Urine Osmolality, Response to Tolvaptan, and Outcome in ADPKD: Results from the TEMPO 3:4 trial

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Suppl. Table 1: Baseline demographics of the ADPKD subjects, by treatment arm.

Parameter	**Tolvaptan (N=700)**	**Placebo (N=337)**	Total (N=1037)
Male, n (%)	366 (52.3)	170 (50.5)	536 (51.7)
Age yrs, mean (SD)	38.4 (7.0)	38.7 (7.3)	38.5 (7.1)
Blood Pressure mmHg, mean (SD)			
Systolic	127 (13.0)	127 (13.2)	127 (13.0)
Diastolic	81.9 (9.9)	82.2 (9.4)	82.0 (9.7)
Race, %			
Caucasian	81.9	82.5	82.1
Asian	14.7	14.2	14.6
Other	4.4	4.3	3.4
eGFR CKD-EPI mL/min/1.73m^2, mean (SD)	80.9 (21.2)	82.1 (23.1)	81.3 (21.8)
TKV mL, mean (SD)	1713 (938)	1681 (914)	1703 (930)
Urine Osmolality mOsm/kg, mean (SD)	500 (173)	514 (186)	504 (177)
Concomitant Medication, % (N)			
Antihypertensives	72.3	72.1	743 (71.7)
Lipid Lowering Drugs	13.6	12.5	137 (13.2)
Anti-depressants	10.7	10.1	233 (22.5)

Abbreviations: TKV, total kidney volume; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Suppl. Table 2: Change from baseline in urine osmolality, per treatment arm.

Visit	Treatment	Average Dose (mg/day)	Change in Uosm from Baseline Mean ± SD (N)	p-value
End of Titration	Tolvaptan	110	-300 ± 186 (657)	<0.0001
	Placebo	117	-65 ± 184 (330)	
Month 12	Tolvaptan	100	-265 ± 186 (592)	<0.0001
	Placebo	113	-63 ± 189 (312)	
Month 24	Tolvaptan	97	-259 ± 181 (554)	<0.0001
	Placebo	111	-75 ± 181 (291)	
Month 36	Tolvaptan	97	-254 ± 186 (523)	<0.0001
	Placebo	111	-85 ± 175 (280)	
Follow-Up	Tolvaptan		-73 ± 174 (525)	0.6553
	Placebo		-81 ± 167 (271)	

Abbreviation: Uosm, urine osmolality.

Suppl. Table 3: Change from baseline in estimated plasma osmolality, per treatment arm.

		Change in Posm from Baseline	
Visit	**Treatment**	**Mean ± SD (N)**	**p-value**
End of Titration	Tolvaptan	2.67 ± 5.55 (659)	<0.0001
	Placebo	-0.46 ± 5.21 (333)	
Month 12	Tolvaptan	1.49 ± 6.02 (586)	0.0005
	Placebo	0.21 ± 5.32 (312)	
Month 24	Tolvaptan	1.61 ± 6.01 (552)	0.0038
	Placebo	0.37 ± 5.81 (295)	
Month 36	Tolvaptan	2.03 ± 6.19 (528)	0.0013
	Placebo	0.64 ± 5.74 (284)	
Follow-Up	Tolvaptan	0.16 ± 5.93 (531)	0.1676
	Placebo	0.64 ± 5.98 (276)	

Abbreviation: Posm, estimated plasma osmolality.

Suppl. Table 4: Change in urine and plasma osmolality levels from baseline to end of titration in the placebo and tolvaptan groups.

	Tolvaptan			Placebo		
	Baseline Mean (SD)	Change from Baseline Mean (SD)	p-value	Baseline Mean (SD)	Change from Baseline Mean (SD)	p-value
Posm (mOsm/kg)	293 (4.96)	+2.67 (5.55)	<0.0001	293 (4.74)	-0.46 (5.21)	0.069
Uosm (mOsm/kg)	500 (173)	-300 (186)	<0.0001	514 (186)	-65.1 (184)	<0.0001
Ratio of Uosm:Posm	1.70 (0.59)	-1.03 (0.64)	<0.0001	1.75 (0.65)	-0.22 (0.63)	<0.0001

Abbreviations: Posm, estimated plasma osmolality; Uosm, urine osmolality.

Suppl. Table 5: Annual change in eGFR and occurrence of composite ADPKD events by quartiles of mean urine osmolality at end of titration in tolvaptan treated subjects.

	Mean Uosm at EOT (mOsm/kg)				
	Q1 <122 (N=156)	**Q2 122, <171 (N=160)**	**Q3 171, <251 (N=158)**	**Q4 ≥251 (N=158)**	**p-value for trend**
Baseline Uosm (mOsm/kg)	461	461	514	548	
Baseline eGFR - CKD-EPI (mL/min/1.73m^2)	77.2	73.3	74.4	80.9	
Median Change in eGFR, 95% CI (mL/min/1.73m^2/yr)	-2.89 (-3.53, -2.04)	-2.98 (-3.44, -2.37)	-2.69 (-3.26, -1.94)	-1.86 (-2.23, -1.36)	0.55
N of subjects with composite secondary end point events (%)[a]	110 (70.5)	92 (57.5)	94 (59.5)	85 (53.8)	0.006[c]
N of subjects with renal pain events or renal function events (%)[b]	29 (18.6)	25 (15.6)	21 (13.3)	15 (9.5)	0.017[c]

Abbreviations: Uosm, urine osmolality; EOT, End of titration; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

[a], The composite secondary end point was the time to investigator-assessed clinical progression, defined as worsening kidney function (a 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 weeks); clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention; worsening hypertension (changes in blood-pressure category or worsening of hypertension requiring an increase in hypertensive treatment); and worsening albuminuria.

[b], Renal pain events and renal function events are defined as above.

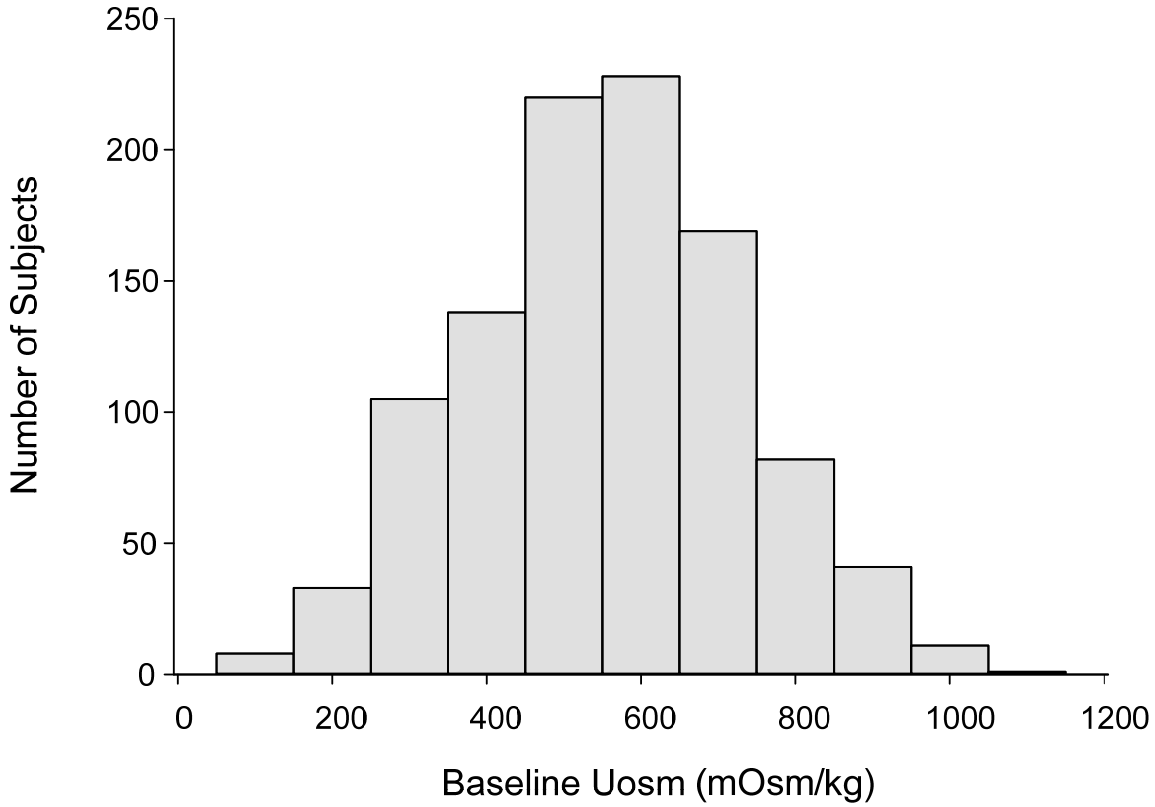
[c], p-value for trend derived from the Cochran-Armitage test.

Suppl. Table 6: Change in urine osmolality in fast and slow progressors (as determined by the highest and lowest quartiles of eGFR slopes during the trial).

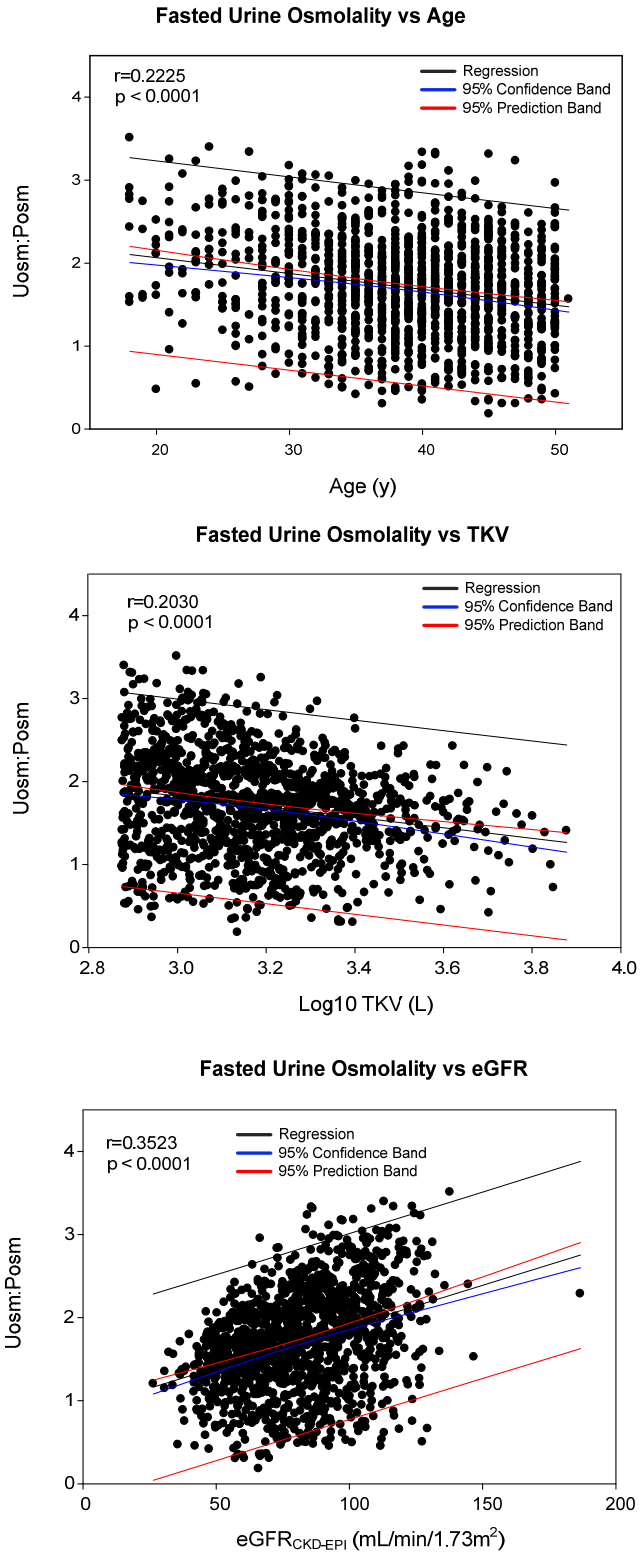
	Change Uosm (EOT - Baseline) Mean ± SD (N), mOsm/Kg		
Treatment	**Fast Progressors:** eGFR Q1 (N)	**Slow Progressors:** eGFR Q4 (N)	**p-value**
Tolvaptan	-229 ± 169 (119)	-293 ± 199 (123)	0.0061
Placebo	-67 ± 137 (69)	-82 ± 190 (68)	0.6129

Quartiles of annual eGFR slopes over 3 years were, for tolvaptan:
Q1, <-4.5 mL/min/1.73m^2/year and Q4, ≥-0.6 mL/min/1.73m^2/year;
and for placebo: Q1, <-5.8 mL/min/1.73m^2 /year and Q4, ≥-1.3 mL/min/1.73m^2/year.
Abbreviations: EOT, End of titration; Uosm, urine osmolality; eGFR, estimated glomerular filtration rate.

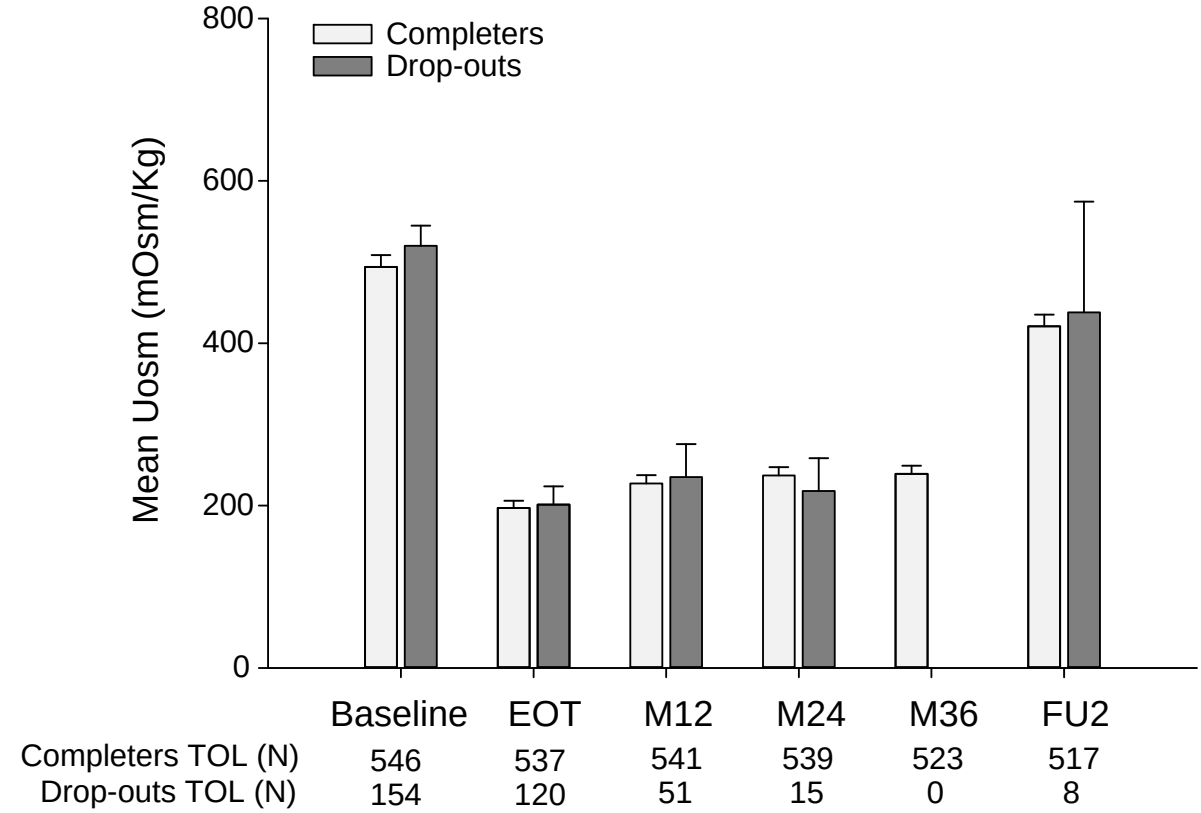
Suppl. Figure 1: Distribution of baseline urine osmolality in the 1037 ADPKD subjects.



Suppl. Figure 2: Correlations of baseline urine:plasma osmolality ratio with age, total kidney volume (TKV) and eGFR in the ADPKD population.



Suppl. Figure 3: Mean urine osmolality in completers and non-completers.



The number of patients (completers or drop-outs) receiving tolvaptan contributing to the average Uosm value for each time point is indicated.

Suppl. Figure 4: Influence of baseline eGFR (tertiles) on the changes in urine osmolality (from baseline to EOT) and the slope of renal function decline (eGFR slope, fast to slow progressors) in the tolvaptan (blue bars) and placebo (red bars) groups.