Otsuka Pharmaceuticals UK Ltd Response to ERG Clarification Questions (02/06/2015)

- It is not clear how the company is proposing the optimised subgroup (CKD stage 2 to 3**)** could be defined in clinical practice, e.g. minimum baseline TKV. Please provide this information.

Response

The requirement for evidence of rapidly progressing disease in order to identify eligible patients for treatment in the overall licensed indication does not change for the proposed optimised subgroup. As outlined in previous correspondence, we do not propose any population-based objective criteria for defining evidence of rapidly progressing disease to be used to assess eligibility of individual patients. This will be guided by clinical judgement of individual patients as per the overall licensed indication (as acknowledged in section 4.4 of the ACD).

The only additional criteria in the proposed optimised subgroup is the requirement for a classification of CKD stage 2-3 at initiation, the knowledge of which is routinely available in clinical practice.

- It is not clear how the relative reduction in renal function decline using CKD-EPI in the CKD stage 2 to 3 subgroup was determined. Please provide details of exactly how the figure of 29.7% was calculated.

Response

Firstly, we would like to acknowledge that the 29.7% treatment effect used in our revised base case was calculated for the subgroup of patients at CKD stage 2-3a (i.e. excluding stage 3b, n=23 in the tolvaptan group and n=15 in the placebo group) at baseline in TEMPO 3:4, not all CKD stage 2-3 combined as originally indicated. We apologise for this oversight.

However the impact of this oversight is marginal and conservative. The recalculated relative treatment effect including the CKD stage 3b patients is [redacted]% ($p<0.0001$). Utilising this number has the effect of reducing our revised base case ICER from £23,503 to £23,045. Therefore the treatment effect used in the revised base case is conservative in this respect.

With respect to the 29.7% relative treatment effect, Table 1 below provides the underlying CKD-EPI renal function results for the CKD stage 2-3a subgroup used to calculate the revised treatment effect (emboldened). These values for the slope of renal function in the tolvaptan ([redacted]) and placebo ([redacted]) groups yield the absolute ([redacted]) and relative ([redacted]) reductions for tolvaptan compared to placebo. This is the same methodology used to calculate the corresponding value for the whole trial population (26.4%) noted in the ACD.

Table 1: Rate of Change per Year[1] in renal function (CKD stage 2-3a at baseline)

Treatment Group	N	Mean	Median	SD	Min	Max	Slope[2]	Treatment Effect[3]	Lower 95% CI	Upper 95% CI	P-value[2]
Tolvaptan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				

SD = standard deviation; Min = minimum; Max = maximum; CI = confidence interval

[1] Summary Statistics are based on slope of change, obtained by regressing renal function data (EOT/Week 3 and beyond) against time by subject.
Time variable used in the regression is equal to (observation date - EOT/Week 3 date)/365.25.

[2] Derived from testing the time treatment interaction using linear mixed model in which both intercept and slope are fixed and random effects.

[3] An estimate of the difference between the slopes of tolvaptan and placebo.

- Regarding the proposed subgroup, please provide some descriptive statistics for baseline age, eGFR and TKV, e.g. mean (already provided), median, range, interquartile range, histograms.

Response

In our revised base case we proposed the following optimised subgroup baseline characteristics:

- Age: 44 years (rounded up to nearest whole year)
- 48.4% female (unchanged from original base case)
- TKV: 2,300 ml (rounded up to nearest 100ml)
- GFR: 60 ml/min/1.73m^2 (midpoint of CKD stages 2-3)

As previously described, these were obtained by utilising the modelled underlying (no active treatment) progression trajectories in our original submission base case. Mean values for TKV and age we observed in the consecutive cycles where GFR was above and below a value of 60.

In order to provide the summary statistics requested, the original model was modified to output patient-level data appropriately at the time point of GFR reaching a mean of 60. These summary statistics are presented below in Table 2. These numbers are slightly different to those provided in the ACD response due to these modifications. However the differences are negligible and do not affect the baseline characteristics selected for the proposed optimised subgroup.

Table 2: Summary descriptive statistics of the proposed optimised subgroup

	Mean	SD	Median	Min	Max
Age (years)	44	0.5	44	43.2	45.2
eGFR (ml/min/1.73m^2)	60	1.7	60	53.6	65.5
TKV (ml)	2307	83.5	2312	2111	2522

- Regarding the handling of missing data and the company's results using a 'jump to placebo' approach as well as from 'tipping point analyses'. While the company reports the assumption for patients in the tolvaptan arm who withdrew from the study ('100% loss of efficacy of tolvaptan'), it is unclear what assumption, if any, was applied to participants who withdrew from the placebo arm. Please provide more information on the 'tipping point analysis', i.e. what software was used, which assumptions were used and ask if a reference can be provided to support this. Also, it is noted that the results of the analyses are discussed but only p-values are given. Please provide effect estimates and corresponding confidence intervals.

Response

The tipping point analyses performed were on the changes from baseline to month 36 for TKV, the secondary composite endpoint and eGFR, and will be presented in the following manner:

- Statistical Methodology for tipping point analyses

    - Tipping Point Analyses for Kidney Cyst Growth as Total Kidney Volume (TKV) and Renal Function as Estimated Glomerular Filtration Rate (eGFR)
    - Tipping Point Analysis for the Key Secondary Endpoint
- Tipping point analyses
    - Primary Endpoint: TKV (Figure A and Table 1).
    - Secondary Efficacy Endpoint: eGFR (Figure B and Table 2)
    - Key Secondary Composite Endpoint (Figure B and Table 2)

Statistical Methodology for tipping point analyses

Tipping Point Analyses for Kidney Cyst Growth as Total Kidney Volume (TKV) and Renal Function as Estimated Glomerular Filtration Rate (eGFR)

In these tipping point analyses, percentage change from baseline in TKV and change from baseline in eGFR (CKD-EPI) were employed using the same multiple imputation (MI) procedure provided below for the key secondary endpoint. The tipping point analysis was applied to all dropouts as well as those who discontinued due to AEs.

This tipping point sensitivity analysis investigated the departure from the "missing at random" (MAR) assumption by progressively increasing a multiplier of the treatment differences to be subtracted from the imputed missing data in tolvaptan discontinued subjects. After imputing missing data following the trend of a discontinued subject's treatment group, this progressive increase in the subtractions was carried out by subtracting *k* times the treatment differences from the imputed missing data after dropout in those tolvaptan subjects, with *k* starting from 0%, 100%, 120%, or higher, until conclusion of the MAR assumption based analysis was overturned (thus called tipping point analysis).

Note that when 0% was used, the MI procedure produced an analysis which was essentially the same as MAR. When 100% was used, the MI procedure produced an analysis which was equivalent to the assumption called "jump to placebo". Beyond 100%, the analysis tested the degree to which a "worst-than placebo" assumption may be applied. Specifically the MI procedure followed these steps:

1. Using Monte Carlo Markov Chain (MCMC) methodology from SAS PROC MI by treatment group to impute the intermittent missing data to a monotone missing pattern. For TKV, the variables included to fill the monotone missing pattern were baseline and percent changes at years 1, 2, and 3. For eGFR, the variables included were Day 1 eGFR observation, Week 3/EOT (End of Titration) eGFR observation, changes from Week 3/EOT baseline at Month 4, Month 8, …, up to Month 36;

2. Using a standard MAR-based multiple imputation approach (regression approach) from SAS PROC MI to impute missing data from monotone missing data by treatment. The variables used in the regression imputation were identical to the variables used to get the monotone missing pattern described in the previous step;

3. For discontinued subjects in tolvaptan group, a delta which was equal to k times their treatment differences obtained from the MMRM (Mixed Model Repeated Measurement) analysis was subtracted from their corresponding imputed values after the dropout time, with k as described in the above paragraph;

4. Using the MMRM model specified in the statistical analysis plan (SAP) to analyse the observed data along with the imputed data;

5. Obtaining the overall results using SAS PROC MIANALYZE.

Thirty imputations were to be used in these tipping point analyses.

Tipping Point Analysis for the Key Composite Secondary Endpoint

Multiple imputation (MI) was used to test the robustness of the key secondary endpoint. Since the key secondary analysis was specified as time to multiple event analysis, it was assumed that the hazard for placebo was constant in each visit interval between two adjacent protocol specified visits, inclusive of the latter visit. A random-number generator of a Poisson process was used in each visit interval based on the hazard and the duration of a discontinued subject in the visit interval. Simulated events in a visit interval were assigned to the end of their visit intervals, since most of the observed clinical events were tied to protocol-specified visits as pre-specified in the SAP.

When more than one event was simulated in a visit interval for a subject, for example, two events, one event was assigned to the end and the other event was assigned to the middle of the visit interval, etc. Then the simulated data of all discontinued subjects were combined with their observed data (regardless of treatment period) for analysis of time to multiple events using Andersen-Gill model with sandwich variance-covariance estimate as specified in the protocol. A multiple of k, with k = 1, 1.1, 1.2, etc., was used to multiply the placebo hazard at each visit interval for tolvaptan subject missing data imputation, in order to explore the tipping point for the key secondary endpoint. Note that when k = 1 the analysis corresponded to an analysis called “jump to placebo”.

Thirty imputations were used in this multiple imputation and the overall result of the imputations is concluded by using SAS PROC MIANALYZE.

Tipping point analyses

Primary Endpoint: TKV (Figure 1, Table 3, Table 4)

For the primary endpoint of total kidney volume (TKV), analyses assuming a total (100%) loss of tolvaptan efficacy (ie, imputation by ‘jump to placebo’) in discontinued subjects continued to show a highly significant benefit for tolvaptan subjects ($p < 0.0001$).

The p-value for the difference between tolvaptan and placebo rises above 0.05 only when 333% of the treatment effect at Month 36 is subtracted from the data imputed for the tolvaptan withdrawn subjects. A 333% reduction in treatment effect would equate to TKV growth at Month 36 of 40.25%, over twice the observed placebo change of 18% and over 4-times the observed tolvaptan change of 9%, a highly conservative assumption.

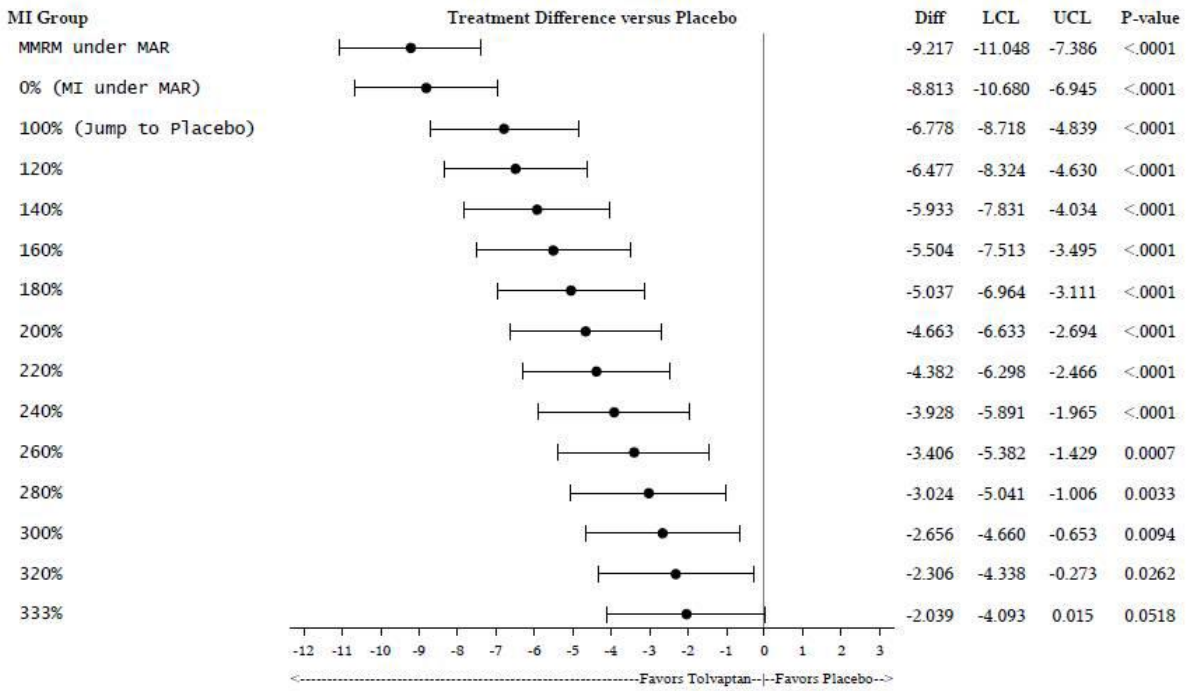

Figure 1: Sensitivity Analysis: Multiple Imputation on MMRM Analysis of Change from Baseline (Using Log Transformation) in TKV to Month 36 - All Withdrawals from Tolvaptan Group were treated as MNAR (Missing Not At Random)

Table 3: Results of Original Efficacy Analyses for TEMPO 3:4 for the Primary Efficacy Variable and tipping point analyses

TKV	**Estimated Treatment Effect (Percent Change at Month 36)**	**p-value**
Original analysis	-9.19	<0.0001
Tipping point analysis at 100%: 'jump to placebo'	-6.778	<0.0001
Tipping point analysis at 333%: 'tipping point'	-2.039	0.0508

Otsuka has produced a table derived from the actual imputation modelling procedure for this tipping point analysis. In this table (Table 4), the mean imputed value in the tolvaptan group for 333% is 43.59% for 3 years of growth.

Table 4: Average Penalty in Imputed Missing Not at Random of Percent Change from Baseline in Total Kidney Volume to Month 36 - All Discontinuations from Tolvaptan Were Treated as Missing Not at Random

Percent of Treatment Effect Subtracted	Treatment Group	Imputed Data			
		N	Mean	Med	SD
0% (MI under MAR)	Tolvaptan	215	12.95	10.52	13.19
	Placebo	64	19.36	18.55	10.91
100% (jump to placebo)	Tolvaptan	215	22.51	20.26	13.21
	Placebo	64	19.98	18.60	11.21
120%	Tolvaptan	215	24.10	21.47	13.54
	Placebo	64	20.33	18.60	10.85
140%	Tolvaptan	215	26.15	23.56	13.31
	Placebo	64	19.77	18.40	11.17
160%	Tolvaptan	215	27.82	25.26	13.46
	Placebo	64	19.33	17.90	11.21
180%	Tolvaptan	215	30.05	27.35	13.40
	Placebo	64	19.59	19.04	11.25
200%	Tolvaptan	215	31.94	29.55	13.05
	Placebo	64	20.01	18.61	11.36
220%	Tolvaptan	215	33.27	30.81	13.29
	Placebo	64	20.00	19.22	10.64
240%	Tolvaptan	215	35.29	32.35	13.63
	Placebo	64	19.97	18.60	11.04
260%	Tolvaptan	215	37.35	34.92	13.43
	Placebo	64	19.59	17.46	10.99
280%	Tolvaptan	215	39.07	36.62	13.43
	Placebo	64	19.69	17.93	11.03
300%	Tolvaptan	215	40.87	38.00	13.43
	Placebo	64	19.84	18.76	10.94
320%	Tolvaptan	215	42.81	40.66	13.20
	Placebo	64	20.44	20.07	10.90
333%	Tolvaptan	215	43.59	41.06	13.26
	Placebo	64	19.84	18.18	11.15

MMRM = mixed model repeat measure, MAR = missing at random, MI = multiple imputation, SD = standard deviation, Trt = treatment, CI = confidence interval.

For TKV, a penalised imputation of 43.59% growth over 3 years (333% of the treatment difference) is believed to be overly conservative. A number of recently published trials which have measured the TKV growth rate in patients with ADPKD who were receiving either placebo or best standard of care indicate the average rate of growth to be between 5% and 8% per year (Grantham 2006 (1) [5.3%/year], Serra 2010 (2) [6.6%/year], Walz 2010 (3) [7.9%/year], Chapman 2012 (4) [7.0%/year], Torres 2012 (5) [5.5%/year], Schrier 2014 (6) [5.6 to 6.6%/year]). Therefore, having a subgroup with over 14.53%/year growth representing nearly 23% of the population enrolled in the TEMPO 3:4 trial (the subject of the Torres 2012 article (5)) is implausible.

The distribution of TKV growth as %/year for both the tolvaptan and placebo subjects as observed clearly indicates a uniform shift towards lower TKV growth for tolvaptan subjects. For each treatment group comparison, a 9% to 10% difference is observed between the 10th and 90th percentile. Therefore it is unlikely that all missing subjects were derived from the highest range of TKV growth.

The imputed value of 43.59 necessary to tip the analysis result to non-significance, falls at the 93rd percentile of placebo subjects in this distribution. This would mean that all 23% of

subjects missing data from the tolvaptan group would have to fall within the top 7% of observed placebo TKV growth. Again, this is highly unlikely and overly conservative.

Secondary Efficacy Endpoint: eGFR (*Figure 2, Table 5, Table 6*)

The estimated glomerular filtration rate (eGFR) change from baseline to Month 36 analyses assuming a total (100%) loss of tolvaptan efficacy in withdrawn subjects (ie, imputation by 'jump to placebo') showed a highly significant benefit for tolvaptan subjects ($p < 0.0001$, Table 5).

The p-value for the difference between tolvaptan and placebo rises above the 0.05 level only when a 267% loss of effect is assumed. At this tipping point of 267%, the Month 36 eGFR decline would be 16.19 mL/min/1.73m^2, an increase of over 60% (1.6 times) of the observed placebo change of 10.41 mL/min/1.73m^2; a highly conservative assumption (Table 6). This level of imputation is equivalent to a TKV growth of 40.25% by Month 36, more than twice the observed placebo TKV growth and over 4 times the observed change for tolvaptan.

At the tipping point of 267%, the Month 36 eGFR decline would be 16.19 mL/min/1.73m^2, which is approximately 1.6 times that observed for placebo and more than 2 times the observed change for tolvaptan. These analyses demonstrated that the original analyses of TKV and eGFR change at Month 36 are robust to the impact of missing data. The results indicate that very substantial, and arguably implausible, rates of disease progression for discontinued tolvaptan subjects have to be assumed before significance is lost.

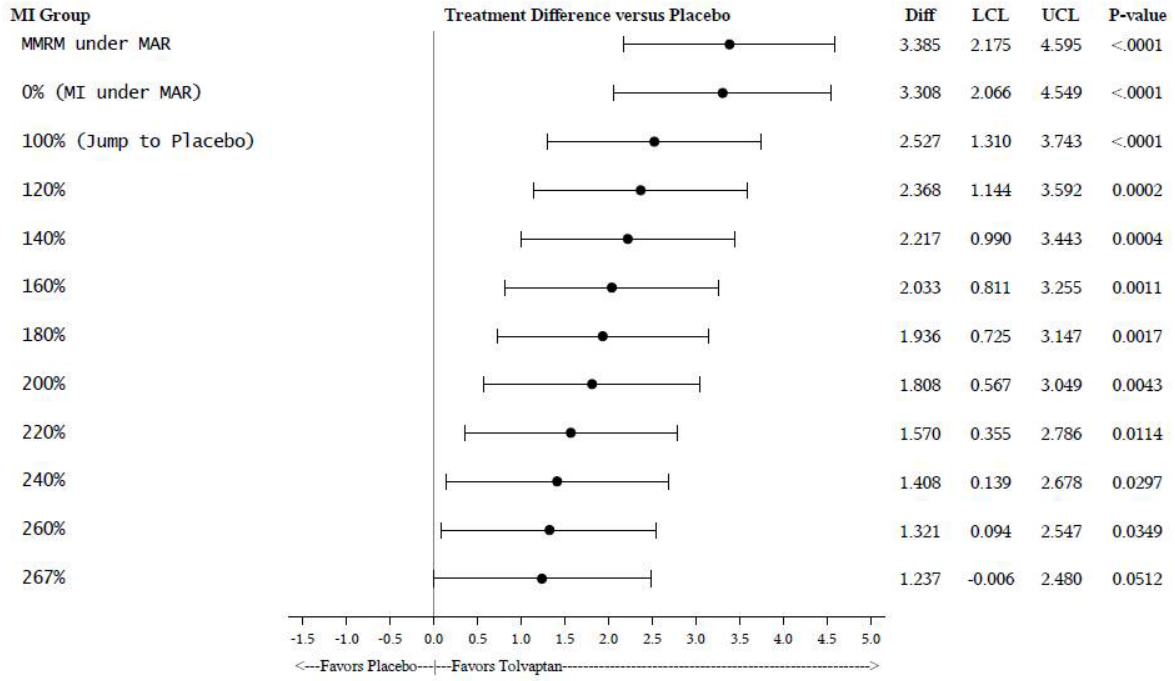

Figure 2: Sensitivity Analysis: Multiple Imputation on MMRM Analysis of Change from Baseline in eGFR (CKD-EPI) to Month 36 - All Withdrawals from Tolvaptan Group were Treated as MNAR

Table 5: Results of Original Efficacy Analyses for TEMPO 3:4 for the Secondary Efficacy Variable of eGFR and tipping point analyses

eGFR	Estimated Treatment Effect (Change at Month 36, mL/min/1.73m2)	p-value
Original analysis	3.26	<0.0001
Tipping point analysis at 100%: 'jump to placebo'	2.527	<0.0001
Tipping point analysis at 333%: 'tipping point'	1.237	0.0512

From Table 6 we can see that at 267% of the treatment difference, the model would impute a value with an average eGFR decline of 15.94 mL/min/1.73m^2.

Table 6: Average Penalty in Imputed Missing Not at Random Data of Percent Change From Baseline in Estimated Glomerular Filtration Rate - All Discontinuations From Tolvaptan Were Treated as Missing Not at Random

Percent of Treatment Effect Subtracted from Imputed Missing Data	Treatment Group	Imputed Data			
		N	Mean	Med	SD
0% (MI under MAR)	Tolvaptan	219	-7.12	-7.04	6.08
	Placebo	65	-10.62	-10.09	8.62
100% (jump to placebo)	Tolvaptan	219	-10.32	-10.30	6.09
	Placebo	65	-10.27	-9.70	8.69
120%	Tolvaptan	219	-10.99	-10.88	6.05
	Placebo	65	-10.20	-9.75	8.95
140%	Tolvaptan	219	-11.62	-11.32	6.06
	Placebo	65	-10.15	-9.43	8.68
160%	Tolvaptan	219	-12.45	-12.56	5.89
	Placebo	65	-10.14	-9.80	8.74
180%	Tolvaptan	219	-12.91	-13.25	6.27
	Placebo	65	-10.30	-10.36	8.97
200%	Tolvaptan	219	-13.41	-13.23	6.10
	Placebo	65	-10.24	-9.84	8.47
220%	Tolvaptan	219	-14.31	-14.33	6.03
	Placebo	65	-9.98	-10.09	8.94
240%	Tolvaptan	219	-15.13	-15.86	6.24
	Placebo	65	-10.24	-10.29	8.98
260%	Tolvaptan	219	-15.71	-15.85	6.14
	Placebo	65	-10.47	-10.99	8.70
267%	Tolvaptan	219	-15.94	-15.67	6.35
	Placebo	65	-10.28	-10.53	8.57

MMRM = mixed model repeat measure, MAR = missing at random, MI = multiple imputation, SD = standard deviation, Trt = treatment, CI = confidence interval.

For eGFR, a penalised imputation of -15.94 mL/min/1.73m^2 in 36 months (or -5.31 mL/min/1.73m^2 per year) is also believed to be overly conservative. Using the same recently published trials which have measured decline in eGFR in patients with ADPKD who were receiving either placebo or best standard of care, the average rate of eGFR decline was as follows: Grantham 2006 (1) [-4.33 mL/min/1.73m^2/year], Serra 2010 (2) [-2.33 mL/min/1.73m^2/year], Walz 2010 (3) [-3.5 mL/min/1.73m^2/year], Chapman 2012 (4) [-2.79 mL/min/1.73m^2/year], Torres 2012 (5) [-3.70 mL/min/1.73m^2/year], Schrier 2014 [-2.9, -3.0, -

3.0, -2.9 mL/min/1.73m^2/year for low blood pressure, standard blood pressure, lisinopril-telmisartan and lisinopril-placebo groups, respectively], Torres 2014 (7) [-3.87 and -3.91 mL/min/1.73m^2/year for lisinopril-telmisartan and lisinopril-placebo groups, respectively]). Therefore, having a subgroup with over 5.3 mL/min/1.73m^2 eGFR decline/year (15.94 ml/min/1.73m^2 divided by 3 years) representing nearly 23% of the population enrolled in the TEMPO 3:4 trial (5) is implausible.

The distribution of eGFR decline as mL/min/1.73m^2/year for both the tolvaptan and placebo subjects as observed clearly indicates a uniform shift towards lower TKV growth for tolvaptan subjects. For each treatment group comparison, a 2.5 to 6 mL/min/1.73m^2/year difference is observed between the 10th and 90th percentile. Again, this demonstrates that the effects of tolvaptan are seen across the range of eGFR decline observed.

The imputed value of 15.94 necessary to tip the analysis result to non-significance, falls at the 30th percentile of placebo subjects in this distribution. While it is possible that all 23% of subjects missing data from the tolvaptan group could fall within the bottom 30% of observed placebo eGFR decline, this is highly unlikely given the baseline characteristics of subjects missing due to aquaretic AE intolerance which would predict a rate of decline less than the average of about 3 mL/min/1.73m^2/year.

Key Secondary Composite Endpoint (Figure 3, Table 7)

In addition to the above, a tipping-point-like analysis was presented for the secondary composite endpoint. It was assumed placebo hazard is constant in each visit interval, and Poisson imputation assuming the observed placebo hazard was used to impute missing data for both placebo and tolvaptan withdrawn subjects. This thereby assumes a total loss of tolvaptan efficacy in tolvaptan withdrawn subjects ("jump to placebo"). The tipping point was then searched by assuming a higher placebo hazard for the imputation of missing data in withdrawn tolvaptan subjects. Figure 23 below illustrates the tipping point analysis.

A hazard rate of 1.11 times the placebo hazard has to be assumed in withdrawn tolvaptan subjects before the p-value for the composite analysis exceeds 0.05. This compares to the HR of 0.865 estimated in the original analysis in which missing data was considered as MAR. As one might expect, the tipping-point results for the composite components of worsening renal pain and worsening renal function are even more robust (data on file).

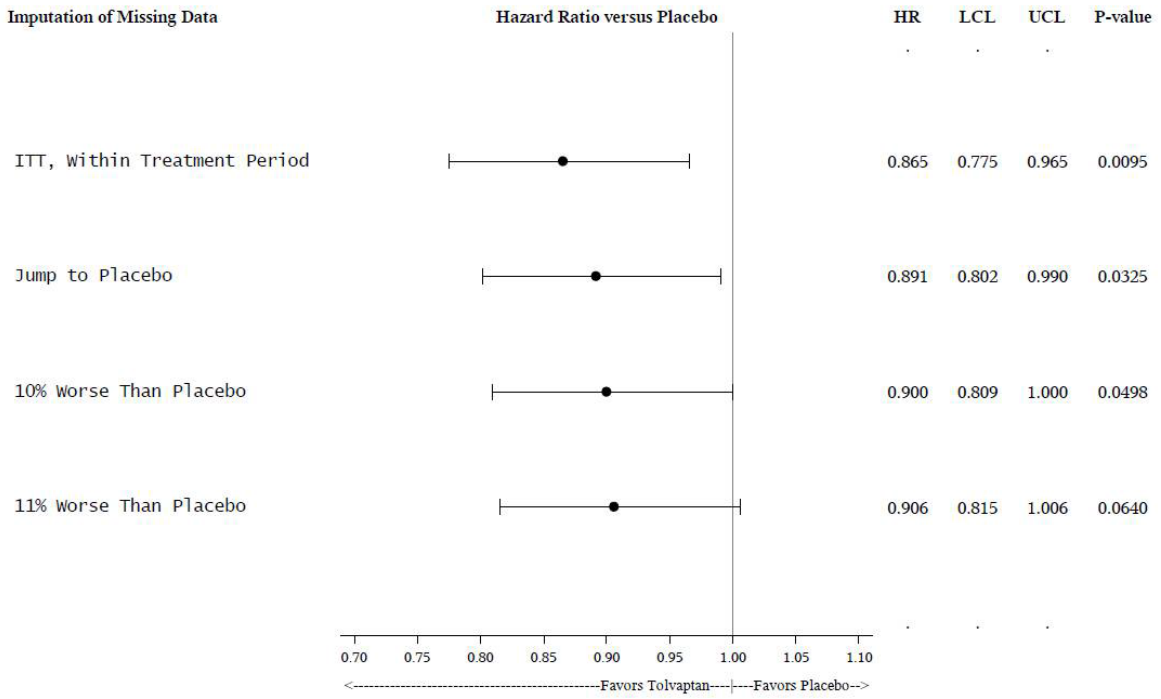

Figure 3: Multiple Imputation of Missing Data in Key Secondary Composite Endpoint with Treatment Effect as Intensity Ratio

Table 7: Results of Original Efficacy Analyses for TEMPO 3:4 for the Secondary Composite Efficacy Variable and tipping point analyses

Key Secondary Composite Endpoint	Estimated Treatment Effect (Percent Change at Month 36)	p-value
Original analysis	0.865	0.0095
Tipping point analysis at 100%: 'jump to placebo'	0.891	0.0325
Tipping point analysis at 333%: 'tipping point'	0.900	0.0498

- The post-hoc power calculations analysis included 1,086 participants "who had an actual month 36 eGFR observation". Please provide a post-hoc power calculation for the optimised subgroup (CKD stage 2 to 3) as well.

<u>Response</u>

In order to provide "post-hoc power" for eGFR (CKD-EPI) slope for CKD Stage 2-3a (corresponding to the 29.7% treatment effect – see above), pre-specific analyses were conducted on this patient population. The delta of treatment difference in eGFR slope is 1.293, with a variance of individual subject slope of 5.8398, and variance of noise of 27.2588.

For this three-year study with three equal space visits within each year, the sample size formula provided by Leffante (8) is used. In this formula, all subjects are assumed to have all the visits, thus the number of subjects who had Month 36 eGFR observation, which is equal to 722 based on this patient population of CKD Stage 2 and 3a, is used in this post-hoc power calculation. We still used 2:1 randomisation since it was used in the sample size calculation for the protocol.

Under these assumptions, using the formula provided by Leffante, with an alpha of 0.05, the 722 subjects would provide 99.8% power to detect a difference of 1.293 in eGFR slope; even with an alpha of 0.01, which was used for the key secondary endpoint, the 722 subjects would still provide 98.9% power to detect a difference of 1.293 in eGFR slope. The post-hoc power would be even higher when discontinued subjects were included in the analysis. Thus the study did have enough power to detect the observed treatment difference in the secondary endpoint of eGFR slope using CKD-EPI formula for subjects in CKD Stage 2-3a (as used in the revised base case).

- Please provide further details regarding the expected availability of the analyses of the ADPKD-specific HRQoL data in the OVERTURE trial.

Response

Since our response to the ACD, the first draft CSR for the OVERTURE study has been made available to Otsuka Europe on a confidential basis (data on file). We recognise the potential importance and value of this ADPKD-specific data on HRQoL from a large, global naturalistic study. Therefore in the short time that has been available, we attempted to assess the likely impact of the EQ-5D data from OVERTURE on the cost-effectiveness results in our revised base case.

EQ-5D estimates were taken in OVERTURE at baseline and at every 6 months thereafter for as long as the patient remained in the study (Figure 4). As can be seen, there is not a great deal of variation in the results within CKD stages by time point.

To take a representative cross-sectional example, at month 12, EQ-5D responses were available for 588, 564, 558 and 196 patients in CKD stage 1, 2, 3 and 4 respectively. The mean values (UK index) for these groups were [redacted], [redacted], [redacted] (weighted average of stage 3a and 3b) and [redacted].

[redacted]

Figure 4: Draft EQ-5D data from OVERTURE by CKD stage and visit

Modifying the health state decrements in the economic model for CKD stages 1-4 according to these values increases the ICER in the revised base case only by a small amount, approximately £641 (from £23,503 to £24,144). This is in line with the low degree of sensitivity demonstrated in scenario analyses on the health state utility decrements for CKD stages 3 and 4 provided in our original submission.

Whilst the example above is draft and preliminary, the EQ-5D data presented in Figure 4 does not greatly vary from the values used in our original submission from published sources. This provides confidence that the ADPKD-specific EQ-5D data from OVERTURE is unlikely to significantly alter the outcome of the revised base case analysis, enabling the decision problem to be fully assessed according to the data already presented.

References

1. Grantham JJ, Torres VE, Chapman AB. Volume progression in polycystic kidney disease. N Engl J Med. 2006;354(20):2122-30.
2. Serra AL, Poster D, Kistler AD, Krauer F, Raina S, Young J. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363(9):820-9.
3. Walz G, Budde K, Mannaa M. Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2010;363(9):830-40.
4. Chapman AB, Bost JE, Torres VE. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012;7(3):479-86.
5. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara Eea. TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18.
6. Schrier RW, Brosnahan G, Cadnapaphornchai MA. Predictors of Autosomal Dominant Polycystic Kidney Disease Progression. JASN. 2014 Epub ahead of print.
7. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Higashihara E, Perrone RD. Tolvaptan-treatment of ADPKD confers persistent eGFR improvement: results from the TEMPO 4:4 extension trial. Nephrol Dial Transplant. 2014;29(suppl 3):iii5-iii6.
8. Lefante JJ. The power to detect differences in average rates of change in longitudinal studies. Statistics in Medicine. 1990;9: 437-46.