Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377:1930-42. DOI: 10.1056/NEJMoa1710030

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SUPPLEMENTARY APPENDIX:

Tolvaptan Slows eGFR Decline in Later-Stage ADPKD

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Trial registration.

Trial was registered ClinicalTrials.Gov on June 6th, 2014. Of the 2292 patients who underwent screening and provided informed consent, 3 had a screening visit in the weeks before the trial registration (between May 21 and June 6, 2014). (This situation occurred because the sponsor followed Section 801 of the Food and Drug Administration Amendments Act rather than the requirements of the International Committee of Medical Journal Editors and the World Health Organization; the trial was registered within the window requirement of ClinicalTrials.gov.) Of these 3 patients, 1 was enrolled in the trial, and the other 2 were excluded at screening.

Analysis of the primary endpoint by a weighted analysis of covariance.

The primary end-point was analyzed by a weighted analysis of covariance (ANCOVA) with treatment and randomization stratification factors as factor and baseline covariates. The SAP pre-specified a weighted analysis since the variance in the primary endpoint may be different from patient to patient. This difference was caused by the number of post-treatment eGFR follow-ups a patient may have (ranged from 1 to 3), and furthermore caused by the annualization, especially for very early dropouts, who would be annualized with a large annualization factor resulting an inflation in their variances. Briefly speaking, the weight was equal to the reciprocal of the estimated variance of the annualized change for each patient, and the estimated variance was depended on the annualization factor and the number of observations at post-treatment follow-up (number of observations at pre-treatment baseline was assumed 3). In order to account for treatment duration on the change in eGFR, an early dropout's post-treatment follow-up was assigned to a visit based on visit windows. We assume the following model for eGFR observations in the trial:

$$y_{i,0,k} = \alpha_i + e_{i,0,k} \quad \textit{where } k = 1, 2, K_{i,0} \tag{1}$$

$$y_{i,j,k} = \alpha_i + \delta_{i,j} + e_{i,j,k} \quad \textit{where } k = 1, 2, K_{i,j} \tag{2}$$

Where $K_{i,0}$ is the number of eGFR observations during the pre-treatment baseline period for patient *i*, and $K_{i,j}$ is the number of eGFR observations during the post-treatment follow-up period for patient *i*, with visit *j* as the visit Month 12 for completers or mapped regular visits for early dropouts. α_i is a random variable for the "real" eGFR baseline of patient *i*, and this variable will be cancelled out for change from baseline. $\delta_{i,j}$ is a random variable for change from pre-treatment baseline for patient *i* to visit *j*. These $\delta_{i,j}$s are normally distributed, with means being $\delta_{P,j}$ for placebo patients and $\delta_{T,j}$ for tolvaptan patients, and variance $\sigma_{\delta,j}^2$. These $\delta_{i,j}$s are supposed to be independent from patient to patient, and each patient has only one post-baseline visit *j* in the primary analysis. In addition, α_is are assumed iid normally distributed, $e_{i,j,k}$ are assumed iid N(0, σ^2), and all these random variables are mutually independent. Assuming each patient had 3 observations at baseline, the average over the 3 observations at baseline and change from baseline to each post-treatment follow-up observation will be

$$\bar{y}_{i,0} = \alpha_i + \bar{e}_{i,0}, \quad \text{where } \bar{e}_{i,0} \sim N(0, \sigma^2/3) \tag{3}$$

$$y_{i,j,k} - \bar{y}_{i,0} = \delta_{i,j} + e_{i,j,k} - \bar{e}_{i,0} \sim N(., \sigma_\delta^2 + \sigma^2(1 + 1/3)) \tag{4}$$

Note that each patient may have up to 3 such individual changes in eGFR to post-treatment follow-ups. Then, a mixed model with terms of treatment nested within visit and replication (for repeated eGFR measures in post-treatment follow-up for each patient) was applied to these data of change from baseline in eGFR to post-treatment follow-ups of all patients who were included for the primary analysis. A compound symmetric variance matrix was used to model the correlation of up to 3 repeated observations for each patient. Variance components were then estimated, and each patient's variance of change (before annualization) was equal to the estimated inter-patient variance ($\sigma\sigma_\delta^2$) plus the estimated intra-patient variance ($\sigma\sigma^2$) multiplied by (1/3 + 1/K), where K was the number of post-treatment eGFR observations a patient had. The estimated variance (before annualization) was multiplied by the annualization factor to estimate the variance of the primary endpoint for each patient, and the reciprocal of this estimated variance was used as the weight of a patient used in the primary analysis. Detailed specification of weight calculation was provided in item (9) of section 8.3 of the statistical analysis plan.

The analysis of the primary endpoint by a weighted analysis of covariance was performed this way because it had been so pre-specified in the statistical analysis plan. Because of a concern that the weights could affect the outcome of the primary analysis, an unweighted analysis was also performed. The result of the unweighted analysis (-2.96 mL/min/1.73m^2 with tolvaptan versus -4.01 mL/min/1.73m^2 with placebo; difference 1.30 mL/min/1.73m^2, 95% CI 0.85-1.76 mL/min/1.73m^2, p<0.001) was similar to that of the weighted analysis.

Table S1. Reasons for exclusion from the modified ITT primary analysis population.

Reason for Exclusion	**Tolvaptan*** N=15	**Placebo*** N=24
No Study Drug Taken	2	2
No Baseline Observation	0	3
No Post-treatment FU	15	21
50% Greater than Screening	1	0
*More than one reason possible in some patients		

Table S2. Baseline Demographic and Clinical Characteristics of Patients Who Withdrew from the Trial

	Withdrew during Tolvaptan Run-In	Non-completers		Off-treatment Completers	
Characteristic	**Tolvaptan** (N=126)	**Tolvaptan** (N=29)	**Placebo** (N=28)	**Tolvaptan** (N=76)	**Placebo** (N=22)
Age, year (SD)	47.4 (8.5)	45.5 (10.3)	46.7 (10.5)	46.9 (8.0)	45.0 (8.6)
Male gender, n (%)	55 (43.7)	15 (51.7)	12 (42.9)	45 (59.2)	12 (54.5)
Height, cm (SD)	175 (10)	173 (11)	174 (9)	172 (10)	173 (10)
Weight, kg (SD)	86.2 (18.5)	86.8 (25.3)	86.0 (16.3)	81.7 (17.2)	78.8 (21.6)
BMI, kg/m^2 (SD)	28.1 (5.1)	28.7 (6.4)	28.2 (4.7)	27.5 (5.4)	26.4 (7.4)
Race, n (%)					
Caucasian	112 (88.9)	23 (79.3)	27 (96.4)	72 (94.7)	19 (86.4)
Asian	3 (2.4)	2 (6.9)	1 (3.6)	1 (1.3)	2 (9.1)
Black	9 (7.1)	4 (13.8)	0 (0)	3 (3.9)	1 (4.5)
Other	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
eGFR (CKD-EPI)	-	38.7 (11.0)	39.2 (12.6)	41.8 (11.1)	39.2 (13.2)

Note: Measurements of serum creatinine by enzymatic assay were not available for patients who were not randomized to the trial.

Baseline demographic and clinical characteristics of the patients who withdrew during the tolvaptan titration and run-in period (n=126), did not complete the 12 month baseline visit (n=57) or completed the 12 month visit off treatment (n=98) were not different from those who completed the 12 month visit on treatment.

Table S3. Sensitivity Analyses of Primary and Secondary Endpoints

Endpoint	Annualized LS mean change in eGFR (SE) mL/min/1.73 m^2 per year		Treatment Difference	95% CI	P-value
	Tolvaptan	**Placebo**			
Primary S1	-2.33 (0.24)	-3.61 (0.24)	1.28	0.86-1.70	<0.001
Primary S2	-3.05 (0.16)	-4.19 (0.14)	1.14	0.73-1.56	<0.001
Primary S3	-2.32 (0,24)	-3.64 (0.24)	1.32	0.91-1.74	<0.001
	Slope of eGFR (SE) mL/min/1.73 m^2 per year		**Treatment Difference**	**95% CI**	**P-value**
	Tolvaptan	**Placebo**			
Secondary S1	-3.19 (0.14)	-4.16 (0.14)	0.98	0.59-1.37	<0.001

To minimize the impact of outliers in the prespecified primary analysis the annualized eGFR change for patients who discontinued the trial early assumed the maximum (or minimum) value of on-treatment completers if their annualized change in eGFR was outside these bounds. In the first sensitivity analysis (Primary S1), annualized eGFR changes were not adjusted for outliers in patients who discontinued early. To evaluate effects of tolvaptan on the primary endpoint without the acute hemodynamic effects of eGFR, a sensitivity analysis (Primary S2) was performed which included the 3 pre-treatment baseline observations, 3 post-treatment follow-up observations and all post-randomization on-treatment eGFR observations in the protocol-specified visits for placebo patients. Patients who discontinued treatment after randomization without withdrawing consent were also followed for additional off-treatment eGFR values up to Month 12. In a sensitivity analysis of primary (Primary S3) and secondary (Secondary S1) endpoints, the post-treatment follow-up eGFR data at Month 12 replaced the post-treatment follow-up eGFR values used in prespecified analyses.

Table S4. MMRM Analysis of eGFR (CKD-EPI) Change Slope from Baseline in Randomized Treatment Period (mL/min1.73m^2 per year)

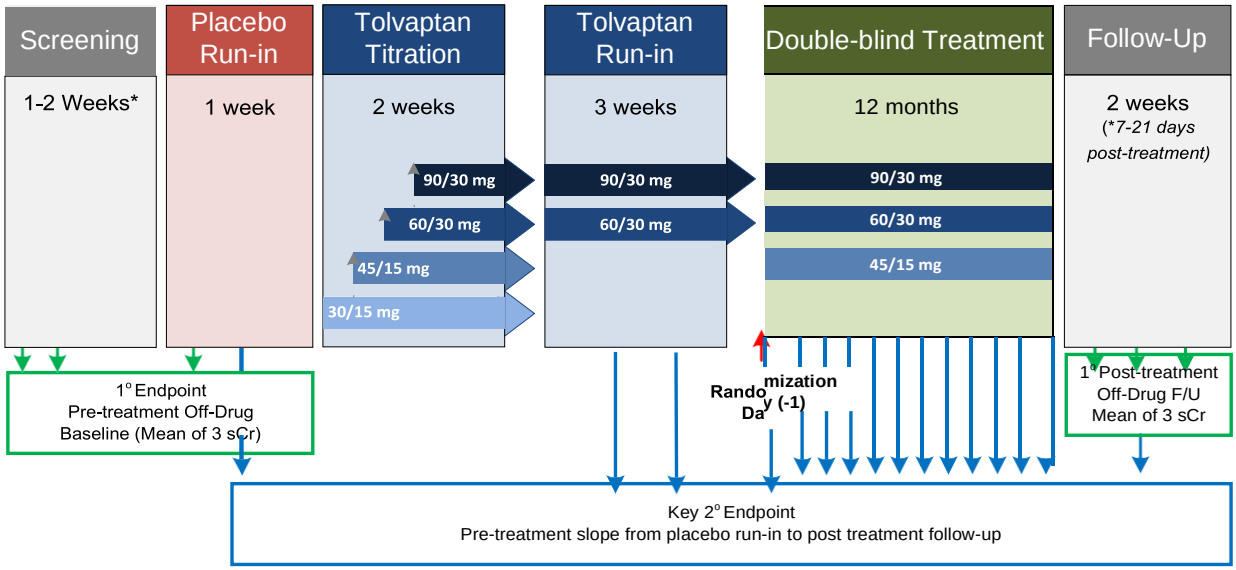
Visit	Tmt Group	N	LS Mean Change from Baseline ± SE	Tmt Effect	95% CI	P-value
Baseline	Tol	680				
	Plc	682				
Month 1	Tol	669	-1.97 ± 0.21	-1.43	-1.84, -1.02	< 0.001
	Plc	666	-0.54 ± 0.21			
Month 12	Tol	565	-4.84 ± 0.24	-0.62	-1.13, -0.11	0.017
	Plc	620	-4.22 ± 0.24			
Follow-Up	Tol	668	-3.02 ± 0.21	1.63	1.15, 2.12	<0.001
	Plc	663	-4.66 ± 0.22			
On-treatment slope (M1-M12)	Tol	668	-3.24 ± 0.17	0.84	0.37, 1.31	<0.001
	Plc	663	-4.08 ± 0.17			

Table S5. Frequency of Potentially Clinically Significant Laboratory Values

		5 wk Single-blind Period	**1year Period**	**Double-blind**
Test (unit), n (%)	**Abnormality***	**Tolvaptan** (N=1491)	**Tolvaptan** (N=681)	**Placebo** (N=685)
ALT (U/L)	Increased	1 (0.1)	38 (5.6)	8 (1.2)
AST (U/L)	Increased	1 (0.1)	24 (3.5)	6 (0.9)
Bilirubin (umol/L)	Increased	0 (0)	0 (0)	0 (0)
Blood urea nitrogen (mg/dL)	Increased	29 (2)	163 (24)	218 (32)
Creatinine, enzymatic (mg/dL)	Increased	1257 (92)	46 (7)	129 (19)
Glucose (mg/dL)	Decreased	0 (0)	4 (0.6)	5 (0.7)
	Increased	0 (0)	22 (3.3)	18 (2.7)
Potassium (mEq/L)	Decreased	0 (0)	2 (0.3)	1 (0.1)
	Increased	1 (0.1)	16 (2.4)	7 (1.0)
Sodium (mEq/L)	Decreased	2 (0.1)	8 (1.2)	18 (2.6)
	Increased	1 (0.1)	4 (0.6)	0 (0)

* Criteria for identifying laboratory values of potential clinical significance include: ALT>3xULN; AST >3xULN; Bilirubin >2xULN; BUN>22; Creatinine>1.33 pre-randomization value; Glucose, decrease ≤65, increase ≥115; potassium, decrease <LLN, increase>ULN; sodium, decrease ≤135, increase ≥146
ULN=upper limit of normal; LLN=lower limit of normal

Figure S1: Schematic design of the REPRISE (Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD) clinical trial.



*SAP allowed for serum creatinine to be collected up to 40 days follow-up to complete the requirement for 3 samples

Figure S2: Forest plot of the tolvaptan treatment effect on the secondary efficacy endpoint (annualized slopes in eGFR) in the intention-to-treat population overall and by baseline subgroups Horizontal bars indicate 95% confidence intervals. The annualized LS mean slope ± SE was -3.16 ± 0.30 versus -4.17 ± 0.22 mL/min/1.73m^2 in the tolvaptan and placebo arms, respectively ($p<0.001$). The analysis of this endpoint used a linear mixed effect model with effects of time (as a continuous variable), treatment, time treatment interaction, acute hemodynamic effect, randomization stratification factors, and a covariate of pre-treatment baseline (of the primary endpoint) to fit the eGFR data. In the model, the intercept and time were both a fixed effect and a random effect, and an unstructured variance covariance matrix was assumed for the random intercept and time. The variable of acute hemodynamic effect in the model was a variable to indicate whether an eGFR observation was while on tolvaptan or not. All the eGFR data observed during tolvaptan run-in period and the eGFR data of the tolvaptan treatment group during the double-blind on-treatment period were assigned with a value 1 and the other eGFR observations were assigned with a value 0 in this variable of acute hemodynamic effect. As tolvaptan on-treatment data were used at the start and off-treatment data were used at the end of this slope analysis, this statistical model adjusts the tolvaptan on-treatment data relative to the observed acute hemodynamic effect during the tolvaptan run-in period and aligns the tolvaptan on-treatment data during the double-blind treatment period to the off-treatment follow-up data in a linear mixed effect model.

Figure S2

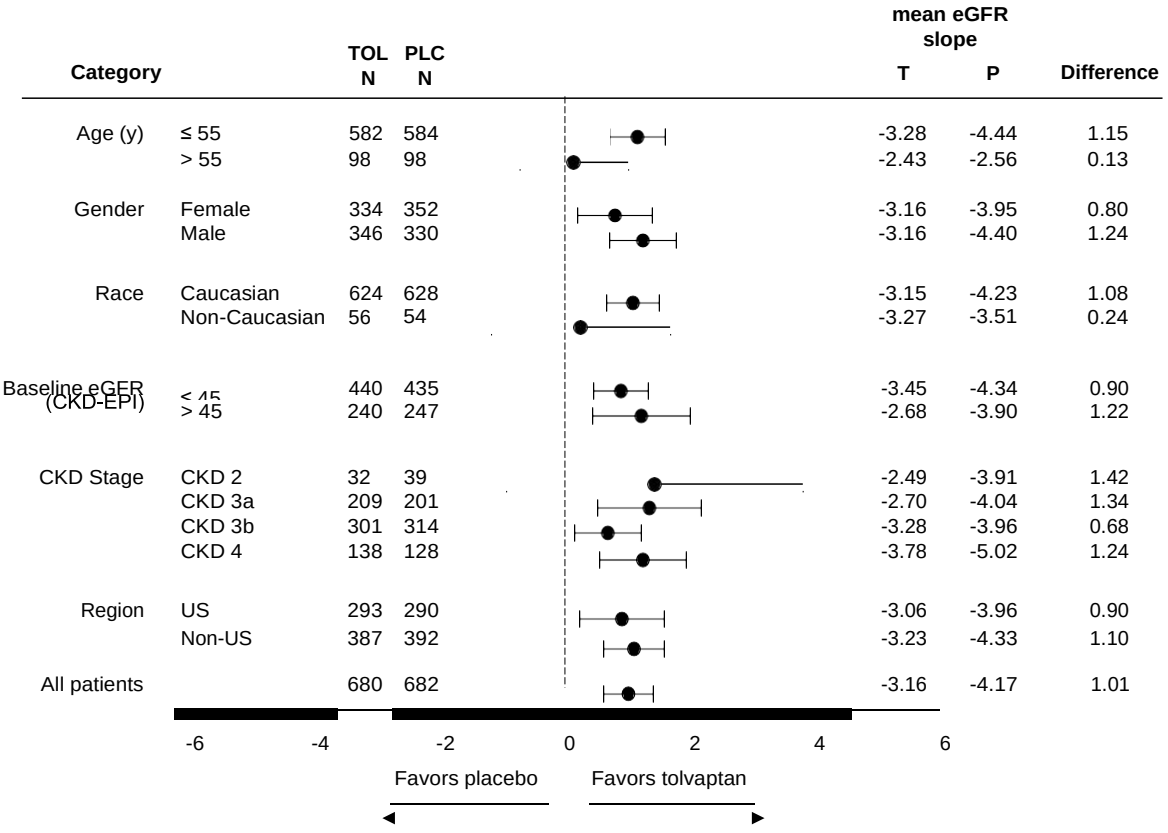

Category
TOL N
PLC N
mean eGFR slope
T
P
Difference
Age (y)
≤ 55 582 584 -3.28 -4.44 1.15
> 55 98 98 -2.43 -2.56 0.13
Gender
Female 334 352 -3.16 -3.95 0.80
Male 346 330 -3.16 -4.40 1.24
Race
Caucasian 624 628 -3.15 -4.23 1.08
Non-Caucasian 56 54 -3.27 -3.51 0.24
Baseline eGFR (CKD-EPI)
< 45 440 435 -3.45 -4.34 0.90
> 45 240 247 -2.68 -3.90 1.22
CKD Stage
CKD 2 32 39 -2.49 -3.91 1.42
CKD 3a 209 201 -2.70 -4.04 1.34
CKD 3b 301 314 -3.28 -3.96 0.68
CKD 4 138 128 -3.78 -5.02 1.24
Region
US 293 290 -3.06 -3.96 0.90
Non-US 387 392 -3.23 -4.33 1.10
All patients 680 682 -3.16 -4.17 1.01
-6
-4
-2
0
2
4
6
Favors placebo
Favors tolvaptan

Figure S3: MMRM analysis of change from baseline in eGFR slope during the randomized treatment period in the intention-to-treat population. The slope of eGFR decline as measured by LS means was slower in tolvaptan treated patients compared to placebo treated patient (-3.24 ± 0.17 versus -4.08 ± 0.17 mL/min/1.73m2/yr) corresponding to a treatment difference of 0.84 mL/min/1.73m2/yr ($p < 0.001$). Baseline represents the mean of 3 baseline serum creatinine values from the screening and placebo run-in periods, prior to initiating tolvaptan treatment. M denotes the month on treatment**.**

Figure S3

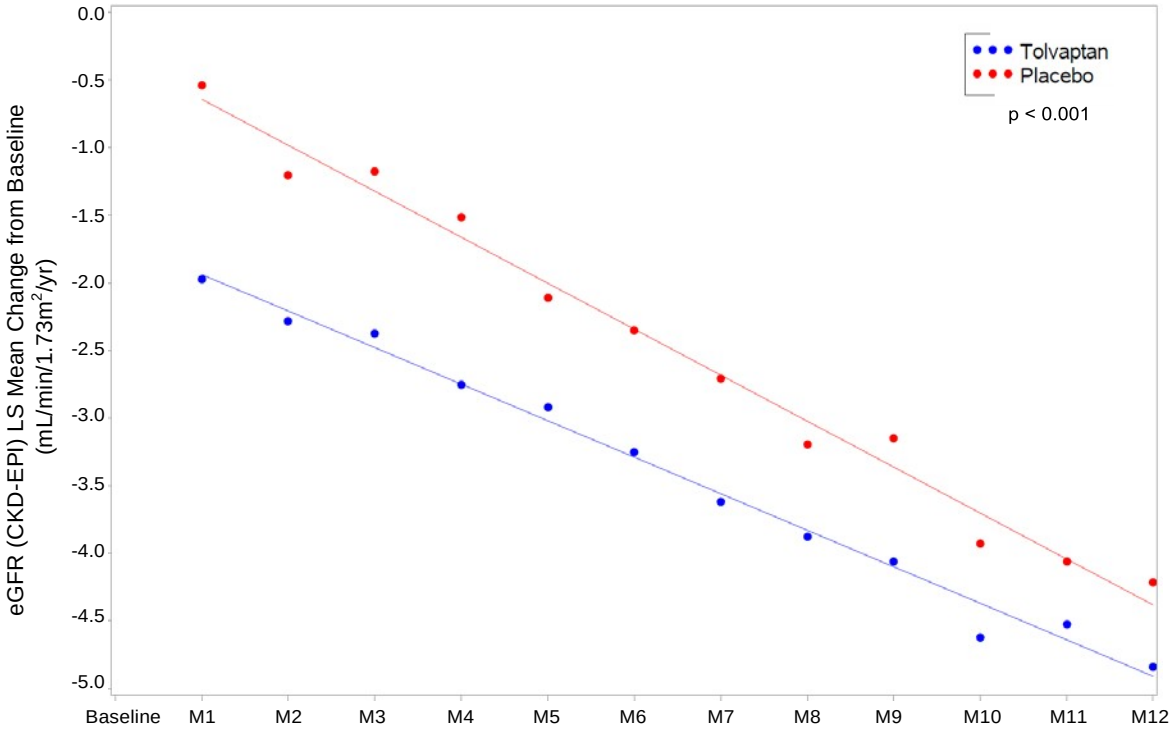


Figure S4: Time from peak ALT to <2 x ULN are shown for tolvaptan (blue) and placebo (red). All patients returned to <2 x ULN, 90% in < 3months.

Figure S4

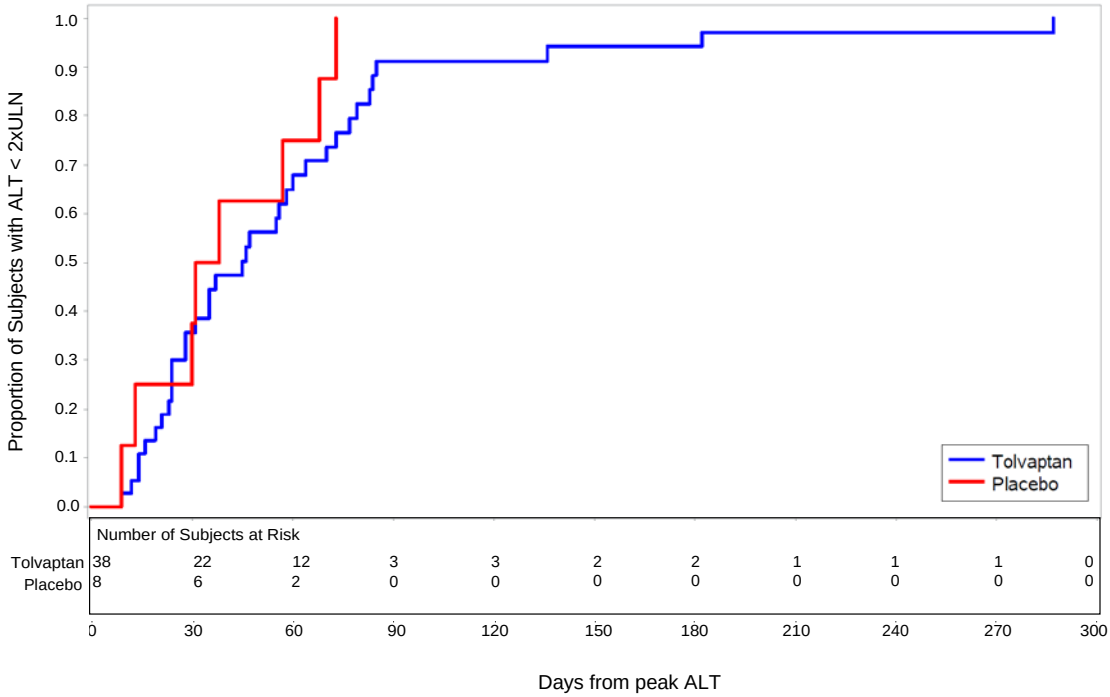


Figure S5. Evaluation of drug-induced hepatotoxicity (e-DISH) plot. Vertical lines correspond to 3 x ULN for ALT. Horizontal lines correspond to 2 x ULN for BT. No patients met Hy's criteria in the upper-right quadrant. The boxes in the box plots represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles and the dots represent the 5th and 95th percentiles for the peak ALT and BT elevations per patient.

Figure S5