CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204441Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Proposed Brand Name	Jynarque®
INN Name	Tolvaptan
NDA Number and Type	204,441
Applicant Name	Otsuka
Submission Date	October 24, 2017
EDR Links	\\cdsesub1\evsprod\nda204441\055 and 0075 \\cdsesub1\evsprod\nda022275
Indication	Treatment of ADPKD
Dosage Form & Strengths	15, 30, 60, 90 mg immediate release tablets
OCP Division	DCPI, Cardiovascular and renal products team
OND Division	ODEI, Division of cardiovascular and renal products
Reviewer	Martina Sahre, PhD
Team Leader	Sudharshan Hariharan, PhD

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1 Executive Summary

The regulatory action for the original application in 2013 was Complete Response, with the requirement to conduct an additional clinical study in patients with more advanced renal impairment. This resubmission provides the results from this newly conducted study (156-13-210, REPRISE) to the FDA, which will be reviewed in detail in the clinical review. In addition, since the drug received a Complete Response in the last review cycle, more detailed labeling review as well as the review of in vitro drug transporter inhibition studies are reviewed in this document.

In vitro assessments show that tolvaptan has the potential to inhibit the following transporters, because the concentrations that can be achieved in vivo in the clinically relevant dose range exceed the concentrations observed to inhibit transporter interactions in vitro: P-gp, BCRP. In addition, the metabolite DM-4103, which is the major circulating moiety in plasma and has a half-life of around 180 h (7.5 days) has the potential to inhibit OATP1B1/3 and OAT3. Of these potential interactions, so far only P-gp has been studied clinically.

The applicant has studied the same doses that had been assessed in study 156-04-251 (TEMPO), which were split doses up to 90/30 mg. The rationale for the doses is reviewed in the clinical pharmacology review for the original submission of tolvaptan for ADPKD (NDA 204,441, DARRTS date 7/2/2013).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 204,441. From a clinical pharmacology perspective, the NDA is acceptable, provided agreement on labeling can be reached.

1.2 Recommended Phase 4 study commitments

To date, the applicant has not conducted clinical studies of the identified potential interactions between tolvaptan and BCRP as well as the metabolite DM-4103 with OATP1B1/B3 and OAT3. A post marketing requirement (PMR) for assessing the interactions with BCRP, OATP1B1/B3 and OAT3, in vivo, will be sent to the Applicant. Until the results from these assessments become available, the risk for drug interactions with these transporters will be addressed in labeling.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The reader is referred to previous reviews for tolvaptan for NDA 22,275 and the previously submission of NDA 204,441 for information about clinical pharmacology. The new information the applicant has provided are centered around in vitro transporter interaction assays, a fluconazole drug-drug interaction study (DDI) to assess interaction with a moderate CYP3A inhibitor as well as a new pivotal clinical study (156-13-210, REPRISE) in ADPKD patients with more advanced renal impairment (eGFR between 25-65 mL/min/1.73 m^2).

2 Review

2.1 Summary of Pharmacokinetic and Pharmacodynamic Information from Previous Reviews

2.1.1 Mechanism of Action

Tolvaptan is a selective antagonist at the Vasopressin receptor Type 2 (V2-receptor) and shows higher affinity for this receptor than its endogenous ligand vasopressin. Vasopressin is also referred to as antidiuretic hormone (ADH). Binding of vasopressin to the V2 receptor on the basolateral membrane of cells in the renal collecting duct causes activation of cAMP and PKA mediated movement of aquaporin 2 water channels to the luminal surface of ductal cells, which enables the reabsorption of water, and thereby antidiuresis, i.e. reduced excretion of water in the urine.

The posited mechanism of action for tolvaptan is that in patients with ADPKD, that pathway could be overstimulated and that constant production of cAMP could promote cyst growth through further down-stream changes in calcium homeostasis in the cell. Therefore, inhibiting cAMP production by blocking the V2 receptor should lead to reduction of the number of new cysts and an arrest of growth of existing cysts.

2.1.2 Pharmacokinetics

Absorption

Cmax of tolvaptan increases with increasing doses until it reaches a limit at around 240 mg. With a 30 mg tablet, absolute bioavailability was 56%, ranging from 42 to 80%.

Distribution

Protein binding was assessed for tolvaptan, DM-4103 and DM-4107.

Table 1. Protein binding of tolvaptan, DM-4103, and DM-4107

Moiety	***Protein Binding***
Tolvaptan (0.5 µg/mL)	99.2
DM-4103 (3 µg/mL)	>99.8
DM-4107 (0.5 µg/mL)	98.5

[Source: Report R017335, Table 7]

Metabolism/Excretion

Incubation of tolvaptan in human liver microsomes produced DM-4103 (Mw 478 g/mol), DM-4104, DM-4105, DM-4107 (Mw 480 g/mol), DM-4110, DM-4111, and MOP21826, as well as unidentified metabolites. The predominant metabolizing enzyme was CYP3A4. DM-4103 is formed through intermediary metabolites MOP-21826 and DM-4105, while DM-4107 is formed via the intermediary DM-4104.

In plasma, after a 60 mg radiolabeled dose, the main circulating moiety is DM-4103 (52.5%), with a half-life of 183 h. Tolvaptan and DM-4107 account for 1.71 and 2.84%, respectively. Approximately 40% of radioactivity was recovered in urine and 59% in feces. The fraction excreted in urine as tolvaptan was about 0.12% in the first 12 h, followed by 0.02% in the twelve hours thereafter. DM-4107 accounted for 3.5, 1.6, and 1% of the excreted dose in the first 0-12, 12-24, and 24-36 h. About 14% of the radioactive dose is recovered as tolvaptan in feces. The amount of DM-4103 and DM-4107 recovered in feces, over 72 h, is approximately 0.7% and 9%, respectively. Neither of these two metabolites are active.

Table 2. Mass-balance study results

Total Recovery	***98.87 (8.06) %***	
Matrix	**Feces**	**Urine**
%of total recovered RA	58.71 (9.12) % of which 65% in 72 h Excretion up to 960 h	40.16 (8.64) % of which 80% in 36 h Excretion up to 216 h
% of RA recovered in matrix	Tolvaptan: 31.91% (18.7% of total) DM-4107: 20.55% (12.1% of total) Other: 22.38% (13.1% of total) Non-identified: 25.16% (or ~14.7% of total administered RA)	DM-4107: 23.28% (9.35% of total) DM-4111: 14.09 (5.66% of total) Other (incl. Tolvaptan): 35.29% (14.2% of total) Non-identified: 27.34% (or ~11% of total administered RA)

[Source: Study Report #156-97-202]

3 Review of New Information

3.1 In vitro transporter assays

To assess the reason for observed increases in hepatic injury markers ALT/AST as well as bilirubin, the applicant has, among other investigations, conducted in vitro studies of the inhibition potential of tolvaptan, DM-4103 and DM-4107, which are two metabolites of tolvaptan.

Transporters that were studied were the following: BCRP, MDR1 (P-gp), BSEP, OAT1 and 3, OATP1B1 and 3, OCT1 and 2, NTCP, MRPs2, 3, and 4, as well as MATE1 and MATE2-K. Individual reviews of these studies are found in the Appendices**Error! Reference source not found.** and the results are summarized in Table 3.

The applicant calculated [I]/IC50 and R values based on FDA guidance. An $[I_{gut}]$/IC50 ratio greater than 10 is calculated for P-gp and BCRP. The interaction of tolvaptan with P-gp has already been assessed in a clinical drug-drug interaction (DDI) study and is included in labeling. It does not rise to the need to adjust the dose. The $[I_{gut}]$/IC50 for tolvaptan towards BCRP is ~90 and has the potential to increase exposure of drugs that are substrates for BCRP.

Based on the R value for OATP1B1 being greater than 1.1 for DM-4103, there is a potential for drug interactions based on this metabolite. In addition, the [I]/IC50 ratio is >0.1 for DM-4103 and OAT3. The applicant has not conducted any clinical studies for these potential interactions. (See Table 4)

Table 3. Summary of results from in vitro transporter assessments

		Mean IC50 [µM]	
Transport Enzyme	*OPC-41061 (TLV)*	*DM-4103*	*DM-4107*
BCRP	8.32	102	>200
BSEP	Ki 34 (noncompetitive)	Ki: 3.77	119
MATE1	7.965	179.1	>200
MATE2-K	>10	>200	121.1
MDR1	15.9	>200	>200
MRP2	50	51	200
MRP3	50	44.6	61.2
MRP4	50	4.26	37.9
OAT1	>30	13	92.8
OAT3	5.47	0.425	0.475
OATP1B1	6.15	0.255	8.37
OATP1B3	4.14	2.9	10.3
OCT1	0.837	4.37	35.1
OCT2	27.2	29.8	>200

[Source: See Appendices]

Table 4. Transporter interactions where thresholds are above guidance limits

Transporter	*Decision Criterion (threshold)*	*Notes*
BCRP (Tolvaptan)	I_{gut}/IC50 = 96* (threshold: ≥10)	Molecular weights: Tolvaptan: 448
OATP1B1	R = 1.56 (threshold: ≥1.1)	DM-4103: 478
OATP1B3	R = 1.05 (threshold: ≥1.1)	DM-4107: 480
OAT3	[I]/IC50 = 0.34 (threshold: ≥0.1)	

*I_{gut}=803.57 µmol/L

** Concentrations based on Table 7

3.2 Phase 3 Study 156-13-210 – Pivotal Study

This study was a phase 3b, multicenter, randomized withdrawal, placebo-controlled, double-blind, parallel-group trial. Patients with ADPKD were enrolled if they had an eGFR between 25-65 mL/min/1.73 m^2. The study was done in three phases: a pre-randomization period consisting of a placebo run-in, a tolvaptan titration and finally a tolvaptan run-in period. The pre-randomization period was followed by the randomized, double-blind treatment period and a follow-up period. During the pre-randomization period, patients underwent a single-blind placebo run-in phase in which they received a daily split dose of 0/0 mg. The placebo run-in was followed by a tolvaptan titration

period. During the titration period, patients were instructed to take a starting dose of 30/15 mg and to titrate every 3 to 4 days in steps of 45/15, then 60/30, to a maximum of 90/30 mg. Following the tolvaptan titration phase, patients who tolerated a 60/30 mg dose or higher (i.e. the 90/30 mg dose) during the titration period were entered a tolvaptan run-in period, to minimize dropout due to tolerability problems. Patients who were unable to tolerate doses higher than 60/30 mg were considered run-in failures and were not randomized to treatment.

The double-blind treatment period lasted for 12 months. In this phase, down titration to 45/15 or 30/15 mg was allowed.

Patients were stratified based on their baseline eGFR (≤/> 45 mL/min/1.73 m^2), age (≤/> 55 years of age) and TKV (≤/> 2000 mL, or a third group of unknown TKV).

Table 5. Study participant disposition

	Tolvaptan (N (%))	*Placebo (N (%))*	*Total (N (%))*
Screened			2292
Entered Placebo run-in			1519
Entered tolvaptan run-in			1496
Randomized	683	687	1370 (91.6)
Completed treatment	578 (84.6)	637 (92.7)	1215 (88.7)
Discontinued treatment	105 (15.4)	50 (7.3)	155 (11.3)
Reason for d/c			
IMP not tolerable	34 (5.0)	6 (0.9)	
IMP related safety	15 (2.2)	6 (0.9)	
Disease progression	6 (0.9)	5 (0.7)	
Hepatic AE	25 (3.7)	4 (0.6)	

[Source: CSR 156-13-210, Tables 10.1-1 and 10.1-2]

Plasma exposures of tolvaptan, DM-4103 and DM-4107

The applicant measured drug concentrations on the following occasions:

End of tolvaptan run-in (Day -1), quarterly during double-blind randomized treatment phase (Month 3, 6, 9, 12 or end of treatment), at the 21-day follow-up visit.

Concentrations at the end of the tolvaptan run-in period and throughout the double-blind treatment period are summarized in Tables 6 and 7. Comparing these concentrations with IC50 values from in vitro assessments of transporters, DM-4103 has the potential to interact with OATP1B1/B3, as well as OAT3. In the gut, tolvaptan has the potential to interact with MDR1 (P-gp) and BCRP. The interaction with P-gp was assessed in a clinical study where digoxin was coadministered with tolvaptan, leading to about a 20% increase in digoxin AUC. The potential interaction with BCRP has not been further studied.

Table 6. Mean (SD) concentrations at the end of the tolvaptan run-in period

Dose	*Tolvaptan*	*DM-4103*	*DM-4107*
90 (60/30 mg)	443.6 (275.7)	5140 (2422)	337.9 (150.8)
120 (90/30 mg)	583.2 (408.7)	6203 (2793)	431.9 (201.2)

[Source: adpc.xpt], Unit: ng/mL

Table 7. Mean (SD) concentrations of tolvaptan, DM-4103 and DM-4107 at the 90/30 mg dose during the double-blind treatment period

Month	*N*	*Tolvaptan*	*DM-4103*	*DM-4107*
3	454	607.1 (397.2)	7271 (4329)	441.6 (199.7)
6	413	595.0 (442.3)	7042 (4142)	433.8 (219.5)
9	392	602.2 (438.0)	6826 (4017)	432.3 (203.0)
12	367	552.7 (444.1)	6830 (3949)	410.6 (210.3)

[Source: adpc.xpt], Unit: ng/mL

3.3 Fluconazole DDI Study

3.3.1 Design

A single dose of 30 mg tolvaptan tablet was administered alone on day 1. Fluconazole was administered as follows: a 400 mg dose on day 3, on days 4 and 5 a 200 mg dose. Coadministration of tolvaptan 30 mg and fluconazole occurred on day 4. All doses were given fasted. The Applicant mentions that this was intended to reduce exposure to tolvaptan and fluconazole in healthy subjects. Fluconazole is dosed as high as 400 mg daily (in single or divided doses) for various candidiases or cryptococcal infections. Therefore, the 200 mg dose represents a half-maximal dose compared to the worst-case scenario of 400 mg, however, the design is acceptable.

PK for tolvaptan, DM-4103 and DM-4107 was collected for 72 h post-last dose. Urine samples were collected from 0-12, 12-24, 24-36, and 36-48 h post-dose for pharmacodynamic assessments.

3.3.2 Demographics

Parameter	*Result*
N (Female/Male)	14 (6/8), all completed
Mean age [years] (SD, range)	35.9 (5.4, 22-45)
Weight [kg] (SD, range)	75.0 (10.4, 55.2-91.6)
Race (White/Black/Asian)	9/3/2

3.3.3 Results

Tolvaptan (Mean (SD))

Parameter	*Tolvaptan alone*	*Tolvaptan + Fluconazole*
Cmax [ng/mL]	222 (72.3)	400 (137)
tmax [h]	2 (1-3)	3 (1-4)
AUClast [ng*h/mL]	1510 (480)	4540 (1190)
AUCinf [ng*h/mL]	1580 (487)	4670 (1190)
t1/2 [h]	6.9 (2.6)	8.5 (1.4)

Geometric mean ratios and their 90% confidence intervals are 1.79 (1.54-2.07) for Cmax and 2.98 (2.67-3.32) for AUCinf, respectively.

DM-4107 (Mean (SD))

Parameter	*Tolvaptan alone*	*Tolvaptan + Fluconazole*
Cmax [ng/mL]	78.4 (27.9)	49.5 (18.1)
tmax [h]	4 (3-8)	8 (4-12)
AUClast [ng*h/mL]	937 (272)	962 (353)
AUCinf [ng*h/mL]	1260 (316)	1410 (398)
t1/2 [h]	8.9 (4.3)	18.8 (16.6)

The applicant has not provided DM-4103 concentrations after tolvaptan and fluconazole administration combined, because, due to the long half-life of DM-4103, not unexpectedly, the pre-dose samples prior to administration of tolvaptan and fluconazole combined had not washed out.

3.3.4 Conclusion

As expected, coadministration with fluconazole increased tolvaptan exposure. Cmax increased 1.8-fold, and AUCinf increased 3-fold. DM-4107 Cmax was reduced, which is expected given that the metabolite is generated by CYP3A4, however, AUC was about 20% increased when coadministered. No conclusions could be drawn about DM-4103. Given that DM-4103 is created through the 3A4 pathway via an intermediary, one could speculate that Cmax would also be reduced. Given the results for DM-4107, it would not be immediately clear whether one could assume the same for AUC. However, the metabolic pathway for DM-4103, once generated, is not clear.

Samples were analyzed using validated methods for detection of each analyte, and performed acceptably during sample analysis for this study.

3.4 Labeling

3.4.1 Contraindication for strong CYP3A4 Inhibitors

The applicant had proposed a dose adjustment for strong CYP3A4 inhibitors in this label, based on exposure matching and assessment of strong CYP3A4 inhibitor use in

clinical studies. The following factors influenced the decision to continue the contraindication for strong CYP3A4 inhibitors:

- Exposures after administration of a strong CYP3A4 inhibitor were characterized in a dedicated DDI study with ketoconazole in which a half-maximal ketoconazole dose (200 mg) was used. Typically, a 400 mg dose is administered. Therefore, there is potential for greater increases in exposure than what the study indicated.
- Most medications that constitute strong CYP3A4 inhibitors would be short-term treatments, for which tolvaptan treatment could be interrupted.
- The applicant made the argument that patients would be able to perceive an exaggerated pharmacological effect on urine osmolality, i.e. increased diuresis, based on increased exposure. However, this appears to be a very subjective measure and will likely depend on many factors. It did not appear that previous studies seemed to show increased reduction in urine osmolality that could be infinite. Further, the amount a patient can produce in urine could also depend on their daily hydration status.

3.4.2 Dose adjustment for moderate CYP3A4 Inhibitors

While the applicant also did not study the highest dose during coadministration with fluconazole, at least the high fluconazole dose was administered on the day before administration with tolvaptan. The applicant approaches dose reduction for this group of comedications by a halving the doses as shown in Table 8. The sponsor justifies this by stating that moderate CYP3A4 inhibitors are defined as those with increases in exposure (AUC ratio) greater than 2-fold, and therefore a halving of dose would be the appropriate means. This discounts that the definition for a CYP3A4 inhibitor of moderate strength lies within a range (2-<5-fold), and is usually adjusted by the clinical data evidence, i.e. here the 3-fold increase in AUC. That said, the dose for tolvaptan can be down-titrated. Further, given the available tablet strengths, 15, 30, 45, 60, 90 mg, a dose adjustment to a third of the original initial dose is not possible. Therefore, the dose adjustment is considered acceptable.

Table 8. Dose adjustment for moderate CYP3A4 inhibitors

Regular daily split dose	*Adjusted split dose*
90/30 mg	45/15 mg
60/30 mg	30/15 mg
45/15 mg	15/15 mg

3.4.3 Transporter Interaction Data

The applicant had not added transporter interaction or metabolite information to their label and an Information Request was sent to the applicant, to which they responded on 3/29/2018.

The applicant proposed to add the following language to the label:

It should be noted, that assessing the potential for the effect of perpetrator drug on potential victim drugs from adverse event data in clinical studies is usually not done because of lack of sensitivity. These studies are not designed to assess these types of interactions, nor is exposure to the potential victim drug measured. Therefore, this type of language should not be added to the label.

The following edits are proposed:

Tolvaptan is a substrate of P-gp and an inhibitor of P-gp and BCRP. The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3. In vitro studies indicate that tolvaptan or the oxobutyric acid metabolite of tolvaptan may have the potential to increase exposure of drugs that are substrates to these transporters (b) (4) *[see Drug Interactions (7.2), (7.3)].*

Sections 7.2 and 3

7.2. OATP1B1/3 and OAT3 Transporter Substrates

The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3. Patients who take JYNARQUE, should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g. statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide) *[see Clinical Pharmacology (12.3)]*.

7.3 BCRP Transporter Substrates

Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin) *[see Clinical Pharmacology (12.3)].*

3.4.4 Metabolite Data

Given that at least one metabolite has the potential to interact with transporters, the applicant was asked to provide language in the label detailing metabolism of tolvaptan. The applicant responded that information was not added, because the metabolites are not considered active. Considering the potential transporter interaction, the statement in the sentence before should be detailed further. While there may not be metabolites that show effect on the pathways that are hypothesized to be important for the clinical effect of tolvaptan, given the potential for transporter interaction, they are not inert. The guidance for Drug Labeling, 2017 clearly states that metabolism of a drug should be

summarized, where necessary. Therefore, this reviewer recommends editing the proposed language by the applicant as follows:

"Fourteen metabolites have been identified in plasma, urine and feces; all but one were also metabolized by CYP3A and none are [redacted] pharmacodynamically active. [redacted] radiolabeled tolvaptan is a minor component in plasma representing 3% of total plasma radioactivity; [redacted] the oxobutyric acid metabolite is present at [redacted] 52.5% of total plasma radioactivity with all others present at lower concentrations than tolvaptan. The oxobutyric acid metabolite shows a plasma half-life of ~180 h."

4 Appendices

4.1 Multidrug Resistance-associated Proteins 2, 3, and 4 (MRP2, 3, 4)

EDR Link	4.2.2.7. Report No. 030786
Moieties and concentrations tested	Tolvaptan and DM-4103: 0, 0.1, 1, 3, 10, 20, 50 µM DM-4107: 0, 10, 20, 50, 100, 200 µM
Substrates	MRP2/3: ^{3}H-estradio 17-beta-D-glucuronide ($E_2$17G) MRP4: ^{3}H-dehydroepiandrosterone sulfate (DHEAS) Final concentration: 2 µCi/mL
Control	Positive: MK-571 Negative: Vehicle only, DMSO
Cells	Inside-out membrane vesicles from Sf9 cells over-expressing the respective transporters MRP2, 3, or 4
Results	Tolvaptan (Values are given as Mean (SD)) (values in % of transport of negative control)

Concentration	MRP2	MRP3	MRP4
0.1	100 (19.1)	92.1 (13.0)	122 (19.6)
1	118 (15.6)	107 (11.2)	107 (11.1)
3	131 (28.1)	112 (6.78)	107 (13.0)
10	138 (13.0)	90.1 (9.64)	106 (19.1)
20	126 (23.0)	91.2 (4.40)	108 (17.9)
50	115 (6.05)	70.8 (22.2)	88.0 (8.48)

IC50 not calculated, since no inhibition of more than 50% was observed

DM-4103 (Values are given as Mean (SD)) (values in % of transport of negative control)

Concentration [µM]	MRP2	MRP3	MRP4
0.1	109 (10.9)	100 (3.39)	99.7 (5.45)
1	112 (16.2)	96.4 (16.7)	88.6 (12.7)

3	103 (8.81)	95.3 (11.8)	58.8 (2.12)
10	94.3 (3.60)	85.0 (12.8)	25.7 (8.98)
20	77.1 (9.14)	74.0 (16.6)	15.0 (3.93)
50	37.4 (1.83)	40.7 (6.93)	-
IC50	**51.0**	**44.6**	**4.26**

DM-4107 (Values are given as Mean (SD)) (values in % of transport of negative control)

Concentration [µM]	MRP2	MRP3	MRP4
10	80.2 (16.9)	82.5 (6.25)	86.1 (8.00)
20	93.6 (1.75)	70.3 (4.23)	65.0 (6.26)
50	100 (15.9)	55 (4.22)	42.7 (5.35)
100	93.4 (14.8)	38.9 (7.48)	24.4 (2.76)
200	67.0 (15.7)	29.9 (4.15)	13.3 (3.37)
IC50	**>200**	**61.2**	**37.9**

MK-571 (negative control at 50 µM) inhibited all three transporters in experiments

4.2 Breast Cancer Resistance Protein (BCRP) and Mannitol Transport

EDR Link	**4.2.2.6. Report No. 030515**
Moieties and concentrations tested	Tolvaptan: 0.1, 0.3, 1, 3, 10, 30, 50 mM DM-4103 and DM-4107: 2, 6, 20, 60, 200, 250 mM
Substrates	Deuterated Prazosin ^{14}C-mannitol
Control	Ko143 1 µM
Cells	MDCKII-BCRP expressing cells
Results	Tolvaptan (Mean % of transport of negative control)

Concentration [µM]	Mannitol Transport	Prazosin Transport
0.1	No inhibition	106.4%
0.3		100.7%
1	-	95.0%
3	-	76.8%
10	No inhibition	46.6%
IC50 [µM]		**8.32**

DM-4103 (Mean % of transport of negative control)

Concentration	Mannitol	Prazosin

[µM]	Transport	Transport
2	No inhibition	
20		143.3
60		116.3
120		30.0
160		11.5
200	No inhibition	7.9
IC50 [µM]		**102**

DM-4107 (Mean % of transport of negative control)

Concentration [µM]	Mannitol Transport	Prazosin Transport
2	No inhibition	105.7
6		103.4
20		105.4
60		105.7
200	No inhibition	100.0
IC50 [µM]		**>200**

4.3 Sodium taurocholate cotransporting polypeptide (NTCP)

EDR Link: 4.2.2.7 Report No. 030787

Moieties and concentrations tested: Tolvaptan: 0.01, 0.1, 1, 5, 25, 50 mM

DM-4103 and DM-4107:

Substrates: Deuterated Prazosin

^{3}H-taurocholic acid

Control: Taurochenodeoxycholic acid (TCDC)

Cells: CHO cells expressing human NTCP

Results: Tolvaptan (Mean (SD) % of transport of negative control)

Concentration [µM]	Tolvaptan	DM-4103	DM-4107
0.01	96.9	86.3 (15.8)	111 (21.2)
0.1	88.5	92.0 (18.2)	106 (18.5)
1	114 (12.6)	87.4 (6.08)	98.1 (35.9)
5	86.1	-	-
10	71.3 (10.3)	52.7 (6.17)	81.9 (22.3)
25	62.5 (13.3)	50.0 (13.1)	78.4 (-)
50	50.6 (13.8)	26.3 (3.46)	65.4 (11.0)
75	-	15.7 (-)	-
100	-	-	49.3 (1.10)

200	-	-	35.8 (2.39)
TCDC Control 100 µM	1.74	Not detected	0.889 (0.635)
IC50 [µM]	**41.5**	**16.3**	**95.6**

4.4 Multidrug and toxin extrusion proteins 1 and 2-K (MATE1, MATE2-K)

EDR Link 4.2.2.6 Report No. 030654

Moieties and concentrations tested
Tolvaptan: 0.03, 0.1, 0.3, 1, 3, 10 µM
DM-4103 and DM-4107: 0.6, 2, 6, 20, 60, 200 µM

Substrates 14C-Metformin (1 µM)

Control Cimetidine 300 µM

Cells MDCKII cells expressing hMATE1 or hMATE2-K

Results Tolvaptan (Mean % of transport of negative control)

Concentration [µM]	*MATE1*	*MATE2-K*
0.03	81.0	113.3
0.1	100.7	116.7
0.3	86.5	122.6
1	83.7	112.4
3	67.0	90.7
10	40.5	65.9
Cimetidine 300 µM	1.8	35.2
IC50 [µM]	**7.965**	**>10**

DM-4103 and DM-4107 (Mean % of transport of negative control)

	DM-4103		*DM-4107*	
Concentration [µM]	MATE1	MATE2-K	MATE1	MATE2-K
0.6	112.0	103.0	96.5	79.3
2	99.3	121.8	99.5	78.1
6	108.5	103.7	91.6	76.9
20	104.7	99.4	87.6	64.1
60	88.0	98.1	79.5	56.1
200	48.0	78.7	53.1	43.0
Cimetidine 300 µM	1.1	26.1	-1.0	17.4
IC50 [µM]	**179.1**	**>200**	**>200**	**121.1**

4.5 Organic anion transporters 1 and 3 (OAT1, OAT3), Organic anion-transporting polypeptides 1B1 and 1B3 (OATP1B1, OATP1B3), Organic cation transporters 1 and 2 (OCT1, OCT2)

EDR Link

4.2.2.6 Report No. 030703

Moieties and concentrations tested

Tolvaptan: 0.0096, 0.048, 0.24, 1.2, 6, 30 µM

DM-4103 and DM-4107: 0.064, 0.32, 1.6, 8, 40, 200 µM

Substrates

OAT1: deuterated aminohippuric acid (3 µM)

OAT3: deuterated estrone sulfate (2 µM)

OATP1B1/3: deuterated estradiol 17beta-D-glucuronide (0.1 µM)

OCT1/2: 14C-Metformin (20 µM)

Control

OAT1: Probenecid (30 µM)

OAT3: Probenecid (30 µM)

OATP1B1/3: Rifampicin (10 µM)

OCT1/2: Quinidine (300 µM)

Cells

HEK293 cells expressing hOAT1, 3, hOATP1B1, 3, hOCT1, 2

Results

Tolvaptan (Mean % of transport of negative control

Concentration [µM]	*OAT1*	*OAT3*	*OATP1B1*	*OATP1B3*	*OCT1*	*OCT2*
0.0096	118.6	98.1	103.4	129.4	109.5	122.6
0.048	88.0	94.6	105.6	116.3	118.7	132.6
0.24	91.6	89.5	107.3	100.4	81.9	65.9
1.2	87.2	78.1	107.0	90.8	46.3	121.5
6	89.4	50.2	54.3	47.6	8.2	104.6
30	54.7	7.8	3.0	7.2	2.9	48.2
Control (see above)	28.5	8.9	2.1	5.8	8.9	17.2
IC50 [µM]	**>30**	**5.47**	**6.15**	**4.14**	**0.837**	**27.2**

DM-4103 (Mean % of transport of negative control

Concentration [µM]	*OAT1*	*OAT3*	*OATP1B1*	*OATP1B3*	*OCT1*	*OCT2*
0.064	124.0	64.9	58.5	82.4	80.9	120.7
0.32	111.1	58.1	56.3	97.3	71.5	126.1
1.6	99.4	37.0	26.3	63.1	72.1	141.4
8	78.6	9.1	2.0	20.1	35.1	99.5

40	11.9	0	0.0	2.9	24.4	38.0
200	0.6	0	0.0	2.1	11.2	35.4
Control	28.5	8.9	2.1	5.8	8.9	17.2
IC50 [µM]	**13.0**	**0.425**	**0.255**	**2.90**	**4.37**	**29.8**

DM-4107 (Mean % of transport of negative control)

Concentration [µM]	*OAT1*	*OAT3*	*OATP1B1*	*OATP1B3*	*OCT1*	*OCT2*
0.064	79.7	60.5	91.5	108.5	80.1	51.0
0.32	79.9	58.6	111.1	107.7	100.5	108.3
1.6	83.0	45.1	105.0	92.4	109.2	57.2
8	85.0	11.6	53.2	60.8	85.0	81.9
40	57.3	1.9	6.4	18.6	44.7	76.0
200	29.4	0.0	0.6	3.3	0	87.9
Control	28.5	8.9	2.1	5.8	8.9	17.2
IC50 [µM]	**92.8**	**0.475**	**8.37**	**10.3**	**35.1**	**>200**

4.6 Bile salt export pump (BSEP)

EDR Link	4.2.2.6 Report No. 030785
Moieties and concentrations tested	Tolvaptan: 0.0096, 0.048, 0.24, 1.2, 6, 30 µM DM-4103 and DM-4107: 0.064, 0.32, 1.6, 8, 40, 200 µM
Substrates	Deuterated Taurocholic acid (TCA) at 2 to 50 µM
Control	Rifampicin
Cells	Inside-out membrane vesicles from Sf9 cells over-expressing hBSEP
Results	Tolvaptan (Mean % of transport of negative control)

Concentration [µM]	
0.1	124
1	113
2	133
5	116
10	101
20	74.4
30	44.4
40	23.4
50	16.4
Rifampicin 50 µM	31.1
IC50 [µM]	**31.6**
Ki	**34.2 (noncompetitive)**

(Mean % of transport of negative control)

Concentration [µM]	*DM-4103*
0.1	108
0.3	91.8
1	83.0
2	70.7
5	43.4
10	30.0
20	17.3
30	8.1
40	5.2
50	0.0
75	1.8
IC50 [µM]	**4.15**
Ki	**3.77 (Competitive)**

(Mean % of transport of negative control)

Concentration [µM]	*DM-4107*
10	97.1
20	85.4
50	82.4
100	57.3
150	41.3
200	24.9
Rifampin 50 µM	49.8
IC50 [µM]	**119**

4.7 Multi-drug resistance gene 1 (MDR1)

EDR Link	4.2.2.6 Report No. 030998
PI and Location	Otsuka, Japan
Moieties and concentrations tested	DM-4103 and DM-4107: 6, 20, 60, 200 µM
Substrates	Deuterated quinidine (0.05 µM)
Control	Verapamil HCl (100 µM)
Cells	Human MDR1 expressing cells from in-house cell bank
Results	(Mean % of transport of negative control)

Concentration [µM]	*DM-4103*	*DM-4107*
2	101.4	91.7
6	90.4	71.7
20	75.8	97.4

60	72.4	84.9
200	81.5	94.9
Verapamil 100 µM		15.3
IC50 [µM]	**>200**	**>200**

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/s/

MARTINA D SAHRE
04/16/2018

SUDHARSHAN HARIHARAN
04/16/2018

MEHUL U MEHTA
04/16/2018

CLINICAL PHARMACOLOGY REVIEW - AMENDMENT

Brand Name	To Be Determined
INN Name	Tolvaptan
NDA Number and Type	204,441
Applicant Name	Otsuka
Submission Date	March 1, 2013
EDR Link	\\cdsesub1\evsprod\nda204441
Indication	Treatment of ADPKD
Dosage Form & Strengths	15, 30, 60, 90 mg immediate release tablets
OCP Division	OCPI, Cardiovascular and renal products team
OND Division	ODEI, Division of cardiovascular and renal products
Reviewer	Martina Sahre, PhD
Pharmacometrics Reviewer	Fang Li, PhD
Team Leader	Rajanikanth Madabushi, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD

Table of Contents

1 Corrections to the previous review

This section serves to correct three errors in the clinical pharmacology review.

- In Section 2.2.3.2 the caption for Figure 11 erroneously refers to study 156-04-251. The correct reference is to study 156-04-250.
- In Section 2.3.1 the following sentence needs to be removed as it is incorrect: "However, the model only included a logical value (Yes/No) for coadministration at any time during trial participation. In addition, information about the duration of the concomitant administration or verification of sample collection for PK during concomitant administration was not collected."
- The eligibility criterion referred to in Section 2.2.4.2 is a baseline creatinine clearance of at least 60 mL/min as measured by the Cockcroft-Gault equation, not the baseline GFR, as was erroneously stated in the original review.
- In the PM review, we added one more question evaluating whether TKV baseline is a prognostic factor for eGFR reduction.

2 Findings from the Office of Scientific Investigation Inspection

The sponsor conducted study 156-11-295 to assess bioequivalence between the currently marketed 30 mg and the to-be-marketed 90 mg tablet. As this constituted the pivotal BE study and the applicant requested a waiver for the 45 mg tablet strength, an inspection of the clinical and bioanalytical sites for study 156-11-295 was requested. The results from this inspection suggest that: (b) (4)

Pending responses from the applicant, the Office of Scientific Investigation has deemed the study unfit for Agency review. Therefore, it may not be possible to draw conclusions from study 156-11-295. Hence, pending additional information that alleviates this concern, the 90 mg strength cannot be approved for marketing.

3 Individual Study Reviews

3.1 Study 156-04-248 (Single Ascending Dose Study)

Report #: 156-04-248	Study Period: 04 Oct 2004 – 23 Oct 2004
EDR Link	\\cdsesub1\evsprod\nda204441\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\study-156-04-248-stf\study-156-04-248.pdf
Title	A phase 2, randomized, double-blind, placebo-controlled, ascending dose study to determine the safety, pharmacokinetics, and pharmacodynamics of orally administered tolvaptan tablets in male and female adults diagnosed with autosomal dominant polycystic kidney disease
Objective	Study 156-04-248 was done to elucidate the PK, PD and tolerability of tolvaptan single doses in ADPKD patients.
Sponsor	Otsuka Maryland Research Institute
Principal Investigator	Thomas Marbury, MD
Study Location	Orlando Clinical Research Center, Orlando, FL

Study Design

Design: Single ascending doses, randomized, double-blind, placebo-controlled, single-center, ADPKD patients
Planned enrollment: 9 to 21 adults with ADPKD
Planned doses

Day 1: 15 mg or placebo
Day 4: 30 mg or placebo
Day 7: 60 or 90 mg or placebo
Day 10: 120 or 180 mg or placebo

In addition all subjects were taking a calcium/vitamin D combination product (Os-Cal 500 + D) twice daily after lunch and a bedtime snack to blunt a potential influence of parathyroid hormone on variability of blood and urine cAMP levels.

Investigational medicinal product

Dose	15 mg	30 mg	60 mg
Batch	02C80A015B	02C80A030B	02C80A060
Dosage form	Tablets		

Administration: Fasted
Concomitant medications were not allowed, except for angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for the treatment of hypertension.

PK Sampling Times
Blood samples for plasma PK analysis were taken at the following time points:

- Days 1, 4, 7, and 10 at pre-dose (0), 1, 2, 3, 4, 8, 12, 16 h post-dose
- Days 2, 5, 8 and 11: 24, 30, 36 h post-dose

- Day 9 only: 48 h post-dose

PK Parameters
Data were analyzed using non-compartmental analysis in WinNonlin software. The following PK parameters were assessed: Cmax, tmax, λz, AUCt, $t_{1/2}$, AUC_{∞}, CL/F.

PD Sampling Times
Urine samples were collected at the following intervals:
- Day -1: 0-4, 4-8, 8-12, 12-16, 16-24 h pre-dose
- Days 1-3, 4-6, 7-9, and 10-11: 0-4, 4-8, 8-12, 12-16, 16-24, 24-28, 28-32, 32-36, 36-40, 40-48 h post-dose

PD Endpoints
The primary PD marker of interest was urine osmolality. The intention for treatment is to lower urine osmolality to below 300 mOsm/kg during the dosing interval. The $AUC_{0\text{-}28\ h}$ for urine osmolality was determined for comparisons among doses and to elucidate drug effect.
In addition, the time it took for patients to reach a less than 300 mOsm/kg urine osmolality was also calculated.

Other PD Parameters
In addition to urine osmolality, the following parameters were also assessed:
- plasma and urine cAMP,
- plasma neurophysin and AVP
- intact parathyroid hormone and ionized calcium in serum
- serum osmolality, sodium, and potassium
- urine sodium, albumin, potassium, aquaporin 2
- urine volume and fluid balance (Fluid intake-urine volume)
- number of times out of bed (after the 16 h collection interval)

Analytical Method

Pharmacokinetic plasma samples were analyzed for tolvaptan and one of its metabolites DM-4103.

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Tolvaptan, DM-4103		

Validation*	▪ Method validated prior to use	Yes
	▪ Method validation acceptable	Yes
Study Sample Analysis*	▪ Samples analyzed within the established stability period	Yes
	▪ Quality control samples range acceptable	Yes
	▪ Chromatograms provided	Yes
	▪ Accuracy and precision of the calibration curve acceptable	Yes
	▪ Accuracy and precision of the quality control samples acceptable	Yes
	▪ Overall performance acceptable	Yes

*Acceptability criteria based on "Guidance for Industry: Bioanalytical Method Validation", 2001

Results

Study Population

Demographics and disposition

Population	Tolvaptan N	Placebo N	Total N
Randomized	8	3	11
Treated	8	3	11
Completed	8	3	11
Discontinued Due to AE	0	0	0
PK Population/Safety Population	8	3	11
Age [Median (range)]	43 (22-47)	33 (27-34)	34 (22-47)
Male/Female	2/6	2/1	4/7
Race (Caucasian/Native American)	7/1	3/0	10/1
Weight [kg]	73.4 (50.1-102.7)	90.0 (79.5-100.0)	77.9 (50.1-102.7)

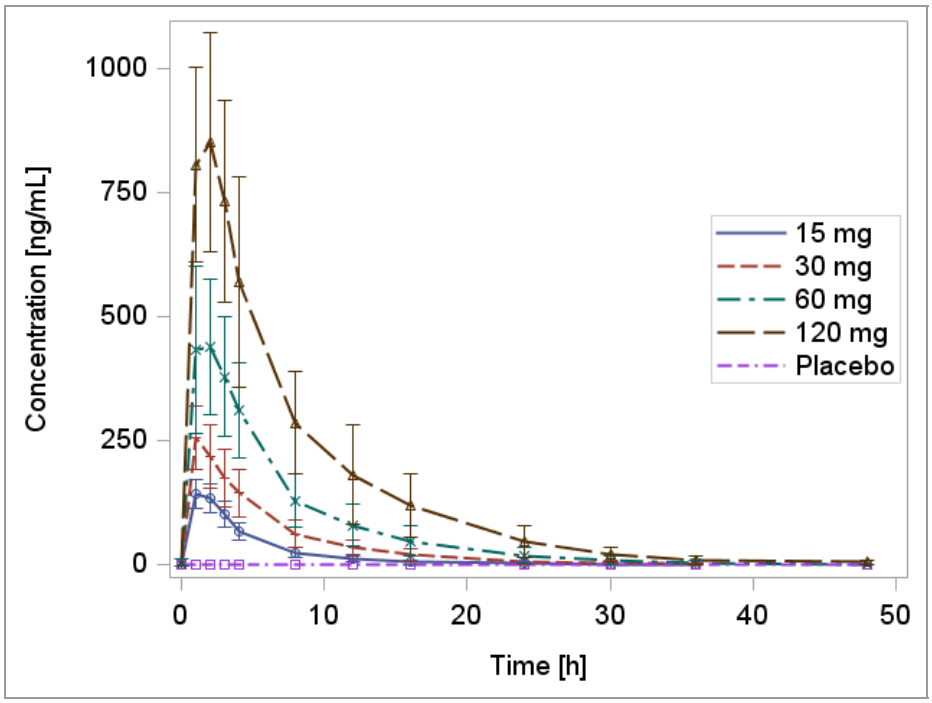
[Source: CSR 156-04-248 Tables 8.1-1 and 8.2-1]

Pharmacokinetics

Pharmacokinetic parameters by dose group, Arithmetic Mean (%CV)

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUCt (ng h/mL)	AUCinf [ng*h/mL]	$t_{1/2}$ (h)	CL/F (L/h)
N	8	8	8	5	5	5
15 mg	146 (24.2)	1.00 (1.00-2.00)	686 (37.5)	880 (36.1)*	3.6 (2.4-8.6)	3.78 (44.8)
30 mg	263 (28.4)	1.00 (1.00-2.00)	1520 (45.9)	1430 (43.0)*	4.1 (2.9-6.2)*	6.03 (38.2)*
60 mg	481 (36.8)	1.50 (1.00-3.00)	3280 (42.7)	4150 (27.6)**	4.8 (4.2-6.5)**	3.99 (48.3)**
120 mg	917 (25.8)	1.50 (1.00-3.00)	6900 (40.5)	7740 (40.1)**	4.9 (3.7-8.3)**	4.45 (59.9)**

[Source: CSR 156-04-248 Figure 9.2.3-2; * n=7, ** n=5]



Mean tolvaptan concentration (Error Bars : 95% CI) in plasma

Dose proportionality

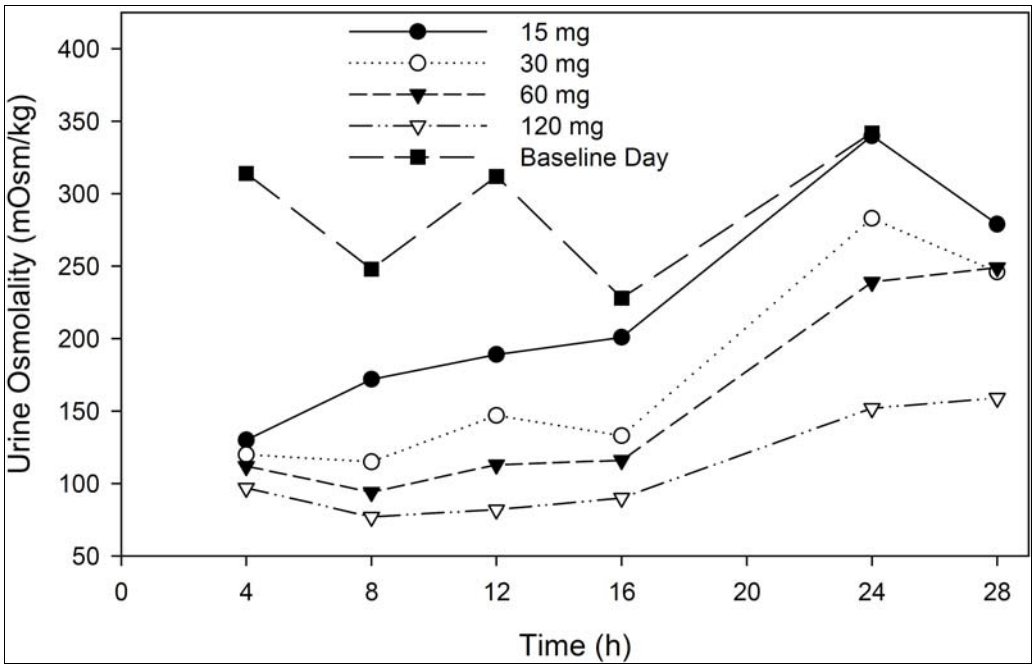
Parameter	Dose Range	Slope	95% CI
AUCt (ng h/mL)	15-120	1.105	0.997, 1.214
C_{max} (ng/mL)	15-120	0.873	0.786, 0.961

Pharmacodynamic Parameters

Table 1. $AUC_{(0-28h)}$ of urine osmolality by dose group

Treatment	$AUC_{(0-28h)}$ [mOsm*h/kg] Mean (SD)	
	Tolvaptan	Placebo
Baseline	8412 (1538)	8346 (1876)
15 mg	6615 (1108)	8788 (3988)
30 mg	5313 (671)	7918 (2451)
60 mg	4663 (807)	7653 (966)
120 mg	3251 (539)	7653 (817)

[Source: CSR 156-04-248 Table 9.3.3-1]



Mean urine osmolality over time, by treatment
[Source: CSR 156-04-248 Figure 9.3.3-1]

Safety

Was there any death or serious adverse events? No
All doses seem to have been well tolerated. The most common treatment emergent adverse events were dry mouth, headache, and somnolence, some of which were ruled potentially related to study drug by the investigator.

Conclusions

Tolvaptan shows dose proportional PK after single doses in the range of 15 to 120 mg. Likewise, a dose-dependent trend for reduction of urine osmolality was observed. Maximum effect was achieved quickly, within the first 4- observation interval. A single 15 mg dose was insufficient to maintain urine osmolality reduced throughout the entire dosing interval. The 120 mg dose showed a sustained decrease in urine osmolality throughout the entire dosing interval.

3.2 Study 156-04-249 (Multiple Dose Study)

Report #: 156-04-249	**Study Period:** 08 Nov 2004 – 03 Mar 2005
EDR Link	\\cdsesub1\evsprod\nda204441\0001\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\study-156-04-249-stf\study-156-04-249.pdf
Title	A Phase 2, Inpatient, Double-Blind, Randomized, Double-Blind, Parallel-Arm Study To Determine The Safety, Pharmacokinetics, Pharmacodynamics And Tolerability Of Multiple QD/BID Doses Of Orally Administered Tolvaptan Tablets In Male And Female Adults Diagnosed With Autosomal Dominant Polycystic Kidney Disease
Rationale	To examine the safety, PK, and PD of multiple dose application of tolvaptan in ADPKD and to compare several regimens of application.
Sponsor	Otsuka Maryland Research Institute, Inc.
Principal Investigator	Thomas Marbury, MD
Study Location	Orlando Clinical Research Center, Orlando, FL

Study Design

Design: Multiple doses, randomized, double-blind, parallel, single-center, ADPKD patients
Planned enrollment: 18 to 48 adults with ADPKD
Planned doses:

A. 15 mg BID x 5 days
B. 30 mg BID x 5 days
C. 30 mg + 15 mg x 5 days
D. 30 mg + placebo x 5 days

Doses were timed so that the second daily dose was taken 8 h after the morning dose, which was taken at around 9 am.
In addition all subjects were taking a calcium/vitamin D combination product (Os-Cal 500 + D) twice daily after lunch and with a snack at bedtime to blunt a potential influence of parathyroid hormone on variability of blood and urine cAMP levels.

Randomization

Subjects were assigned to treatment, stratified by gender, in two cohorts. Cohort 1 was assigned to treatment in blocks of size 3 (one each for treatments 15 mg BID, 30 mg BID, and 30/15 mg). Cohort 2 was assigned to treatment in blocks of size 6 (one each for treatments 15 mg BID, 30 mg BID, and 30/15 mg and three for treatment 30/0 mg).

Dose	15 mg	30 mg	Placebo
Batch	02C80A015A	02C80A030B	02C80P000C
Dosage form	tablet		

Administration: Breakfast given after scheduled dose time (not further specified)
Concomitant medications were not allowed, except for angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) for the treatment of hypertension.

PK Sampling Times

Blood samples for plasma PK analysis were taken at the following time points:

- Days 1 and 5: pre-dose (0), 1, 2, 3, 4, 8, 9, 10, 11, 12, 16 h post-dose
- Day 2: 24 h
- Day 6: 24, 30, 36 h post-dose
- Day 7 only: 48 h post-dose

PK Parameters

Data were analyzed using non-compartmental analysis in WinNonlin software.
The primary PK parameters were estimated from PK samples on Day 5: Cmax, Tmax, AUC24.
Parameters for Day 1 and Day 5 were Cmax, Tmax and AUC24, in addition to Day 5 values for accumulation ratios for Cmax and AUC24 and terminal t1/2.

PD Sampling Times

Urine samples were collected at the following intervals:
Day -1: 0-4, 4-8, 8-12, 12-16, 16-24 h pre-dose
Day 1: 0-4, 4-8, 8-12, 12-16, 16-24
Day 6: 0-4, 4-8, 8-12, 12-16, 16-24, 24-28, 28-32, 32-36, 36-40, 40-48 h post-dose

PD Endpoints

The primary PD marker of interest was urine osmolality. The intention for treatment is to lower urine osmolality (Uosm) to below 300 mOsm/kg during the dosing interval, which is thought to show efficacious response, however, most patients should show maximal suppression of urine osmolality to <100 mosm/kg. The AUC0-28 h for urine osmolality was determined for comparisons among doses and to elucidate drug effect.
In addition, the time it took for patients to reach a less than 300 mOsm/kg urine osmolality was also calculated.
In addition to urine osmolality, the following parameters were also assessed:
plasma and urine cAMP,
plasma neurophysin and AVP
intact parathyroid hormone and ionized calcium in serum
serum osmolality, sodium, and potassium
urine sodium, albumin, potassium, aquaporin 2
urine volume and fluid balance (Fluid intake-urine volume)
number of times out of bed (after the 16 h collection interval)

Analytical Method

Pharmacokinetic plasma samples were analyzed for tolvaptan and one of its metabolites DM-4103.

Method Type	LC/MS/MS	Matrix	Plasma

Analytes	Tolvaptan, DM-4103

Validation*	Method validated prior to use	Yes
	Method validation acceptable	Yes
Study Sample Analysis*	Samples analyzed within the established stability period	Yes
	Quality control samples range acceptable	Yes
	Chromatograms provided	Yes
	Accuracy and precision of the calibration curve acceptable	Yes
	Accuracy and precision of the quality control samples acceptable	Yes
	Overall performance acceptable	Yes

*Acceptability criteria based on "Guidance for Industry: Bioanalytical Method Validation", 2001

Results

Study Population

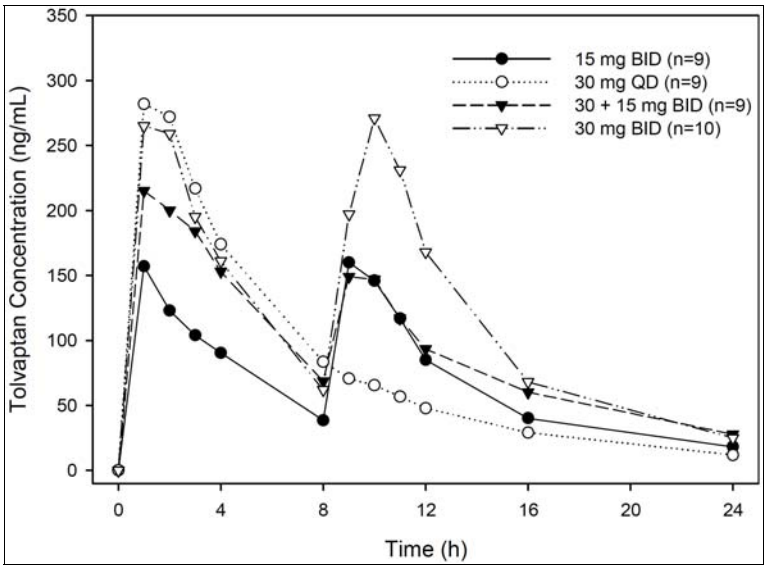
Population	15 mg BID	30 mg BID	30/15 mg	30/0 mg	Total N
Randomized	9	10	9	9	37
Treated	9	10	9	9	37
Completed	9	10	9	9	37
Discontinued Due to AE	0	0	0	0	0
PK Population/Safety Population	9	10	9	9	37
*Age	41 (25-50)	45 (34-54)	42 (32-48)	40 (27-58)	42 (25-58)
Male/Female	2/7	2/8	2/7	2/7	8/29
Race (Caucasian/Black or African American/Other)	8/1/0	9/0/1	9/0/0	9/0/0	35/1/1
**Weight [kg]	96.6 (28.0)	68.7 (10.5)	72.2 (16.1)	74.8 (13.8)	77.9 (20.6)
*Total kidney volume (TKV) [mL]	1295 (307-3177)	1264 (799-3201)	1545 (881-3683)	1072 (760-1289)	1226 (307-3683)
Right	262 (145-1003)	845 (536-1373)	446 (433-459)	502.5 (408-768)	536 (145-1373)
Left	293 (108-2513)	1264 (799-3201)	1545 (881-3683)	513 (455-820)	1226 (307-3686))

*[Median (range)], **[Mean (SD)]

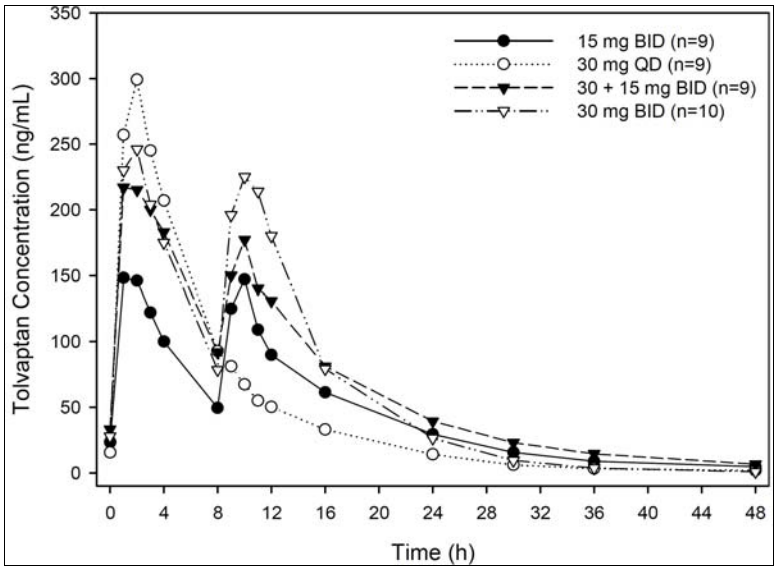
Pharmacokinetics

Dose (mg)	Cmax (ng/mL)	*Tmax (h)	AUC24 (ng*h/mL)	t1/2 (h)	Rac (Cmax)	Rac (AUC)
N**	9	9	9	9	9	9
15 mg BID						
Day 1	201 (88.5)	8.97 (1.00-11.00)	1650 (774)			
Day 5	190 (60.5)	9.00 (0.95-9.98)	1890 (1070)	6.2 (3.3)	1.04 (0.45)	1.16 (0.38)
30 mg BID						
Day 1	335 (135)	2.00 (1.00-10.000)	2900 (1340)			
Day 5	295 (122)	5.47 (0.93-12.02)	2990 (1640)	4.7 (1.8)	0.91 (0.22)	1.02 (0.13)
30/15 mg						
Day 1	262 (55.1)	1.00 (1.00-10.00)	2270 (1650)			
Day 5	269 (69.2)	0.98 (0.97-9.95)	2770 (2020)	6.4 (3.7)	1.04 (0.26)	1.21 (0.24)
30/0 mg						
Day 1	312 (205)	2.00 (1.00-4.00)	1950 (1490)			
Day 5	330 (230)	1.98 (0.98-2.98)	2140 (1620)	4.3 (1.2)	1.03 (0.18)	1.09 (0.22)

*[Median (range)], Rac= accumulation ratio, **N=10 in 30 mg BID group



Mean plasma concentrations of tolvaptan on Day 1
[Source: CSR 156-04-249 Figure 9.3.3-1]



Mean plasma concentrations of tolvaptan on Day 5

[Source: CSR 156-04-249 Figure 9.2.3-2]

Pharmacodynamic Markers

Urine osmolality

Arithmetic mean (SD) AUC0-28h [mOsm*h/kg] of urine osmolality at Baseline and on Day 5

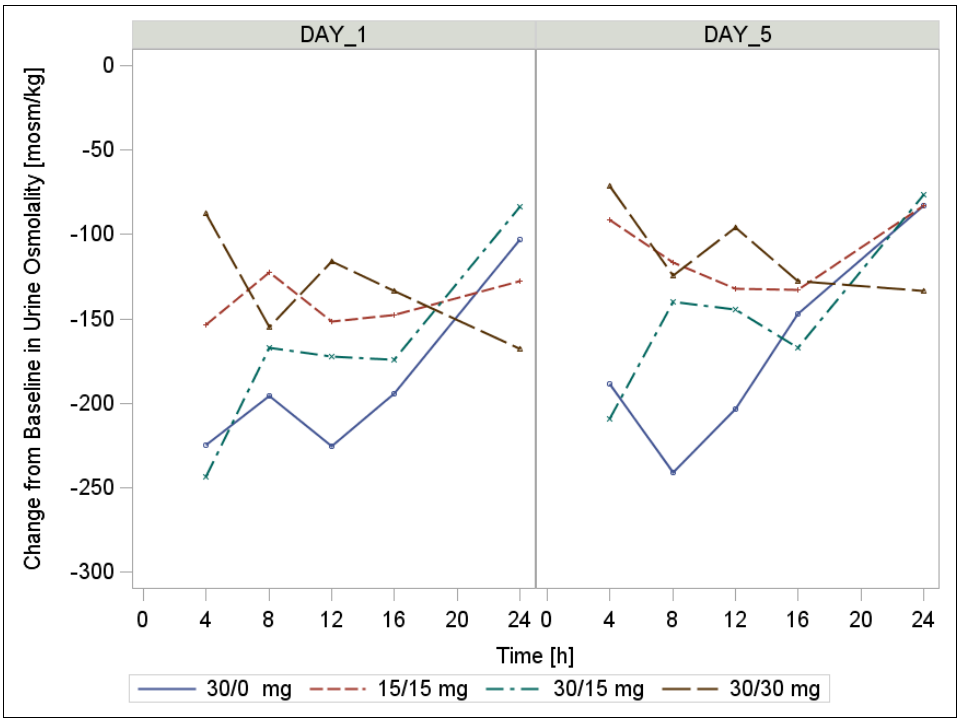
Study Day	TLV 15 mg BID (N = 9)	TLV 30 mg QD (N = 9)	TLV 30 + 15 mg BID (N = 9)	TLV 30 mg BID (N = 10)
Baseline (Day -1)	8331 (3686)	10881 (6408)	9412 (3431)	8054 (5422)
Day 5	4871 (1672)	6322 (3060)	4942 (1796)	4216 (1863)

[Source: CSR 156-04-249 Table 9.3.3-1]

Duration and number of patients with Uosm < 300 mOsm/kg

Parameter	15 mg BID	30 mg BID	30/15 mg	30/0 mg
Duration <300 mOsm/kg [h] Baseline (observed 24 h) Day 1 (observed 24 h) Day 5 (observed 48 h)	24.0 (0.0-24.0) 24.0 (16.0-24.0) 36.0 (0.0-48.0)	20.0 (0.0-24.0) 24.0 (24.0-24.0) 48.0 (8.0-48.0)	8.0 (0.0-24.0) 24.0 (16.0-24.0) 32.0 (4.0-48.0)	4.0 (0.0-24.0) 16.0 (4.0-24.0) 16.0 (8.0-48.0)
n/N (%) <300 mOsm/kg for 24 h Baseline Day 1 Day 5	 5/9 (55.6) 8/9 (88.9) 8/9 (88.9)	 5/10 (50.0) 10/10 (100) 9/10 (90.0)	 1/9 (11.1) 8/9 (88.9) 7/9 (77.8)	 2/9 (22.2) 4/9 (44.4) 4/9 (44.4)

[Source: CSR 156-04-249 Tables 6.1.1, 6.1.2, and 6.1.3]



Urine osmolality over time at Baseline, Day 1 and after 5 days of dosing
[Source: Analysis dataset urin0.xpt]

Safety

Was there any death or serious adverse events? No
All doses seem to have been well tolerated. The most common treatment emergent adverse events were dry mouth, headache, somnolence., some of which were ruled potentially related to study drug by the investigator.

Conclusions

Urine osmolality decreased similarly between the dosing regimens and total daily doses studied. Based on the results from this study, it is not completely clear that a single daily dose regimen would be significantly inferior to a twice daily regimen with or without split dosing. Higher total daily doses did not yield greater decreases from baseline in urine osmolality.

3.3 Study 156-09-284 (Renal Function Study)

Report #	156-09-284
Study Period	October 6, 2010 – November 11, 2011
EDR Link	\\cdsesub1\evsprod\nda204441\0001\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\study-156-09-284-stf\report-body.pdf
Title	A Phase 2a, Single-center Study Investigating the Short-term Renal Hemodynamic Effects, Safety and Pharmacokinetics/Pharmacodynamics of Oral Tolvaptan in Subjects With Autosomal Dominant Polycystic Kidney Disease at Various Stages of Renal Function
Rationale	Results from earlier trials for the hyponatremia indication and in ADPKD patients indicated that there is a small, but significant increase in uric acid and transiently in serum creatinine, while there is also a small decrease in blood urea nitrogen after administration of tolvaptan. A study testing the effect of 30 mg tolvaptan treatment on renal hemodynamics in heart failure patients showed no effect on the above mentioned laboratory parameters, however it has been observed in ADPKD patients. This study was therefore done to assess whether there is an impact of tolvaptan treatment at higher doses (total daily dose 60 to 120 mg).
Principal Investigator	Ron T. Gansevoort, MD, PhD
Study Location	University Medical Center Groningen, Netherlands

Study Design

Design	Multiple dose, single center
Subjects	ADPKD patients stratified by degree of renal impairment

Planned enrollment
36 female and male patients, with a minimum of 6 patients per stratum were to be enrolled in the trial.

Strata
The renal impairment strata were based on $eGFR_{MDRD}$ at baseline as follows:
Group A: $eGFR_{MDRD}$ >60 mL/min/1.73 m2,
Group B: $eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m2,
Group C: $eGFR_{MDRD}$ <30 mL/min/1.73 m2.

Reviewer's Note: As in previous trials assessing impact of tolvaptan on renal impairment, or impact of renal impairment on tolvaptan PK, patients with normal function and mild renal impairment were included in one group. For the purpose of this study, this seems acceptable, as renal function seems to remain unaffected in the early stages of the disease.

Planned doses
Patients received tolvaptan in a split BID dose, with the higher dose administered in the mornings and the smaller dose given approximately 8 h later.
The doses were titrated weekly based on tolerability and safety from a dose of 45/15 in week 1, to 60/30 in week 2, up to 90/30 in week 3.

Table 1. Investigational medicinal product

Dose	15 mg	30 mg
Batch	09I94A015A	09J77A030A
Dosage form	tablets	

Reviewer's Note: The doses administered in this trial are those that were studied in the pivotal phase 3 study (TEMPO trial).
All but two patients were titrated to the highest dose of 90/30 mg tolvaptan. Two patients discontinued the study as described in the Safety section.

Administration: Fasted

Concomitant medications
For hypertensive patients, ACE inhibitors or ARBs were required co-medications. If patients were receiving diuretics at screening, they could be enrolled if they were able to be controlled on another blood pressure medication. Patients who were still hypertensive while receiving an ACE inhibitor or an ARB could have received other antihypertensives, except for diuretics. Other medications for the treatment of ADPKD were not allowed. Potent CYP3A4 inhibitors (with the exception of amiodarone) were to be avoided during the trial.

Overall Study Procedures Summary

PK Sampling Times:
Blood samples for plasma PK analysis were taken at the following time points:
Day 0: prior to start of infusion,
Day 21 ± 1 or within 1 week of reaching maximum dose (Final treatment day): prior to infusion, and at 1, 2, 3, 4, and 5 h post dose,
Post treatment (3 weeks ± 3 days after last dose): prior to start of infusion.
If a patient discontinued prematurely, a blood sample was collected on the discontinuation day.

PK Parameters:
Data were analyzed using non-compartmental analysis in WinNonlin software. The following PK parameters were assessed: Cmax, Tmax, λz, AUCt, t1/2, AUC∞, CL/F.

PD Sampling Times:
24-h split urine samples were collected by patients at home in the 24 h prior to admission to the renal function ward. The collection intervals went from 7 am to 5 pm, 5 pm to bedtime and bedtime to 7 am on the following days:
- one day prior to the baseline visit,
- one day prior to the final treatment visit, and
- one day prior to the post treatment visit.

PD Endpoints:
Measured Glomerular Filtration Rate (mGFR), Effective Renal Plasma Flow (ERPF), Filtration Fraction (FF)
On renal function testing days, patients received 20 mL priming solution containing 0.04 MBq of ^{125}I-iothalamate (for determination of mGFR) and 0.03 MBq ^{131}I-hippuran (for

determination of ERPF) at 8 am, which was followed by a constant infusion of 6-12 mL/h of the infusion solution for 1.5 h. The infusion rate was lowest in patients with lowest renal function. Following the infusion were two periods of two hours each from 9:30 to 11:30 am and from 11:30 am to 1:30 pm to assess clearance of iothalamate and hippuran. Blood was drawn at 1, 2, 3, 4, and 5 hours post dose.

Calculation of mGFR: $$CL_{iothalamate} = \frac{(U_{iothalamate} * V)}{P_{iothalamate}},$$

Calculation of ERPF: $$CL_{hippuran} = \frac{(U_{hippuran} * V)}{P_{hippuran}},$$

where U=concentration of tracer in urine, V=volume of urine collected, and P=plasma concentration of tracer at the end of either clearance collection interval.

Measured GFR was adjusted for voiding errors as follows:

$$CL_{iothalamate,\,corr.} = \frac{\frac{I_{hippuran} * V}{P_{hippuran}}}{\frac{U_{hippuran} * V}{P_{hippuran}}} * CL_{iothalamate} = \frac{CL_{hippuran,\,plasma}}{CL_{hippuran,\,urine}} * CL_{iothalamate}$$

where I is measured in counts/mL of infusion.

Other PD markers measured were:

- urine volume and free water clearance (FWC)
- urine sodium, potassium, osmoles, creatinine, urea, uric acid, aldosterone, albumin
- serum sodium, potassium, creatinine, osmoles, urea, uric acid, albumin, cystatin C, active plasma renin, copeptin, aldosterone
- urine albumin to creatinine
- MAP

Magnetic Resonance Imaging:
MRI was performed to assess total kidney volume (TKV), but without gadolinium contrast. MRI was done at the following time points, and had to fall within the visit window:

- baseline
- final treatment visit
- post-treatment visit
- early termination.

Safety Measures

- AEs,
- vital signs,
- safety labs (CBC with differential, Hct, Hb, Platelets, INR, aPTT, urinalysis, CMP, cholesterol, lactic dehydrogenase, triglycerides, uric acid),
- physical exams,

- ECG.

Statistical Analysis
All patients who took trial medication and had a post-baseline renal function measurement were included in the analysis of PD data.
For calculation of descriptive statistics for PK data, values below LLOQ were set to 0 and non-compartmental analysis was conducted using WinNonlin 5.2 software.
Pharmacodynamic data was also analyzed using descriptive statistics by group and visit.
Group comparisons were made using a paired t-test as well as Wilcoxon's singed-rank test and between group comparisons were made using Wilcoxon's rank-sum test.

Analytical Method
The pharmacokinetic plasma samples were analyzed for tolvaptan and its metabolites DM-4103 and DM-4107.

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Tolvaptan, DM-4103, DM-4107		

Validation*	Method validated prior to use	Yes
	Method validation acceptable	Yes
Study Sample Analysis*	Samples analyzed within the established stability period	Yes
	Quality control samples range acceptable	Yes
	Chromatograms provided	Yes
	Accuracy and precision of the calibration curve acceptable	Yes
	Accuracy and precision of the quality control samples acceptable	Yes
	Overall performance acceptable	Yes

*Acceptability criteria based on "Guidance for Industry: Bioanalytical Method Validation", 2001

Results

Disposition and Demographics

Population	$eGFR_{MDRD}$ >60 mL/min/1.73 m2	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m2	$eGFR_{MDRD}$ <30 mL/min/1.73 m2
Randomized	10	10	9
Treated	10	10	9
Completed	9	9	9
Discontinued Due to AE	1	1	0
PD Population	9	9	9
Safety Population	10	10	9
Age [Median (range)]	35.5 (32-54)	46.5 (25-69)	51 (40-61)
Male/Female	4/6	4/6	7/2
Race (Caucasian/Other)	10	9/1	9/0
Hypertension (Yes/No)	7/3	9/1	9/0
ACE inhibitor/ARB	7	9	8

Beta blocker	0	2	2
CCB	2	2	6
TKV [mL]	1376.7 (605.5-2527.8)	1812.8 (528.7-3775.7)	4360.7 (2106.9-10280)
Weight [kg]	74.8 (18.1)	78.3 (15.1)	90.11 (18.1)

	$eGFR_{MDRD}$ >60 mL/min/1.73 m2		$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m2		$eGFR_{MDRD}$ <30 mL/min/1.73 m2	
	Male	Female	Male	Female	Male	Female
eGFRMDRD at Screening [mL/min]	87.2 (67.5-105.2)	82.2 (64.5-110.0)	44.1 (41.0-47.0)	46.8 (32.8-60.0)	20.7 (14.0-29.0)	16.5 (16.0-17.0)

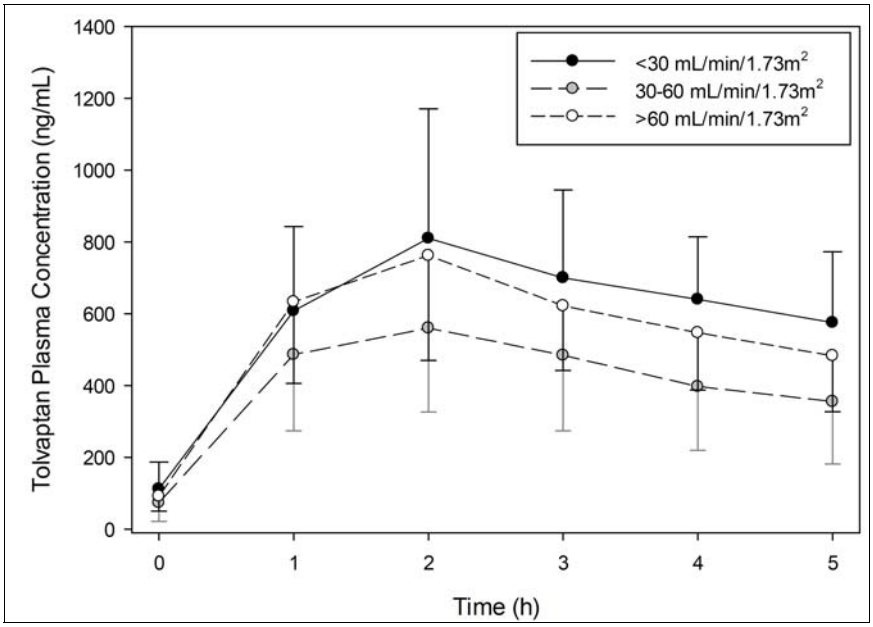
[Source: CSR 156-09-284 Tables 8.1-1 and 8.2-1]

Pharmacokinetics

Parameters by Dose Group, Arithmetic Mean (%CV)

Group	Cmax (ng/mL)	Tmax (h)	AUC0-5 (ng h/mL)
A (N=8)	828 (297)	2.00 (1.00-3.00)	2850 (774)
B (N=9)	591 (235)	2.00 (1.00-3.00)	2140 (863)
C (N=9)	840 (355)	2.00 (1.00-5.00)	3100 (1060)

[Source: CSR 156-09-284 Table 9.2.3.4-1]



Mean (SD) tolvaptan concentrations in plasma after one week of treatment at 90/30 mg dose

[Source: CSR 156-09-284 Figure 9.2.3.1-1]]

Reviewer's Note: AUC and Cmax are higher in the <30 and >60 mL/min GFR groups compared to patients with a GFR between 30 and 60 mL/min. This is different from results found from study 156-09-282, which studied the impact of renal impairment on tolvaptan PK. In that study, patients in the <30 and 30-60 mL/min GFR groups showed

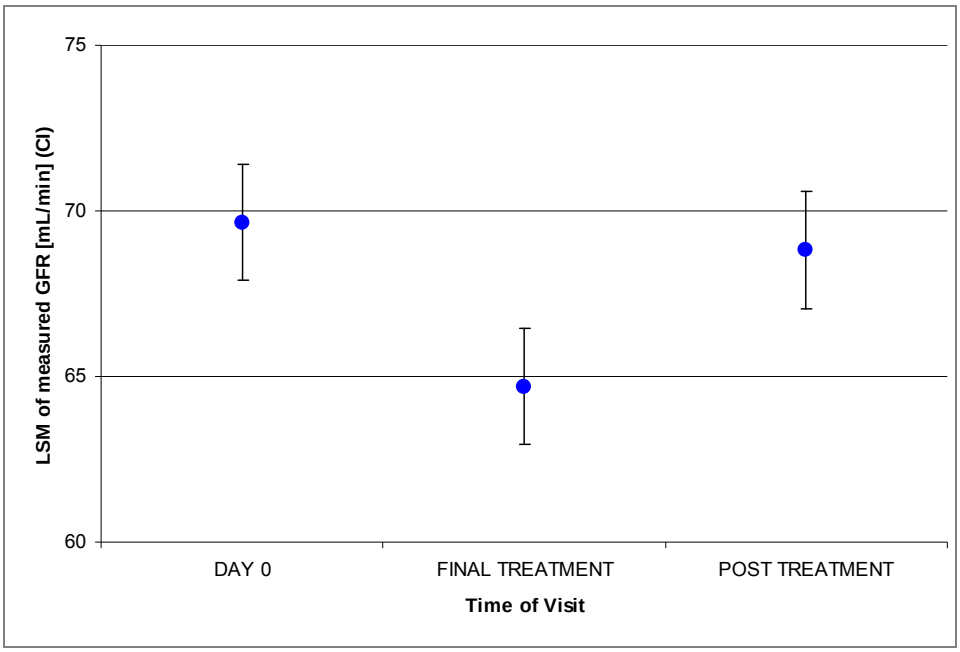
higher exposure than those in the >60 mL/min group. The reason for these inconsistent findings is not clear.

Pharmacokinetics

Pharmacodynamic Parameters

Population		$eGFR_{MDRD}$ >60 mL/min/1.73 m2	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m2	$eGFR_{MDRD}$ <30 mL/min/1.73 m2
Absolute Values				
mGFR [mL/min]	Baseline	112.3 (21.9)	66.3 (20.3)	29.3 (10.6)
	Final Trt	104.3 (22.7)	60.1 (16.6)	28.6 (10.0)
	Post Trt	112.3 (23.1)	64.8 (18.1)	26.9 (8.7)
ERPF [mL/min]	Baseline	335.9 (62.8)	222.8 (57.2)	98.1 (30.1)
	Final Trt	319.0 (77.6)	211.7 (47.0)	96.4 (28.6)
	Post Trt	340.2 (77.8)	214.3 (48.1)	91.5 (23.8)
FF	Baseline	0.335 (0.029)	0.296 (0.022)	0.303 (0.030)
	Final Trt	0.330 (0.024)	0.283 (0.023)	0.293 (0.029)
	Post Trt	0.333 (0.030)	0.301 (0.031)	0.289 (0.035)
Change from BL				
mGFR [mL/min]	Baseline			
	Final Trt	-8.0 (9.1)	-6.2 (6.2)	-0.7 (1.5)
	Post Trt	0.1 (4.9)	-1.5 (4.0)	-2.4 (4.6)
ERPF [mL/min]	Baseline			
	Final Trt	-16.9 (36.4)	-11.1 (18.4)	-1.7 (5.1)
	Post Trt	4.3 (30.2)	-8.4 (17.7)	-1.3 (10.3)
FF	Baseline			
	Final Trt	-0.005 (0.017)	-0.013 (0.016)	-0.010 (0.014)
	Post Trt	-0.003 (0.018)	0.006 (0.015)	-0.016 (0.023)

[Source: CSR 156-09-284 Table CT-5.1.1]



Least square mean measured GFR pooled across groups, adjusted by baseline GFR
Source: 156-09-284, pdparm0.xpt

Reviewer's Note: Measured GFR and ERPF decrease after initiation of treatment, with the smallest decrease seen in the group with severe renal impairment. Both measures return to baseline levels within three weeks after the last dose.

Safety

Were there any deaths or serious adverse events? No

Two patients discontinued treatment due to an AE. One each in group A and B. No patients discontinued treatment in group C (GFR <30 mL/min). The discontinuation in group A was due to a serious treatment emergent AE of polyuria on Day 2 (treatment: 45/15 mg tolvaptan). The patient (Subject number: (b) (6)) was discontinued and the last dose was taken on Day 4. The AE resolved without intervention on Day 5. The event was judged as a moderate TEAE and is considered related to tolvaptan.

One patient (Subject number: (b) (6)) in group B (GFR=30-60 mL/min) had experienced a mild AE of worsening dry mouth on Day 2 of treatment (45/15 mg) and had been sequentially titrated to 60/30 mg tolvaptan on Day 8. With the morning dose on Day 14 the event severity increased to moderate. The patient had a prior history of salivary gland dysfunction due to radiological treatment of throat cancer twelve years earlier. The patient discontinued treatment on Day 14 and the study on Day 22 for worsening dry mouth, which was judged to be moderate in severity and possibly related to tolvaptan. The AE resolved without medical intervention by Day 53.

Conclusions

Once tolvaptan treatment is initiated, GFR decreases, in all three renal function groups and returns to baseline within three weeks after drug is discontinued. This return to baseline is more complete the better the residual renal function. In patients with <30 mL/min renal function, the drop in GFR was lowest, but these patients, on average, had not fully returned to baseline.

The population being studied in Group A ($eGFR_{MDRD}$ >60 mL/min/1.73 m2) in this trial is similar to the population studied in trial 156-04-251 with regards to age, weight, renal function and kidney volume.

Comments

The >60 mL/min GFR group contains patients with what would be considered normal renal function and those that would, according to the guidance for renal impairment studies, be considered to have mild renal impairment. If there are changes in mild renal impairment with regard to PK or PD, disregarding mild levels of impairment in renal function may lead to underestimation of the effect of tolvaptan in renal impairment.

3.4 Study 156-11-295 (Bioequivalence and Food Effect Study)

Report # 156-11-295	Study Period: 04 Oct 2011 – 30 Nov 2011
EDR Link	\\cdsesub1\evsprod\nda204441\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-156-11-295-stf\report-body.pdf
Title	An Open-label, Randomized, Crossover Trial to Assess Dose Strength Equivalence Among 30 and 90 mg Strengths of Oral Tolvaptan Tablets and to Determine the Effect of Food (Standard Food and Drug Administration High-fat Breakfast) on Tolvaptan Pharmacokinetics Following the 90-mg Tablet in Healthy Subjects
Objective	To determine the dose strength equivalence between marketed 30 mg tablets and to be marketed 90 mg tablets. In addition the food effect after a standard high-fat breakfast was assessed.
Sponsor	Otsuka Pharmaceutical Development & Commercialization, Inc.
Principal Investigator	(b) (4)
Study Location	

Study Design

Design: Open-label, single center, single dose, randomized, 2 period, crossover, healthy volunteers.

Screening: -21 to -2 days

Washout: 96 h

Inpatient/Outpatient Stay, Duration: 8 day inpatient stay

Period 1: Days 1 to 4 → Period 2: Days 5-8 → Follow-up: Days 8-15 (+2) (by phone)

Doses: Part 1 - BE: 1 x 90 mg vs 3 x 30 mg tablets

Part 2 - Food Effects: 90 mg tablets fasted vs 90 mg tablets fed

Treatments

The study had two parts. Part one assessed the BE between the clinical trial formulation (30 mg tablets) compared to 90 mg to-be-marketed tablets. Part two assesses the food effect of a high fat, high calorie breakfast on the PK of a 90 mg dose.

For either part one or part two, volunteers were screened from three weeks to 2 days prior to randomization. On Day -1 subjects were checked into the clinical research unit as inpatients and were discharged on Day 8.

Possible sequences for Part 1 and Part 2

		Sequence 1	Sequence 2
Part 1	Period 1	3 x 30 mg	90 mg
	Period 2	90 mg	3 x 30 mg
Part 2	Period 1	90 mg Fasted	90 mg Fed
	Period 2	90 mg Fed	90 mg Fasted

Investigational medicinal products

	Reference	Test
Dosage Form	tablet	tablet
Dosage Strength	3 x 30 mg	90 mg
Batch #.	0K81TB1SW	11F82A090A
Administration	per os	

Sampling Times

Plasma samples for PK analysis were taken on Day 1 (through 4) and Day 5 (through 8) at the following time points: pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 72 h post-dose

Analytical Method: The performance of the analytical method is acceptable. Yes

Bioanalytical sample analysis for this study was done using a validated analytical method. The report number for the method is 157209 and the validation report is available in the submission.

The method was developed for the analysis of both tolvaptan and the metabolite DM-4103. Since only the tolvaptan levels were of interest, calibration and QC samples contained both analytes, but only tolvaptan levels were monitored.

Properties of the analytical method

Method	LC/MS/MS with SPE
Validation Protocol #	157209
Internal Standard	OPC-41100
Matrix	Plasma
Linear Range	5.00-1000.00 ng/mL
Calibration Samples	5.000, 10.00, 50.00, 250.0, 500.0, 750.0, 1000 ng/mL
Accuracy	95.8-105.4%
Precision	1.92-3.80%
QC Samples	15.0, 80.0, 800 ng/mL

Accuracy	91.1-94.0%
Precision	4.11-6.55%
Stability	Bench top: 168 h
	Freeze/Thaw: 7 cycles
	Extract: 10 d at 4 C, 114.5 h at room temperature
	-70 C: 1518 d
	-20 C: 705 d

Reviewer's Note: There were 21 samples with reported concentrations greater than 1000 ng/mL, they were re-assayed, presumably diluted and their concentration reassessed, however, the procedure for doing this is not included in the bioanalytical report or the validation report. An SOP for the method conduct has not been provided in the submission.

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Reviewer's Note: The design of the study and chosen PK sampling scheme is acceptable for the intended purpose of testing bioequivalence and food effect.

Results

Study Population

Healthy males and females age 18 to 45, inclusive

Part 1 Bioequivalence

Disposition and demographics (Part 1, BE)

Parameter	N
Randomized	44
Completed	43
Discontinued	1
Age [Mean (range)]	32.3 (19-45)
Male/Female	24/20
Race (Caucasian/Black/American Indian or Alaska Native/other)	25/16/1/2

[Source: CSR 156-11-295 Tables 8.1.1-1 and 8.2.1-1]

Reviewer's Note: One subject discontinued the study for a personal emergency 24 h after the intake of study drug in the second period of study (part 1). The PK results were excluded from BE assessment, because AUC and terminal half-life could not be determined and no comparisons could be made to the reference formulation..

(b) (4)

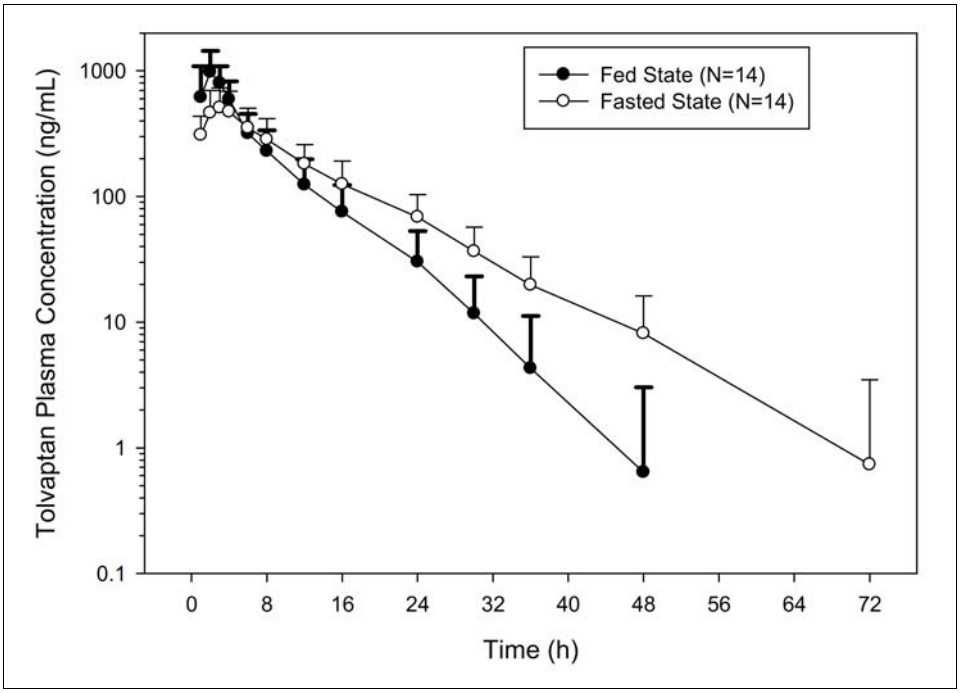
(b) (4)

Part 2 Food Effect

Disposition and demographics (Part 2, FE)

Parameter	N
Randomized	14
Completed	14
Discontinued Due to AE	0
Age [Mean (range)]	34.6 (24-44)
Male/Female	10/4
Race (Caucasian/Black /other)	9/4/1

[Source: CSR 156-11-295 Tables 8.1.2-1 and 8.2.2-1]



Mean concentrations of tolvaptan over time (Part 2, FE)

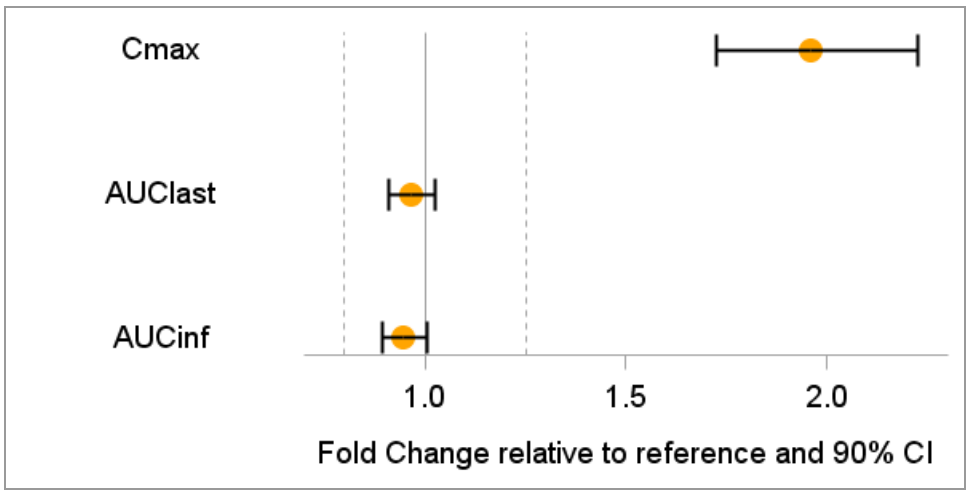
[Source: CSR 156-11-295 Figure PKF-2]

Table 2. Geometric mean ratios (Part 2, FE)

	N	Fasted	Fed	Mean Ratio	95% CI
Cmax [ng/mL]	14	496	972	1.960	1.726, 2.226
AUCt [ng*h/mL]	14	5480	5310	0.968	0.912, 1.026
AUC∞ [ng*h/mL]	13	5640	5780	0.948	0.894, 1.005

[Source: CSR 156-11-295 Tables 9.2.3.4-1 and 2]

Reviewer's Comment: Based on a previously reviewed absolute bioavailability study, tolvaptan is known to demonstrate flip-flop kinetics. Being a very lipophilic drug with a logP value of approximately 5, tolvaptan is practically insoluble in water. Therefore it could be hypothesized that a high fat meal could increase the solubility of tolvaptan and provide more drug to be absorbed faster, whereas in the fasted situation, a slow but continuous release from the dosage form occurs, which resembles flip-flop kinetics. Hence, the elimination appears to be faster in fed state compared to fasted condition.



Forest plot for food effect study (Part 2)

Site Inspected

Requested: Yes ☑ No ☐ Performed: Yes ☑ No ☐ N/A ☐

The OSI report on the inspection of clinical and analytical sites for study 156-11-295 are available in DARRTS (M. Skelly PhD, 8/20/2013). While there were no objectionable observations at the analytical site, at the clinical site a Form 483 was issued. (b) (4) The authors of the report conclude that the clinical results from the herein reviewed study are unfit for agency review, stemming from violations (b) (4)

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

The 90 mg dose strength cannot be approved for marketing, as the clinical results are deemed unfit for agency review.

4 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

NDA	204-441
Drug Name:	Tolvaptan (b) (4)
Strength and Dosage Form:	Tablets: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg
Sponsor:	Otsuka
Submission Date:	February 27, 2013
Submission Type:	Original NDA
Proposed Indication:	To slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)
Priority Classification:	Fast Track
Clinical Division	Division of Cardiovascular and Renal Products
Primary Pharmacometrics Reviewer:	Fang Li, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there significance difference between tolvaptan and placebo in slowing down kidney growth? Is the difference dose-dependent?

Yes, in study 156-04-251 (or referred as study 251 in this document), all tested tolvaptan doses showed significantly lower kidney growth than the placebo after three years of treatment, but no clear dose-response relationship was observed for TKV slope based on the modal doses. Tolvaptan treatment demonstrated a TKV slope that was about half of the placebo, indicating a favorable effect for tolvaptan. However, the effect was not dose-dependent under the tolerability based titration design. Lower slope values were not associated with higher modal tolvaptan doses. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect, e.g. less tolerable patients were more sensitive to the drug's desired effect. The numerical trend among the three modal dose groups suggested that those patients who could only

tolerate the lower dose seemed to be more sensitive to tolvaptan's effect in reducing the TKV slope.

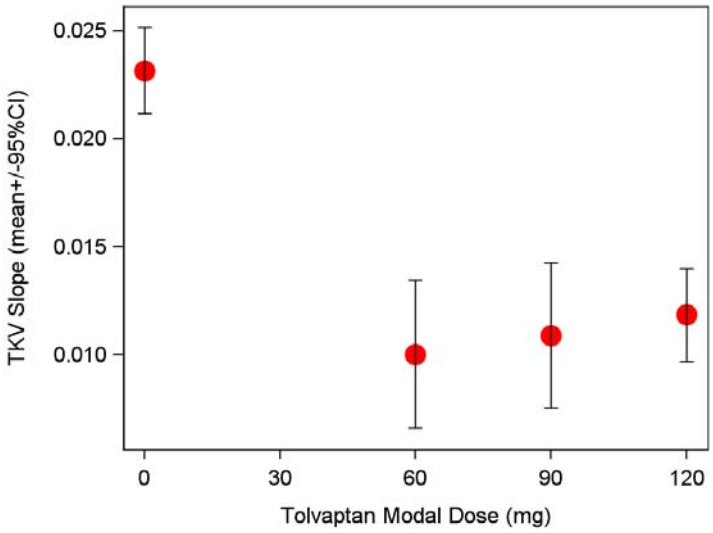


Figure 1: Relationship between total kidney volume (TKV) slope and varying tolvaptan modal doses. The dose of 0 mg is the placebo treatment

1.1.2 Is baseline TKV a prognostic factor for eGFR reduction?

Yes, baseline TKV is a prognostic factor for eGFR reduction. The patients were divided into two groups based on the median value of their baseline eGFR_MDRD (eGFR<= 70 ml/min/1.73m2 and eGFR > 70 ml/min/1.73m2). The percentage change from baseline was plotted over time stratified by their baseline TKV (TKV>=1.5L or TKV<1.5L where 1.5L is the median baseline TKV, Figure 2). As shown in Figure 2, both subgroups in each treatment arm demonstrated that the subgroup with larger baseline TKV consistently showed larger eGFR reduction at month 36, suggesting the prognostic feature of TKV for eGFR reduction. The interaction between eGFR and KTV is more evident when the upper 25% (TKV>2L) was compared to the lower 25% (TKV<1L) as shown in Figure 3, suggesting that the prognostic feature of TKV is more significant for those patients with low eGFR. In addition, the larger difference between tolvaptan and placebo at month 36 within the subgroup with < 70 ml/min/1.73m2 and TKV>2L suggests that this subgroup may be a more sensitive subgroup to demonstrate the benefit of tolvaptan in a future trial. Given the obvious linear relationship between eGFR percentage reduction and time in the placebo group, a linear mixed model was applied to estimate the individual slope. These individual slopes were summarized in four ranked subgroups (25% patients in each subgroup) based on the baseline TKV values (Figure 4). It is evident that the larger the baseline TKV, the faster the eGFR reduction. This relationship is more evident in the subgroup with eGFR<70 ml/min/1.73m2.

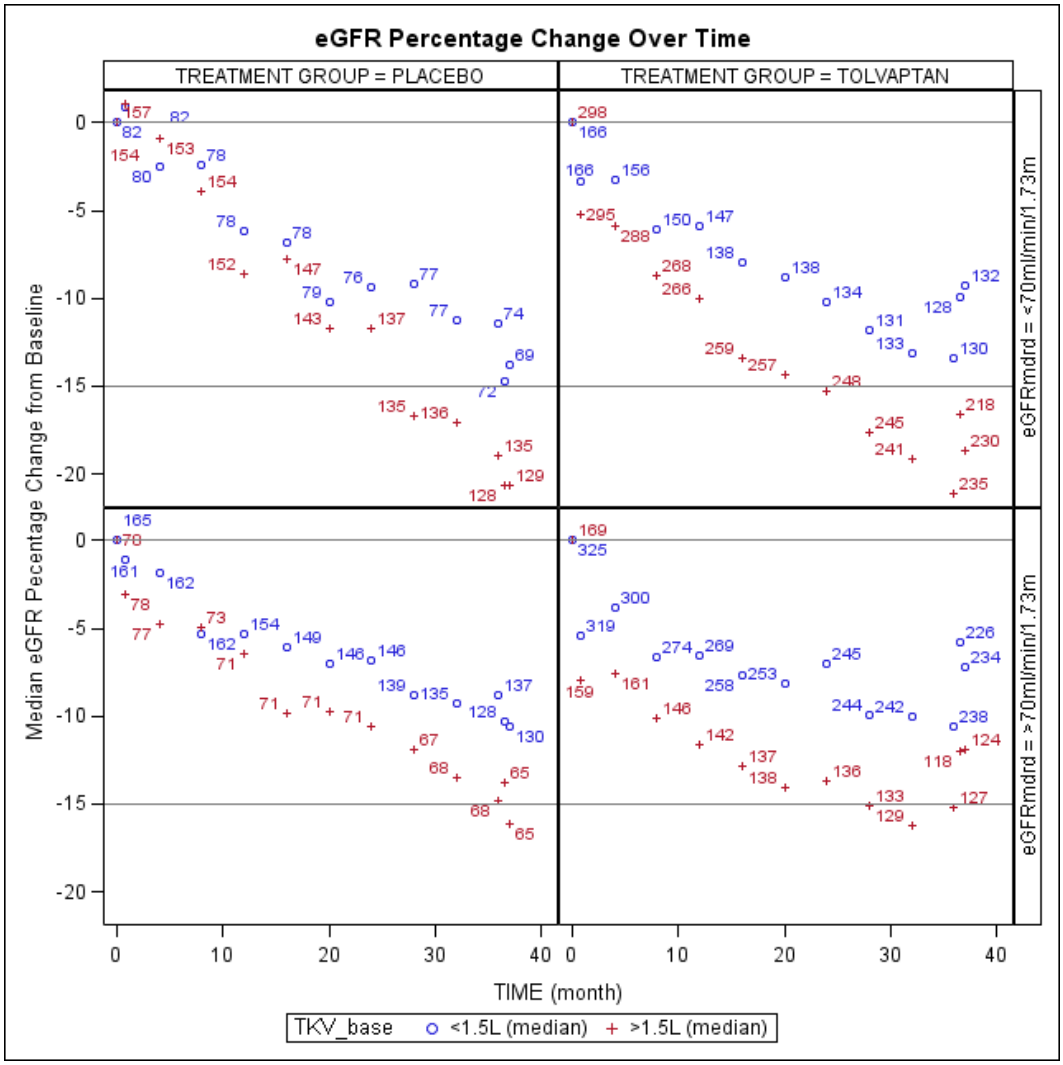


Figure 2: eGFR percentage change over time stratified by baseline eGFR and TKV (numbers are the sample size at each point)

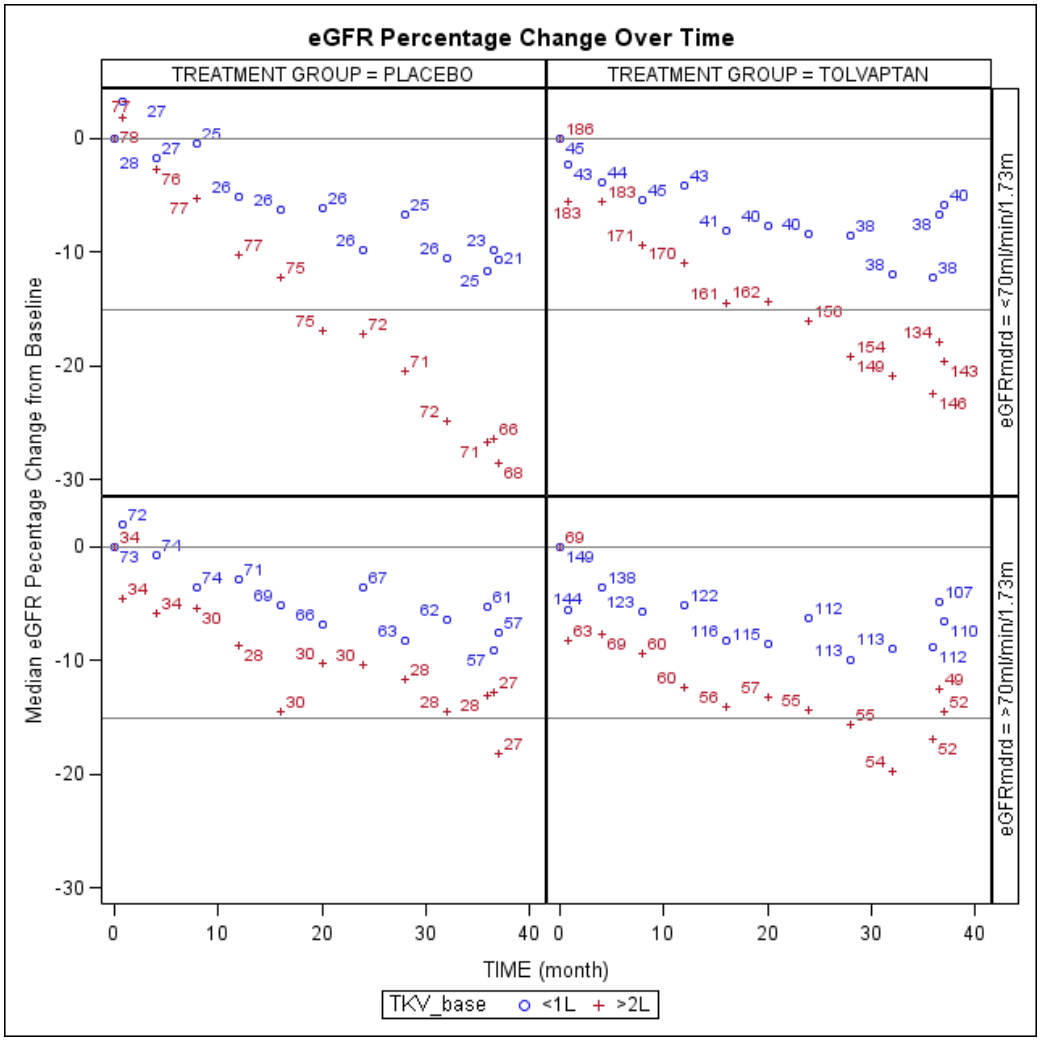


Figure 3: eGFR percentage change over time stratified by baseline eGFR and TKV (numbers are the sample size at each point and only patients with TKV<1L or TKV>2L are included)

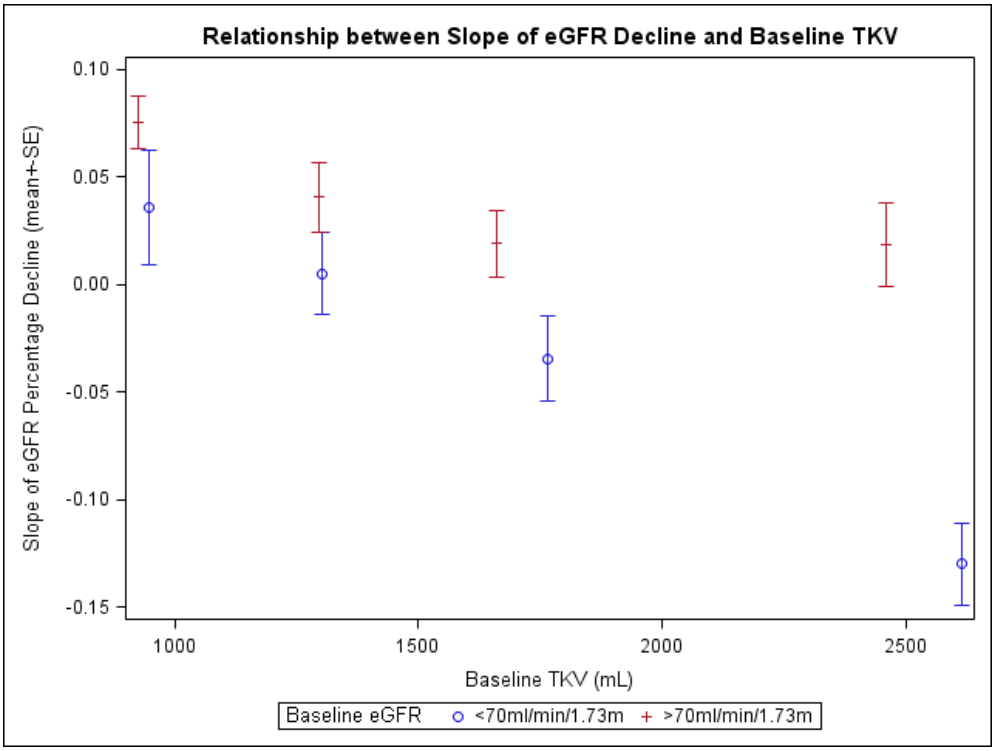


Figure 4: Relationship between slope of eGFR reduction over time and baseline TKV in placebo group.

1.1.3 Is there any correlation between increase in kidney volume and worsening of renal function?

Yes. There existed moderate but statistically significant association between TKV and worsening of renal function measured as GFR using CKD-EPI equation. Higher volume of total kidney was associated with lower renal function. Correlation between percent changes of last visit TKV and last visit renal function was -0.21415 (p value <.0001). Patients in tolvaptan and the placebo arms showed similar trend, as indicated by the smooth lines in Figure 5.

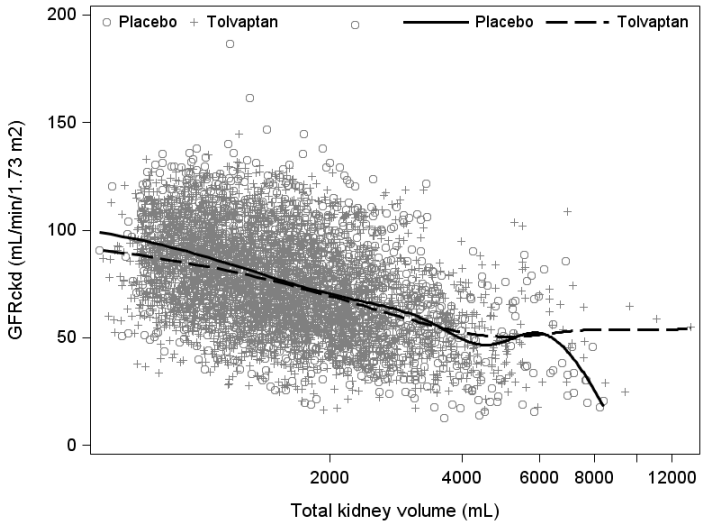


Figure 5: Relationship between GFR using CKD-EPI equation and total kidney volume

1.1.4 Is there any evidence of dose-response relationship for time to first severe renal pain?

Yes. First severe renal pain was defined as the first occurring event being severe renal pain requiring a prescribed intervention from Day 1 onwards. As indicated in the Figure 6, tolvaptan showed a clear treatment effect in delaying the occurrence of renal pain. There was a dose-response relationship for renal pain even though the dose was not a randomized. Higher split-doses, especially the 120 mg daily doses (90 mg+30 mg), appeared to have a better effect, while the lowest daily doses (60 mg) showed an effect being no different from the placebo. This observed relationship was also subjective to the confounding issue due to the titration trial design.

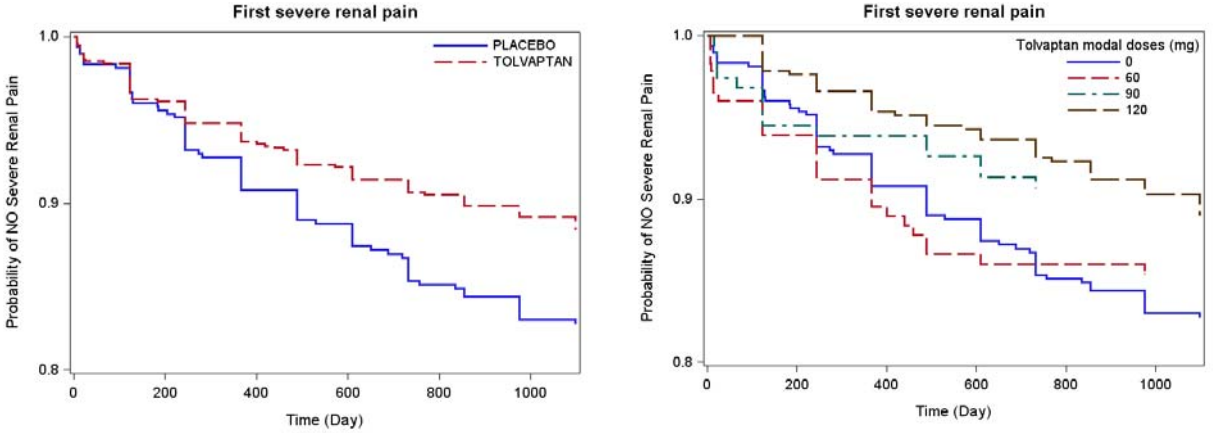


Figure 6: Kaplan-Meier plot of time to first severe renal pain stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan modal doses (right)

1.1.5 Is there any evidence of dose-response relationship for time to first worsening of renal function?

No. First severe worsening of renal function was defined as a reproducible 25% decrease in reciprocal serum creatinine from Week 3/EOT onwards. As demonstrated in Figure 7, tolvaptan showed a clear treatment effect in delaying the occurrence of severe worsening of renal function. However, there was no apparent modal dose-response relationship for worsening of renal function. Higher doses were not associated with longer time to the first severe worsening of renal function. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.

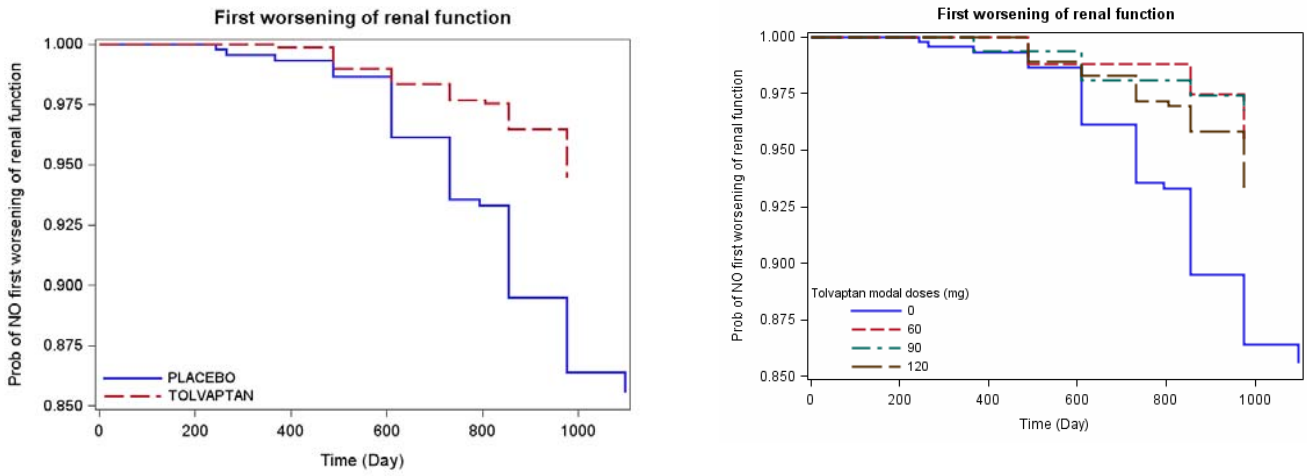


Figure 7: Kaplan-Meier plot of time to first severe worsening of renal function stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan doses (right)

1.1.6 Is there any evidence of exposure-response relationship for liver safety?

One major concern for tolvaptan in ADPKD patients is liver safety. After the completion of trial 156-04-251, an abnormal elevation of serum alanine aminotransferase (ALT) was revealed with incidence in the tolvaptan arm much higher than in the placebo. The potential of tolvaptan for development of drug-induced liver injury (DILI) was then evaluated. In study 156-04-251, three cases (two during treatment) were found matching Hy's law, with serum ALT >3 x ULN and total bilirubin > 2 xULN. The eDISH plot for study 251 was followed below. It can be observed that there is a clear imbalance between tolvaptan and placebo subjects experiencing serum ALT elevation exceeding 3 x ULN. In the right-upper (Hy's Law) quadrant, there are two tolvaptan treated subjects and no placebo treated subjects.

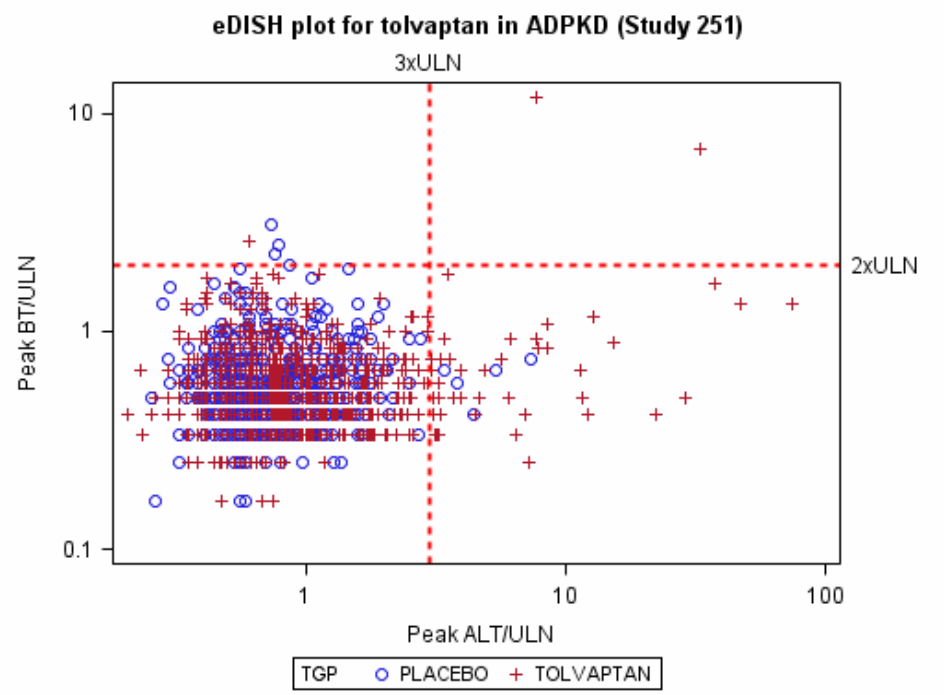
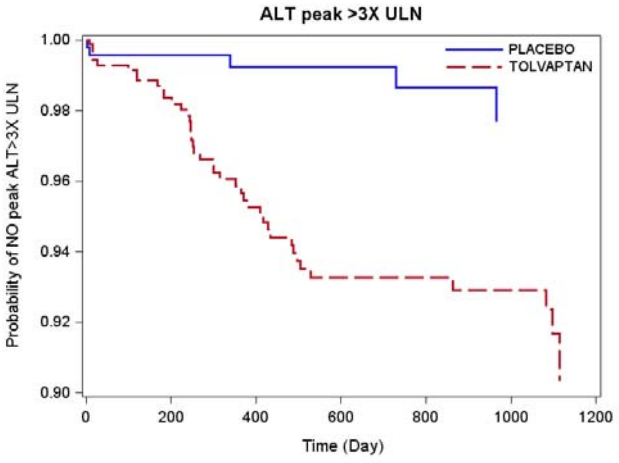


Figure 8: eDISH plot for peak total bilirubin vs. peak ALT in patients receiving placebo or tolvaptan in study 156-04-251

The Kaplan-Meier plot for time to peak ALT >3 x ULN was followed. Tolvaptan showed a much higher probability than the placebo to have peak ALT >3 x ULN. However, the risk was not dose-related based on the modal doses. There was no dose-response relationship for the risk of elevated ALT levels. The lack of dose-response relationship could be due to the titration trial design based on the tolerability.



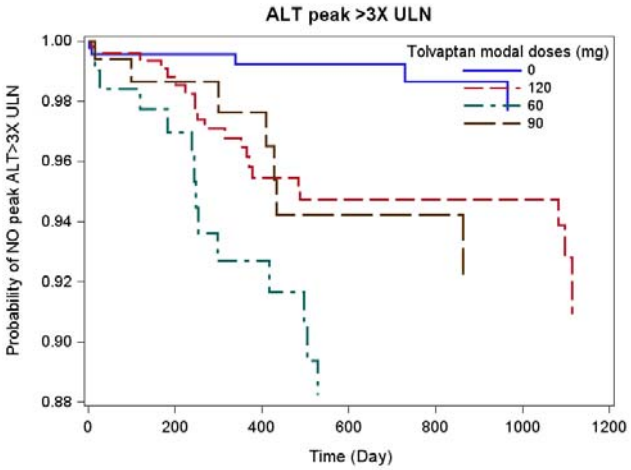


Figure 9: Kaplan-Meier plot for time to peak ALT > 3 x ULN stratified by treatment (tolvaptan vs. placebo, left) and various tolvaptan modal doses (right)

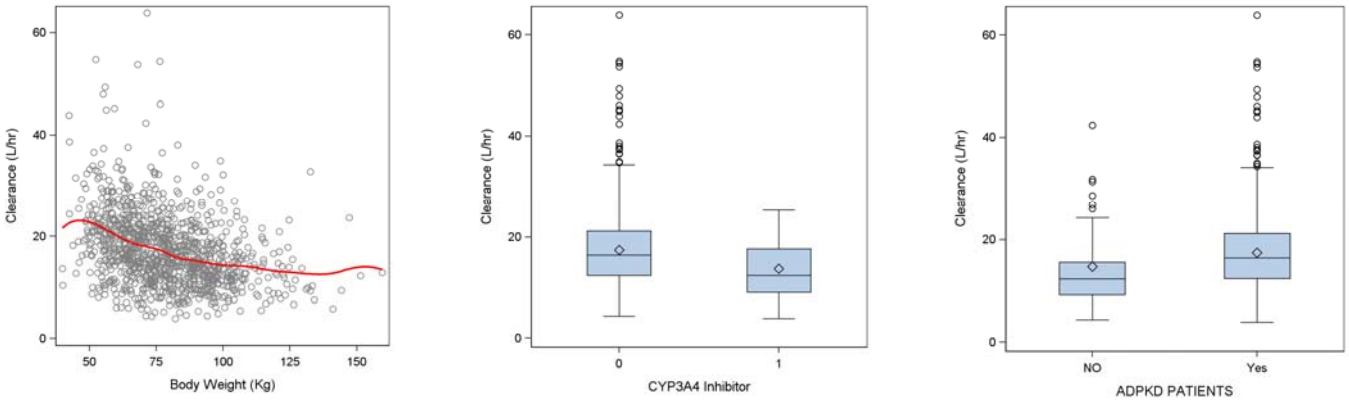
1.1.7 Is there any covariates that significantly influence PK parameters of tolvaptan in patients with ADPKD

In a population PK study, body weight and renal function (measured as GFRckd) was found to have significant effect on tolvaptan clearance.

Individual PK parameters were estimated by the sponsor's final population PK model. The reviewer explored relationships between tolvaptan clearance (CL/F), absorption (Ka) and selected covariates, including body weight, age, sex, GFR, race, and patient group. As demonstrated in figure below, identified significant covariates included body weight and GFRckd. Tolvaptan clearance increased with GFRckd and decreased with body weight. Co-administration of CYP3A4 inhibitor reduced CL/F by 22%.

Female patients showed a clearance that was 15% higher than male. Female patients were also observed to have 52% faster absorption than male. ADPKD patients showed an average clearance that was 18% higher than non-ADPKD patients. Age showed no significant effect on tolvaptan clearance.

There was no strong relationship between volume of distribution (V/F) and the selected covariates except race. Asian patients were found to have a lower mean V/F than all other races.



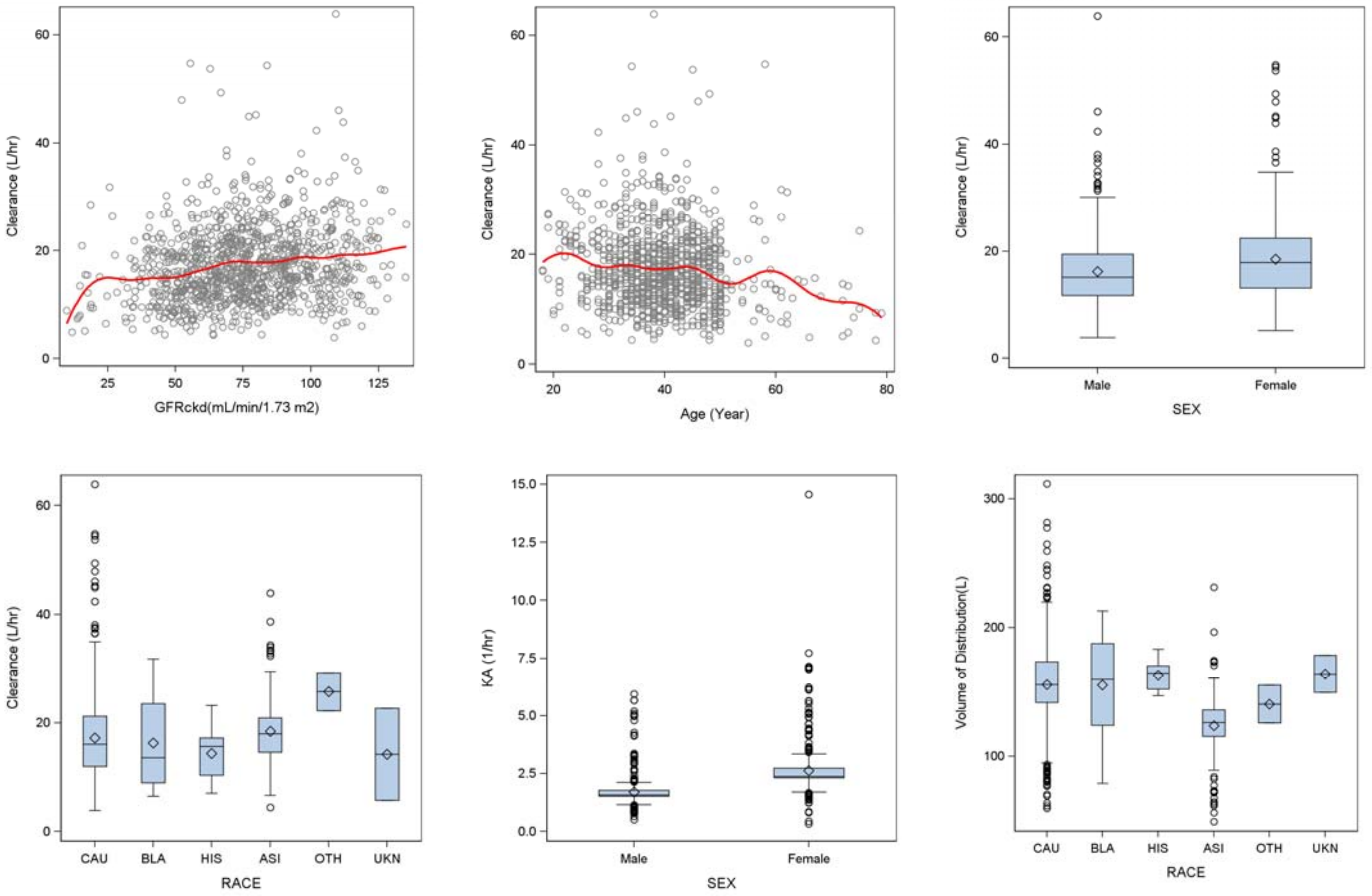


Figure 10: PK parameter-covariates relationships. The red lines are smooth lines showing the trend. The box plots and black circles are based on empirical Bayes individual estimates.

1.2 Recommendations

The sponsor's PK/PD analysis is acceptable from the pharmacometric perspective.

1.3 Label Statements

None

2 Pertinent regulatory background

The sponsor (Otsuka Pharmaceutical Co., Ltd) submitted this application to seek the approval of tolvaptan for the treatment of Autosoaml Dominant Polycystic Kidney Disease (ADPKD). ADPKD is a serious medical condition characterized by progressive development of cysts that impinge on and destroy normal kidney tissue, culminating in fibrosis, and ultimately kidney failure. There is no cure for ADPKD at this time. Existing therapies are symptomatic targeting pain, infection, and hypertension.

Tolvaptan is a selective arginine vasopressin (AVP) V_2 receptor antagonist discovered by the same sponsor and was previously approved by FDA on 19 May 2009 under trade name Samsca® for the treatment of clinically significant hyponatremia. The approved dose strengths were 15, 30 and 60 mg as immediate release oral tablets. In addition to

the approved doses, new strengths of 45- and 90- mg are being sought for approval for the new indication.

One pivotal Phase III trial (156-04-251) was conducted to evaluate the long-term safety and efficacy of oral tolvaptan titrated to a maximum tolerated dose in adults with ADPKD for three years. The primary efficacy endpoint was the rate of change in total kidney volume (TKV) of both kidneys. The key secondary composite endpoint was a time to multiple-event analysis of clinical progression events of renal function, renal pain, hypertension, and albuminuria. The results of the pivotal study showed that tolvaptan treatment reduced progression of cyst growth by nearly 50%. However, FDA did not agree with using change in kidney size as primary efficacy endpoint. FDA has reiterated to the sponsor that, to obtain approval, in addition to positive result in the primary efficacy endpoint, tolvaptan should also show favorable effect on key secondary composite endpoints, such as slower rate in reduction of renal function, renal pain etc.

3 Results of Sponsor's Analysis

3.1 Population PK Analysis

3.1.1 Objectives

The sponsor conducted population PK analysis and PK/PD analysis in this submission.

The objectives of the population PK analysis were to:

- develop a population PK model to describe tolvaptan pharmacokinetics in ADPKD subjects following oral administration of tolvaptan;
- evaluate the effects of covariates on selected PK parameters;
- derive individual estimates of daily (0-24h) tolvaptan exposure, including AUCss, Cmax,ss, and Cmin,ss).

The primary objective of the PK/PD analysis was to:

- explore the relationships between tolvaptan exposure and the four clinical endpoints, e.g. the change in TKV, the time to multiple ADPKD clinical progression events defined as either severe renal pain or worsening of renal function, the rate of eGFR change with time and the rate of log-transformed percentage TKV change with time.

3.1.2 Datasets

The sponsor used dense and sparse datasets pooled from 10 short-term and long-term clinical trials in ADPKD patients for population PK analysis. Studies included in the analysis were 156-04-001, 156-05-002, 156-04-248, 156-04-249, 156-04-250,156-04-251, 156-06-260, 156-09-282, 156-09-284, and 156-09-285. The PK datasets comprised of 1067 subjects contributing a total of 6437 observations evenly split into dense and

sparse PK data. The average age of the subjects was 40 with a range from 18 to 79 years old. The average body weight was 77.1 kg, and the average eGFR was 72.2 ml/min/1.73 m^2. Of the 940 subjects enrolled outside Japan, 892 were Caucasians, 19 were blacks, 4 were Asians, and 16 were others. There were 50 subjects with at least one instance of strong, moderate or weak CYP3A4 inhibitor co-administration and 61 subjects with at least one instance of strong, moderate, or weak CYP3A4 inducer co-administration.

Table 4.1.1-1 Distribution of Continuous Covariates

Descriptive statistics	Age (years)	Body weight (kg)	BMI ($kg.m^{-2}$)	eGFR ($mL/min/1.73m^2$)
Median	40	77.1	25.4	72.2
[Min;Max]	[18;79]	[38.0;162.9]	[15.4;54.7]	[9.8;144.7]

Table 4.1.1-2 Distribution of Categorical Covariates

Sex (male/female) number of subjects	Site (Japan/Non Japan) Number of subjects	Number of observations with co-administration of CYP3A4 inhibitor (Yes/No)	Number of observations with co-administration of CYP3A4 inducer (Yes/No)
541/526	136/931[a]	161/6276	165/6272

[a] 940 subjects enrolled outside Japan were 892 Caucasians, 19 Blacks, 4 Asians and 16 Other.

3.1.3 Population PK Model

Base Model: The base model developed by the sponsor was a one-compartment model with first-order absorption and elimination, and a combined additive and proportional error structure adequately described the dense PK data. Model parameters for the base model are summarized in table below:

Table 4.1.2-1 Parameters for the Base PK Model for Tolvaptan

Parameter	Unit	Estimate	SE	RSE (%)	Shrinkage(%)
Fixed effects					
Ka at 120 mg	h^{-1}	1.34	0.130	10	
CL/F	$L{\cdot}h^{-1}$	16.2	0.278	2	
Vc/F	L	142	3.62	3	
t_{lag}	h	0.221	0.0146	7	
Power dose effect on Ka	1	-0.585	0.0858	15	
Random effects: variance (CV)					
Ka at 120 mg	1	0.400 (63%)	0.0798	20	66
CL/F	1	0.219 (47%)	0.0132	6	13
Covariance CL/F-Vc/F	1	0.0619	0.0105	17	
Vc/F	1	0.132 (36%)	0.0142	11	43

Table 4.1.2-1 Parameters for the Base PK Model for Tolvaptan					
Parameter	**Unit**	**Estimate**	**SE**	**RSE (%)**	**Shrinkage(%)**
Residual variability: variance					
Proportional, dense	1	0.0777	0.00845	11	6
Additive, dense	1	8.35	1.47	18	6
Proportional, sparse	1	0.200	0.0120	6	12
Additive, sparse	1	176	68.1	39	12
runTLV12DV1cpt_b47, minimum value of objective function 54908.555					

Reviewer's Comments: All parameters were well estimated with low η-shrinkage except for Ka.

Final Population PK Model:

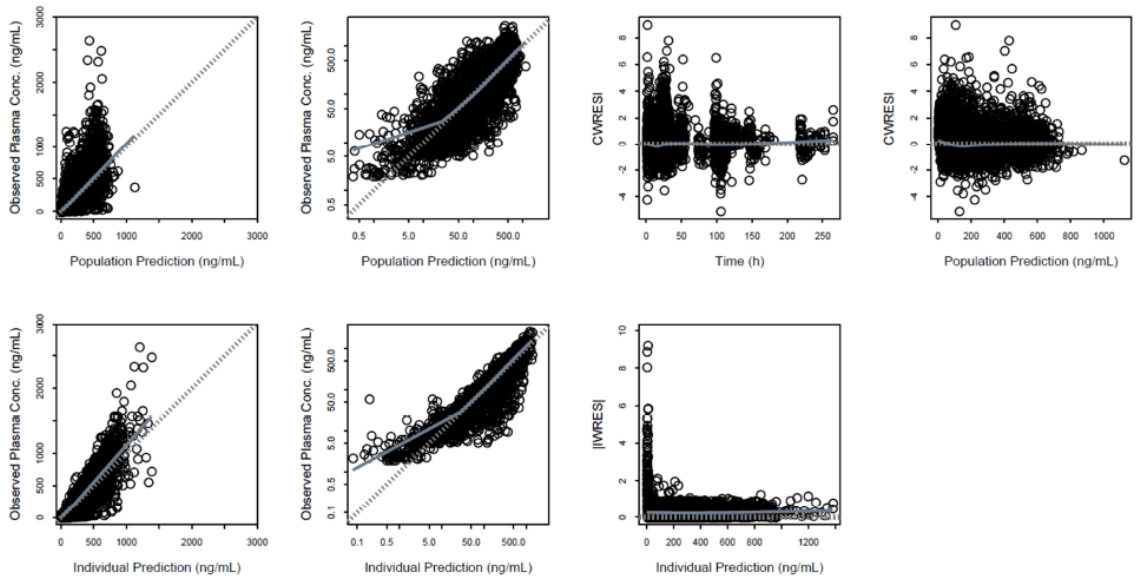
Full population PK model was constructed via forward inclusion of covariates of interest and then reduction step by removing covariates to check MVOF. The resulted model was then refined to the final model by removing the effect of the co-administration of CYP3A4 inducer on tolvaptan CL/F as it was poorly estimated (RSE of 56%). The parameter estimates of the final model were summarized as followed.

Table 4.1.4-1 Parameters for the Final PK Model for Tolvaptan					
Parameter	**Unit**	**Estimate**	**SE**	**RSE (%)**	**Shrinkage(%)**
Fixed effects					
Ka at 120 mg	h^{-1}	1.40	0.125	9	
CL/F	$L \cdot h^{-1}$	16.4	0.296	2	
Vc/F at 120 mg	L	163	5.04	3	
t_{lag}	h	0.236	0.00927	4	
Power dose effect on Ka	1	-0.385	0.0923	24	
Power dose effect on Vc/F	1	0.121	0.0227	19	
Power BMI on CL/F	1	-0.976	0.0884	9	
Power eGFR on CL/F	1	0.195	0.0420	21	
Fractional change on CL/F with Inh[a]	1	-0.270	0.0639	24	
Fractional change in Ka in female	1	0.501	0.192	38	
Power age on Vc/F	1	-0.265	0.0744	28	
Fractional change in Vc/F in Japanese sites	1	-0.197	0.0384	19	
Random effects: variance (CV)					

Table 4.1.4-1 Parameters for the Final PK Model for Tolvaptan					
Parameter	**Unit**	**Estimate**	**SE**	**RSE (%)**	**Shrinkage(%)**
Ka at 120 mg	1	0.450 (67%)	0.0967	21	66
CL/F	1	0.182 (43%)	0.0116	6	15
Covariance CL/F-Vc/F	1	0.0615	0.00964	16	
Vc/F	1	0.114 (34%)	0.0133	12	43
Random effects: variance					
Proportional, dense	1	0.0735	0.00764	10	6
Additive, dense	1	8.27	1.40	17	6
Proportional, sparse	1	0.194	0.0101	5	12
Additive, sparse	1	152	41.7	28	12
final_backward_TLV_PK_reduced_wV_indDose, minimum value of objective function 54486.993					

[a] Co-administration of CYP3A4 inhibitors.

General Goodness-of-fit plots for the final model:



Reviewer's Comment:

- *The population PK model is acceptable. The structural PK model used for ADPKD patients is the same as the one previously used for hyponatremia patients. The final model reasonably described the observed data. The estimated key PK parameters such as CL/F and Vc/F are reasonable.*
- *Tolvaptan clearance increases with body weight. This is consistent with previous observations in hyponatremia patients.*
- *Female patients showed 52% faster absorption than male patients.*
- *Co-administration with CYP3A4 inhibitor increases tolvaptan clearance by 22%. However, in a total of 1067 subjects, there were only 50 subjects with at least*

one instance of strong, moderate or weak CYP3A4 inhibitor co-administration. Of the 6437 observations, less than 3% observations were associated with CYP3A4 inhibitor co-administration.

3.2 Exposure-response analysis for efficacy

3.2.1 Change in TKV

The sponsor compared effect of tolvaptan and the placebo in change of total kidney volume after 36 months of treatment. Log10-transformation of TKV was used to balance for the natural skewness of volume data distribution. The following figure showed TKV ratio at month 36 to the baseline for each quartile of baseline. The values of tolvaptan Cmin,ss of each quartile were shown in the figure

As demonstrated, a clear tolvaptan treatment effect was observed. However, no dose-response relationship within the range of Cmin,ss from 82.0 to 126.3 ng/mL can be identified. The mean ratio at Month 36 was 1.18, 1.09, 1.07, and 1.09 for placebo, and 45/15 mg, 60/30 mg, 90/30 mg split-dose regimens, respectively.

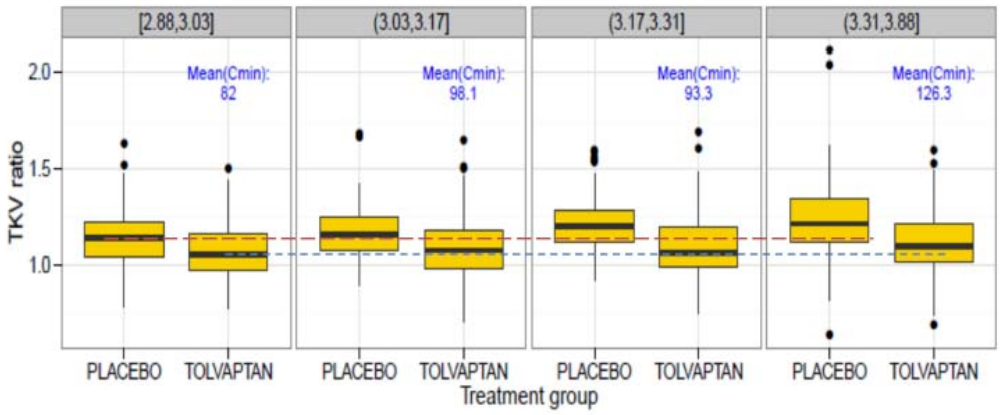


Figure 4.2.1.2.1-2 Box-and-Whisker Plot for TKV ratio at Month 36 for each Quartile of Baseline Log-Transformed TKV

3.2.2 TKV Slope

TKV slope of each individual reported by the sponsor was estimated by the equation $TKV=TKVbase*e^{2.3*slope*year}$. TKV slopes were compared between subjects in the placebo group and subjects treated with tolvaptan. A clear treatment effect of tolvaptan was estimated, with a mean value of 0.011 $year^{-1}$ in treated subjects versus a mean value of 0.023 $year^{-1}$ in placebo group.

The following linear regression model was fitted to the TKV slope data:

$$TKV\ slope = Intercept + \beta_{TLV} \cdot TLV + \beta_{BSLN} \cdot log_{10}(TKV_{BSLN}) + \beta_{AUC} \cdot AUC + \beta_{AUC\text{-}BSLN} \cdot log_{10}(TKV_{BSLN}) \cdot AUC$$

Where *Intercept* is the intercept of the linear regression model. TLV is an indicator variable for treatment group (TLV=0 for placebo and TLV=1 for tolvaptan). TKV_{BSLN} is the baseline TKV, AUC is the overall modal daily steady-state tolvaptan AUC in $\mu g \cdot mL^{-1} \cdot h$ and βx are the coefficients reflecting the impact of those factors listed above on TKV slope. As shown in Table below, while treatment (tolvaptan versus placebo) and the log-transformed TKV baseline had a significant effect on TKV slope, neither the overall AUC nor the interaction between AUC and tolvaptan baseline has a statistically significant effect on TKV slope.

Table 4.2.1.2.2-1 Parameter Estimates for the Linear Regression Model for TKV Slope

Parameter	Units	Estimate	RSE (%)	p-value
Intercept	$year^{-1}$	-0.0420	35	0.0045
θ_{TLV}	$year^{-1}$	-0.0163	12	<0.001
θ_{BSLN}	$log_{10}(cm^3)^{-1} \cdot year^{-1}$	0.0204	23	<0.001
θ_{AUC}	$(\mu g \cdot mL^{-1} \cdot h)^{-1} \cdot year^{-1}$	0.00335	67	0.139
$\theta_{AUC\text{-}BSLN}$	$(\mu g \cdot mL^{-1} \cdot h)^{-1} \cdot log_{10}(cm^3)^{-1} \cdot year^{-1}$	-0.000840	82	0.226

3.2.3 eGFR Slope

The sponsor defines eGFR as GFR estimated by the CKD-EPI formula (the term GFRckd was used by the reviewer). eGFR slope was defined as the rate of eCFR change with time. Estimated GFR slopes were compared between placebo subjects and subjects treated with tolvaptan. The mean values was -2.68 ml?min/1.73 $m^2 \cdot year^{-1}$ in tolvaptan subjects versus a mean value of -3.57 mL/min/1.73 $m^2 \cdot year^{-1}$ in placebo subjects.

The following linear regression model was fitted to the eGFR slope data:

$$eGFR\ slope = Intercept + \beta_{TLV} \cdot TLV + \beta_{BSLN} \cdot eGFR_{BSLN} + \beta_{AUC} \cdot AUC + \beta_{AUC\text{-}BSLN} \cdot eGFR_{BSLN} \cdot AUC$$

where *Intercept* is the intercept of the linear regression model, *TLV* is an indicator variable for treatment (*TLV*=0 for placebo and *TLV*=1 for tolvaptan), $eGFR_{BSLN}$ is the baseline eGFR, *AUC* is the overall daily steady-state tolvaptan AUC in $\mu g \cdot mL^{-1} \cdot h$, and β_X are the coefficients reflecting the impact of those factors listed above on eGFR slope. While treatment (tolvaptan versus placebo) and eGFR baseline had a significant effect on eGFR slope, the overall AUC did not have a statistically significant effect on eGFR slope, as shown in Table 4.2.1.2.3-1.

Table 4.2.1.2.3-1 Parameter Estimates for the Linear Regression Model for eGFR Slope

Parameter	Units	Estimate	RSE (%)	p-value
Intercept	$mL/min/1.73\ m^2 \cdot year^{-1}$	-5.54	18	<0.001
θ_{TLV}	$mL/min/1.73\ m^2 \cdot year^{-1}$	1.75	34	0.0037
θ_{BSLN}	$year^{-1}$	0.0246	48	0.038
θ_{AUC}	$(\mu g \cdot mL^{-1} \cdot h)^{-1} \cdot mL/min/1.73\ m^2 \cdot year^{-1}$	0.210	72	0.16
$\theta_{AUC\text{-}BSLN}$	$(\mu g \cdot mL^{-1} \cdot h)^{-1} \cdot year^{-1}$	-0.00431	46	0.031

Reviewer's comment: 1) In the pivotal trial of study 251, the sponsor used post-randomization eGFR value (eGFR at three weeks after treatment) as eGFR baseline. This is not the true baseline and is not considered appropriate;2) the sponsor's model above did not include TKV baseline, which was also found to be significant by the reviewer.

3.2.4 Time to Multiple Clinical Events

Time to multiple ADPKD clinical progression events was defined as the first occurring event being either severe renal pain requiring a prescribed intervention from Day 1 onwards or worsening of renal function by a reproducible 25% decrease in reciprocal serum creatinine from Week3/EOT onwards. There were a total of 251 events of which 173 were renal pain events. The modal dose corresponding to the time of occurrence of each event was recorded and the modal Cmin,ss was derived. The percentage of subjects with at least one event post dose was recorded in Table 4.2.1.2.4-3 per modal dose. There was clearly a tolvaptan treatment effect but no apparent dose-response relationship as confirmed by the Kaplan-Meier plot performed by quartiles of modal Cmin,ss.

Table 4.2.1.2.4-3 Percentage of Subjects With at least One ADPKD Clinical Progression Event in Placebo Subjects and by Modal Split-dose Regimen		
Dose regimen	**Multiple ADPKD clinical progression event (% subjects with at least one event)**	**Severe renal pain event (% subjects with at least one event)**
Placebo	25.1	15.9
45/15 mg	10.5	9.0
60/30 mg	7.5	6.4
90/30 mg	16.5	11.6

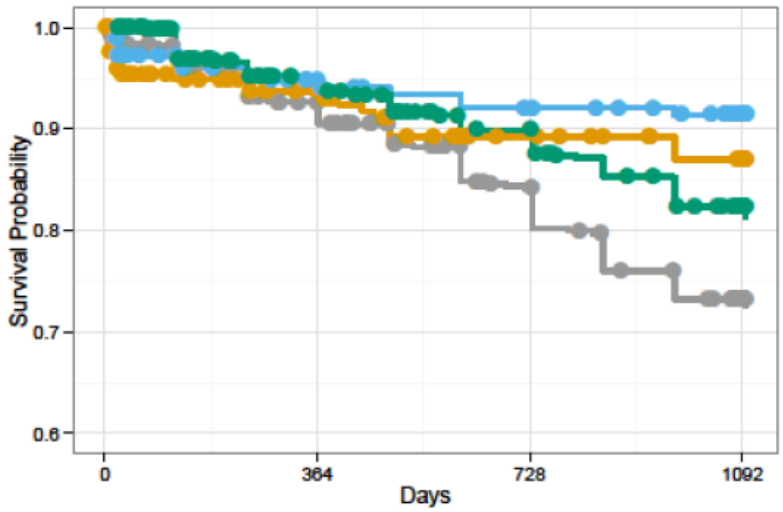


Figure 4.2.1.2.4-1 Kaplan-Meier Plot of Time to Multiple ADPKD Clinical Progression Events in Placebo and per Modal dose at the Time of the Event

Table 4.2.1.2.4-4 Mean Number of Severe Renal Pain Events per Subject in Placebo and per Overall Modal AUCss quartiles	
Quartiles of overall modal AUC_{SS} values ($\mu g \cdot mL^{-1} \cdot h$)	**Mean number of severe renal pain events per patient**
Placebo	0.20
[1.36, 4.42]	0.10
(4.42, 5.89]	0.12
(5.89, 8.17]	0.12
(8.17, 26.7]	0.13

3.2.5 Relationship between Urine Osmolality and Clinical Endpoints

Time to multiple ADPKD clinical progression events has also been investigated as a function of change in Uosm, The percentage of subjects with at least one event was recorded in Table 4.2.1.3-1 by quartiles of Uosm change at the corresponding time of the event. There was clearly a trend of a decreasing occurrence of events with the

magnitude or reduction in Uosm. This was confirmed by the Kaplan-Meier plot in figure below.

Table 4.2.1.3-1 Percentage of Subjects with at Least One ADPKD Clinical Progression Event by Quartiles of Change from Baseline in Uosm	
Quartile of change from baseline in urine osmolality ($mOsm \cdot kg^{-1}$)	**Subjects with at least one ADPKD clinical progression event (%)**
[-1119, -300]	12.1
(-300, -105]	19.5
(-105, 0]	19.2
(0, 548]	23.3

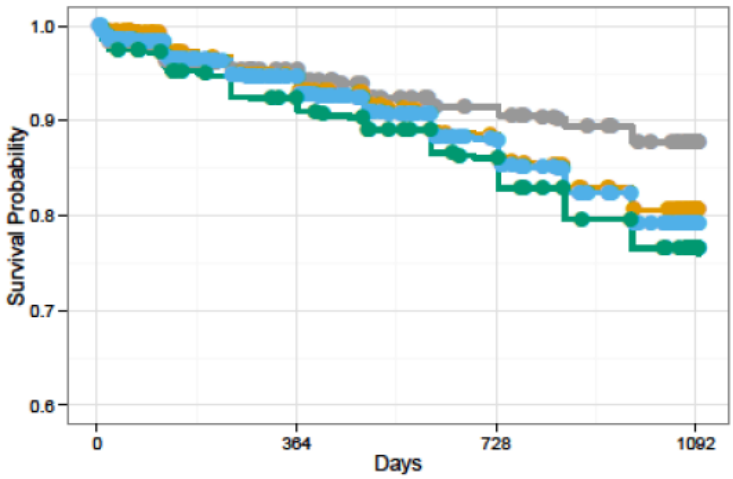


Figure 4.2.1.3-2 **Kaplan-Meier Plot of Time to Multiple ADPKD Clinical Progression Events by Quartiles of Change in Uosm at the Corresponding Time of the Event**

Reviewer's comments:

The sponsor compared the effect of tolvaptan and the placebo on change in TKV, TKV slope, eGFR slope, and time to multiple clinical events. In all these analyses, tolvaptan showed significant and favorable effect than the placebo in slowing down the progression of ADPKD . However, no apparent dose/exposure-response relationship for efficacy was observed. As mentioned repeatedly, the titration design has limited our capability to fully reveal such relationship. The reviewer's analyses are followed in section 4. The overall conclusion of the reviewer is consistent with that of the sponsor.

4 Reviewer's Analysis

4.1 Introduction

The Division of Pharmacometrics has reviewed the data and reports in the pivotal trial (study 251) and population PK/PD study (trial 156-11-296). We were interested in exploring the dose-response relationship for efficacy and safety, however, the nature of titration design used in study 251 has limited our capability to fully reveal such relationship. When tolvaptan doses were titrated to each individual's maximally tolerated doses, the final dosing groups were not randomized, i.e. patient baseline characteristics were not evenly distributed among treatment arms. With this limitation in mind, we compared the treatment effect of tolvaptan and placebo in slowing the progression of ADPKD and explored possible dose-response relationship for efficacy and safety.

4.2 Objectives

Analysis objectives are:

1. to evaluate the adequacy of the sponsor's population PK analysis and to determine if there are any factors that could significantly influence tolvaptan PK parameters in ADPKD patients.
2. to evaluate the efficacy of tolvaptan and placebo in slowing down the growth in total kidney volume
3. to evaluate the efficacy of tolvaptan and placebo in slowing down the worsening of renal function
4. to evaluate dose-response relationship for liver safety.

4.3 Methods

4.3.1 Experimental Design and Primary Endpoints

The data for reviewer's analysis were mostly from the pivotal trial 156-04-251, which was a Phase 3, multi-center, double-blind, placebo-controlled, parallel-arm trial to determine long-term safety and efficacy of oral tolvaptan in 1444 adults with ADPKD. Tolvaptan and placebo treatments were randomized in a ratio of 2:1. Treatment started with a 3-week titration during which tolvaptan or placebo was titrated in weekly intervals from lowest to highest tolerated levels in split-dose regimen of 45/15 mg, 60/30 mg, and 90/30 mg. The afternoon dose was given 8-9 hours after the morning dose. During the maintenance phase (to Month 36) following the up-titration, down-titration and up-titration were allowed based on tolerability to tolvaptan.

The primary efficacy endpoint by the sponsor was the rate of kidney volume change from baseline for tolvaptan relative to placebo. The key secondary composite efficacy endpoint was the time to multiple investigator-reported ADPKD clinical progression events, including, severe renal pain, worsening of renal function, worsening of albuminuria, onset or progression of hypertension. As mentioned before, FDA did not agree with using change in kidney volume as the primary efficacy endpoint. The agency is more interested in positive effect on key secondary efficacy endpoint.

4.3.2 Data Sets

Data sets used are summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
156-11-296	Exposure.xpt, fevall.xpt, gfr.xpt, kidpn.xpt, mri.xpt, tkvsl.xpt	\\cdsesub5\EVSPROD\NDA204441\0001\m5\datasets\156-11-296\listings
156-04-251	gfr0.xpt, slp-tkv.xpt Mri0.xpt	\\cdsesub5\EVSPROD\NDA204441\0001\m5\datasets\156-04-251\analysis

4.3.3 Software

NONMEM (Version 7.2) installed on a 48-core Linux cluster was used for the population PK analysis. An R package “popPK” developed by FDA was used for population PK graphing and reporting; SAS for windows 9.3 was used for all graphing and statistical analyses.

4.3.4 Models

The population PK model was a one-compartment model. Survival analyses were conducted using PROC LIFETEST in SAS.

4.4 Results

4.4.1 Effect on TKV and Change in TKV

Using data from study 251, the reviewer plotted TKV, log-transformed TKV, as well as change in TKV from baseline versus time. As demonstrated in figure below, in patients with the placebo treatment, the TKV or log-transformed TKV increased linearly over time. In those with tolvaptan treatment, TKV or log-transformed TKV progressed nonlinearly. TKV showed a flat growth or a slight decrease after first year then progress linearly afterwards. Overall, tolvaptan showed a slower rate of growth than the placebo. The percent change in TKV was consistently lower in patients in tolvaptan than in the placebo. However, no apparent dose-response relationship was identified for TKV change. As shown in Figure 11, all tested tolvaptan modal doses showed similar magnitude of decrease across the trial duration.

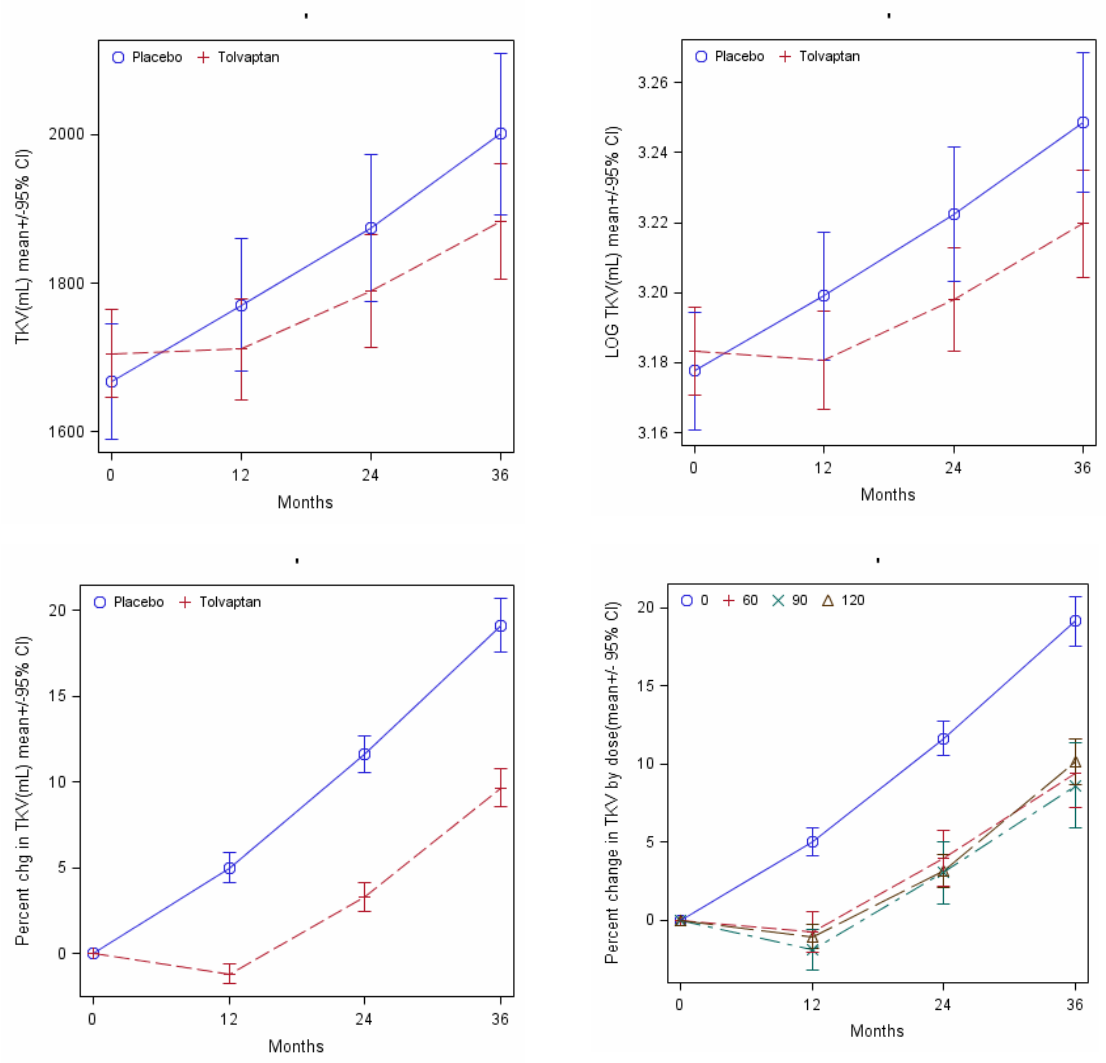


Figure 11: Time profile of TKV, log-transformed TKV, and percent Change in TKV from baseline.

4.4.2 Effect on Events of Renal Pain

Time to first severe renal pain was explored. The results are shown in Figure 6. Tolvaptan treatment demonstrated longer time to first severe renal pain. However, as shown in Table **4.2.1.2.4-4**. The number of renal pain events was not exposure-dependent. High tolvaptan exposure (AUC) values were not observed with less events.

4.4.3 Effect on Events of Worsening of Renal Function

Time to first severe worsening of renal function was studied. The results are shown in Figure 7. Tolvaptan treatment showed longer time to first sever renal pain. However, no clear dose/exposure response was identified.

4.4.4 Effect on Liver Toxicity

The effect of tolvaptan on abnormal elevation of ALT was studied. The results are shown in Figure 8 and 9. An imbalance elevation of ALT was observed after tolvaptan and placebo treatment with incidence of tolvaptan >placebo. While the elevation is reversible, tolvaptan has potential to cause drug-induced liver injury. Two cases in study 251 were found matching the Hy's law during treatment.

4.4.5 Population PK analysis

The sponsor's population PK model was reviewed and verified by the reviewer. The PK-covariate plots are shown in Figure 10. Tolvaptan clearance decreases with the increase of body weight but increase with eGFR.

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
postNM.sas	Diagnosis and covariate analysis for the final model	~\Tolvaptan_NDA204441_FL_LOCAL\PPK Analyses\reviewer\final
dose_efficacy_251.sas	Dose-response relationship for efficacy using data from study 251	~\Tolvaptan_NDA204441_FL_LOCAL\ER Analyses\Study251\ER

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

/s/

MARTINA D SAHRE
08/30/2013

RAJANIKANTH MADABUSHI
08/30/2013

FANG LI
08/30/2013

YANING WANG
08/30/2013

GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Brand Name	TBD
INN Name	Tolvaptan
NDA Number and Type	204,441
Applicant Name	Otsuka
Submission Date	March 1, 2013
EDR Link	\\cdsesub1\evsprod\nda204441
Indication	Treatment of ADPKD
Dosage Form & Strengths	15, 30, 60, 90 mg immediate release tablets
OCP Division	OCPI, Cardiovascular and renal products team
OND Division	ODEI, Division of cardiovascular and renal products
Reviewer	Martina Sahre, PhD
Pharmacometrics Reviewer	Fang Li, PhD
Team Leader	Rajanikanth Madabushi, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD

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1 Executive Summary

Otsuka Pharmaceutical Company, Ltd., is seeking approval of tolvaptan (NDA 204441) to slow progressive kidney disease in adults with autosomal dominant polycystic kidney disease (ADPKD). There are no approved treatments for this indication. Tolvaptan is currently approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (NDA 022275) with the proprietary name SAMSCA®.

In support of this indication, the submission consists of 10 clinical pharmacology study reports, a single pivotal, placebo controlled efficacy (Study 156-04-251 also referred to as TEMPO) and an uncontrolled clinical efficacy trial enrolling ADPKD patients from PK/PD studies.

The pivotal efficacy trial followed a 3-week dose titration of a split dose regimen starting from 45 mg AM/15 mg PM (45/15 mg) to 90 /30 mg dose based on tolerability. Following the titration phase, the maintenance phase began at the dose level tolerated at the end of titration. The applicant states that the rate of total kidney volume (TKV) over 3 years was significantly less for tolvaptan subjects than for placebo and the occurrence of renal pain and albuminuria was significantly reduced in the tolvaptan arm. With regard to safety, there were 3 cases of Hy's Law identified in trial 156-04-251 (Study 251), two during the main trial phase and one in a patient who switched from placebo to tolvaptan active treatment in the extension phase. Increases in ALT also seem to be more common in patients treated with tolvaptan.

The clinical pharmacology program was aimed at elucidating the pharmacokinetics, pharmacodynamics and efficacy in patients with ADPKD. The applicant is seeking approval of a 90 mg strength, which is to-be-marketed based on the results of a bioequivalence study.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 204441. From a clinical pharmacology perspective, the NDA is acceptable.

1.2 Identify recommended Phase 4 study commitments if the NDA is judged approvable

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

- Tolvaptan exhibits dose proportional pharmacokinetics following single dose (15 to 120 mg).

- The multiple dose study at doses of 15 mg BID, 30 mg BID, 30+15 mg split dose BID and a single 30 mg QD dose given for 5 days, likewise showed proportional increases in exposure and little accumulation at steady state.
- The to-be-marketed 90 mg formulation was demonstrated to be bioequivalent to 3x30 mg tablets in a healthy volunteer study. With a high fat meal, Cmax increased about 2-fold compared to administration in fasted state. Administration of food did not alter the AUC. This finding is consistent with that previously reported for SAMSCA®. In the phase 3 study tolvaptan was administered without regard to food intake. While the impact of food (varying fat content) may not be significant with respect to maintaining effect, the possibility that a higher Cmax may manifest tolerability issues such as dizziness, increased polyuria, or thirst cannot be ruled out.
- A renal impairment study (not done in ADPKD patients) showed that in subjects with moderate renal impairment, AUC of total tolvaptan increased by 100%, whereas the unbound AUC was increased negligibly by 5%. In subjects with severe impairment of renal function (10 – 28 mL/min/1.73 m^2) the, total AUC and unbound AUC were increased by 114% and 92% respectively.
- A trend for dose-dependent decrease in urine osmolality over the range of 15 – 120 mg was observed following single dose of tolvaptan in ADPKD patients. Near maximum effects were observed within the first urine collection interval from 0 to 4 h post dose. A trend for dose dependent increase in the duration of the effect was also observed. The effect on urine osmolality with 15 mg dose reached baseline levels by 24 hrs.
- Multiple dose study in ADPKD patients indicates that there was no difference between once daily dosing or twice daily dosing with respect to lowering of urine osmolality (after correcting for baseline). Further, there was no trend for dose dependent effects.
- In ADPKD patients, glomerular filtration rate (GFR) decreased acutely (at week 3) after initiation of tolvaptan treatment (duration: 3 weeks) and returned to baseline 3 weeks after discontinuation. This decrease is larger in the patients with normal renal function or mildly impaired renal function compared to patients with moderate and severe impairment of renal function.

1.4 Summary of Pharmacometric Findings

- In the pivotal Phase III trial of study 251, all tested tolvaptan doses showed significantly lower kidney growth than the placebo after three years of treatment. The slope in total kidney growth of tolvaptan treatment was about half of the placebo, indicating favorable treatment effect. However, based on the modal

doses, the effect was not dose-dependent under the tolerability based titration design. Lower slope values were not observed in patients with higher modal tolvaptan doses. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect, e.g. less tolerable patients were more sensitive to the drug's desired effect.

- In study 251, tolvaptan treatments showed significantly slower rate in the worsening of renal function than the placebo over three years of therapy. Tolvaptan treatment effect was evident but not dose-dependent based on the modal doses. Higher tolvaptan doses were not associated with lower pace of renal worsening. The lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.
- There existed significant association between total kidney volume (TKV) and worsening of renal function measured as GFR using CKD-EPI equation. Higher volume of total kidney was associated with lower renal function. Correlation between percent changes of last visit TKV and last visit renal function was significant (p value <.0001)
- There was a clear dose-response relationship for time to first severe renal pain based on the modal doses. Higher modal doses were associated with longer time to first severe renal pain. This observed relationship was also subjective to the confounding issue due to the titration trial design.
- There was no dose-response relationship for time to first severe worsening of renal function based on the modal doses. The lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.
- There was an imbalance in subjects experiencing abnormally elevated serum ALT between tolvaptan and the placebo. Tolvaptan are more likely to have peak ALT > 3 x ULN and carries higher risk of hepatocellular injury. However, the risk is not dose-related based on the modal doses. The lack of dose-response relationship could be due to the titration trial design based on the tolerability.

2 Question-Based Review (QBR)

This is an abbreviated review of the drug tolvaptan. Tolvaptan was approved by the FDA under the brand name Samsca® in May 2009. The approved doses for Samsca are 15 to 60 mg of tolvaptan daily. The clinical pharmacology of this drug has been extensively reviewed for NDA 22,275 (Peter Hinderling, 6/9/2008). This review will focus on studies that have been submitted for the ADPKD indication.

The IND for the ADPKD indication has been active since 2005 and the drug was given Fast Track designation in 2006. Subsequently, the drug was given orphan drug status in 2012 and rolling review was granted. The final submission for this indication was received on March 1, 2013.

2.1 General attributes of the drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Tolvaptan belongs to a class of drugs that are developed as antagonists at the vasopressin receptors. The structure of tolvaptan is shown in Figure 1; the molecular weight is 448.94 g/mol and it appears as a white crystalline powder. The tolvaptan molecule has one stereoisomeric center and thus two enantiomers. The drug substance is a racemic mixture of both enantiomers. The solubility was measured in various solvents at 25°C and showed higher solubility in lipophilic solvents as compared to water, where it was practically insoluble (0.00005% w/v). In Britton-Robinson buffer (phosphoric acid, acetic acid, boric acid and sodium hydroxide) at pH levels ranging from 2 to 12 no change in solubility was observed (0.00004% w/v) and partition coefficients between buffer and octanol showed an overwhelming preference for the lipophilic phase ($P_{O/W}$ >5000).

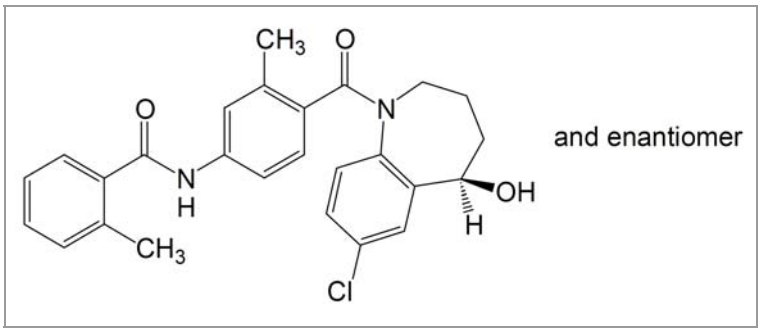

Figure 1. Tolvaptan structure

2.1.2 What is the proposed mechanism of action and therapeutic indication?

ADPKD is a hereditary genetic disease that is characterized by mutations in the genes encoding for polycystin-1 and polycystin-2. These two proteins are found expressed on cilia that protrude into the lumen of the collecting duct and they are thought to be working together on flow-induced calcium signaling. It is hypothesized that in ADPKD, due to the mutations, intracellular calcium level homeostasis might be impaired and as a result, cyclic adenosine monophosphate (cAMP) levels are not suppressed as they ordinarily would be. The second messenger cAMP is involved in promoting an environment for cyst growth.

Vasopressin binding to the V2-receptor uses the second messenger cAMP to elicit the downstream effect of incorporation of water channels (aquaporins) in the luminal membranes of collecting duct cells. Therefore, binding of vasopressin would increase intracellular cAMP and therefore promote a proliferative environment for cyst growth.

Tolvaptan is a selective antagonist at the vasopressin 2 receptor (V2R) located in cells in the collecting duct and distal convoluted tubules of the kidney. The antagonism at the receptor leads to decreased influence of vasopressin (aka arginine vasopressin (AVP) or antidiuretic hormone (ADH)) on the kidney and, by virtue of counteracting vasopressin's antidiuretic activity, leads to increased free water clearance and retention of sodium, which in turn increases sodium concentrations in plasma. Tolvaptan is also hypothesized to limit the increase in second messenger cyclic adenosine mono phosphate (cAMP) after the binding of vasopressin to the receptor and thus provide its effect in ADPKD.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

For treatment of ADPKD, tolvaptan is to be taken orally. Daily doses are to be split unevenly between a morning dose and an afternoon dose taken approximately 8 hours after the morning dose. Tolvaptan is titrated to the highest tolerated dose, with initial dose (morning/afternoon) being 45/15 mg, followed by a first titration step to 60/30 mg to the target dose of 90/30 mg. The label recommends weekly intervals between titration steps, which is consistent with the titration implemented in the pivotal clinical trial. To facilitate this dosing regimen, the applicant is seeking approval of two new strengths of 45 mg and 90 mg tablets in addition to the previously approved strengths of 15 mg, 30 mg and 60 mg tablets.

2.2 General clinical pharmacology

This section provides information about the PK and PD properties of tolvaptan that are pertinent to the current indication, population and the dose ranges studied.

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

As a part of their clinical pharmacology package in support of the current indication, the applicant provides 10 clinical pharmacology study reports. These included: PK/PD studies in healthy volunteers, ADPKD patients following single and multiple doses, studies exploring the impact or tolvaptan on renal function and the impact of renal function impairment on the pharmacokinetics of tolvaptan, and lastly a bioequivalence study that provides the information to bridge the new 90 mg to-be-marketed strength with the 30 mg strength that was studied in the Phase 3 trial. This study also evaluated the impact of high fat meal on the pharmacokinetics of tolvaptan for this new strength of 90 mg tablets.

The applicant performed one randomized, double-blind, placebo controlled trial in subjects with ADPKD who had a total kidney volume of >750 mL, as this was thought to define a population at for progression of the disease. The trial lasted 36 months. The titration scheme used in the trial is the same that is proposed for the label.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The biomarker measured to ascertain effect of study drug in clinical pharmacology studies was urine osmolality. Vasopressin increases urine osmolality by increasing reabsorption of water from the collecting duct. Inhibition of vasopressin action should therefore lead to lower urine osmolality as was observed in clinical pharmacology studies.

Urine osmolality is measured in two ways in clinical and clinical pharmacology studies in this submission. One way was to collect urine in defined intervals over a 24-hour period and then determine osmolality for each pooled interval. Another way was to take a spot urine sample and determine urine osmolality in the spot sample. Healthy, normal values of urine osmolality range from 300 to 800 mOsm/kg in spot urine samples. Normal daily variation of urine osmolality exists; it is usually larger in the morning sample. Water consumption will usually decrease urine osmolality, as the release of vasopressin precursor from the anterior pituitary is prevented.

Total kidney volume (TKV) is the primary efficacy response in Phase 3 (156-04-251). It is measured using magnetic resonance imaging (MRI) at 12, 24, and 36 months. The Agency indicated to the applicant that TKV is not an acceptable surrogate. The Agency suggested that the applicant study the proposed secondary endpoints in the TEMPO trial, such as pain, hematuria, infection, nephrolithiasis and considered rate of GFR change to be important. The applicant's final secondary endpoint consisted of renal pain, albuminuria, hypertension, and worsening renal function.

One of the expected impacts of the treatment of ADPKD would be a decreased progression of renal function decline and the slope of renal function was another secondary endpoint in trial 156-04-251. The main marker to measure renal function was

reciprocal serum creatinine. Other metrics of renal function considered in the study were estimated creatinine clearance as measured by either the Cockcroft-Gault equation, or the Modification of Diet in Renal Disease method (MDRD), or using the Chronic Kidney Disease Epidemiology Collaboration method (CKD-EPI). Of note, the applicant chose to assess the baseline at the end of titration, with the intention of excluding the acute decrease in GFR due to hemodynamic changes.

2.2.3 Exposure-response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Urine Osmolality

After single doses of 15, 30, 60, or 120 mg tolvaptan, urine osmolality decreased quickly, within the first urine collection interval from 0 to 4 h post dose. The effect of tolvaptan on urine osmolality was numerically ordered in a dose dependent fashion as shown in the Figure 2 below. However, by 24 hrs, there was loss of the treatment effect with the 15 mg dose returning to baseline levels.

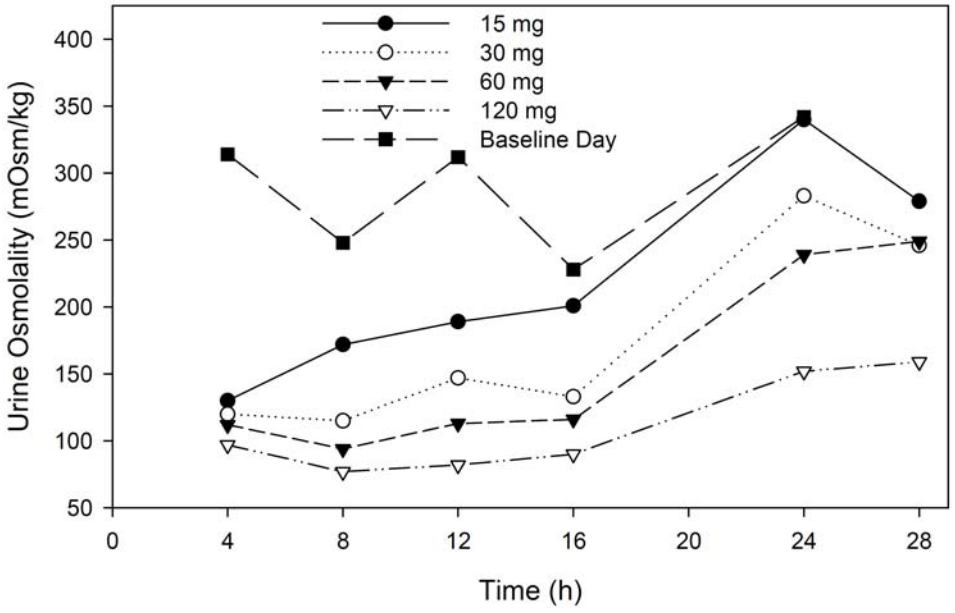

Figure 2. Mean urine osmolality [mOsm/kg] after single oral doses of tolvaptan
Source: CSR 156-04-248 Figure 9.3.3-1, page 78

Similar effects were observed following repeat administration as shown in Figure 3. The urine osmolality remained below 300 mOsm/kg for the entire dosing interval after twice daily dosing, while the 30 mg QD arm showed that urine osmolality gradually increased following the last dose reaching 300 mOsm/kg.

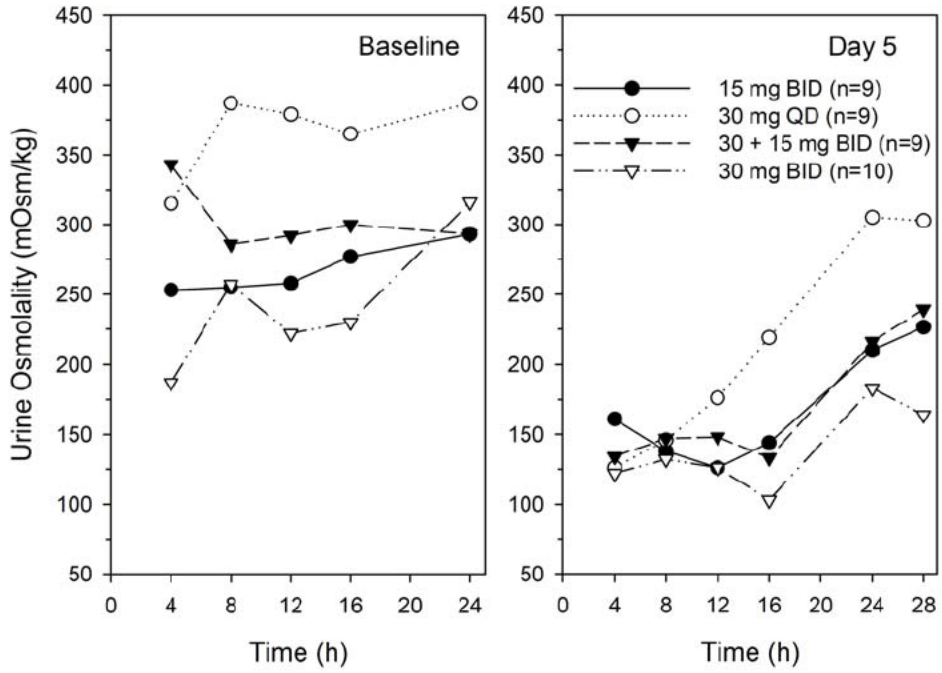

Figure 3. Mean urine osmolality [mOsm/kg] at baseline and after 5 days of dosing with tolvaptan
Source: CSR 156-04-249 Figure 9.3.3-1, page 86

The baseline values were not similar between dose groups. When corrected for baseline, there did not seem to be any dose or dosing regimen related difference in the effect of tolvaptan on urine osmolality as shown in Figure 4.

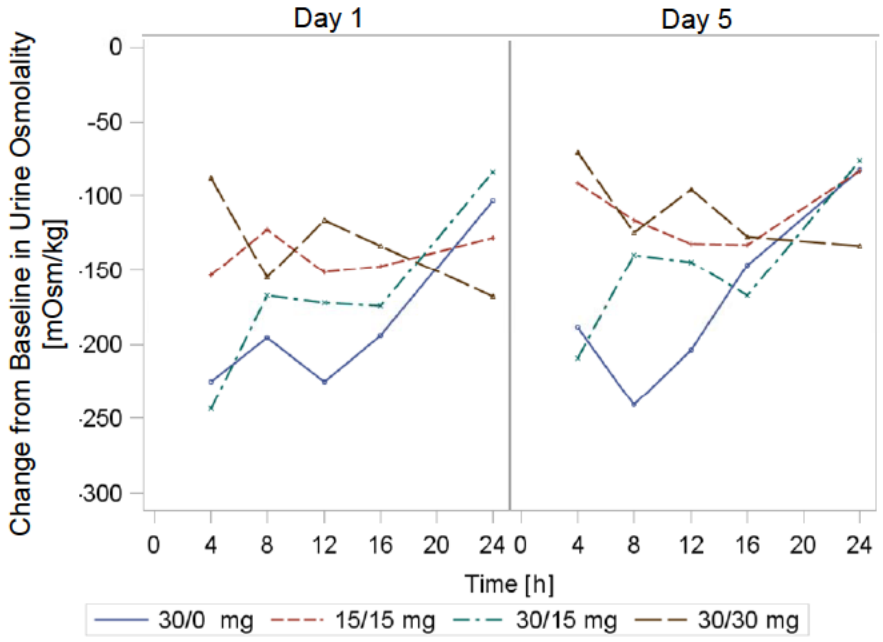

Figure 4. Change from baseline in urine osmolality in study 156-04-249
Source: CSR 156-04-294, urin0.xpt

Change in Total Kidney Volume

In study 251(Phase 3 study 156-04-251) all tested tolvaptan doses showed significantly lower kidney growth than the placebo after three years of treatment, but no clear dose-response relationship was observed for TKV slope based on the modal doses. Tolvaptan treatment demonstrated a TKV slope that was about half of the placebo, indicating a favorable effect for tolvaptan. However, the effect was not dose-dependent under the tolerability based titration design. Lower slope values were not associated with higher modal tolvaptan doses. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect, e.g. less tolerable patients were more sensitive to the drug's desired effect. The numerical trend among the three modal dose groups suggested that those patients who could only tolerate the lower dose seemed to be more sensitive to tolvaptan's effect in reducing the TKV slope.

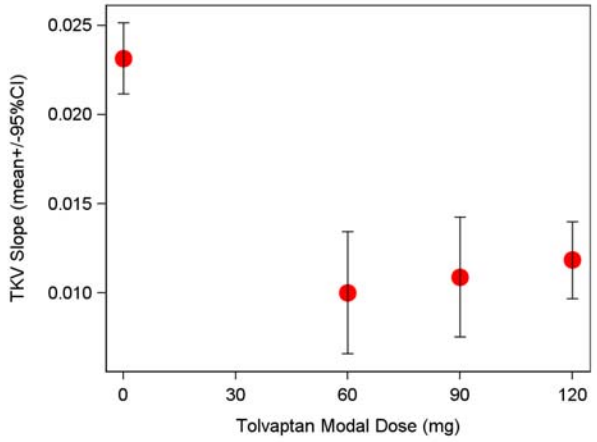

Figure 5: Relationship between total kidney volume (TKV) slope and varying tolvaptan modal doses. The dose of 0 mg is the placebo treatment.

Change in Renal Function

In study 251, after three years of treatment, the tolvaptan arm showed significantly slower slope in worsening of renal function than the placebo. Tolvaptan treatment effect was evident but there was no clear modal dose-response relationship for the decrease in GFR values using CKD-EPI equation. Higher modal tolvaptan doses were not associated with lower slope of renal worsening. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.

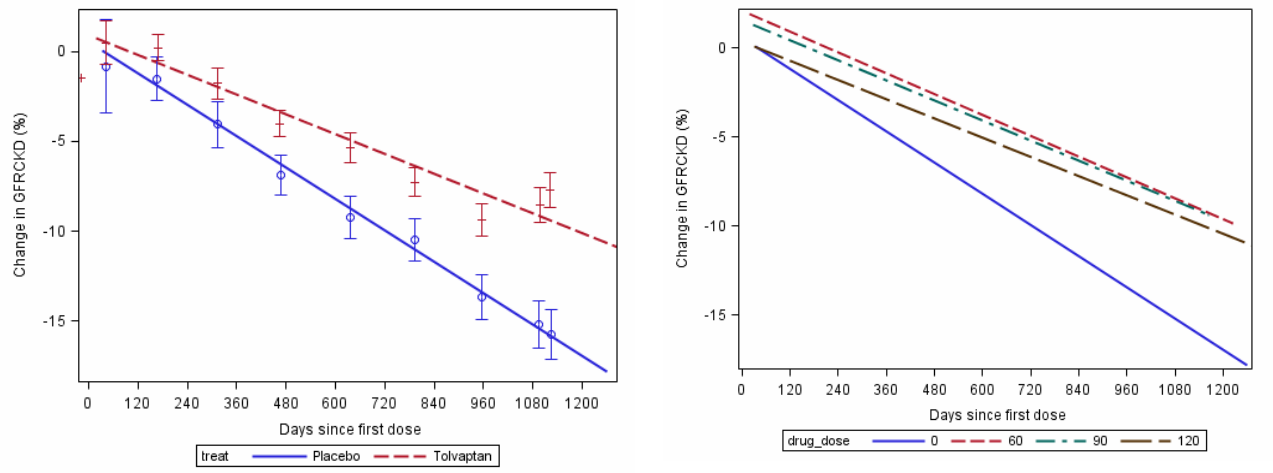

Figure 6: Percent change in renal function measured as GFR (mean with 95% CI) using CKD-EPI equation over time since first dose stratified by treatment (tolvaptan vs. placebo; left) and varying tolvaptan modal doses (right); the lines were regression lines.

Correlation between Change in Total Kidney Volume and Worsening of Renal Function

There existed significant association between TKV and worsening of renal function measured as GFR using CKD-EPI equation. Higher volume of total kidney was associated with lower renal function. Correlation between percent changes of last visit TKV and last visit renal function was significant (p value <.0001)

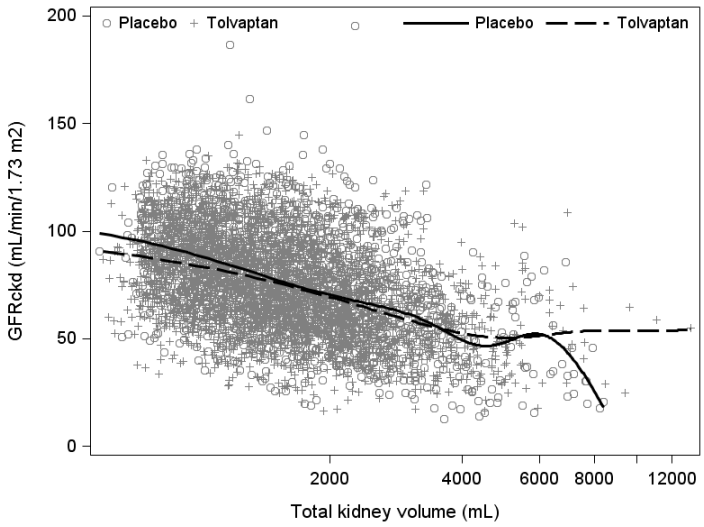

Figure 7: Relationship between GFR using CKD-EPI equation and total kidney volume

Time to First Severe Renal Pain

First severe renal pain was defined as the first occurring event being severe renal pain requiring a prescribed intervention from Day 1 onwards. As indicated in the figure below, tolvaptan showed a clear treatment effect in delaying the occurrence of renal pain. There was a dose-response relationship for renal pain even though the dose was not a randomized dose but a modal dose. Higher doses, especially the 120 mg daily doses (90 mg+30 mg), appeared to have a better effect, while the lowest daily doses (60 mg) showed an effect being no different from the placebo. This observed relationship was also subjective to the confounding issue due to the titration trial design.

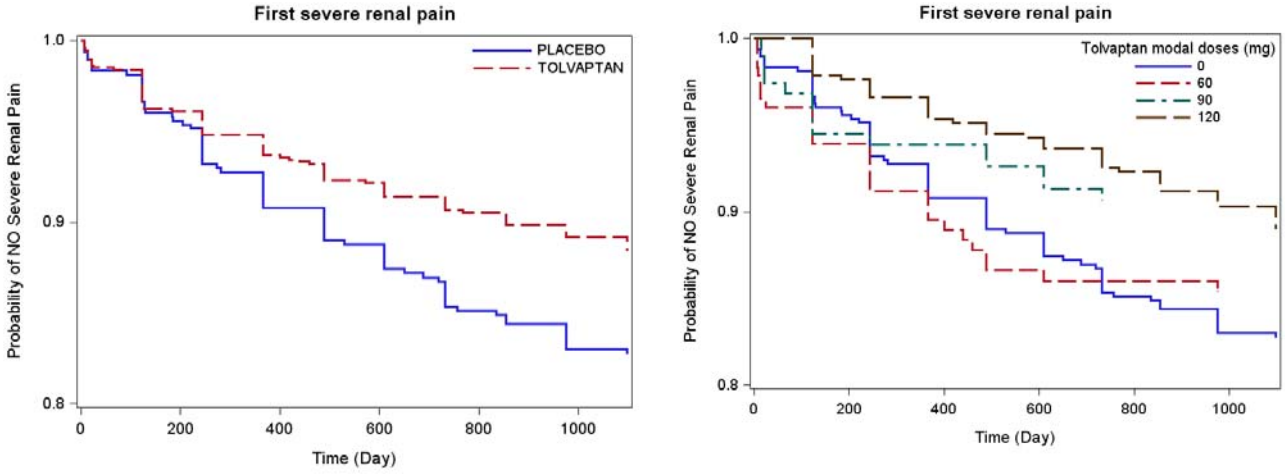

Figure 8: Kaplan-Meier plot of time to first severe renal pain stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan modal doses (right)

Time to First Severe Worsening of Renal Function

First severe worsening of renal function was defined as a reproducible 25% decrease in reciprocal serum creatinine from Week 3/EOT onwards. As demonstrated in figure below, tolvaptan showed a clear treatment effect in delaying the occurrence of severe worsening of renal function. However, there was no apparent modal dose-response relationship for worsening of renal function. Higher doses were not associated with longer time to the first severe worsening of renal function. However, the lack of dose-response relationship could be due to the trial design if the patients' tolerability to tolvaptan was associated with the patients' sensitivity for the desired effect.

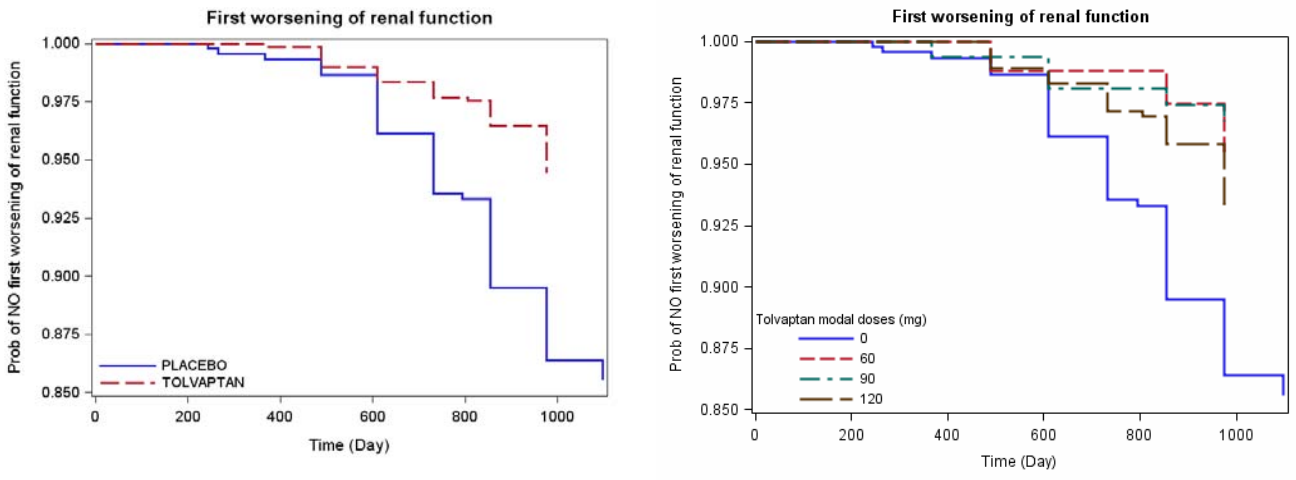

Figure 9: Kaplan-Meier plot of time to first severe worsening of renal function stratified by treatment (Tolvaptan vs. Placebo, left) or varying tolvaptan doses (right)

2.2.3.2 What is the time-course of treatment effects?

The time-course of effects on urine osmolality is already described under Section 2.2.3.1

Glomerular Filtration Rate (GFR)

Acute effect on GFR after tolvaptan dosing was assessed in a clinical study in patients with varying degrees of renal function. A pooled analysis adjusted for baseline GFR showed that at the end of treatment period, i.e., 3 weeks of forced titration from 45/15 mg to 90/30 mg, there was a statistically significant reduction in GFR (Figure 10). Three weeks after discontinuation of tolvaptan treatment, the GFR returned to baseline levels (Figure 10). The acute decrease in renal function was largest in patients with GFR >60 mL/min/1.73 m^2, compared to the moderate and severe renal impairment groups.

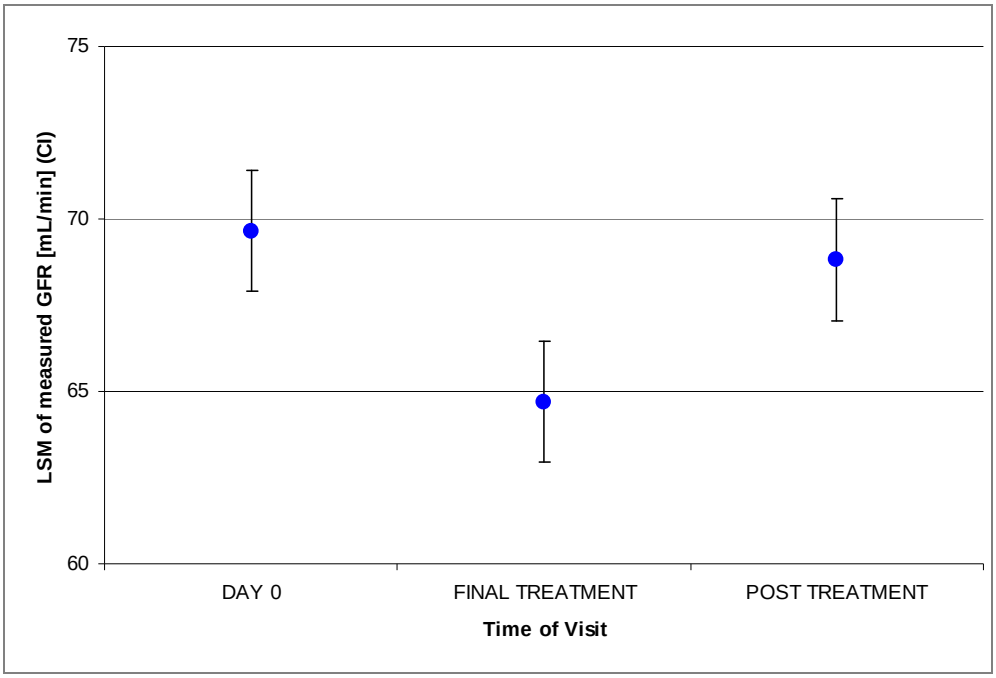

Figure 10. Least square mean measured GFR pooled across groups, adjusted by baseline GFR
Source: 156-09-284, pdparm0.xpt

Total Kidney Volume (TKV)

Change in total kidney volume at two dose levels was assessed in study 156-04-250, which enrolled patients who had been previously enrolled in the single and multiple dose PK/PD studies. Patients had an MRI measurement at screening (baseline) and at 2 months, 12, 24, and 36 months after treatment initiation. The results are shown in Figure 11 below. It is difficult to interpret the impact of treatment on progression, as there is no placebo group for comparison; however, after an initial drop in TKV by month 2, it increases with approximately the same rate between the dose groups.

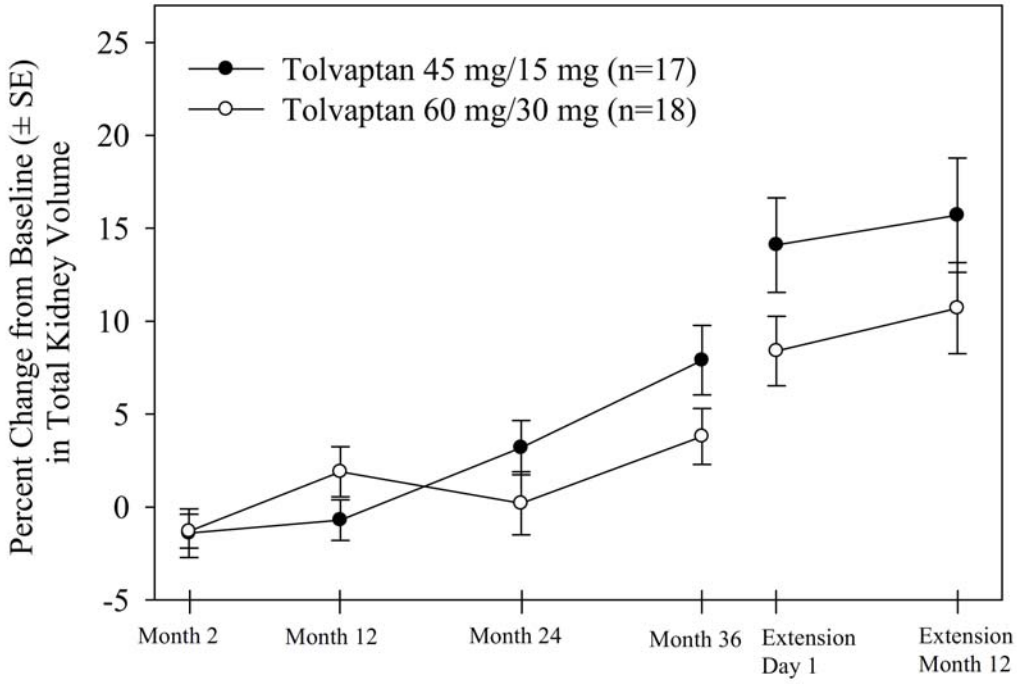

Figure 11. Percent change from baseline in TKV by dose regimen assigned at month 2
Source: CSR 156-04-251 Figure 9.4.2.1-3, page 82

A similar time-course of effect on total kidney volume was observed in a shorter duration study after 3 weeks on tolvaptan treatment and subsequently after 3 weeks off treatment in patients with varying renal function. Changes in TKV were highest in patients with normal renal function or those with mild-moderate impairment of renal function. The reduction in TKV from baseline was ~4.5%. In contrast, the severe renal impairment group had a reduction in TKV of ~2%. Three weeks after the end of tolvaptan treatment, TKV increased. The TKV at the end of treatment was not found to be different compared to baseline (see Table 1 below).

Table 1. Mean TKV [mL] after 3 weeks on treatment and 3 weeks after the end of treatment with tolvaptan

Parameter	$eGFR_{MDRD}$ > 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ 30 to 60 mL/min/1.73 m^2 (N = 9)	$eGFR_{MDRD}$ < 30 mL/min/1.73 m^2 (N = 9)
Baseline	1376.7 (723.6)	1812.8 (1126.3)	4360.7 (3252.5)
Final Treatment	1315.1 (703.5)	1735.3 (1093.8)	4276.2 (3187.0)
Percent Change from Baseline	−4.5 (3.7)[a]	−4.6 (2.7)[a,b]	−1.9 (1.9)[a]
Post Treatment	1359.3 (729.3)	1759.3 (1101.3)	4558.2 (3415.1)
Percent Change from Baseline	−1.5 (2.3)	−2.4 (3.8)	−0.7 (2.5)

[a] P-value for assessment of significance for the change from baseline < 0.05.

[b] P-value for comparison of change in $eGFR_{MDRD}$ 30 to 60 group to change in $eGFR_{MDRD}$ < 30 group < 0.05.

Source: CSR 156-09-284 Table 9.3.3.4-1, page 86

2.2.3.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

One major concern for tolvaptan in ADPKD patients is liver safety. After the completion of trial 156-04-251, an abnormal elevation of serum alanine aminotransferase (ALT) was revealed with incidence in the tolvaptan arm much higher than in the placebo. The potential of tolvaptan for development of drug-induced liver injury (DILI) was then evaluated. As mentioned early, three cases (two during treatment) were found matching Hy's law, with serum ALT >3 x ULN and total bilirubin > 2 xULN. The eDISH plot for study 251 was followed below. It can be observed that there is a clear imbalance between tolvaptan and placebo subjects experiencing serum ALT elevation exceeding 3 x ULN. In the right-upper (Hy's Law) quadrant, there are two tolvaptan treated subjects and no placebo treated subjects.

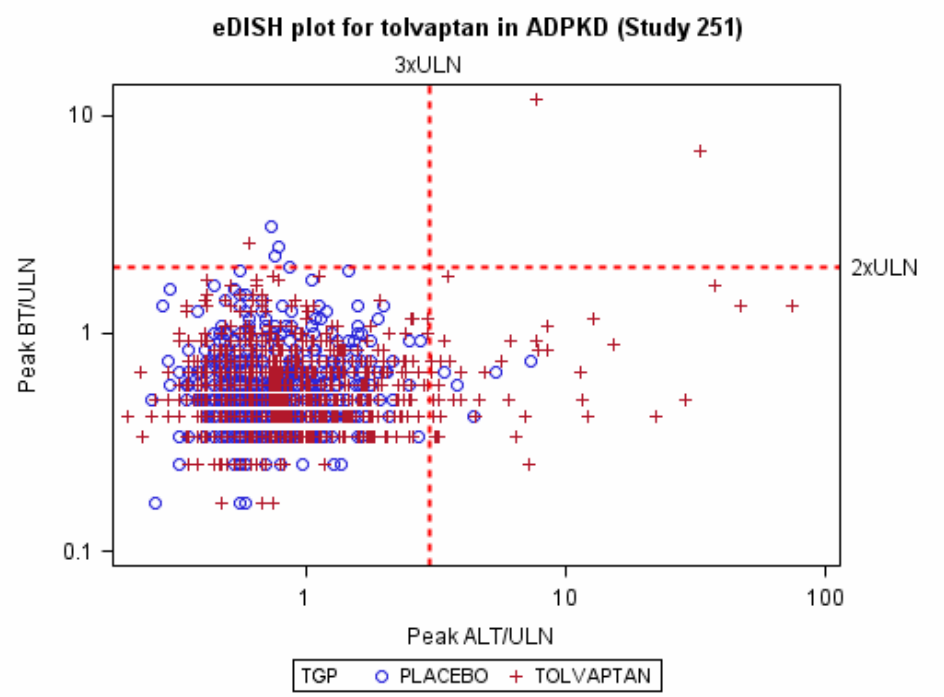

Figure 12: eDISH plot for peak total bilirubin vs. peak ALT in patients receiving placebo or tolvaptan in study 156-04-251

The Kaplan-Meier plot for time to peak ALT >3 x ULN was followed. Tolvaptan showed a much higher probability than the placebo to have peak ALT >3 x ULN. However, the risk was not dose-related based on the modal doses. There was no dose-response relationship for the risk of elevated ALT levels. The lack of dose-response relationship could be due to the titration trial design based on the tolerability.

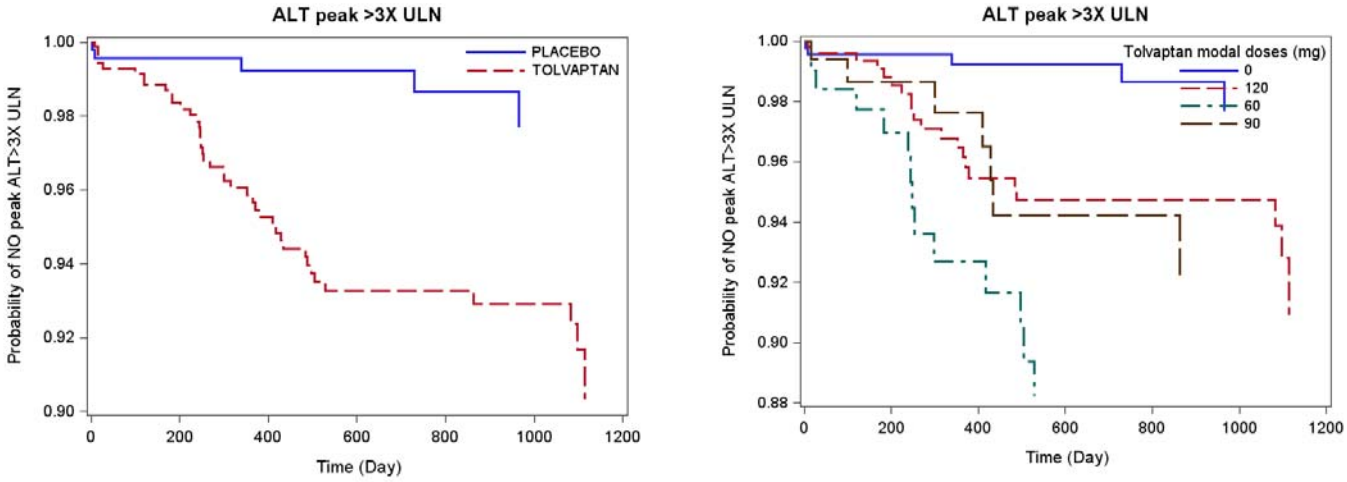

Figure 13: Kaplan-Meier plot for time to peak ALT > 3 x ULN stratified by treatment (tolvaptan vs. placebo, left) and various tolvaptan modal doses (right)

2.2.3.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant's goal for dose selection during the development of tolvaptan for the treatment of ADPKD was to lower urine osmolality to below 300 mOsm/kg and to maximally decrease the marker throughout the dosing interval.

A single dose study (see results in Figure 2) showed that a 15 mg dose was too low, as urine osmolality returned to baseline at the end of the dosing interval. Likewise, higher doses of 30 and 60 mg kept urine osmolality below the threshold of 300 mOsm/kg, but increased towards the end of the dosing interval. Only the 120 mg single dose depleted urine osmolality until the end of the dosing interval. Based on the single-dose study, a multiple dose approach with split doses was chosen to potentially decrease occurrences of nocturia in patients. In the multiple dose Phase 2 study, the following doses were studied: 30 mg QD, 15 mg BID, 30 /15 mg, and 30 mg BID. The first dose was given at around 8-9 am and the second dose approximately 8 h later. The time course of change from baseline in urine osmolality in the multiple dose study can be seen in Figure 4. There does not seem to be a dose response associated with urine osmolality, i.e. all doses achieved a reduction in urine osmolality to approximately the same degree and it is not clear that a case for a BID dosing, split or otherwise, provides a clear advantage over a once daily dose of tolvaptan.

In another study (Study 250), ADPKD patients who were enrolled in the single and multiple dose trials (and thus not eligible to enroll in the pivotal trial) were able to receive study drug for a three year duration. It is not clear how much time was required to elapse between the end of the single or multiple dose studies and enrollment in study 156-04-

250. Both studies 1(Study 56-04-248 and 249) had follow-up periods of 5 days, which would allow enough washout time for tolvaptan from a PK perspective. In study 250, patients were started on a dose of 30/15 mg tolvaptan and were up-titrated weekly to 45/15, 60/30, and finally 90/30 mg. At 2 months, patients were randomized to either 45/15 mg or 60/30 mg doses for the remaining 34 months on trial. Spot urine osmolality was measured throughout and the results of the marker during the titration period are shown in Table 2 below.

Table 2. Mean (SD) urine osmolality[mOsm/kg] after one week of treatment at each dose

Time of Day	Week of Treatment and Dose					
	Day 0	Week1	Week 2	Week 3	Week 4[a]	
	Baseline n=45[b]	30+15 mg n=45	45+15 mg n=43	60+30 mg n=43	45+15 mg n=14	90+30 mg n=27
Prior to First Dose	467 (227)	276 (143)	264 (104)	239 (122)	300 (99)	174 (98)
Prior to Second Dose	455 (237)	191 (108)	154 (66)	140 (70)	175 (85)	136 (58)
Prior to Bedtime	438 (207)	170 (106)	163 (75)	136 (110)	206 (109)	108 (28)

Source: CSR 156-04-250 Table 9.4.1.1-1 (page 76)

At the end of titration, the 90/30 mg dose achieved a mean urine osmolality of 108 mOsm/kg prior to bedtime and 174 mOsm/kg prior to the morning dose. Prior to the morning dose, 15% of patients were below a 300 mOsm/kg threshold, which is the lowest achieved percentage of patients below this threshold compared to the other titration doses. Presumably as a result, the applicant chose 90+30 mg as the target dose.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

This part of the review will focus on the pharmacokinetics in ADPKD patients. For a review of the PK in healthy volunteers and hyponatremic as well as heart failure patients please refer to the clinical pharmacology review for NDA 22,275 (Peter Hinderling, 6/9/2008).

Briefly, in healthy subjects, peak exposure of tolvaptan is reached with 2-4 hours post dose and about 56% of administered drug is absorbed from the intestines. The drug is >99% protein bound and is a substrate of CYP3A4 and MDR1 (P-gp). It is also an inhibitor of P-gp. Two metabolites are of interest, metabolite DM-4103 because of its long half-life of ~180 h, and DM-4107 because is the major circulating metabolite. The drug is mostly eliminated hepatically and its terminal half-life is around 8-10 h.

2.2.4.1 What are the single dose and multiple dose PK parameters?

Pharmacokinetics of tolvaptan following single and multiple doses were similar to that previously observed in healthy volunteers. After, oral administration in ADPKD patients, peak plasma concentrations are observed around 1 – 3 hrs. Tolvaptan generally follows a monoexponential decline with an elimination half-life of 4 – 6hrs as shown in Figure 14 below. Tolvaptan exhibits dose proportional pharmacokinetics following single dose (15 to 120 mg).

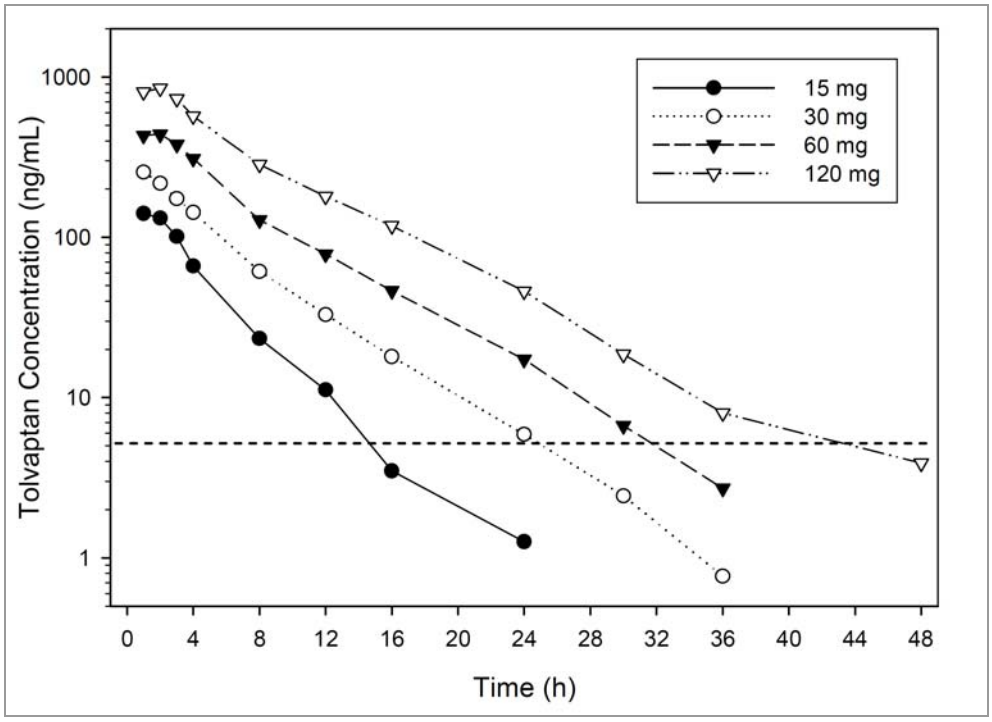

Figure 14. Semi-log plot of mean plasma concentrations of tolvaptan after ascending single oral doses

Source: CSR 156-04-248 Figure 9.2.3-1, page 74

The multiple dose study at doses of 15 mg BID, 30 mg BID, 30+15 mg split dose BID and a single 30 mg QD dose given for 5 days, showed slightly less than proportional increases in exposure and little accumulation at steady state as shown in Figure 15 below.

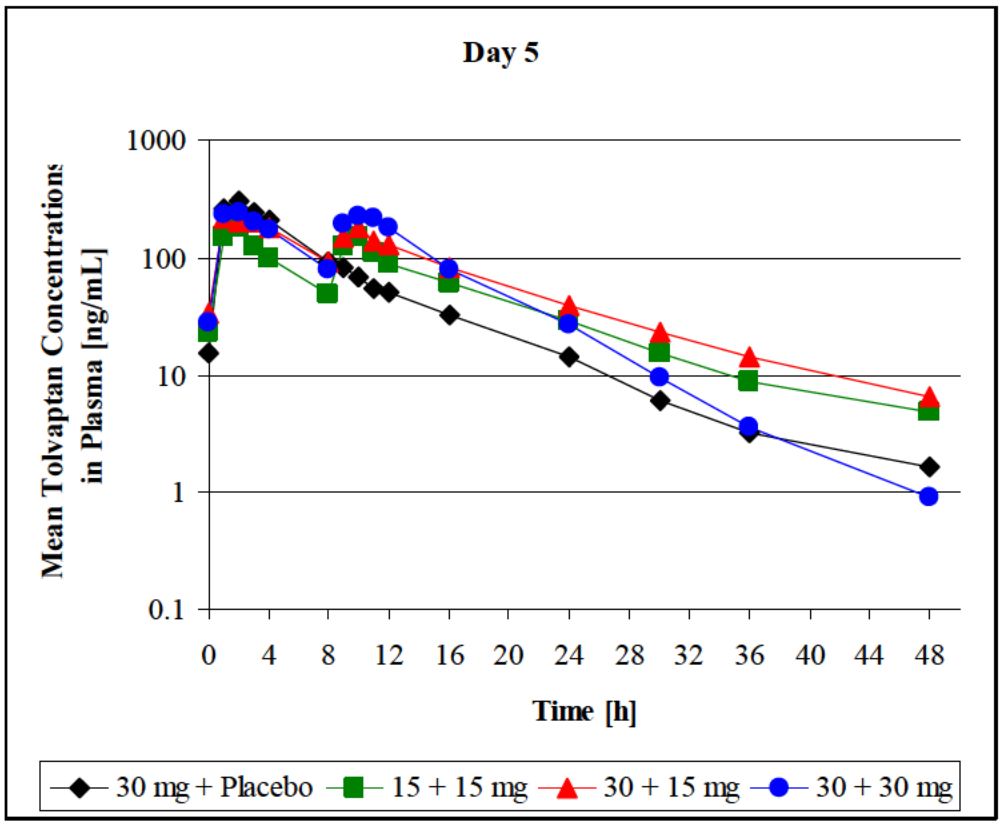

Figure 15. Mean tolvaptan concentrations in plasma after 5 days of dosing
Source: 156-04-249 pk0.xpt

2.2.4.2 Renal Impairment

A study on the effect of renal impairment on tolvaptan PK (not ADPKD patients) had been previously reviewed (Dr. Peter Hinderling, 12/15/2011, IND 54,200). The study showed that in subjects with moderate renal impairment, AUC of total tolvaptan increased by 100%, whereas the unbound AUC was increased negligibly by 5%. In subjects with severe impairment of renal function (10 – 28 mL/min/1.73 m^2) the, total AUC and unbound AUC were increased by 114% and 92% respectively.

No dose adjustment is required for patients with mild or moderately impaired renal function, as this population was studied in the TEMPO trial. One entry criterion for the TEMPO trial was a baseline GFR of at least 60 mL/min/1.73 m^2. Based on the results observed in Study 284, tolvaptan may not be the treatment of choice for patients with severe renal impairment.

2.3 Extrinsic Factors

2.3.1 CYP3A4 Inhibition

The interactions of tolvaptan with other drugs have previously been reviewed. Tolvaptan is a substrate for CYP3A4 and is thus subject to drug-drug interactions with CYP3A4 inhibitors and inducers.

A 200 mg once daily dose of ketoconazole caused a 3.5-fold and 5-fold increase in tolvaptan Cmax and AUC, respectively. A 50% increase in the terminal half-life is also observed. Concomitant administration with the CYP3A4 inducer rifampin reduced Cmax and AUC of tolvaptan to 10 and 20%, respectively as compared to tolvaptan administered alone.

The US package insert for SAMSCA® recommends not using tolvaptan with strong CYP3A4 inhibitors and avoiding use with moderate CYP3A4 inhibitors while considering a dose adjustment with CYP3A4 inducers.

In the pivotal clinical trial (156-04-251, TEMPO) in ADPKD patients, the applicant cautioned against the use of potent CYP3A4 inhibitors. A total of 287 out of 1444 patients in the study received CYP3A4 inhibitors (163/961 on tolvaptan and 124/483 placebo). Co-medication that inhibited CYP3A4 included ketoconazole (topical application) and itraconazole, other azole antimycotics, diltiazem, alprazolam, atorvastatin, fluoxetine and ranitidine, among others. Side effects such as fatigue were observed more commonly in patients on a CYP3A4 inhibitor for both placebo and tolvaptan groups, however, the occurrence was higher in the tolvaptan group. Numerically, there did not appear to be a difference in the occurrence of ALT or AST elevations in either the tolvaptan or the placebo arm when coadministered with a CYP3A4 inhibitor (CSR 156-04-251 Table ST-1.9.1, page 4754); however, numbers were small overall. For bilirubin, a clear trend was not observed, again because of a limited number of observations. Dizziness, polyuria, nocturia did not occur more often in the CYP3A4 inhibitor treated groups, however, renal pain and hematuria did (Table ST-1.9.1, page 4771 f.).

A population pharmacokinetic study (156-11-296) assessed the impact of CYP3A4 inhibitors and found that on average CL/F was reduced by 27% when tolvaptan was coadministered with an inhibitor. In a total of 1067 subjects, there were only 50 subjects with at least one instance of strong, moderate or weak CYP3A4 inhibitor co-administration. Of 6437 observations, less than 3% observations were associated with CYP3A4 inhibitor co-administration. However, the model only included a logical value (Yes/No) for coadministration at any time during trial participation. In addition, information about the duration of the concomitant administration or verification of sample collection for PK during concomitant administration was not collected. Hence

the impact of strong or moderate CYP3A4 inhibitors may not be fully elucidated from this analysis.

The applicant proposes dose adjustment only for patients on potent CYP3A4 inhibitors as shown in Table 3 below.

Table 3. Proposed dose adjustment when tolvaptan is coadministered with strong CYP3A4 inhibitors

Standard Split Dose	Adjusted Daily Dose
90/30 mg	30 mg upon waking
45/15 mg	15 mg upon waking

Source: Annotated label, (b) (4)®

While the proposal to decrease the daily dose by a factor of ¼ seems reasonable, it should be noted that the reported increase with ketoconazole in AUC to tolvaptan was 5-fold. This was observed at a ketoconazole dose of 200 mg dose QD, which is a sub-maximal dose. Hence the proposed dose adjustment may not fully alleviate the interaction. Further, there is no proposed recommendation for patients who might be stabilized on a tolvaptan dose of 60/30 mg. Based on the above proposal, such patients may need a dose of ~20 mg, however the applicant does not have a dose strength of 20 mg available.

Hence, it may be prudent to avoid concomitant administration of systemically (i.e. not topically) administered strong CYP3A4 inhibitors.

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed 90 mg formulation was demonstrated to be bioequivalent to 3x30 mg tablets in a healthy volunteer study as shown in Figure 16.

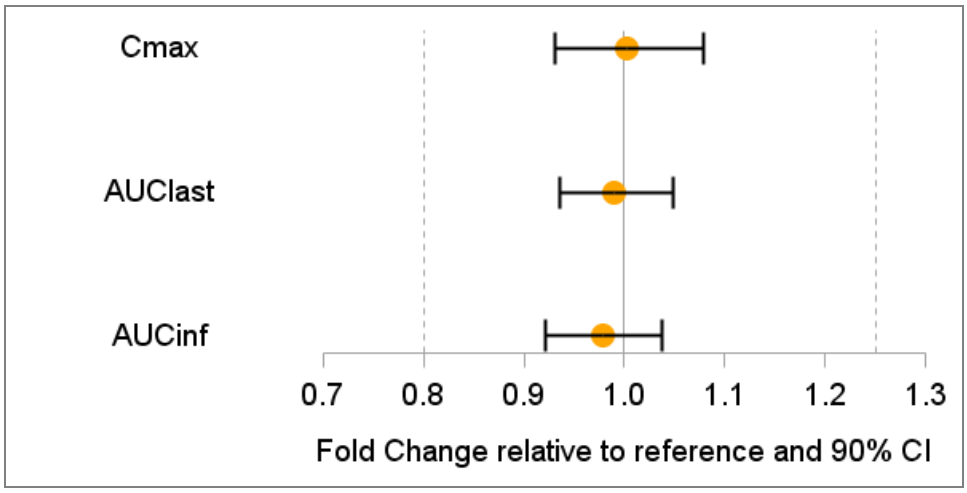

Figure 16. Forest plot of geometric mean ratios for bioequivalence study
Source 156-11-295 pk0.xpt

2.4.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

With a high fat meal, Cmax increased about 2-fold compared to administration in fasted state as shown in Figure 17. Administration of food did not alter the AUC.

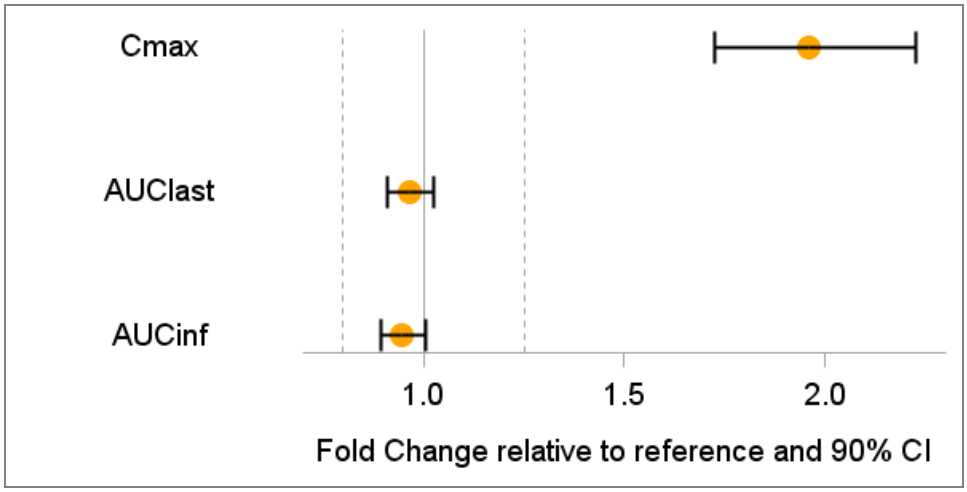

Figure 17. Forest plot of geometric mean ratios for food effect study
Source 156-11-295 pk0.xpt

This increase in Cmax was also observed in a previously reviewed food effect study for tolvaptan and was deemed not clinically relevant. The pivotal phase 3 study for ADPKD (156-04-251) was conducted without regard to food intake. While the impact of food (varying fat content) may not be significant with respect to maintenance of effect, the

possibility that a higher Cmax may manifest tolerability issues such as dizziness, increased polyuria, or thirst cannot be ruled out.

The plot of the concentration-time course shows that half-life is longer in the fasted compared to the fed dose group (Figure 18).

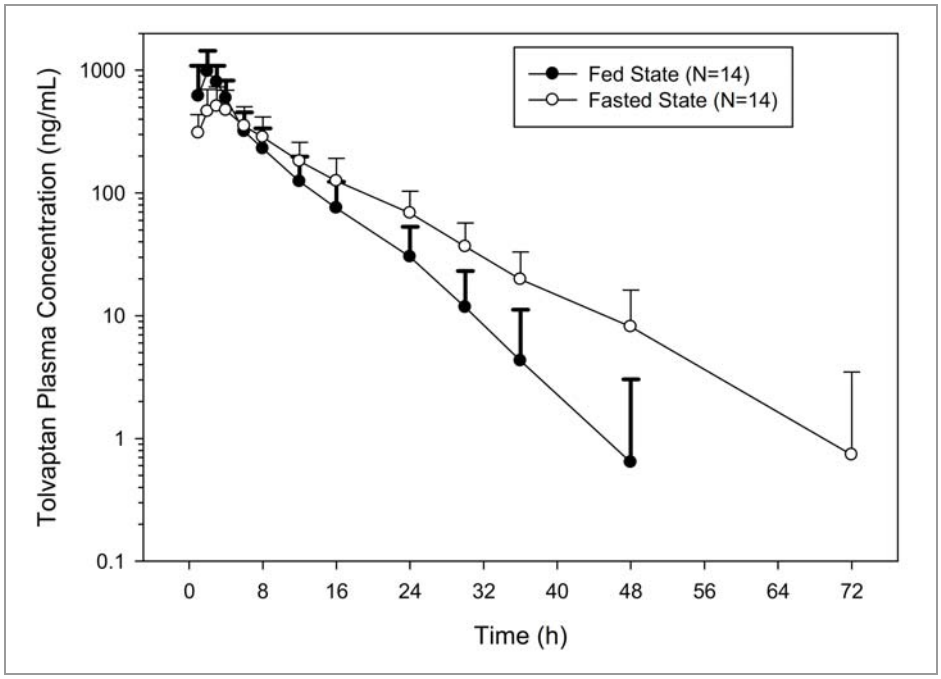

Figure 18. Mean tolvaptan concentrations over time, fed vs fasted
Source: CSR 156-11-295 Figure PKF-2, page 294

This is an unusual finding for a food effect study. One potential explanation can be provided based on physicochemical properties (refer to Section 2.1.1): Tolvaptan is a very lipophilic drug with a logP value of approximately 5. The drug is practically insoluble in water. Therefore it could be hypothesized that a high fat meal could increase the solubility of tolvaptan and provide more drug to be absorbed faster, whereas in the fasted situation, a slow but continuous release from the dosage form occurs, which resembles flip-flop kinetics. Tolvaptan oral tablets demonstrated flip-flop kinetics in an absolute BA study (study 156-05-254).

2.5 Analytical section

2.5.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tolvaptan, the only clinically active moiety, is quantified using liquid chromatography separation with tandem mass spectrometry quantification (LC/MS/MS).

2.5.2 Which metabolites have been selected for analysis and why?

Selected metabolites are DM-4103, chosen for its long half-life of ~180 h, and DM-4107, of interest because it is the major circulating metabolite.

2.5.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For all trials done for the ADPKD indication, total concentrations were assessed.

2.5.4 What bioanalytical methods are used to assess concentrations?

For ADPKD studies, the method used was LC/MS/MS for all three molecules (tolvaptan, DM-4103, and DM-4107).

Properties of the methods used to characterize concentrations are shown in Table 4 below.

Table 4. Characteristics of methods used to quantify tolvaptan and its metabolites

Parameters	Method 1		Method 2			Method 3		
Study	156-04-248, 156-04-249, 156-11-295		156-09-284			156-06-260		
Method Report	157209 (Lot: 001)		176574 (Lot: 001)			167151 (Lot: 001)		
Matrix	Plasma		Plasma			Plasma		
Analytes	Tolvaptan	DM-4103	Tolvaptan	DM-4103	DM-4107	Tolvaptan	DM-4103	DM-4107
Calibration Range [ng/mL]	5.0-1000.0	12.5-2500.0	5.0-1000.0	12.5-2500.0	12.5-2500.0	5.0-1000.0	12.5-2500.0	12.5-2500.0
Calibration Curve Fit*	0.998	0.998	0.998	0.997	0.998			
QC Concentrations [ng/mL]	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	37.5, 200.0, 2000.0	15.0, 80.0, 800.0	37.5, 200.0, 2000.0	37.5, 200.0, 2000.0
Accuracy	91.26-98.00%	92.85-105.60%	-5.4188	-9.973	-10.725	<4%	<7%	<5.5%
Precision	2.37-8.30%	3.10-9.11%	<5%	<12%	<5%	<7.7%	<7.5%	<7.9%
Stability	Yes		Yes			Yes		
Internal Standard	OPC-41100		OPC-41100			OPC-41100		

* Weight = $1/concentration^2$

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