defined as a baseline serum sodium of < 130 mEq/L.

Table 9. Completed HDS by Hyponatremia Severity

Baseline Group		HDS completed Day 1	HDS completed Day 7	HDS completed Day 30
		105/108	79/108	72/108
Mild Hyponatremia	40/108	39/40	26/40	24/40
Severe Hyponatremia	62/108	61/62	49/62	44/62

SEALD's Comments:

Table 9 suggests that there is a considerable amount of missing data associated with HDS completion. For example, out of 117 enrolled patients with severe hyponatremia, only 44 completed the HDS at Day 30 (38%).

Based on discussion with Otsuka, four items were not used for the purposes of psychometric validation of the properties of the instrument. The self reported sensation of thirst and the self reported sodium concentration level were excluded due to questionable significance as a symptom of hyponatremia and the difficulty in self assessment of sodium level, respectively. The patient and physician reported effects of treatment on activity, symptoms and emotional well-being were also excluded due to the inclusion of treatment effect as part of the assessment as well as inconsistent recall from the first 9 items. Item response values for the 9 HDS items were

STUDY ENDPOINT REVIEW

coded such that a higher item response value was indicative of worse health or more severe impairment.

The post-hoc analyses of the HDS included the following:

- Descriptive Statistics:
- Computed means, standard deviations, missing data rates, and frequency distributions for each item response at each time point in study when HDS was administered
- Factor Analyses
- Exploratory factor analyses were conducted to obtain a general understanding of the relationship of HDS items
- Multi-Trait Analyses
- Validation Analyses
- Construct validity of the HDS scale in relation to physical and mental health was tested by correlating HDS scales with SF-12 MCS and PCS scales

SEALD Comments: None of the post-hoc analyses establish the content validity of the HDS as an adequate measurement of the signs and/or symptoms of hyponatremia.

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/s/

Ann Marie Trentacosti
7/17/2008 11:40:42 AM
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STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2008.002.A.00031
APPLICATION NUMBER	NDA 22-275
LETTER DATE/SUBMISSION NUMBER	October 23, 2007
PDUFA GOAL DATE	August 23, 2008
DATE OF CONSULT REQUEST	March 4, 2008
REVIEW DIVISION	Division of Cardiovascular and Renal Products
MEDICAL REVIEWER	Aliza Thompson
REVIEW DIVISION PM	Dan Brum
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	April 14, 2008
ESTABLISHED NAME	Tolvaptan
TRADE NAME	Samska (proposed)
APPLICANT	Otsuka Pharmaceutical Development & Commercialization, Inc.
ENDPOINT(S) CONCEPT(S)	Functioning and Quality of Life in Hyponatremic Patients
INSTRUMENT(S)	SF-12 Physical Component Summary (PCS); SF-12 Mental Component Summary (MCS)
INDICATION	Treatment of Hypervolemic and Euvolemic Hyponatremia and for Prevention of Worsening Hyponatremia.
INTENDED POPULATION(S)	Patients with Hyponatremia

STUDY ENDPOINT REVIEW

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Cardiovascular and Renal Products regarding NDA 22-275 and the proposed indication of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for prevention of worsening hyponatremia. This review addresses the adequacy of the patient-reported outcome efficacy measurements, the Short Form (SF) -12 Physical Component Summary (PCS) and Mental Component Summary (MCS) utilized in the pivotal clinical studies to support the proposed indication.

The review concludes that the SF-12 PCS and MCS are not adequate measurements of function and health related quality of life (HRQL) as proposed and cannot be utilized to support efficacy claims.

The SF-12 is a generic instrument and is not specific in accessing function or health related quality of life (HRQL) in the target population of patients. The PCS and MCS are composite measures that combine weighted scores for all 8 SF-12 domains into a single score, in order to assess physical and mental functioning, respectively. The weights for each respective measure vary, however, the patient responses that are used to calculate the scores are identical. Therefore, each summary score includes domains that are not directly associated to the concept of interest (i.e. mental summary score includes domains of bodily pain and physical functioning.) Since the content validity of the SF-12 PCS and MCS for the target population has not been clearly defined, it cannot be determined what concepts these summary scores are measuring or if the patient has achieved a clinically significant improvement, even if a statistically significant improvement compared with placebo is achieved.

2 STUDY ENDPOINT REVIEW

2.1 Instrument(s)

The SF-12 health survey was administered in Studies 156-02-235 and 156-03-238 in order to assess the treatment effects of study drug on functioning and quality of life in hyponatremic patients.

The SF-12 is a 12-item generic measure of overall health status and quality of life. Version 1 of the instrument, which includes a one-week recall, was administered in the pivotal tolvaptan clinical trials. The SF-12 includes the following domains:

- Physical functioning (PF) (2 items)
- Role physical (RP) (2 items)
- Bodily pain (BP) (1 item)
- General health (GH) (1 item)
- Vitality (VT) (1 item)

STUDY ENDPOINT REVIEW

- Social functioning (SF) (1 item)
- Role emotional (RE) (2 items)
- Mental health (MH) (2 items)

The summary scores calculated using variably weighted SF-12 item scores are named the Physical Component Score (PCS) and the Mental Component Score (MCS). The PCS and MCS scores range from 0 to 100, with higher scores suggesting better functioning.

Comments: The SF-12 is a generic instrument and it not specific to accessing health related quality of life (HRQL) or symptoms of hyponatremia. The content validity of the instrument has not been demonstrated in the target population. At face value, some of the items may not be appropriate for the target population (i.e. assessment of pain). In order to effectively assess the patient's symptomatic response to treatment, it is recommended that the sponsor develop a PRO instrument that based upon patient input, is shown to be appropriate, comprehensive, and interpretable.

In addition, the PCS and MCS are composite measures that combine weighted scores for all 8 SF-12 domains into a single score. For example, the MCS scale only includes 2 items that are specific to mental functioning. All of the other domains of the parent SF-12 instrument which are not specific to mental functioning, such as, bodily pain, physical functioning, and general health, are included in calculating the total score. Therefore, since the PCS and MCS contain items that are not directly associated with physical and mental functioning, respectively, they are not adequate measurements of the concepts proposed.

3 PROTOCOL AND ANALYSIS PLAN

In support of their efficacy claims, the sponsor submitted the data from several trials, include 2 Phase III trials: Studies 156-02-235 (SALT-1) and 156-03-238 (SALT-2). Both studies had similar studies designs, which are delineated below. The overview emphasizes the PRO endpoints of SF-12 MCS and PCS, which are the focus of this review

Study 156-02-235/Study 156-03-238:

Title: Sodium Assessment with Increasing Levels of Tolvaptan in Hyponatremia (SALT)

Objectives: The primary objective of this study was to demonstrate that tolvaptan is a safe, effective, and useful agent for achieving and maintaining increased serum sodium level for the treatment of nonhypovolemic hyponatremia arising from a variety of etiologies.

Efficacy Variables:

Primary:

The primary efficacy variable was serum sodium level. The primary efficacy endpoints were as follow:

STUDY ENDPOINT REVIEW

- Average daily area under the curve (AUC) of change from baseline in serum sodium level up to Day 4 within the double-blind treatment period;

and/or

- Average daily AUC of change from baseline in serum sodium level up to Day 30 within the double-blind treatment period.

Secondary:

The secondary efficacy variables included the change from Baseline in the SF-12 (health survey) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores at Weeks 1 and Day 30. (For Study 156-03-238 the SF-12 was administered at Baseline, Week 2, and Day 30.)

Study Design:

The studies were multicenter, randomized, double-blind, placebo-controlled, efficacy and safety studies of the effects of oral tolvaptan as adjunct to standard therapy in subjects with nonacute hyponatremia in euvolemic or hypervolemic states.

Subjects who met the inclusion and exclusion criteria were randomized to either placebo or 15 mg tolvaptan for up to 30 days. 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. Study drug was titrated based upon the patient's serum sodium. Subjects who discontinued from the study early were to complete all Day 30 assessments on or near the date of early termination.

Individual study results are presented below.

Results: Study 156-02-235:

As noted by the sponsor, in Study 156-02-235, tolvaptan was found superior to placebo for the primary endpoint of increasing the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 and Day 30. This efficacy was seen regardless of the general type (euvolemic or hypervolemic), severity, or etiology (CHF, cirrhosis, or SIADH/other) of hyponatremia.

SF-12:

As noted by the sponsor, and as shown in Table 1, for the ITT population, the PCS score was improved in the tolvaptan group by 1.14 over placebo at Week 1 (OC), and by 0.03 (OC) and 0.39 (LOCF) over placebo at Day 30; however, the differences between treatment groups were not statistically significant. At Day 30, the relative shifts in PCS scores from baseline were from 33.37 to 34.46 in the tolvaptan group, and from 33.88 to 34.57 in the placebo group (LOCF). In the hyponatremia subgroup analysis, as noted in Table 2, the PCS score was also improved in the tolvaptan group over placebo at Week 1 (OC) and Day 30 (and LOCF) for the mild hyponatremia subgroup and at Week 1 (OC) for the severe hyponatremia subgroup. None of the differences between treatment groups reached statistical significance.

STUDY ENDPOINT REVIEW

Table 1. Analysis from Baseline in SF-12 PCS- ITT Population; Study 156-02-235

Visit	Treatment Group	N	Original Value				Change from Baseline						P-Value*	ESD	95% CI	95% CI		
			Mean	Med	SD	Min	Max	N	Mean	Med	SD	Min					Max	Effect
Baseline	OPC41061	69	33.37	21.42	10.73	15.30	59.07											
	PLACEBO	64	33.88	32.55	10.51	16.19	60.79											
Week 1 (OC)	OPC41061	84	34.95	31.45	11.91	14.32	60.64	80	0.57	0.00	7.93	-22.8	22.81	0.8167	1.14	-1.64	3.92	
	PLACEBO	71	34.15	29.59	10.94	17.91	56.59	68	-0.52	-0.27	10.10	-22.5	20.07					
Day 30 (OC)	OPC41061	73	34.85	33.82	10.23	14.06	59.34	76	0.37	0.78	1.27	-15.0	21.24	0.3643	0.03	-2.63	2.89	
	PLACEBO	59	36.06	33.83	9.21	17.14	58.32	57	0.29	0.39	9.06	-24.1	16.75					
Day 30 (LOCF)	OPC41061	87	34.46	33.07	10.59	14.06	59.34	83	0.36	0.42	1.84	-15.8	21.24	0.7436	0.35	-1.97	2.75	
	PLACEBO	74	34.57	32.27	10.22	17.14	58.32	71	0.04	0.00	8.73	-23.1	20.07					

Table 2. Analysis of Change from Baseline in SF-12 PCS-by Hyponatremia Subgroup, Study 156-02-235

Visit	Treatment Group	N	Original Value				Change from Baseline						P-Value*	ESD	95% CI	95% CI		
			Mean	Med	SD	Min	Max	N	Mean	Med	SD	Min					Max	Effect
Mild Hyponatremia	Baseline	OPC41061	41	36.13	34.55	10.13	15.30	59.07										
	PLACEBO	44	34.76	33.91	10.42	18.80	60.79											
Week 1 (OC)	OPC41061	40	38.07	35.28	11.84	20.96	59.73	37	1.02	1.00	7.93	-16.6	17.59	0.2891	2.35	-2.07	6.89	
	PLACEBO	34	34.05	33.82	11.18	17.91	56.60	32	-0.78	-1.16	11.39	-23.9	20.07					
Day 30 (OC)	OPC41061	39	37.37	36.10	9.13	20.04	57.30	43	0.54	-0.12	7.38	-15.9	19.92	0.7019	0.38	-2.35	4.11	
	PLACEBO	23	36.17	33.89	8.83	17.14	54.24	25	-0.48	-0.04	7.85	-19.6	15.62					
Day 30 (LOCF)	OPC41061	42	37.19	35.33	9.67	20.04	57.26	39	1.08	-0.76	1.84	-15.8	19.52	0.1567	1.31	-2.32	4.80	
	PLACEBO	25	36.06	33.99	10.07	17.14	54.24	23	-0.44	-0.28	8.33	-19.8	20.07					
Severe Hyponatremia	Baseline	OPC41061	18	30.46	28.51	10.66	17.89	57.32										
	PLACEBO	44	32.05	30.35	10.64	16.19	59.04											
Week 1 (OC)	OPC41061	11	32.10	29.32	12.86	14.32	60.64	13	0.12	0.00	6.00	-22.8	22.81	0.9752	0.07	-3.53	3.67	
	PLACEBO	37	33.23	28.65	10.73	20.14	56.58	34	-0.48	-0.00	8.37	-22.5	14.33					
Day 30 (OC)	OPC41061	38	31.52	31.15	10.73	14.06	59.34	37	0.22	2.34	0.37	-13.6	21.24	0.7061	-0.75	-4.82	3.35	
	PLACEBO	20	33.95	34.40	10.15	19.35	56.92	25	0.10	1.21	10.23	-24.1	16.75					
Day 30 (LOCF)	OPC41061	45	31.95	29.82	11.05	14.06	59.34	44	0.17	1.05	7.93	-13.6	21.24	0.9334	-0.15	-3.58	3.30	
	PLACEBO	39	31.83	31.52	10.33	16.19	56.92	35	-0.31	0.00	8.36	-24.1	16.75					

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As noted by the sponsor, and delineated in Table 3, for the ITT population, the MCS score was statistically significantly improved at Day 30 in the tolvaptan group over placebo by 5.24 (p = 0.0052) (OC) and 3.89 (p = 0.0210) (LOCF). At Day 30, the relative shifts in MCS scores from baseline were from 42.44 to 48.40 in the tolvaptan group, and from 44.74 to 46.22 in the placebo group (LOCF). The MCS score was also statistically significantly improved in the tolvaptan group over placebo in the severe hyponatremia subgroup at Day 30 by 7.07 (p = 0.0056; OC), and by 5.14 (p = 0.0193; LOCF). As noted in Table 4, at Day 30 for the severe hyponatremia subgroup, the relative shifts in MCS scores from baseline were from 42.86 to 47.92 in the tolvaptan group, and from 44.77 to 44.64 in the placebo group (LOCF). The MCS score improved at Day 30 in the mild hyponatremia subgroup by 3.39 (OC) and 2.36 (LOCF) in the tolvaptan group over placebo; however, no other statistically significant differences between treatment groups were observed.

STUDY ENDPOINT REVIEW

Table 3. Analysis from Baseline in SF-12MCS- ITT Population; Study 156-02-235

Visit	Treatment Group	Original Value						Change from Baseline						p-value	Std. Error	95% CI Lower	95% CI Upper
		N	Mean	Med	SD	Min	Max	N	Mean	Med	SD	Min	Max				
Baseline	OPC41061	85	42.44	40.91	11.62	17.72	63.83										
	PLACEBO	84	44.74	43.70	11.93	19.05	64.91										
Week 1 (OC)	OPC41061	84	46.44	47.36	11.86	16.15	67.22	80	3.98	1.62	10.25	-26.3	37.42	0.8108	-0.35	-3.39	2.69
	PLACEBO	71	48.32	48.02	11.84	18.06	67.65	89	3.37	3.72	11.27	-28.1	34.61				
Day 30 (OC)	OPC41061	73	49.55	50.75	10.59	22.42	67.20	70	8.01	6.43	11.47	-16.4	37.42	0.0052	3.24	1.60	6.89
	PLACEBO	59	48.65	48.07	12.84	22.39	67.04	67	0.75	-9.10	12.95	-26.9	31.13				
Day 30 (LOCF)	OPC41061	87	49.40	50.41	11.26	21.44	67.22	82	6.30	6.10	11.76	-16.4	37.42	0.0210	3.87	0.59	7.18
	PLACEBO	74	46.22	47.75	12.80	19.05	67.04	71	1.12	0.00	12.02	-26.9	31.13				

Table 4. Analysis of Change from Baseline in SF-12 MCS – by Hyponatremia Subgroup; Study 156-02-236

Visit	Treatment Group	Original Value						Change from Baseline						p-value	Std. Error	95% CI Lower	95% CI Upper	
		N	Mean	Med	SD	Min	Max	N	Mean	Med	SD	Min	Max					
Mild Hyponatremia	Baseline	OPC41061	41	41.94	40.07	13.37	11.12	63.95										
		PLACEBO	40	43.71	43.63	11.62	20.89	64.91										
	Week 1 (OC)	OPC41061	40	46.31	45.36	12.33	16.15	63.83	37	4.36	0.93	12.77	-26.0	37.42	0.0427	-0.51	-2.57	4.16
		PLACEBO	34	48.42	50.01	12.67	20.37	63.45	32	3.90	4.55	13.41	-26.1	26.07				
	Day 30 (OC)	OPC41061	35	49.15	51.74	9.68	20.95	63.28	32	8.63	0.95	15.34	-31.53	37.42	0.0275	3.39	2.10	6.76
		PLACEBO	26	48.07	52.30	14.83	22.39	67.04	29	3.39	1.13	12.25	-17.4	31.13				
Severe Hyponatremia	Baseline	OPC41061	48	42.36	41.53	11.05	24.74	63.09										
		PLACEBO	43	44.77	43.93	12.10	19.05	64.31										
	Week 1 (OC)	OPC41061	41	46.10	46.15	11.54	23.28	67.22	43	3.65	3.66	7.39	-11.3	21.59	0.3010	-0.21	-3.97	3.55
		PLACEBO	37	48.21	48.02	10.81	18.06	67.65	36	2.90	3.34	11.27	-21.7	34.61				
	Day 30 (OC)	OPC41061	35	49.27	50.55	11.95	22.42	63.20	31	7.46	1.52	10.77	-16.4	31.94	0.0086	3.87	2.14	6.77
		PLACEBO	30	46.72	47.49	10.11	20.37	64.11	28	1.78	1.13	12.15	-26.9	21.53				
Day 30 (LOCF)	OPC41061	45	47.32	51.42	12.45	22.42	67.22	44	5.85	5.22	10.80	-16.4	31.64	0.0193	5.13	0.85	9.42	
	PLACEBO	39	44.14	45.54	11.30	19.06	64.11	38	-0.33	0.00	11.13	-26.9	21.53					

Results: Study 156-03-238:

As noted by the sponsor, tolvaptan was superior to placebo for the primary endpoint of increasing the average daily AUC of change from baseline in serum sodium level from the start of treatment to Day 4 and Day 30. This efficacy was seen regardless of the general type (euvoletic or hypervolemic), severity, or etiology (CHF, cirrhosis, or SIADH/other) of hyponatremia.

SF-12:

The analysis of change from baseline in SF-12 (health survey) PCS is presented in Table 5 for the ITT population and in Table 6 for the hyponatremia subgroups. As noted by the sponsor, for the ITT population, the PCS score was improved in the tolvaptan group by 2.48 over placebo at Week 2 (OC) (p = 0.0500). The PCS score was also improved in the tolvaptan group at Day 30; however, no statistically significant difference between treatment groups was observed (LOCF and OC). The relative shifts in PCS scores in the tolvaptan group were from 33.01 at baseline to 36.02 at Week 2 (OC) and to 35.39 at Day 30 (LOCF); in the placebo group, the relative shifts were from 33.10 at baseline to 34.46 at Week 2 (OC) and to 34.37 at Day 30 (LOCF).

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STUDY ENDPOINT REVIEW

For the mild and severe hyponatremia subgroups, the PCS score was improved in the tolvaptan group compared to placebo at all time points except for the mild hyponatremia subgroup at Day 30 (OC); however, no statistically significant differences between treatment groups were noted.

Table 5. Analysis of Change from Baseline in SF-12-PCS ITT Population; Study 156-03-238

Visit	Treatment Group	N	Original Value				Change from Baseline				P-value	Est'd Effect	95% CI				
			Mean	Med	SD	Min	Max	N	Mean	Med			SD	Min	Max	Lower Limit	Upper Limit
Baseline	OPC41061	114	35.01	31.13	10.61	15.74	60.44										
	PLACEBO	114	33.10	30.99	10.80	11.22	61.15										
Week 2 (OC)	OPC41061	101	36.32	34.33	11.43	14.21	57.65	29	2.51	0.93	9.84	-19.2	35.34	0.0500	2.46	0.00	4.86
	PLACEBO	92	31.74	32.68	10.87	14.13	56.78	91	0.12	-0.25	9.22	-24.8	23.51				
Day 30 (OC)	OPC41061	97	35.97	35.63	11.06	16.83	60.83	85	2.55	1.52	10.64	-17.7	29.65	0.4463	1.04	-1.65	3.74
	PLACEBO	95	35.45	33.89	10.97	15.62	56.89	85	1.20	0.00	10.16	-24.6	32.16				
Day 10 (LOCF)	OPC41061	104	35.33	34.73	11.01	16.33	60.83	103	1.65	0.75	10.34	-17.7	29.65	0.2245	1.51	-0.53	3.55
	PLACEBO	104	34.17	32.66	10.84	13.62	56.89	103	0.35	-0.25	9.76	-24.6	32.55				

Table 6. Analysis of Change from Baseline in SF-12 PCS by Hyponatremia Subgroups; Study 156-03-238

Visit	Treatment Group	N	Original Value				Change from Baseline				P-value	Est'd Effect	95% CI				
			Mean	Med	SD	Min	Max	N	Mean	Med			SD	Min	Max	Lower Limit	Upper Limit
Mild Hyponatremia	Baseline																
	OPC41061	56	34.20	31.55	10.27	16.20	60.44										
	PLACEBO	57	32.97	33.13	10.31	11.22	63.18										
	Week 2 (OC)																
	OPC41061	49	35.16	35.13	11.23	14.71	57.65	46	4.10	2.63	11.02	-18.2	35.34	0.1078	3.11	-0.59	6.84
	PLACEBO	48	34.76	32.73	10.37	14.83	56.78	48	1.73	0.29	9.47	-20.3	23.51				
Day 30 (OC)																	
OPC41061	42	37.66	36.51	10.53	16.83	60.83	44	3.20	2.74	10.78	-17.7	29.65	0.3082	-0.75	-4.75	3.24	
PLACEBO	41	30.15	30.70	11.57	13.88	55.92	44	0.16	0.88	9.52	-11.8	32.55					
Day 10 (LOCF)																	
OPC41061	51	37.88	36.51	10.63	16.63	60.83	50	2.53	1.78	10.34	-17.7	29.65	0.8497	0.35	-1.70	4.00	
PLACEBO	53	35.97	34.71	12.03	13.89	55.92	54	2.30	0.48	10.21	-11.8	32.55					
Severe Hyponatremia	Baseline																
	OPC41061	56	31.69	29.85	10.32	11.74	59.46										
	PLACEBO	57	32.23	28.13	11.38	13.08	60.78										
	Week 2 (OC)																
	OPC41061	52	33.07	32.64	10.91	16.74	57.24	50	0.47	-0.04	9.39	-15.5	21.50	0.2324	1.99	-1.30	5.27
	PLACEBO	44	34.13	32.68	10.90	14.13	56.02	43	-2.17	-4.17	9.25	-24.6	18.08				
Day 30 (OC)																	
OPC41061	42	34.16	33.94	11.44	16.17	55.12	41	1.85	1.00	10.57	-17.4	29.55	0.1322	2.73	-0.86	6.44	
PLACEBO	41	32.56	31.74	9.36	13.62	56.08	41	-2.00	-2.01	9.55	-24.6	24.44					
Day 10 (LOCF)																	
OPC41061	53	32.49	30.49	11.34	16.17	56.15	51	0.78	1.11	10.58	-17.4	29.55	0.1745	2.29	-1.63	5.55	
PLACEBO	50	32.64	31.62	9.52	13.62	56.05	49	-2.47	-2.01	9.67	-24.6	24.14					

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The analysis of change from baseline in SF-12 (health survey) MCS is presented in Table 7 for the ITT population and in Table 8 for the hyponatremia subgroups. The MCS score improved at each time point in the tolvaptan group over placebo; however, no statistically significant differences between treatment groups were noted at any time point for the ITT population or for the mild or severe hyponatremia subgroups. In the ITT population, the relative shifts in MCS scores at Day 30 were from 44.34 at baseline to 49.07 in the tolvaptan group, and from 44.93 at baseline to 47.18 in the placebo group (LOCF).

As noted by the sponsor, for the severe hyponatremia subgroup, the MCS score was improved in the tolvaptan group by 4.35 over placebo at Day 30 (OC), approaching statistical significance at $p = 0.0762$. Here, the relative shifts in MCS scores from baseline to Day 30 were from 43.87 to 50.60 for tolvaptan and from 42.79 to 45.45 for placebo (OC).

STUDY ENDPOINT REVIEW

Table 7. Analysis of Change from Baseline in SF-12 MCS-ITT Population; Study 156-03-238

Visit	Treatment Group	N	Original Value				Changes from Baseline					P-value ¹	Est'd Effct	95% CI			
			Mean	Med	SD	Min	Max	N	Mean	Med	SD			Min	Max	Lower Limit	Upper Limit
Baseline	OPC41061	114	44.54	45.85	11.89	19.36	68.78										
	PLACEBO	114	44.93	45.95	11.83	11.97	68.17										
Week 3 (OC)	OPC41061	101	48.31	50.44	10.98	20.20	69.72	98	4.33	3.51	11.70	-27.5	35.45	0.1660	2.08	-1.01	5.16
	PLACEBO	82	47.23	49.84	12.02	19.06	70.42	91	2.06	0.82	14.10	-31.4	31.00				
Day 30 (OC)	OPC41061	87	50.00	51.34	11.10	20.78	67.78	85	4.90	3.37	10.31	-35.3	35.45	0.1062	2.40	-0.88	5.07
	PLACEBO	65	47.79	49.57	12.51	17.25	64.25	85	2.59	0.90	12.40	-36.9	32.31				
Day 30 (LOCF)	OPC41061	104	49.07	50.67	11.60	19.06	67.78	101	4.44	3.47	12.51	-35.3	35.45	0.1643	2.13	-0.98	5.14
	PLACEBO	104	47.18	48.87	11.82	17.29	64.25	103	2.09	0.90	13.44	-36.9	32.31				

Table 8. Analysis of Change from Baseline in SF-12 MCS by Hyponatremia Subgroups; Study 156-03-238

Visit	Treatment Group	N	Original Value				Changes from Baseline					P-value ¹	Est'd Effct	95% CI			
			Mean	Med	SD	Min	Max	N	Mean	Med	SD			Min	Max	Lower Limit	Upper Limit
Mild Hyponatremia	Baseline																
	OPC41061	59	44.75	44.10	12.85	23.51	68.78										
	PLACEBO	57	47.07	49.14	11.41	17.10	65.17										
Week 3 (OC)	OPC41061	48	48.18	48.15	10.85	23.59	68.78	48	3.57	1.04	11.82	-27.5	35.27	0.58	-1.73	4.89	
	PLACEBO	48	48.03	53.52	11.70	15.06	73.42	48	1.42	-0.21	13.87	-26.5	41.00				
Day 30 (OC)	OPC41061	45	45.43	48.95	11.55	20.78	67.78	44	4.43	2.23	10.31	-14.5	32.28	0.6676	0.86	-3.11	4.83
	PLACEBO	44	49.36	53.01	10.50	20.63	64.29	44	2.86	0.41	11.73	-15.5	32.31				
Day 30 (LOCF)	OPC41061	51	45.17	50.43	11.64	20.78	67.78	50	4.48	2.86	10.61	-14.5	32.28	0.3020	2.02	-1.30	6.07
	PLACEBO	34	48.93	52.75	12.53	15.36	64.23	51	1.25	-0.04	12.82	-26.5	42.31				
Severe Hyponatremia	Baseline																
	OPC41061	56	43.87	45.22	13.98	19.36	66.82										
	PLACEBO	57	42.74	43.70	13.55	11.97	63.79										
Week 3 (OC)	OPC41061	31	45.52	51.30	11.17	20.20	66.39	50	5.09	4.06	11.45	-17.4	35.44	0.1392	3.50	-1.05	8.05
	PLACEBO	41	48.43	48.38	12.44	15.35	63.60	43	2.78	3.14	13.45	-31.4	11.00				
Day 30 (OC)	OPC41061	42	50.60	52.45	10.70	24.58	67.00	41	5.33	3.65	14.10	-35.3	32.45	0.0762	4.38	-0.47	8.17
	PLACEBO	41	45.45	48.44	12.21	17.25	62.02	41	1.85	0.90	10.21	-36.9	25.36				
Day 30 (LOCF)	OPC41061	53	48.98	50.81	11.67	19.06	67.00	51	4.35	3.55	14.24	-35.3	32.45	0.1228	2.67	-0.95	5.15
	PLACEBO	50	45.71	48.70	12.05	17.25	62.42	45	2.75	1.52	14.25	-36.5	31.00				

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Sponsor Summary:

The sponsor summarized the results of the 2 pivotal studies, with respect to the SF-12 data as follows:

There was a demonstrable effect on the Mental Component Summary (MCS) Score of the 12-item Short-form (SF-12) Health Survey. In the prespecified combined analysis of the two phase 3 trials (Trials 156-02-235 and 156-03-238), there was a significant beneficial effect of tolvaptan versus placebo on the MCS Score of the combined group ($p = 0.0036$). Severe hyponatremic patients achieved statistical significance ($p = 0.0025$). The size of this effect would be considered clinically significant. The MCS finding was supported by improvements in memory, concentration and calculating ability and general well-being in a prespecified but not validated disease-specific questionnaire. No effect was observed on the Physical Component Summary (PCS).

Comments:

The data concerning the SF-12 PCS and MCS are presented by the sponsor in order to support the primary efficacy claim of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for prevention of worsening hyponatremia. The sponsor has not proposed any labeling claims, specifically related to the SF-12.

STUDY ENDPOINT REVIEW

Overall, the treatment effect of tolvaptan on the HRQL of patients with hyponatremia cannot be determined based upon the data from the SF-12 MCS and PCS. As noted above, the SF-12 PCS and MCS do not represent adequate measures of either physical or mental functioning and are not specific to assess HRQL in the target population of patients. The lack of statistically significant improvement in SF-12 PCS scores and inconsistent statistically significant improvement in SF-12 MCS scores between study drug and placebo, observed in Studies 156-02-235 and 156-03-238, cannot be effectively interpreted. Since the content validity of the SF-12 PCS and MCS for the target population has not been clearly established, it cannot be determined what concepts these summary scores are measuring and what score represents a clinically significant improvement for the patient. In addition, the sponsor's claim is unfounded that the small but statistically significant improvements in MCS score are clinically significant. Developers of the SF-12 may claim that changes less than 10 points on a 0-100 scale are detectable by patients, however, the meaningfulness of such scores has not (to our knowledge) been established in this or any other population. Moreover, clinical significance cannot be assumed for measures that fail to represent an established concept of measurement demonstrated to be meaningful and important in the study population (i.e., content validity).

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4/15/2008 11:26:25 AM
INTERDISCIPLINARY

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	022275
Brand Name	SAMSKA®
Generic Name	Tolvaptan (OPC-41061)
Sponsor	Otsuka Maryland Research Institute, Inc.
Indication	_____ hypervolemic or euvoletic hyponatremia
Dosage Form	Tablet
Drug Class	Nonpeptide arginine vasopressin V ₂ receptor antagonist
Therapeutic Dose	15 mg – 60 mg
Duration of Therapeutic Use	_____ Chronic for Hyponatremia
Maximum Tolerated Dose	MTD not determined. Maximum studied doses are 480 mg SD and 300 mg QD for 5 days
Application Submission Date	22 Oct 2007
Review Classification	Standard NDA
Date Consult Received	29 Nov 2007
Clinical Division	DCRP / HFD 110

b(4)

b(4)

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study was designed and conducted adequately to exclude a clinically significant QTc prolongation over the tolvaptan dose range studied. The largest upper limit of the two-sided 90% CI for the mean difference between tolvaptan (30-mg and 300-mg) and placebo was below 10 ms.

In this parallel-arm, double-blind (for tolvaptan and placebo), placebo- and positive-controlled, multiple dose study, two different dose regimens of tolvaptan (30 mg and 300 mg) on QTcF interval were compared with placebo. The primary analysis performed by the sponsor is not recommended by the ICH E14 guidance. The overall findings of the FDA analysis are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for tolvaptan and the Largest Lower Bound for Moxifloxacin

Treatment	Day	Time (h)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Tolvaptan 30 mg OD	1	2	0.9	(-3.0, 4.8)
Tolvaptan 30 mg OD	5	3	0.5	(-4.1, 5.0)
Tolvaptan 300 mg OD	1	1	2.4	(-1.6, 6.3)
Tolvaptan 300 mg OD	5	24	4.6	(0.1, 9.1)
Moxifloxacin OD	1	2*	12.3	(6.1, 18.6)
Moxifloxacin OD	5	1*	16.7	(9.4, 24.0)

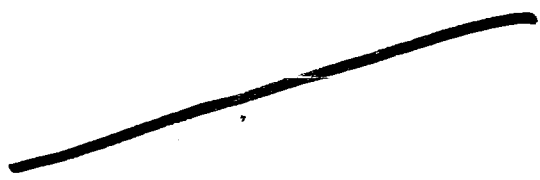
*Bonferroni adjusted

At the supratherapeutic dose (300 mg), tolvaptan plasma concentrations were 4.5-fold higher than peak concentrations following the 30-mg dose. The 300-mg dose covers the expected increase in tolvaptan concentrations due to the known intrinsic and extrinsic factors (Clinical Pharmacology Table, Appendix 6.1). There was no relationship between the tolvaptan plasma concentration and $\Delta\Delta\text{QTcI}$ interval.

Moxifloxacin increased the $\Delta\Delta\text{QTcI}$ interval by 12 ms at 2 hours after dosing on Day 1 and 17 ms at 1 hour after dosing on Day 5. These results are consistent for Moxifloxacin indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

2 PROPOSED LABEL

The sponsor did not include any labeling for QT evaluation. **The following recommendations are suggestions for labeling only. We defer all final labeling decisions to the review division.**



b(4)

3 BACKGROUND

Tolvaptan (OPC-41061), is an oral, non-peptide, selective vasopressin V₂-receptor antagonist whose action on the distal nephron causes loss of electrolyte-free water (ie, aquaresis). Its intended use is for clinical conditions associated with AVP-mediated fluid retention include heart failure, cirrhosis, syndrome of inappropriate diuretic hormone secretion, and associated hyponatremia.

3.1 MARKET APPROVAL STATUS

Tolvaptan is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

Source: Non-clinical Summary

The effect of tolvaptan was investigated on hERG (human ether-a-go-go related gene) channel current in CHO-K1 cells stably expressing the transfected gene. Tolvaptan was tested at 0 (vehicle), 1×10^{-6} , and 2×10^{-6} M. The vehicle and tolvaptan at 1×10^{-6} M and 2×10^{-6} M reduced the hERG channel current to 94.2%, 92.3% and 90.2% of the pretreatment value, respectively. Thus the test drug at 1×10^{-6} M and 2×10^{-6} M had no significant effects on the hERG channel current in comparison with the vehicle control. On the other hand, the positive control E-4031 significantly decreased the hERG channel current to 3.9% of the pretreatment value. In conclusion, tolvaptan did not affect the hERG channel current at the tested concentrations up to 2×10^{-6} M, which was the solubility limit.

In isolated guinea pig papillary muscle, tolvaptan at 1×10^{-6} , 1×10^{-5} , and 3×10^{-5} M showed no effects on any action potential parameters such as resting membrane potential (RMP), action potential amplitude (APA), the maximum upstroke velocity of the action potential (V_{max}) and the action potential duration at 30%, 60% and 90% of repolarization (APD30, APD60, and APD90, respectively). After-depolarizations were never observed with tolvaptan at these concentrations. Thus, the study provided conclusive evidence that tolvaptan did not affect the action potential parameters at any of the tested dosages.

In conscious dogs 10, 100, and 1000 mg/kg of tolvaptan were sequentially administered to each animal at intervals of 7 to 14 days. Relevant endpoints such as the general condition, respiratory rate, heart rate and mean blood pressure and of electrocardiogram parameters such as ST segment, T-wave amplitude, PR interval, QRS width, QT interval, and QTc (QT interval corrected by Van de water's formula) were monitored for 5 hours post-dosing. Oral tolvaptan at 1000 mg/kg significantly decreased the T-wave amplitude and at 100 and 1000 mg/kg significantly shortened the PR interval with no significant changes in respiratory rate, heart rate, mean blood pressure, ST segment, QRS width, QT interval and/or QTc when compared with the same parameters of the control group. The C_{max} of the unchanged compound were 0.15, 0.46, and 2.83 $\mu\text{g/mL}$ at the 10, 100 and 1000 mg/kg dosages of tolvaptan, respectively. These observations suggested that tolvaptan had no influence on the respiratory and cardiovascular systems at up to serum concentration of 0.15 $\mu\text{g/mL}$, but it did shorten the PR interval at 0.46 $\mu\text{g/mL}$ or higher and decreased the T-wave amplitude at 2.83 $\mu\text{g/mL}$ in conscious dogs which were not allowed free access to water.

Reviewers Comment: No effects on cardiac repolarisation reported per in vitro data. However dose dependent shortening of the PR interval and decreased T wave amplitude has been reported in whole animal studies.

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical safety

A total of 4339 subjects have received a tolvaptan oral dose in the 55 completed/ongoing pooled phase 1 to 3 trials. Critical findings and conclusions were drawn from the intended treatment population (ie, “the primary safety population”) and relevant subsets based on each treatment indication. The primary safety population consisted of subjects with a baseline diagnosis of heart failure and/or hyponatremia treated in any of the completed placebo-controlled, phase 2 and 3, multiple-dose trials with tolvaptan. The phase 3 outcome trial in subjects with worsening heart failure (Trial 156-03-236) was the only tolvaptan trial powered to detect a difference between groups in mortality in the ITT population. A total of 537/2072 (25.9%) subjects in the tolvaptan 30 mg group and 543/2061 (26.4%) subjects in the placebo group died for any cause (hazard ratio, 0.98; 95% CI, 0.87-1.11; p = 0.68). The upper limit of the one-sided 95% CI for the comparison of tolvaptan 30 mg with placebo was within the pre-specified margin for non-inferiority with regard to mortality (p < 0.001)

Approximately 50% of subjects reported serious adverse events: 47.2% of subjects in the any tolvaptan dose group and 51.1% of subjects in the placebo group. Cardiac arrest was reported more frequently (1.5% versus 0.9%) in subjects receiving tolvaptan than in subjects receiving placebo. Because of slight variances in the reported verbatim terms, and the resultant MedDRA coding, relating to cessation of cardiac activity, the following terms were combined: cardiac arrest, cardio-respiratory arrest, sudden cardiac death, sudden death. The overall combined incidence was 5.2% in tolvaptan-treated subjects and 5.8% in placebo-treated subjects.

The analysis of pooled events relating to both atrial and ventricular demonstrated no clear signal related to the use of tolvaptan (ISS Section 18.5). The aggregate incidence rate for this category for atrial arrhythmias in the All Heart Failure and Hyponatremia Subjects population was 6.3% (208/3294) for any tolvaptan dose versus 6.3% (172/2738) for placebo. The aggregate incidence rate of ventricular arrhythmias for all subjects was 12.8% (420/3294) for any tolvaptan dose versus 13.0% (357/2738) for placebo.

Generally, modest differences between the any-oral-dose-tolvaptan and placebo groups were observed in mean changes for ECG parameters for All Heart Failure Subjects from the multiple-dose trials. Mean changes from baseline were slightly increased for placebo compared with tolvaptan for PR interval, QRS interval, and RR interval, whereas greater mean decreases were observed for placebo compared with tolvaptan for ventricular rate. Greater mean decreases were observed for tolvaptan compared with placebo for QT interval, QTcB interval, and QTcF interval. In hyponatremia subjects, changes in QTcB and QTcF were either similar between groups or favored tolvaptan, except that the incidences of increase in QTcB of 30 to 60 ms were greater for tolvaptan than placebo (64/211, 30.3% for tolvaptan 15 to 60 mg, 163/551, 29.6% for the total tolvaptan group, and 130/472, 27.5% for placebo). No other differences in QTc abnormalities were evident.

Reviewers Comment: No clinically significant QT prolongation or increased risk for cardiovascular related events has been noted so far.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of tolvaptan’s clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted a thorough QT study report and supporting electronic datasets. Digital ECGs were submitted to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Parallel Arm, Double-Blind, Placebo-Controlled, Multiple Dose Administration Study of Tolvaptan Oral Tablets and Moxifloxacin Oral Tablets on ECG QTc Interval in Healthy Men and Women

4.2.2 Protocol Number

156-03-245

4.2.3 Study Dates

25 Mar 2004 – 29 Jun 2004

4.2.4 Objectives

The primary objective of this study was to quantitate the effect of tolvaptan on individually corrected QT (QTcI).

The secondary objectives were:

- 1) to examine the dose-effect relationship of tolvaptan on QTcI,
- 2) to examine the concentration-effect relationship of tolvaptan and moxifloxacin on QTcI from 0-24 hours postdose, and
- 3) to quantitate the effect of moxifloxacin on QTcI.

4.2.5 Study Description

4.2.5.1 Design

This study was a single center, parallel-arm, double-blind (for tolvaptan and placebo), placebo- and positive-controlled, multiple dose study of 30 mg or 300 mg doses of tolvaptan once daily. Assay sensitivity was established using once daily doses of 400-mg moxifloxacin on Day 1 and Day 5.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

On Day -1, subjects were randomized to 1 of 4 treatment arms:

- Arm 1: 1 x 400-mg moxifloxacin tablet + 4 tolvaptan placebo tablets
- Arm 2: 5 tolvaptan placebo tablets
- Arm 3: 1 x 30-mg tolvaptan tablet + 4 tolvaptan placebo tablets
- Arm 4: 5 tolvaptan 60-mg tablets (300 mg total dose)

All subjects received 5 placebo tablets on Day 0 for the baseline day evaluations and received study treatments on Day 1 through Day 5. Treatments were administered orally once daily.

4.2.6.2 Sponsor's Justification for Doses

If a heart failure subject currently taking ketoconazole was given 30 mg tolvaptan, peak tolvaptan plasma concentrations would be expected to be increased about 3.5-fold and exposure, as determined by AUC, would be expected to be increased 5.4-fold. A four-fold higher dose, ie, 120 mg, was well-tolerated by heart failure subjects. "

If a hyponatremia subject with liver disease currently taking ketoconazole was given 15 mg tolvaptan, the recommended starting dose, tolvaptan concentrations would again be expected to be about 4-fold higher. Doses of 60 mg have been well-tolerated by hyponatremia subjects with liver disease.

Multiple oral doses of 300 mg in healthy subjects also produce exposures similar to the scenarios above and have been well tolerated.

Reviewer's Comments: The rationale for the selection of therapeutic dose by the sponsor is justified. The exposures achieved at worst case scenario are covered by the oral dose of 300 mg tolvaptan.

4.2.6.3 Instructions with Regard to Meals

All doses were given orally with 240 mL of room temperature water to subjects in the fasted state. Subjects were prohibited from drinking any liquids, other than that given with drug administration, for 2 hours before and 2 hours after drug administration.

Reviewer's Comments: High fat meal is known to increase the C_{max} of tolvaptan 12% – 40%. The supratherapeutic dose covers the range of exposures expected to be seen with high fat meal.

4.2.6.4 ECG and PK Assessments

Table 1: Sampling Schedule

Study Day	0	1	2-4	5
Intervention	5 Placebo tablets (Baseline)	Placebo / Moxifloxacin 400mg / Tolvaptan 30 mg / Tolvaptan 300 mg	Placebo / Moxifloxacin 400mg / Tolvaptan 30 mg / Tolvaptan 300 mg	Placebo / Moxifloxacin 400mg / Tolvaptan 30 mg / Tolvaptan 300 mg
12-Lead ECGs	Predose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18 and	Predose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18 and	None recorded	Predose, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18 and

	24 h postdose	24 h postdose		24 h postdose
PK Samples for drug	Predose, 1, 2, 4, 8, 12 and 24 h postdose	Predose, 1, 2, 4, 8, 12 and 24 h postdose	None collected	Predose, 1, 2, 4, 8, 12 and 24 h postdose

4.2.6.5 Baseline

Baseline collected ECG on Day 0 were used to perform a time-matched baseline correction of QTcI.

4.2.7 ECG Collection

Digital ECGs for QTc analysis were obtained using the [REDACTED] ECG continuous recorder at the specified time points on day 0, 1 and 5. The ECGs were stored on a flash card approximately every 10 seconds and were not available for review by the clinic staff. In order to optimize consistent recording by the ECG device, subjects were to remain in a supine position starting 20 minutes prior to ECG sampling times and lasting for at least 16 minutes. The start and stop times of the ECG resting period were recorded. b(4)

ECGs were read centrally by [REDACTED] ECG readers were blinded to subject, time and treatment. As part of [REDACTED] standard practice, to assess inter-reader variability, second reader interpretations were performed for 2% of the ECGs processed on a per protocol basis. b(4)

Safety ECGs were performed at screening and check-in for the determination of subject eligibility. Similar ECGs were obtained at approximately 3.5 hours postdose on Days 0, 1, and 5 and then on Day 6 (or early termination) for safety screening purposes. Any subject on therapy with a QTc of > 500 ms defined automatically at the site at any time point was to be further evaluated by the principal investigator for possible discontinuation of the subject.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 172 subjects (88 males, 84 females), 18-45 yrs of age, with a normal baseline ECG and body weight within $\pm 15\%$ of ideal body weight, were enrolled in this study. Of these, 171 (99.4%) subjects received at least one dose of study medication and 169 (98.3%) completed the study. Two subjects discontinued the study due to AEs: Subject 1085, randomized to receive moxifloxacin, withdrew due to dizziness prior to receiving any study medication and was therefore excluded from the safety and QTc analyses, and Subject 2031 (300 mg tolvaptan) discontinued on Day 2 due to an AE of rash and was excluded from the QTc analysis at Day 5. Subject 1060 (moxifloxacin) voluntarily withdrew consent on Day 2 and was excluded from QTc analysis at Day 5. Overall, 171 (99.4%) subjects were analyzed for safety; 171 (99.4%) were analyzed for QTc at Day 1; and 168 (97.7%) subjects were analyzed for QTc at Day 5.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary analysis was based on the change in mean QTcI from Day 0 (baseline) to Day 5 following tolvaptan treatment (30 and 300 mg). Mean QTcI of a day (Day 0 or Day 5) was defined as the average QTcI over time points of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, and 24 hours postdose. The analysis was performed on subjects who were eligible for QTcI correction (i.e., had no less than 50 complexes on Day 0), and who had taken study medication consecutively from Day 0 to Day 5 (with placebo at Day 0) and had ECG assessments at Day 0 and Day 5. Baseline for this variable was the mean QTcI assessments on Day 0. Missing data points at Day 0 or Day 5 were ignored in deriving their means. Ninety-five percent confidence intervals (CIs) of the mean change in mean QTcI from Day 0 to Day 5 for each of the tolvaptan doses were constructed by adding (and subtracting) the 97.5% quintile from the t distribution multiplied by the standard error of the change from baseline for each treatment group. The degree of freedom of the t distribution was equal to the number of subjects in the treatment group minus 1.

The changes from mean baseline in mean QTcI following either single (Day 1) or multiple QD (Day 5) oral doses of either 30 or 300 mg tolvaptan, 400 mg moxifloxacin, or placebo are summarized in Table 2.

Table 2 Mean Change in Time-averaged QTcI from Mean Baseline and 95% Confidence Intervals

	Mean (ms)	95% CI	P-value ^a
Day 5 Treatment			
30 mg tolvaptan	-5.02	-7.02 to -3.03	0.1151
300 mg tolvaptan	-0.74	-3.65 to 2.18	0.3786
400 mg moxifloxacin	8.20	5.89 to 10.50	<0.0001
Placebo	-2.21	-4.43 to 0.02	
Day 1 Treatment			
30 mg tolvaptan	-6.31	-8.04 to -4.58	0.0036
300 mg tolvaptan	-6.26	-8.21 to -4.30	0.0032
400 mg moxifloxacin	3.79	2.21 to 5.36	<0.0001
Placebo	-2.67	-4.23 to -1.12	

QTcI = individually corrected QT; CI = confidence interval; ANCOVA = analysis of covariance.

^aDerived from ANCOVA with factors of treatment group and gender, and covariate baseline for least squares mean difference from Placebo. P < 0.05 is considered significant.

Source: Table 9.3.3.1-1 of sponsor's Study Report.

For the primary endpoint analysis, there was no significant change from mean baseline in mean QTcI on Day 5 following multiple QD oral doses of either 30 or 300 mg tolvaptan.

Reviewer's comments: The sponsor's primary analysis was based on the average QTcI over all postdose time points. However, to the ICH E14 Guidance recommends that the mean difference between the drug and placebo after baseline adjustment be evaluated at each time point. This analysis was performed by the FDA and is presented in the Statistical Assessments (Section 5.1)..

4.2.8.2.2 Categorical Analysis

The incidence of maximum change from the Day 0 (baseline) in QTcI interval between 30 and 60 ms on Days 1 and 5, the incidence of maximum change from Day 0 (baseline) in QTcI interval > 60 ms on Days 1 and 5, and the new incidence of maximum QTcI interval > 450, > 480, and > 500 ms on Days 1 and 5 are presented in Table 3. Maximum at Day 0, Day 1, or Day 5 was defined as the maximum QTcI over all postdose time points.

Table 3 Incidence of Categorical Changes in Maximum QTcI from Maximum Baseline on Day 1 or Day 5

	Tolvaptan 30 mg (N=42)	Tolvaptan 300 mg (N=43)	Placebo (N=43)	Moxifloxacin 400 mg (N=42)
Category Change	n (%)	n (%)	n (%)	n (%)
30-60 ms	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
> 60 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New onset (> 450 ms)	2 (4.8)	0 (0.0)	1 (2.3)	4 (9.5)
New onset (> 480 ms)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New onset (> 500 ms)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 9.3.3.4-1 of sponsor's Study Report..

4.2.8.2.3 Additional Analyses

A single delta analysis results (change from baseline) are presented in Table 4. This is not the analysis recommended by the ICH E14 guidance.

Table 4 Largest Time-matched Mean Difference in QTcI and the Upper Limit of the One-sided Confidence Interval on Day 1 and Day 5

	Time Postdose (h)	Mean (ms)	Upper Limit of One-sided 95% CI ^a
Day 1 Treatment			
30 mg tolvaptan	2	-1.48	1.15
300 mg tolvaptan	2	0.62	3.70
400 mg moxifloxacin	2	10.07	12.66
Placebo	24	2.28	4.82
Day 5 Treatment			
30 mg tolvaptan	5	0.60	3.63
300 mg tolvaptan	3	2.68	6.75
400 mg moxifloxacin	1	15.78	19.35
Placebo	12	1.34	3.83

QTcI = individually corrected QT; CI = confidence interval.

^aAn upper limit of > 8 ms indicates a positive effect on QTcI prolongation.

Source: Table 9.3.3.10-1 of sponsor's Study Report.

The upper limits of the one-sided 95% CIs for all days and all doses of tolvaptan were less than 8. The mean differences and upper limits for each day of moxifloxacin (positive control) were greater than 8.

4.2.8.3 Safety Analysis

There were no deaths or SAEs reported in this study.

Two subjects withdrew from the study due to an AE. Of these, one subject randomized to receive moxifloxacin, withdrew due to dizziness prior to receiving any study medication. Another subject was discontinued from the study due to an AE of maculopapular rash that occurred after receiving two doses of 300 mg tolvaptan.

For subjects treated with tolvaptan, the most commonly occurring TEAEs ($\geq 5\%$ of subjects in either dose group) considered potentially drug-related were thirst (27.9% and 48.8% in the 30 mg and 300 mg dose groups, respectively), urinary frequency (23.3% and 46.5%), dry mouth (7.0% and 18.6%), abdominal pain (2.3% and 9.3%), nausea (0.0% and 9.3%), and headache (4.7% and 7.0%).

Increases of 30-60 ms for QTcB were noted in 4/43 (9.3%), 5/43 (11.6%), 3/43 (7.0%) and 10/42 (23.8%) subjects in the 30 mg tolvaptan, 300 mg tolvaptan, placebo, and moxifloxacin groups, respectively, and for QTcF in 1/43 (2.3%), 2/43 (4.7%), 1/43 (2.3%), and 8/42 (19.1%) subjects, respectively. New onset of QT >500 ms was noted in 1/43 (2.3%) subject in the placebo group. New T wave changes were noted for 1/43 (2.3%) subject in the 30 mg tolvaptan group. A notable change in HR (25% decrease

from baseline and HR < 50 bpm) was noted in 1/43 (2.3%) subject in the 300 mg tolvaptan group. No TEAEs relating to ECG findings were reported in any subject.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Summary statistics for Tolvaptan pharmacokinetics for both the studied doses are shown in Table 5 below. The plasma concentrations for 30 and 300 mg doses of Tolvaptan following Days 1 and 5.

Table 5: Summary statistics for Tolvaptan pharmacokinetic parameters following multiple oral doses of 30 and 600 mg on Days 1 and 5

Parameter	30 mg Tolvaptan		300 mg Tolvaptan	
	Day 1 (n=42)	Day 5 (n=41)	Day 1 (n=43)	Day 5 (n=42)
C _{max} (ng/mL)	212 (90.5)	238 (104)	971 (397)	994 (348)
t _{max} (h) ^a	2.00 (1.00-4.02)	2.00 (1.00-4.00)	2.02 (1.00-23.92)	2.00 (1.00-8.00)
AUC _t (ng·h/mL)	1430 (718)	1550 (739)	ND	ND
AUC ₀₋₂₄ (ng·h/mL)	1830 (659) ^b	1800 (730) ^c	11700 (5030)	11500 (3540)
R _{ac} (C _{max})	ND	1.14 (0.31)	ND	1.07 (0.30)
R _{ac} (AUC ₀₋₂₄)	ND	1.16 (0.22) ^d	ND	1.03 (0.23)
CL _{ss} /F (mL/min/kg)	ND	0.484 (0.218) ^c	ND	0.703 (0.278)

SD = standard deviation; QD = once daily; ND = not determined; BQL = below the quantitation limit.

^aValues are median (minimum - maximum).

^bn=25. Value could not be determined if 24-hour postdose sample was BQL.

^cn=28. Value could not be determined if 24-hour postdose sample was BQL.

^dn=21. Ratio only determined if values present for Day 1 and Day 5.

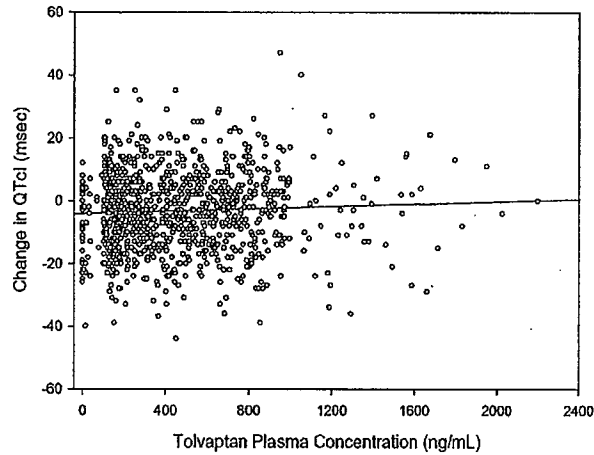
Source: Table 9.2.3.2-1 of sponsor's Study Report.

4.2.8.4.2 Exposure-Response Analysis

A plot of change in QTcI from time-matched baseline versus tolvaptan concentration (all days and doses combined) is presented in Figure 1. A similar plot for moxifloxacin is presented in Figure 2.

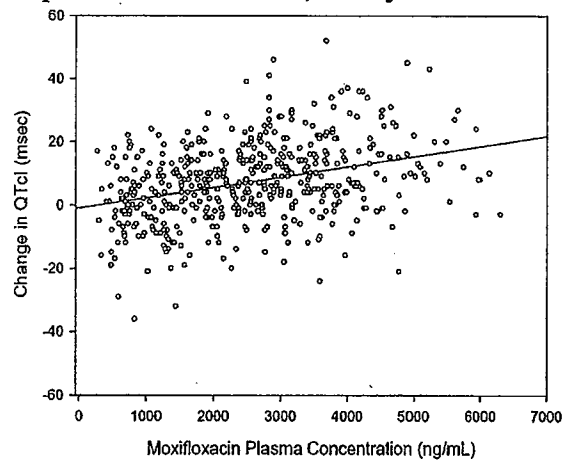
The sponsor concludes that no concentration-effect relationship was seen for tolvaptan.

Figure 1: Change from baseline in QTcI (Time-matched) versus Tolvaptan plasma concentration, all days and all doses combined



Source: SF-1 Section 16 of sponsor's Study Report

Figure 2: Change from baseline in QTcI (Time-matched) versus Moxifloxacin plasma concentration, all days combined



Source: SF-2 Section 16 of sponsor's Study Report.

Reviewer's comment: Sponsor's analysis does not take into account the placebo effects on the change from baseline in QTcI. Further the effect of tolvaptan on the QTcI is not quantified by the sponsor. See Reviewer's analysis for the exposure-response analysis.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

QTcI is the pre-specified primary endpoint, and this reviewer conducted independent analysis for Δ QTcI using mixed-effect model with repeated measurements. The model included the following factors: treatment, gender, and time-point as fixed effect, the subjects as random effect, and the treatment-by-time interaction. Model-adjusted means

were derived for each treatment at each time-point as well as 90% CI of the differences between each active treatment and placebo at each time-point ($\Delta\Delta QTcI$). The results are presented in Table 6 and

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Table 7.

Table 6 Point Estimates and 90% CIs for $\Delta\Delta\text{QTcI}$ (Day 1)

Treatment	Time	Estimate	Standard Error	Lower Bound	Upper Bound
30 mg tolvaptan	1	-0.32	2.39	-4.26	3.62
	2	0.92	2.37	-2.97	4.82
	3	0.14	2.38	-3.77	4.06
	4	-3.11	2.39	-7.05	0.83
	6	-4.13	2.39	-8.07	-0.19
	8	-4.96	2.42	-8.94	-0.98
	10	-6.63	2.38	-10.55	-2.71
	12	-7.19	2.41	-11.15	-3.23
	14	-5.38	2.39	-9.32	-1.44
	16	-3.73	2.38	-7.65	0.19
	18	-4.91	2.41	-8.87	-0.95
	24	-5.38	2.41	-9.34	-1.42
300 mg tolvaptan	1	2.33	2.40	-1.63	6.28
	2	2.71	2.37	-1.18	6.61
	3	-1.74	2.37	-5.63	2.16
	4	-1.22	2.37	-5.12	2.67
	6	-3.16	2.39	-7.09	0.78
	8	-3.08	2.43	-7.08	0.92
	10	-6.09	2.38	-10.00	-2.17
	12	-9.16	2.39	-13.10	-5.23
	14	-6.70	2.39	-10.64	-2.76
	16	-7.20	2.38	-11.12	-3.29
	18	-9.94	2.39	-13.87	-6.00
	24	-2.30	2.38	-6.21	1.62
400 mg moxifloxacin	1	8.57	2.39	4.64	12.51
	2	12.31	2.37	8.41	16.21
	2*	12.31	2.37	6.05	18.57
	3	11.17	2.38	7.26	15.09
	4	9.95	2.38	6.03	13.86
	6	6.55	2.42	2.56	10.53
	8	8.67	2.42	4.69	12.65
	10	1.55	2.37	-2.34	5.45
	12	2.91	2.39	-1.03	6.85
	14	3.46	2.43	-0.54	7.46
	16	5.32	2.41	1.36	9.28
	18	3.47	2.42	-0.52	7.45
24	0.93	2.38	-2.98	4.85	

*: Results presented here are not multiple-endpoint adjusted. If Bonferroni adjustment is applied, the largest lower bound is 6.05 ms.

Table 7 Point Estimates and 90% CIs for $\Delta\Delta\text{QTcI}$ (Day 5)

Treatment	Time	Estimate	Standard Error	Lower Bound	Upper Bound
30 mg tolvaptan	1	-2.01	2.77	-6.56	2.55
	2	-1.56	2.74	-6.07	2.95
	3	0.46	2.75	-4.08	4.99
	4	0.42	2.75	-4.12	4.95
	6	-5.60	2.77	-10.16	-1.05
	8	-3.59	2.75	-8.12	0.95
	10	-4.46	2.74	-8.98	0.05
	12	-6.57	2.75	-11.10	-2.04
	14	-5.29	2.75	-9.82	-0.75
	16	-2.03	2.77	-6.58	2.53
300 mg tolvaptan	1	2.54	2.79	-2.05	7.13
	2	0.35	2.75	-4.18	4.88
	3	3.07	2.75	-1.46	7.59
	4	0.20	2.74	-4.30	4.71
	6	-1.67	2.75	-6.20	2.85
	8	3.20	2.76	-1.35	7.75
	10	2.66	2.76	-1.89	7.20
	12	-4.97	2.75	-9.50	-0.45
	14	-1.40	2.76	-5.95	3.14
	16	4.06	2.78	-0.51	8.63
400 mg moxifloxacin	1	16.67	2.77	12.12	21.23
	1*	16.67	2.77	9.36	23.99
	2	13.24	2.74	8.73	17.75
	3	16.35	2.75	11.81	20.88
	4	13.71	2.74	9.20	18.23
	6	7.99	2.78	3.41	12.56
	8	10.79	2.77	6.23	15.34
	10	11.28	2.74	6.77	15.79
	12	5.24	2.75	0.71	9.77
	14	8.11	2.77	3.56	12.67
	16	5.08	2.78	0.51	9.66
	18	9.36	2.78	4.78	13.93
24	1.52	2.78	-3.06	6.10	

*: Results presented here are not multiple-endpoint adjusted. If Bonferroni adjustment is applied, the largest lower bound is 9.36 ms.

The following two graphs show the time profile of $\Delta\Delta\text{QTcI}$ by treatment groups over time.

Figure 3 $\Delta\Delta$ QTcI by Treatment over Time (Day 1)

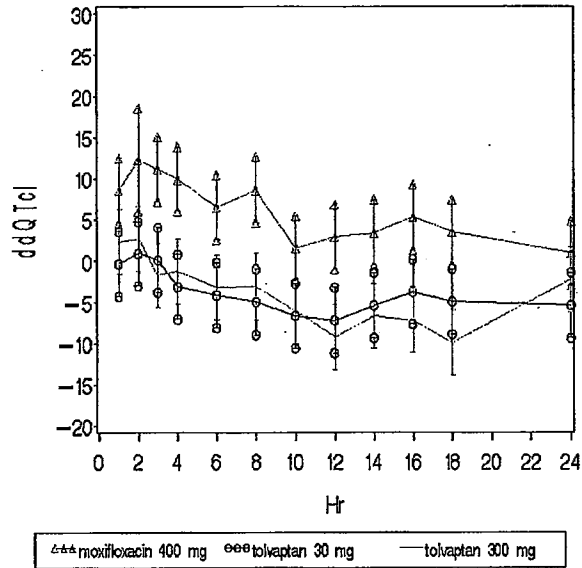
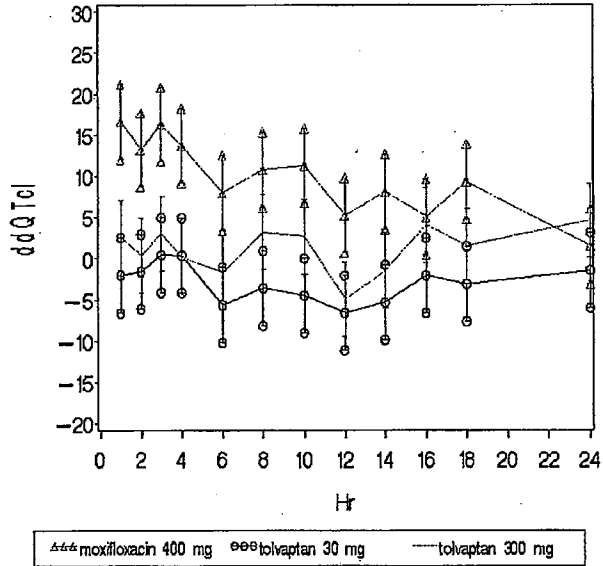


Figure 4 $\Delta\Delta$ QTcI by Treatment over Time (Day 5)



The categorical analysis result is presented in the following tables. No subject's QTcI value greater than 480 ms. There is no subject whose Δ QTcI values were greater than 60 ms.

Table 8 Frequency for QTcI>450 ms

Treatment	Total Subject (N)	No.	%	Total Obs.	No.	%
30 mg tolvaptan Baseline	42	3	7.1	500	4	0.8
300 mg tolvaptan Baseline	43	1	2.3	505	1	0.2
400 mg moxifloxacin Baseline	42	0	0	508	0	0
Placebo Baseline	43	1	2.3	505	5	1
30 mg tolvaptan Day 1	42	2	4.8	504	2	0.4
300 mg tolvaptan Day 1	43	0	0	508	0	0
400 mg moxifloxacin Day 1	42	2	4.8	499	3	0.6
Placebo Day 1	43	1	2.4	511	4	0.8
30 mg tolvaptan Day 5	42	2	4.8	495	2	0.4
300 mg tolvaptan Day 5	43	2	4.7	491	5	1.0
400 mg moxifloxacin Day 5	42	3	7.1	485	4	0.8
Placebo Day 5	43	2	4.7	505	9	1.8

Table 9 Frequency for ΔQTcI: 30~60 ms

Treatment	Total Subject (N)	No.	%	Total Obs.	No.	%
30 mg tolvaptan Day 1	42	1	2.4	504	1	0.2
300 mg tolvaptan Day 1	43	0	0	508	0	0
400 mg moxifloxacin Day 1	42	2	4.8	499	3	0.6
Placebo Day 1	43	1	2.3	511	1	0.2
30 mg tolvaptan Day 1	42	1	2.4	495	1	0.2
300 mg tolvaptan Day 5	43	6	14.0	491	10	2.0
400 mg moxifloxacin Day 5	42	11	26	485	18	3.7
Placebo Day 5	43	1	2.3	505	1	0.2

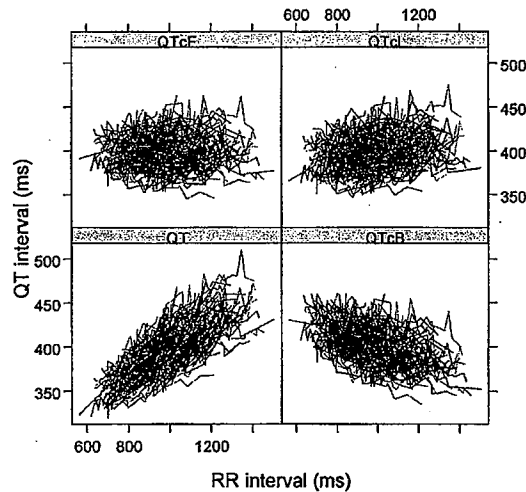
This reviewer also performed the same analysis for $\Delta QTcF$, and the same conclusions can be reached. Basically, for both doses of tolvaptan, all the upper bounds of the 90% confidence interval for the mean difference in $\Delta QTcI$ and $\Delta QTcF$ between the drug and placebo after baseline adjustment are below 10 ms. The largest lower bounds for moxifloxacin with and without multiple endpoint adjustment are greater than 5 ms at both Day 1 and Day 5.

In conclusion, this reviewer's results support the sponsor's conclusion of no prolongation to a clinically significant degree of QTcI interval for tolvaptan 30 mg or 300 mg compared with placebo at any time point.

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between QT (raw and different correction methods) and RR interval at baseline is illustrated in the Figure 5. The Fredericia's and Individual correction seem to be reasonable.

Figure 5: QT (Raw QT measurements, Bazett's, Fredericia's and Individual corrected QT)-RR interval relationship



The comparative time course for mean $\Delta \Delta QTcF$ on Day 1 and 5 are illustrated in the

Figure 6. It appears that tolvaptan does not prolong the QT interval at both the studied doses.

Figure 6: Time course of mean $\Delta\Delta\text{QTcF}$

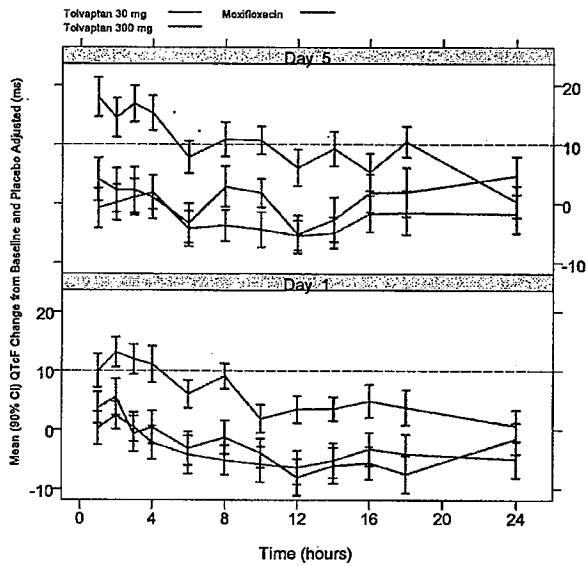
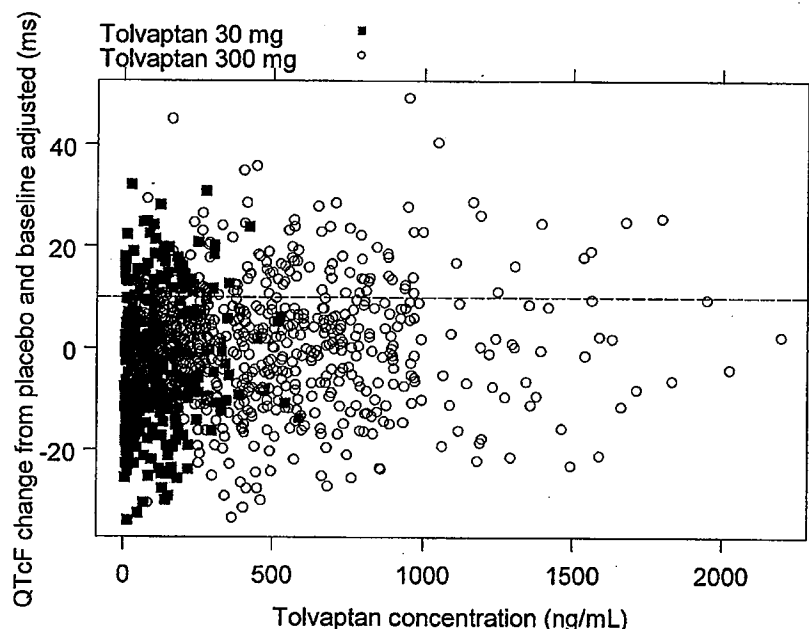


Figure 7 illustrates no relationship between Tolvaptan concentrations and $\Delta\Delta\text{QTcF}$. The mean (upper CI) effect at mean C_{max} (982.5 ng/mL) after supratherapeutic dose is 3.1 (5.6) ms.

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Figure 7: 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.

5.3 CLINICAL ASSESSMENTS

5.3.1 SAFETY ASSESSMENTS

Three of the clinical events identified to be of particular importance per the ICH E14 guidelines (i.e. death, serious ventricular arrhythmia, and seizures) were not observed in this study. There was one case of syncope which lasted for 1 minute on day 2 after receiving 300 mg tolvaptan. The subject continued in the study and no ECG abnormalities were reported.

5.3.2 ECG ASSESSMENTS

Review of waveforms sent to the warehouse show that lead II was primarily used (96%) for interval measurements but the percentage of ECGs with significant QT bias in this study compared to the automated algorithm was 15%. On review of these tracings there appears to be problems with waveform quality and T wave offset abnormalities.

However, when analyzed by treatment, the mean, standard deviation, of the distributions of QT bias were similar for drug, placebo and moxifloxacin were similar after removing two outliers. Hence ECG acquisition and interpretation in this study appears acceptable.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	For Heart Failure • 30 mg, QD For Hyponatremia • 15, 30 or 60 mg, QD															
Maximum tolerated dose	Single oral doses up to 480 mg and multiple oral doses up to 300 mg, QD for 5 days have been well tolerated. The maximum tolerated dose has not been determined.															
Principal adverse events	Most common adverse events (>2% and/or greater than placebo) for multiple dose Phase 2/3 trials are presented in Attachment 1. There were no dose-limiting adverse events.															
Maximum dose tested	Single Dose	Healthy Subjects • 480 mg Heart Failure Subjects • 120 mg Hyponatremia Subjects (Secondary to Liver Disease) • 60 mg														
	Multiple Dose	Healthy Subjects • 300 mg, QD, 5 days Heart Failure Subjects • 120 mg, QD, 13 days Hyponatremia Subjects (of any origin) • 60 mg, QD, 29-34 days														
Exposures Achieved at Maximum Tested Dose	Single Dose	<table border="1"> <thead> <tr> <th rowspan="2">Subject Population, Dose</th> <th colspan="2">Mean (%CV)</th> </tr> <tr> <th>C_{max} (ng/mL)</th> <th>AUC_{0-24h} (ng·h/mL)</th> </tr> </thead> <tbody> <tr> <td>Healthy, 480 mg</td> <td>1073 (22.8)</td> <td>25700 (34.8)*</td> </tr> <tr> <td>Heart Failure, 120 mg</td> <td>686 (73.9)</td> <td>8700 (101)</td> </tr> <tr> <td>Hyponatremia (Secondary to Liver Disease), 60 mg</td> <td>423 (58.6)</td> <td>5430 (31.7)</td> </tr> </tbody> </table> * AUC _∞	Subject Population, Dose	Mean (%CV)		C _{max} (ng/mL)	AUC _{0-24h} (ng·h/mL)	Healthy, 480 mg	1073 (22.8)	25700 (34.8)*	Heart Failure, 120 mg	686 (73.9)	8700 (101)	Hyponatremia (Secondary to Liver Disease), 60 mg	423 (58.6)	5430 (31.7)
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Range of linear PK	Single Doses			
	Linear Range			
	Subject Population	C_{max}	AUC	
	Healthy ^a	30 to 300 mg	30 to 480 mg	
	Heart Failure	10 to 60 mg	10 to 60 mg	
	Hyponatremia (Secondary to Liver Disease)	5 to 60 mg	5 to 60 mg	
	^a For healthy subjects, linear PK was observed for 5 to 60 mg doses administered as a capsule formulation			
	Multiple Doses			
	Linear Range			
	Subject Population	C_{max}	AUC	
Healthy ^a	30 to 60 mg, QD	30 to 60 mg, QD		
Heart Failure	10 to 60 mg, QD	10 to 60 mg, QD		
Hyponatremia (Secondary to Liver Disease)	5 to 60 mg, QD	5 to 60 mg, QD		
^a With the exception of 300 mg, doses outside this range were not tested.				
Accumulation at steady state	Accumulation Ratio, Mean (%CV)			
	Subject Population	Dose Range	C_{max}	
	Healthy	30 to 60 mg	1.19 (29.4)	
	Stable Heart Failure	10 to 60 mg	0.97 (34.0)	
	Hyponatremia (Secondary to Liver Disease)	5 to 60 mg	1.72 (39.0)	
Steady state concentrations are achieved after the first dose in healthy and heart failure subjects.				
Metabolites	Metabolites detected in plasma, urine and feces include: DM-4103*, DM-4107*, MOP-21826, DM-4104, DM-4105, DM-4110, DM-4111, DM-4119, DM-4128, DM-4129, DM-4130, DM-4131, DM-4132, and DM-4133. *Major metabolite None have pharmacological activity at the concentrations observed during clinical trials.			
Absorption	Absolute Bioavailability (Mean, %CV)	Absolute Bioavailability of 30 mg tablet, Healthy Subjects • 56 (17.9)		
	Relative Bioavailability (Geometric mean ratios and 95% confidence intervals)	Relative Bioavailability Ratio of 2 x 15mg Tablet/2 x 15mg Capsule Formulation • C_{max}, 0.818 (0.653-1.025) • AUC_∞, 0.860 (0.692-1.069)		
	T _{max} (h)	> Tolvaptan		
		Subject Population	Dose Range	Median (range)
		Healthy	30 to 60 mg, QD	2.00 (0.50-4.20)
	Stable Heart Failure	10 to 60 mg, QD	2.00 (0.98-8.00)	
	Hyponatremia (Secondary to	5 to 60 mg, QD	2.00 (1.00-12.17)	

		Liver Disease)												
		➤ Metabolites • A median for all subjects was not determined as none have pharmacological activity												
Distribution	Vd/F or Vd	Not evaluated												
	% unbound, Mean (%CV)	Healthy Subjects • 1.04 (25.0) Hyponatremia Subjects (Secondary to Liver Disease) • 1.57 (33.1)												
Elimination	Route	• Metabolism mediated via cytochrome P-450 CYP3A4 • ~19% excreted unchanged in feces • <1% excreted unchanged in urine												
	Terminal t _{1/2} (h)	➤ Tolvaptan <table border="1"> <thead> <tr> <th>Subject Population</th> <th>Dose Range</th> <th>Mean (%CV)</th> </tr> </thead> <tbody> <tr> <td>Healthy</td> <td>30 to 60 mg, QD</td> <td>9.4 (60.6)</td> </tr> <tr> <td>Stable Heart Failure</td> <td>10 to 60 mg, QD</td> <td>9.7 (41.2)</td> </tr> <tr> <td>Hyponatremia (Secondary to Liver Disease)</td> <td>5 to 60 mg, QD</td> <td>10.5 (63.8)</td> </tr> </tbody> </table> ➤ Metabolites • A mean for all subjects was not determined as none have pharmacological activity	Subject Population	Dose Range	Mean (%CV)	Healthy	30 to 60 mg, QD	9.4 (60.6)	Stable Heart Failure	10 to 60 mg, QD	9.7 (41.2)	Hyponatremia (Secondary to Liver Disease)	5 to 60 mg, QD	10.5 (63.8)
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CL (mL/min/kg)	IV Administration Healthy Subjects, 1 mg, 1-hour infusion • 2.34 (33.3)													
Intrinsic Factors	Age (60 mg, QD, 7 days)	Age has no effect on tolvaptan C_{max} or AUC_t. <table border="1"> <thead> <tr> <th>Comparison</th> <th>C_{max} Ratio</th> <th>AUC_t Ratio</th> </tr> </thead> <tbody> <tr> <td>Men >65 years/ Men 18-45 years</td> <td>0.90</td> <td>0.93</td> </tr> <tr> <td>Women >65 years/ Women 18-45 years</td> <td>1.06</td> <td>1.33</td> </tr> </tbody> </table> None of the changes were statistically significant.	Comparison	C _{max} Ratio	AUC _t Ratio	Men >65 years/ Men 18-45 years	0.90	0.93	Women >65 years/ Women 18-45 years	1.06	1.33			
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Drug (Dose)	TLV Dose	Analyte	C _{max}	AUC
CYP3A4 -mediated				
Amiodarone (200 mg) ^a	30 mg	Amio- darone	1.08	1.00
Amiodarone (200 mg) ^a	90 mg	Amio- darone	1.03	0.96
Amiodarone (200 mg) ^a	30 mg	Des- ethylami odarone	1.00	1.01
Amiodarone (200 mg) ^a	90 mg	Des- ethylami odarone	0.99	0.98
Lovastatin (80 mg) ^b	60 mg	Lovastatin	1.36*	1.33*
Lovastatin (80 mg) ^b	90 mg	Lovastatin	1.34*	1.38*
Lovastatin (80 mg) ^b	60 mg	Lovastatin β- hydroxy acid	1.21	1.29
Lovastatin (80 mg) ^b	90 mg	Lovastatin β- hydroxy acid	1.02	1.09
Warfarin (25 mg) ^c	60 mg	S- Warfarin	1.06	1.05
Warfarin (25 mg) ^c	60 mg	R- Warfarin	1.08	1.07
Warfarin (25 mg) ^c	60 mg	7- hydroxy warfarin	1.01	1.09
Warfarin (25 mg) ^c	60 mg	10- hydroxy warfarin	1.05	1.14
P-glycoprotein-mediated				
Digoxin (0.25 mg) ^d	60 mg	Digoxin	1.30**	1.18**
Other diuretics				
Furosemide (80 mg) ^e	60 mg	Furo- semide	0.90	0.91
Hydroxy- chloro- thiazide (100 mg) ^e	60 mg	Hydroxy- chloro- thiazide	1.08	1.10

^aSubjects were on amiodarone, 200 mg QD, for at least 28 days prior to study entry. Tolvaptan 30 mg and 90 mg were given on Day 4 and Day 5, respectively, of study.

^bSequential study. Period 1, lovastatin alone. Period 2, lovastatin+TLV 60 mg. Period 3, lovastatin+TLV 90 mg.

^cSingle dose of 25 mg warfarin. TLV given QD for 10 days beginning with warfarin dose.

		^d TLV administered QD on Days 8-12 of QD regimen for digoxin. ^e Single dose, randomized crossover study. [*] Statistically significant change, not considered clinically significant. ^{**} Statistically and clinically significant change.																													
	Food Effects	<table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="2">Geometric mean ratios and 95% confidence intervals Fed/Fasted State</th> </tr> <tr> <th>Subject Population</th> <th>Meal*, Tolvaptan Dose</th> <th>C_{max}</th> <th>AUC</th> </tr> </thead> <tbody> <tr> <td>Healthy Men and Women</td> <td>HFM, 60 mg tablet</td> <td>1.40 (1.17-1.67)</td> <td>1.06 (0.97-1.16)</td> </tr> <tr> <td>Caucasian Men</td> <td>HFM, 30 mg tablet</td> <td>1.182 (1.031-1.354)</td> <td>1.166 (1.085-1.253)</td> </tr> <tr> <td>Japanese Men</td> <td>HFM, 30 mg tablet</td> <td>1.119 (0.955-1.312)</td> <td>1.178 (1.041-1.332)</td> </tr> <tr> <td>Caucasian Men</td> <td>JSM, 30 mg tablet</td> <td>1.065 (0.930-1.221)</td> <td>1.021 (0.957-1.088)</td> </tr> <tr> <td>Japanese Men</td> <td>JSM, 30 mg tablet</td> <td>1.185 (1.006-1.397)</td> <td>1.107 (0.973-1.261)</td> </tr> </tbody> </table> *HFM= High Fat Meal, JSM= Japanese Standard Meal (5 g sodium)				Geometric mean ratios and 95% confidence intervals Fed/Fasted State		Subject Population	Meal*, Tolvaptan Dose	C _{max}	AUC	Healthy Men and Women	HFM, 60 mg tablet	1.40 (1.17-1.67)	1.06 (0.97-1.16)	Caucasian Men	HFM, 30 mg tablet	1.182 (1.031-1.354)	1.166 (1.085-1.253)	Japanese Men	HFM, 30 mg tablet	1.119 (0.955-1.312)	1.178 (1.041-1.332)	Caucasian Men	JSM, 30 mg tablet	1.065 (0.930-1.221)	1.021 (0.957-1.088)	Japanese Men	JSM, 30 mg tablet	1.185 (1.006-1.397)	1.107 (0.973-1.261)
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Expected High Clinical Exposure Scenario	If a heart failure subject currently taking ketoconazole was given 30 mg tolvaptan, peak tolvaptan plasma concentrations would be expected to be increased about 3.5-fold and exposure, as determined by AUC, would be expected to be increased 5.4-fold. A four-fold higher dose, ie, 120 mg, was well-tolerated by heart failure subjects. If a hyponatremia subject with liver disease currently taking ketoconazole was given 15 mg tolvaptan, the recommended starting dose, tolvaptan concentrations would again be expected to be about 4-fold higher. Doses of 60 mg have been well-tolerated by hyponatremia subjects with liver disease. Multiple oral doses of 300 mg in healthy subjects also produce exposures similar to the scenarios above and have been well tolerated. Tolvaptan's primary pharmacological effect is to increase the rate of urine output and, consequently, urine volume. Following doses of 60 to 480 mg to healthy subjects, the 24-hour urine volume and peak excretion rate were similar. The increases seen in mean serum Na⁺ concentrations (4-6 mEq/L), plasma osmolality (~8 mOsm/kg) and free water clearance (~6 mL/min) were also similar throughout the 0-24 hour period across the dose range. Changes in serum K⁺, creatinine clearance, and Na⁺, K⁺ and osmolality urinary excretion were similar to the placebo group. Some changes in plasma arginine vasopressin, serum aldosterone concentrations and plasma renin activity were observed but had large intersubject variability and were not clinically significant. Only total urine volume excretion (0-72 hours postdose) increased linearly with dose. In conclusion, as plasma tolvaptan concentrations increase above those achieved with 60 mg doses, the duration of pharmacological effect increases but the magnitude of response does not.																														

6.2 TABLE OF STUDY ASSESSMENTS

Table 5.5-1 Schedule of Assessments - Screening	
Procedure	Days -21 to -2
Informed consent ^a	X
Inclusion/exclusion criteria	X
Medical history	X
Physical examination ^b	X
Vital signs (including body weight) ^c	X
Hematology/serum chemistry/urinalysis ^d	X
Serum pregnancy test - females	X
Resting 12-lead ECG ^e	X
Concomitant medications	X
Adverse event assessment	X

ECG = electrocardiogram.

^aSubjects must have given written informed consent prior to any study procedures, including rescreening.

^bIncluded elbow breadth and height.

^cBlood pressure, pulse, and temperature. All were assessed after sitting ≥ 3 minutes.

^dClinical labs also included urine alcohol and drug screen, serum Hepatitis B and C, and HIV screens.

^eStandard 12-lead ECG was performed after the subject had been recumbent and at rest for ≥ 10 minutes prior to the ECG.

Source: Appendix I-1.

Appears This Way
On Original

Procedure	Day -1 (Check-in)
Admit to clinic in PM	X
Verify inclusion/exclusion criteria	X
Physical examination ^a	X
Vital signs (including body weight) ^b	X
Resting 12-lead ECG ^c	X
Hematology/serum chemistry/urinalysis ^d	X
Serum pregnancy test - females	X
Concomitant medications	X
Adverse event assessment	X
Randomization	X
Begin fasting at 10 PM (2200 hours)	X

ECG = electrocardiogram.

^aElbow breadth and height at screening only.

^bBlood pressure, pulse, and temperature. All were assessed after sitting ≥ 3 minutes.

^cStandard 12-lead ECG was performed after the subject had been recumbent and at rest for ≥ 10 minutes prior to the ECG.

^dClinical laboratory tests also included urine alcohol and drug screen.

Source: Appendix I-1.

Procedure	Study Day						
	0	1	2	3	4	5	6/ET
Vital Signs	X ^a	X ^a				X ^a	X
Body weight							X
Physical examination ^b							X
Resting period (for digital ECG)	X ^c	X ^{c,d}	X ^{c,d}			X ^c	X ^d
Resting 12-lead ECG (for safety)	X ^c	X ^c				X ^c	X
Hematology/serum chemistry/urinalysis							X ^f
Serum pregnancy test - females							X

Procedure	Study Day						
	0	1	2	3	4	5	6/ET
PK blood draws	X ^g	X ^{g,h}	X ^h			X ^g	X ^{f,h}
Dosing ⁱ	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X
Meals ^j	X ^j	X ^j	X	X	X	X ^k	X
Begin fasting at 10 PM (2200 hours)	X				X		

ECG = electrocardiogram; PK = pharmacokinetic.

^aBlood pressure, pulse and temperature. Vital signs were to be performed predose, after being seated for ≥ 3 minutes within 30 minutes prior to dosing. Vital signs were to be taken before ECGs.

^bElbow breadth and height at screening only.

^cSubjects were to remain in a supine position starting 20 minutes prior to digital ECG sampling times and lasting for at least 16 minutes. Digital ECG sampling times were at predose, 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose.

^dSubjects were to remain in a supine position starting 20 minutes prior to digital ECG sampling times and lasting for at least 16 minutes. Digital ECG sampling times were at 16, 18, and 24 hours postdose. (Note: Day 1 predose draw was the same as the 24-hour postdose evaluation on Day 0.)

^eStandard 12-lead ECGs were recorded at 3.5 hours postdose for safety purposes.

^fBlood draws for clinical chemistry and PK analysis were to be performed after vital signs measurements were taken.

^gPK blood draws: predose (5 minutes), followed by 1, 2, 4, 8, and 12 hours postdose. (Note: predose sample on Day 1 was the same sample as the 24-hour postdose sample for Day 0.)

^hPK blood draw 24 hours postdose. Sample was to be taken 5 minutes prior to dosing Days 1 and 2, and at 24 hours on Day 6.

ⁱDosing at approximately 0800 hours.

^jMeals were breakfast, morning snack, lunch, dinner and evening snack except on Day 6 where only breakfast was offered.

^kNo breakfast or morning snack was given. Lunch and dinner were to be served at ~4 and 10 hours postdose, respectively, and after the ECG rest period and/or PK draw.

Source: Appendix I-1.

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

/s/

Joanne Zhang
3/31/2008 12:32:46 PM
BIOMETRICS

Jingyu Luan
3/31/2008 12:34:55 PM
BIOMETRICS

Suchitra Balakrishnan
4/1/2008 10:17:13 AM
MEDICAL OFFICER

Rajnikanth Madabushi
4/1/2008 11:49:50 AM
BIOPHARMACEUTICS

Christine Garnett
4/2/2008 04:39:42 AM
BIOPHARMACEUTICS