Otsuka Pharmaceuticals (UK) Limited - New evidence in response to the preliminary recommendations in the ACD of Tolvaptan for treating autosomal dominant polycystic kidney disease [ID652]

Otsuka Pharmaceuticals (UK) Limited (OPUK) has reviewed the appraisal committee decision (ACD) in detail and believes that the concerns raised by NICE about the cost-effectiveness of tolvaptan can be addressed. In this appendix we present a revised cost-effectiveness analysis which accounts for the ACD's conclusions, including a revised (optimised) population and incorporates the revised patient access scheme (PAS) submitted to the Department of Heath (DH).

Most plausible base case

In points 4.14 and 4.15 of the ACD NICE outline the changes that they feel should be incorporated in the most plausible base case for tolvaptan treatment.

ERG/Committee's proposed changes:

1. Correcting the model code error
2. Applying a lower disutility of 0.02 for dialysis complications
3. A treatment discontinuation rate of 2.9% after year 3 (point 4.11)
4. Assuming equal costs for chronic kidney disease (CKD) stages 3 and 4
5. Decreased post-transplant costs
6. Increased pre-ESRD mortality, instead of the general population mortality data (hazard ratio 2.0)
7. Assess eGFR with CKD-EPI equation
8. Disutility of tolvaptan
9. Applying an equal probability of kidney pain to both treatment groups
10. All Hy's Law cases would have a liver transplant at year 1 and would die immediately after
11. Increased monitoring costs for being on tolvaptan treatment

Code error, disutility of dialysis, discontinuation, CKD 3 costs and post-transplant costs

We agree that the most plausible base case should include the corrected model code, a disutility of 0.02 for dialysis complications and a discontinuation rate of 2.9% after year three. As requested by NICE we will incorporate the conservative assumptions of equal costs for CKD 3 and CKD 4, and decreased transplant costs.

Pre-ESRD mortality

As discussed in the main Otsuka response to the ACD, evidence from Florijn *et al*. (1) confirms that the mortality hazards ratio of 2.0 arbitrarily selected by the ERG is excessively high. We propose to apply the conservative assumption of a hazard ratio of 1.6 as reported in Florijn *et al*. (1).

Patient population

We clearly note the uncertainty expressed by the Committee regarding the cost-effectiveness of tolvaptan. One way in which we can move to significantly reduce this uncertainty is by applying the decision problem to a well-defined subgroup of patients within the licensed indication.

At the outset, it is important to re-affirm that Otsuka believes strongly that the greatest benefit from tolvaptan treatment can be achieved through early intervention, i.e. in CKD stage 1 ADPKD patients with evidence of rapidly progressing disease, prior to irreversible damage to the kidneys. In the absence of long-term data reflecting the chronic nature of the disease, this belief is difficult to prove, however the biological plausibility of this belief is not in doubt.

With that said, we recognise it unfortunately does not necessarily follow that patients with the greatest capacity to benefit from treatment clinically will also the most cost-effective to treat. The key driver of cost-effectiveness in our economic evaluation is delay to ESRD. For those patients initiating tolvaptan in CKD stage 1, this driver would be typically realised further into the future relative to those initiating treatment in CKD stage 2 or 3, simply by virtue that CKD stage 2 or 3 patients are (by definition) closer to ESRD at initiation. This leads to the following downward pressures on cost-effectiveness for eligible patients initiating in CKD stage 1:

- More time on treatment, incurring more upfront cost
- More uncertainty associated with their predicted rate of ADPKD progression
- Disproportionate erosion of the value of benefits due to discounting in line with the NICE Reference Case

The reduction in confidence that treatment is cost-effective in this patient group may be compounded further by the lack of clinical guidance to ensure consistent patient assessment in CKD stage 1 for "evidence of rapidly progressing disease", and therefore eligibility for treatment with tolvaptan.

In our original submission we presented subgroup analyses of efficacy from the TEMPO 3:4 trial by CKD stage at baseline (Table B12 and B13). These analyses served to show that whilst the treatment effect of tolvaptan on TKV growth was consistent across the CKD stages, the positive effect on renal function decline was more pronounced in later disease stages. This is an expected outcome, i.e. an effect on renal function decline is more easily detected in patients already experiencing significant renal dysfunction.

In totality, these factors lead to the reasonable conclusion that the cost-effectiveness of tolvaptan may be optimised in patients initiating in CKD stage 2 or 3 with evidence of rapidly progressing disease. As such, we propose that the Committee focuses its discussions at the 2nd Committee meeting on a revised decision problem:

"*To appraise the clinical and cost effectiveness of tolvaptan within its licensed indication for treating autosomal dominant polycystic kidney disease,* ***specifically in patients at CKD stage 2 or 3 at initiation with evidence of rapidly progressing disease***."

Our revised base case is restricted to this subgroup of patients, for which we seek an optimised recommendation from NICE.

For avoidance of doubt, this proposal is made purely on the grounds of reducing uncertainty in cost-effectiveness. Based on the TEMPO 3:4 study data, and the nature of ADPKD progression, Otsuka remains firmly of the belief that the greatest clinical benefit of tolvaptan treatment can be achieved with early intervention, prior to irreversible damage of the kidneys.

Definition of proposed optimised subgroup

In our economic evaluation, the modelled patient cohort is defined at baseline by the following factors:

- Age
- % female
- TKV
- GFR

Accordingly, in order to model the proposed optimised subgroup it is necessary to define representative baseline values for these variables. In our original submission, and in the absence of reliable real-world data, we approximated the full licensed indication population in the economic model to the average baseline characteristics of the included patients from the TEMPO 3:4 trial. This appears to have been accepted by the ERG and Committee as appropriate.

Utilising the modelled underlying (no active treatment) progression trajectories in our original submission base case, it is possible to "read off" mean characteristics for a population that would represent the proposed optimised subgroup.

Our proposed optimised subgroup is patients at CKD stage 2 or 3 at initiation within the licensed indication (i.e. with evidence of rapidly progressing disease). According to the KDOQI classification, CKD stage 2 begins at GFR values below 90 and CKD stage 3 ends at a GFR value of 30. The midpoint of this range is a GFR value of 60, which is reached on average approximately by the end of year 5 in the no active treatment cohort. Reading off the average modelled values from this cycle for TKV and age allows a set of baseline characteristics for the optimised subgroup to be defined.

Table 1: Mean progression trajectory of no active treatment group in original modelled base case

	GFR (ml/min/1.73m^2)	Age (years)	TKV (ml)
Baseline	82	39	1692
Year 1	78	40	1778
Year 2	74	41	1888
Year 3	70	42	2012
Year 4	65	43	2150
Year 5	60	44	2287

*Values rounded to nearest whole number

Proposed 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)

We regard this to be the most appropriate way of defining the proposed optimised subgroup as it is based on a population representative of the licensed indication, and an underlying disease progression trajectory that appears to have been accepted as reasonable by the ERG and Committee.

Ideally, we would prefer to define the proposed optimised subgroup based on real-world data sources. However this is problematic due to the patient characteristics required by the licensed indication (i.e. subjective evidence of rapid progressing disease) and the absence of TKV data in such sources.

Similarly, the two Otsuka study data sources including reliable TKV measurements are problematic for this purpose. In TEMPO 3:4 only 17% of patients were CKD 3 at baseline, and therefore the baseline characteristics of the proposed subgroup are unlikely to be representative of those who would be seen in practice. The OVERTURE study, as a naturalistic observational study, included a broad range of ADPKD patients (including CKD stage 4 and 5 at baseline) that does not reflect the specific targeted population in the licensed indication (i.e. evidence of rapidly progressing disease). OVERTURE is therefore also unsuitable for this purpose.

Estimate of treatment effect in the proposed optimised subgroup

We note the Committee's conclusion in section 4.10 of the ACD that CKD-EPI should be preferred as the method of assessing eGFR. We maintain the view, as clearly laid out in our original submission that assessment of eGFR is not straightforward and no single method can be said to be applicable for every patient and every purpose. It is our belief that there exists a margin of error in assessment of renal function that is well illustrated by the range of variability across the four measures of renal function collected in TEMPO 3:4 (i.e. reciprocal serum creatinine, CKD-EPI, MDRD and Cockcroft-Gault).

Each of the equation-based techniques incorporate various patient factors such as age, gender, ethnicity and body mass/surface area, and are associated with greater or lesser degrees of accuracy depending on specific patient characteristics and the objective of the assessment (i.e., diagnosis or evaluation of change). Therefore the optimal choice of correct estimation technique is individualised.

It should be noted that CKD-EPI produced the lowest relative treatment effect for tolvaptan out of all four measures. Our original base case utilised reciprocal serum creatinine, the primary renal function measure in TEMPO 3:4 per protocol, which did not produce the highest relative treatment effect (Cockcroft-Gault produced the highest relative treatment effect). Since our original methodology used a value within the range of alternatives and the Committee's preference is at the bottom of the range, we believe the Committee's conclusion can be regarded as conservative.

With that said, we recognise that a choice is required and that CKD-EPI is named as the GFR estimate of choice in NICE CG 182. Therefore our revised base case utilises CKD-EPI as the measure of renal function, both for underlying disease progression and for assessment of relative treatment effect.

The relative reduction on the slope of renal function decline estimated in TEMPO 3:4 for tolvaptan compared to placebo, as measured by CKD-EPI, was 26.4% (as compared to 31.6% in our original base case utilising reciprocal serum creatinine). However this value is for the included trial cohort as a whole, including patients in CKD 1 at initiation. In light of the proposed optimised subgroup in our revised base case, we apply the corresponding value derived for the subpopulation of trial patients at CKD stage 2 and 3 at baseline (approximately 29.7%).

Revised PAS net price

Otsuka has requested that the Department of Health approve a revision in the PAS for tolvaptan to a discount of [redacted]% of the NHS list price (originally [redacted]%) £[redacted] for each 28 day pack (£[redacted] per day; originally £[redacted] per day). The simple fixed price discount patient access scheme approved by the department of health in March 2015 (subject to marketing authorisation) is not being revised in any other way.

Table 2: NHS list and PAS price of tolvaptan

NHS list price	Acquisition cost under proposed PAS scheme
[redacted]	[redacted]

Treatment disutility and equal pain

Please refer to the corresponding section in our main response which outlines our complete rationale with regard to these variables. This is summarised below:

- The Committee's conclusions on these combined issues lead to a disproportionate bias against tolvaptan that is contradictory to the available evidence
- The ERG and Committee have not accounted for the impact of discontinuation from tolvaptan treatment due to AEs on patient HRQoL
- We are firm in the belief that tolvaptan's positive impact on TKV growth will lead to indirect benefits, most notably a reduction in significant kidney pain events, supported by evidence and expert opinion
- There exists no evidence to suggest that tolvaptan treatment leads to significant and long-term reductions in patient HRQoL due to adverse effects
- The disutility value applied in exploratory analyses was extreme, and in no way do we regard it as a true effect
- The net impact on patient HRQoL of tolvaptan AEs, relative to reduction in ADPKD complications, is no worse than neutral
- Testimony from patient and clinical experts, and the evidence from TEMPO 3:4 support this view

In our revised base case we suggest a new value for tolvaptan treatment disutility which is in line with this conclusion.

Net effect on patient HRQoL

In order to illustrate the relative weight each of these factors has on patient HRQoL we conducted a "direction of bias" analysis isolating each of the factors in turn. The table below presents the impact on incremental QALYs, in our revised base case, of each of the individual factors discussed above.

Table 3: Direction of bias analysis

HRQoL factor	Included?	Included?	Included?	Included?
Discontinuation due to AEs*	No	Yes	No	No
Benefit from reduced pain events (as per our original submission)	No	No	Yes	None
Treatment disutility (as per ERG exploratory analysis)	No	No	None	Yes
Incremental QALYs	**0.71**	**0.59**	**0.72**	**0.62**
Influence		**-0.12**	**<0.01**	**-0.09**

*Annual rates of discontinuation for reasons excluding AEs are always included and were derived from data from TEMPO 3:4 as follows: 2.19 (±0.47)% in year 1, 4.30 (±0.717)% in year 2 and 2.23 (±0.54)% in year 3.

This analysis clearly illustrates the relative impact of each factor on patient HRQoL. Discontinuation due to AEs leads to a reduction of 0.12 QALYs (17% of the total); the exploratory treatment disutility analysis leads to a reduction of 0.09 QALYs (13% of the

total); the inclusion of differential rates of kidney pain has a negligible impact on overall HRQoL.

As such, far from being conservative, it is clear that the conclusion of the Committee regarding kidney pain and treatment disutility leads to a disproportionate negative impact of tolvaptan on patient HRQoL. This is true irrespective of whether one considers discontinuation from treatment due to AEs to be relevant in this regard.

With this in mind, we have proposed a new treatment disutility value in our revised base case (0.0025) which effectively neutralises the positive impact of the benefit of tolvaptan on kidney pain. This value was calculated by performing a "goal seek" until the net effect of these two variables was zero on incremental QALYs. It is worth noting that in order to neutralise HRQoL change due to both kidney pain and discontinuation due to AEs, a *positive utility* of tolvaptan treatment (0.017) would be required. We therefore regard the approach adopted in our revised base case to be extremely conservative.

Monitoring cost

As five year data from TEMPO 3:4 and TEMPO 4:4 (2) shows that the risk of alanine aminotransferase (ALT) elevation is equal after the first 18 months (across study arms), the assumption of doubling the monitoring frequency for patients with raised ALTs is plausible for the first 24 months of the model; however there is no evidence to support double monitoring frequency for the remainder of the model time horizon. We propose to apply double monitoring only for the first two years of the model for the 4.4% of patients with ALT elevation above three times the upper limit of normal (ULN).

Otsuka disagree with the assumption that after the second year all patients receiving tolvaptan would require an additional consultant visit due to adverse events. Consultant visits would only be required for serious adverse events (SAEs) and data from Table 2 of TEMPO 3:4 (3) shows that for SAEs more common in tolvaptan and placebo groups, that tolvaptan had less SAEs (5.3% [31+ 20 / 961] vs 7.45% [6 + 309 / 483]). We propose to assume no additional consultant visits for tolvaptan patients in the base case. This is a conservative approach given that placebo patients have 2.15% more SAEs.

Hy's Law

As a worst case the ERG modelled a scenario where all Hy's law cases would have a liver transplant in the first year and die immediately after transplant. We are very surprised that the committee accepted this scenario given that they acknowledged in point 4.8 of the ACD that:

- All three cases of Hy's law in TEMPO 3:4 and 4:4 resolved after discontinuing the drug
- The Hy's law cases could be avoided through increased monitoring

It should be noted that in TEMPO 3:4 liver function testing (LFT) was conducted every three months. As part of the risk management plan UK patients will have far more stringent LFT testing; once a month for the first 18 months and three monthly thereafter. Otsuka believe that this exploratory scenario is too extreme even for a worst case scenario.

It should be noted that there are issues with the method in which the scenario was implemented by the ERG. Firstly, we believe the ERG have misinterpreted the FDA guidance for industry on drug-induced liver injury (4), assuming a 3 per 958 Hy's Law patients would experience liver injury, the figure should be approximately 1 per 3000 (3 Hy's Law ÷ 958 total number of patients X 10% risk of liver failure/mortality ≈ 1/3000) (4). As a result the numbers of liver failure patients have been over estimated approximately nine fold.

Secondly, immediate death following transplant was assumed to be 100%. This is extremely severe as European Liver Transplant Registry from 2012 lists 1-year post–transplant survival at 79% and 5-year survival at 72% (5)

Thirdly, the ERG had a coding error in their Hy's law calculations. They applied costs excluding the patient access scheme in their Hy's law calculation which overestimated costs and the ICER.

Methods

Other than correcting the model code error identified by the ERG no programming or structural changes have been made to the model. The changes made to the variables specified in the model for the most plausible base case are described below and presented in Table 4.

a) The percentage of relative reduction in renal function decline (slope) is now measured using CKD-EPI for patients in CKD 2 to 3. The values calculated from the TEMPO 3:4 data are 29.7% and a standard error (SE) of 5.63%. Annual change in renal function (slope) over the first three years was modelled as there was insufficient time to calculate this data by year.
   The baseline patient profile was amended to represent the average ADPKD patient in CKD stage 2 to 3 with evidence of rapidly progressing disease
b) The baseline values for definition of the subgroup were approximated from modelled projections of the original base case (no active treatment) cohort. The baseline values used are age 44 years (SE 0.190), female 48.4% (SE 1.3%), eGFR 60 ml/min/1.73m^2 (SE 0.570), total kidney volume 2,300 ml (SE 23.82).
c) Treatment discontinuation in year 4 and beyond has been amended to 2.89% (SE 0.61%) as found in year 3 of the TEMPO 3:4 study.
d) The risk of serious kidney pain events for tolvaptan-treated patients in CKD 1 to 4 is set to 0.05 (SE 0.004) as seen in TEMPO 3:4.
e) The PAS discount has been set to [redacted]%.
f) Monitoring and administration costs in year one and two have been set 1.044 times the annual monitoring cost , accounting for doubling the intensity of monitoring for the estimated 4.4% of patients with raised ALT (above 3). Monitoring costs in year three and beyond are unchanged as the ALT elevation is equal to placebo after the first 18 months. Increased nephrology visit costs in year three and beyond are set to zero as tolvaptan patients are less likely to experience SAEs.
g) CKD 3 costs and the standard error were set equal to those for CKD 4 (£3,357.65, SE £503.65).
h) The annual cost of the background management of ADPKD (£5,238.59) has been removed for patients that have received a kidney transplant. Year one maintenance cost has been reduced to £13,805.85 (SE £2,070.88) and the year two and beyond cost has been reduced to £2,637.93 (SE £395.69).
i) Disutility associated with tolvaptan treatment is set to 0.0025
j) The disutility associated with haemodialysis and peritoneal dialysis were set to 0.02 (SE 0.003).

Table 4: Revised parameter values and model settings

Item	Sheet	Cell	Cell value / adjustment
Set the model to CKD-EPI			
	Control	L7	*select:* TEMPO equation (CKD-Epi)
	Control	K28	*Select:* 0
	Control	T28	*Select:* 0
CKD-EPI % slope - Mean	Control	E45	29.7074%
CKD-EPI % slope - SE	Control	F45	5.6342%
Baseline patient profile			
Current age (years) - Mean	Control	E17	44
Current age (years) - SE	Control	F17	0.190
Sex (% female)	Control	E18	48.40%
Sex (% female) - SE	Control	F18	1.3%
eGFR (ml/min/1.73m^2) - Mean	Control	E20	60.00
eGFR (ml/min/1.73m^2) - SE	Control	F20	0.570
Kidney volume (ml) - Mean	Control	E21	2300.00
Kidney volume (ml) - SE	Control	F21	23.820
Treatment discontinuation			
Assuming treatment discontinuation of 2.9% after year 3 - Mean	Control	E53	2.89093298291721%
Assuming treatment discontinuation of 2.9% after year 3 - SE	Control	F53	0.607374527829829%
Tolvaptan kidney pain			
Tolvaptan kidney pain probability - Mean	Control	H59:H62	0.05
Tolvaptan kidney pain probability - SE	Control	I59:I62	0.003
PAS discount	Cost & Utility Input	E11	[redacted]
	Cost & Utility Input	H11	[redacted]
	Cost & Utility Input	K11	[redacted]
Assuming increased monitoring costs	Cost & Utility Input	E20	=1.044*£308.57
	Cost & Utility Input	H20	=1.044*£224.42
	Cost & Utility Input	K20	£112.21
	Cost & Utility Input	K21	£0.00
Equal CKD 3 & 4 costs			
Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4 - Mean	Cost & Utility Input	E30	£3357.65
Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4 - SE	Cost & Utility Input	F30	£503.65
Assuming decreased post-transplant costs			
Maintenance Year 1 Mean	Cost & Utility Input	E78	£13805.85
Maintenance Year 1 SE	Cost & Utility Input	F78	£2,070.88
Maintenance Year 2+ Mean	Cost & Utility Input	E79	£2637.93
Maintenance Year 2+ SE	Cost & Utility Input	F79	£395.69
Disutility			
Disutility associated with treatment	Cost & Utility Input	E92	0.0025
Disutility of HD and PD complications	Cost & Utility Input	E102:E103	0.02
Mortality			
Assuming increased mortality hazard ratio	Life tables	C6:D106	*all values in life tables (C6:D106) multiplied by:* 1.6

Results

Clinical outcomes from the model

Table 5: Summary of model results compared with clinical data

Outcome	Clinical trial/study result	Model result
Survival at 3 years	100% in both arms	99.1% control; 99.1% treatment
Mean age at ESRD (years)	55[a] (45 – 67)[b]	52.42[c]
Mean age at death (years)	70[d]	65.19

[a] UK Renal Registry data for ADPKD patients, median age of commencing RRT (Shaw *et al*., 2014)

[b] Range of estimates from published studies reporting age of ESRD onset in ADPKD patients; see section 7.8.1 of main submission.

[c] Model estimate for the control (no active treatment) arm.

[d] UK Renal Registry data for ADPKD patients, median age of death (Shaw *et al*., 2014)

The model estimate for the mean age at ESRD was similar to that observed in the UK renal registry and other published studies, and within the plausible range that may be expected for a patient population with evidence of rapidly progressing disease.

Underlying life expectancy is estimated to be a mean of 65 years of age for patients receiving no active treatment and eligible for tolvaptan. In the UK, registry data indicate that the mean age of death of patients with ADPKD and ESRD is approximately 70 years (6). Since this analysis focusses on patients in CKD 2 or 3 at initiation of treatment with evidence of rapidly progressing disease the modelled value for underlying life expectancy appears plausible.

1.1.1 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of patients in each ESRD health state over time in the no active treatment and the tolvaptan cohorts is presented in Figure 1 and Figure 2, respectively. The distribution of patients among the CKD health states is presented in Table 6.

Patients in the tolvaptan cohort spend longer in CKD stages 3 and 4, and less time in ESRD (1.28 years) than patients in the control (no active treatment) cohort. Tolvaptan patients are

associated with approximately 0.24 years less on dialysis and 14% fewer transplants compared to no active treatment.

Table 7: Time spent in each CKD health state (years)

Health State	Control (no active treatment)	Tolvaptan	Incremental
CKD 1	-	-	-
CKD 2	0.50	0.50	0.00
CKD 3	5.42	6.96	1.54
CKD 4	2.43	2.98	0.56
ESRD	12.74	11.55	-1.20

Figure 3: Distribution of patients among ESRD treatment modalities: no active treatment cohort

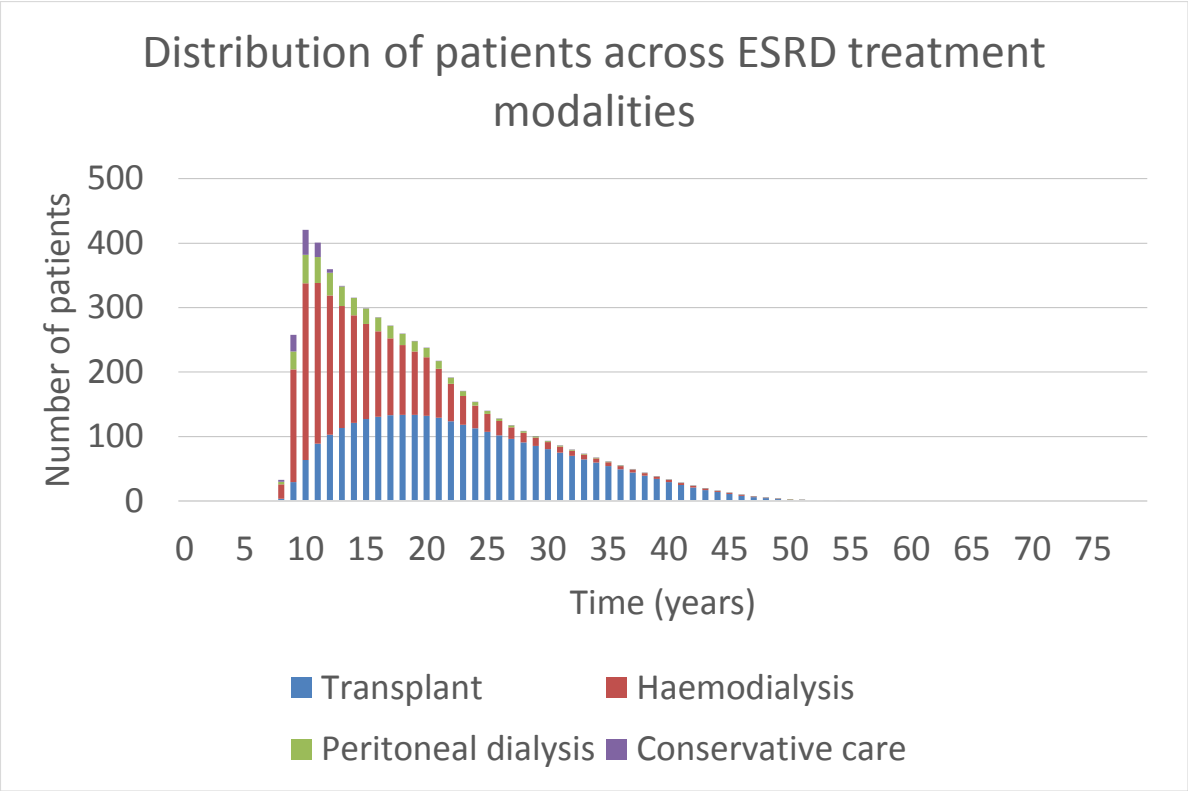
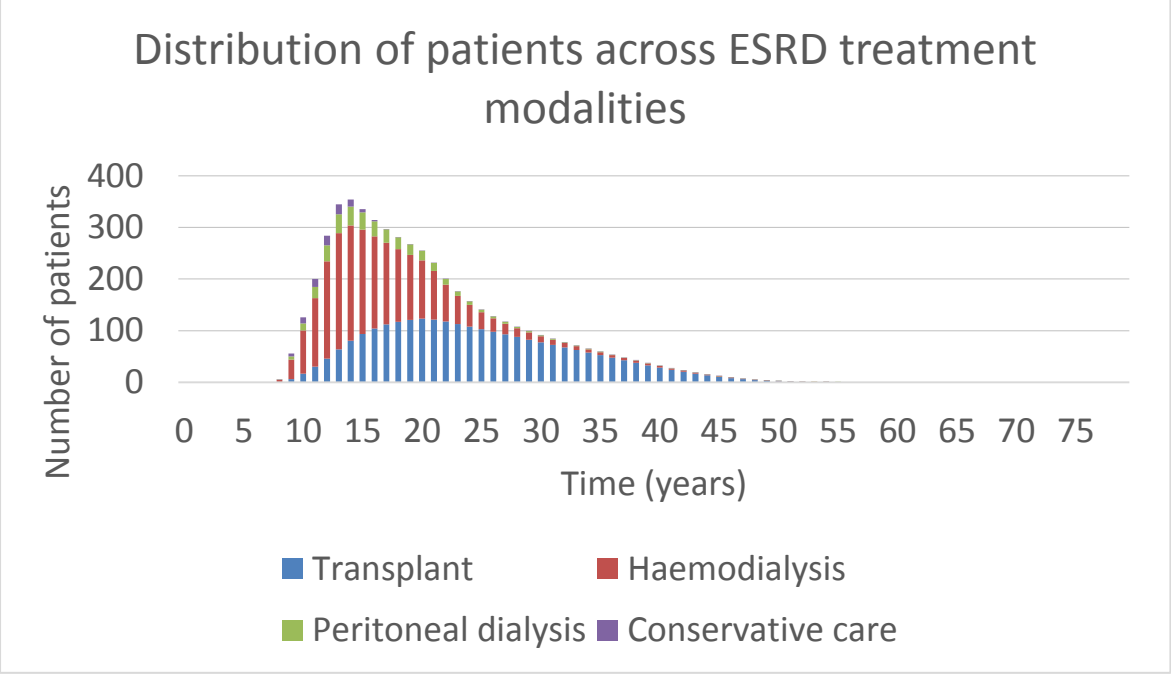


Figure 4: Distribution of patients among ESRD treatment modalities: tolvaptan cohort



1.1.2 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

1.1.3 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

1.1.4 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

As the model is an individual patient simulation model, these data are not presented. However a series of transparency reports are included within the Excel model provided with the submission, including reports of each simulation run, patient-level TKV and GFR outputs stratified by cycle, and event counts.

Base-case analysis

1.1.5 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental

analysis ranking technologies in terms of dominance and extended dominance.

The probabilistic mean base-case results are presented in
Table **8** (excluding the PAS) and (including the PAS), based on 500 patients simulated with sampling of baseline characteristics; 1,000 PSA iterations.

The discounted estimates for total expected lifetime costs were [redacted] for the control (no active treatment) cohort. For the tolvaptan cohort, the cost estimates were higher at [redacted] (including the PAS). The health outcomes in the form of QALYs and life years gained were higher for the tolvaptan patient cohort at 10.42 QALYs (discounted) and 14.71 life year (undiscounted) than for the control (no active treatment) cohorts at 9.83 QALYs and 14.13 life years. The ICER for tolvaptan was £23,503 per QALY gained including the PAS.

Table 8: Mean discounted base-case results per patient (probabilistic mean estimates, including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	[redacted]	14.13	9.83				
Tolvaptan	[redacted]	14.71	10.42	[redacted]	0.58	0.59	£23,503

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Total expected lifetime results, mean per patient, based on 500 patients simulated with sampling of baseline characteristics; 1,000 PSA iterations.

1.1.6 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

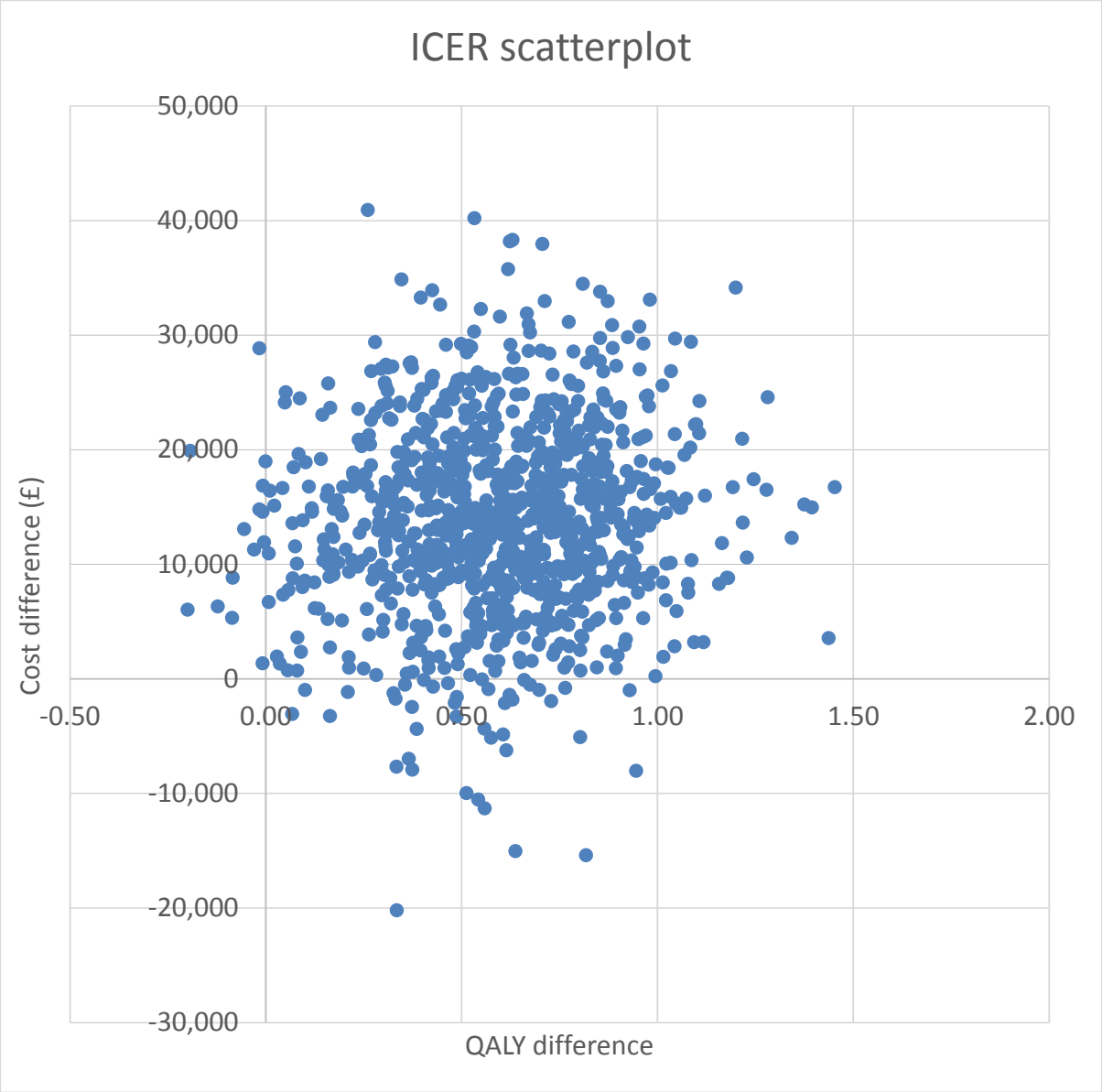
The results of 1,000 probabilistic simulations (each including 500 patients with identical characteristics) are presented on the cost-effectiveness plane in Figure **5** (including the PAS). The vast majority of simulations fell in the north east quadrant in both cases.

The cost-effectiveness acceptability curve is presented in

Figure **6** (including the PAS). Including the PAS the probability of cost-effectiveness at a willingness-to-pay threshold of £30,000 per QALY gained was 64.90%.

The variability of the ICER estimates as the number of probabilistic simulations was increased is presented in Figure 7. The ICER became stable after approximately 200 simulations. 1,000 simulations were performed for all analyses.

Figure 5: Probabilistic ICER estimates presented on the cost-effectiveness plane [including PAS)



Note: within each probabilistic iteration, 500 patients with identical baseline characteristics were simulated. Between each successive probabilistic iteration, the baseline characteristics of the 500 identical patients were sampled from their distributions.

Figure 6: Cost-effectiveness acceptability curve [including PAS]

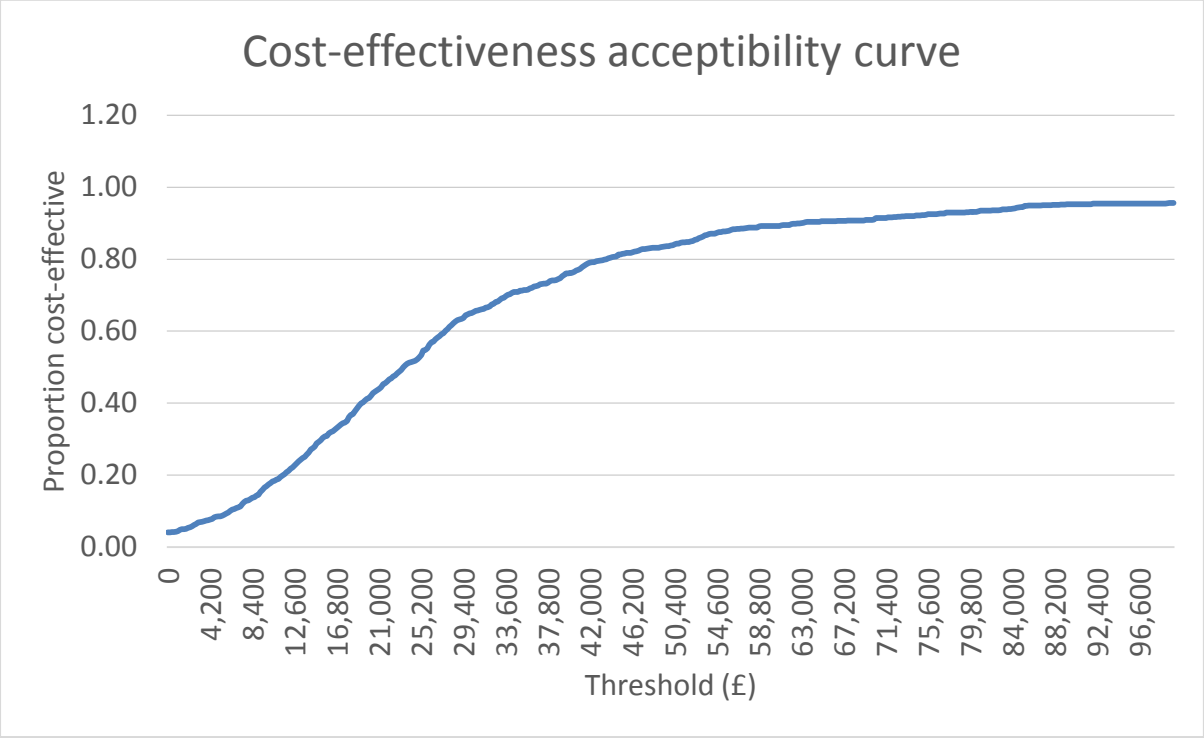
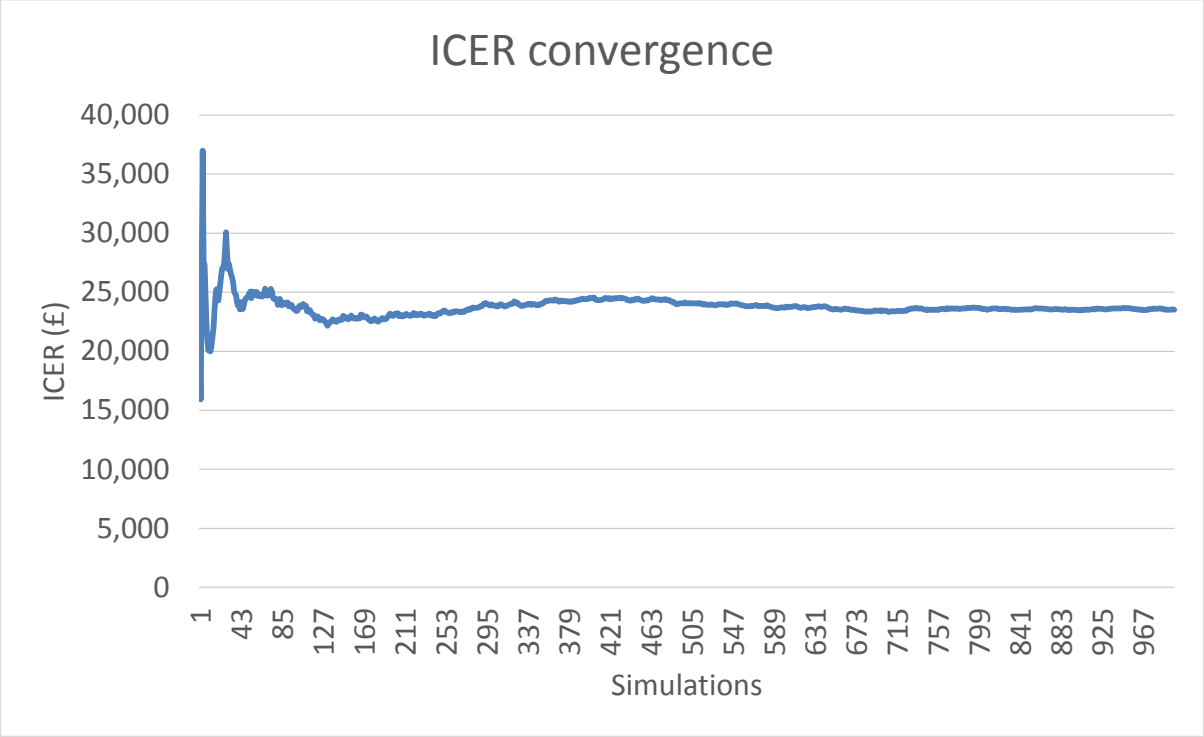


Figure 7: ICER estimates with increasing number of probabilistic simulations [including PAS]



Note: within each probabilistic iteration, 500 patients with identical baseline characteristics were simulated. In each successive probabilistic iteration, the baseline characteristics of the 500 identical patients were sampled from their distributions (based on the baseline characteristics of the TEMPO 3:4 trial population) and the mean values of all model parameters were sampled from their individual distributions (see section 7.3.6).

Discussion and conclusions

The economic evaluation presented here has addressed the issues highlighted by NICE in the ACD. We have outlined why it would be inappropriate to apply a significant disutility to tolvaptan treatment, to assume equal probability of kidney pain for tolvaptan and the no active treatment arm, and to apply the ERG scenario for Hy's law. We have corrected the model code errors and amended the values of the remaining parameters identified in the ACD.

We reiterate that tolvaptan represents a step-change in the management of ADPKD, being the first treatment proven to delay ADPKD renal progression, leading to clinically meaningful long-term benefits for patients, whilst reducing the burden on transplant and dialysis services for the NHS. Under the terms of the PAS and in the proposed optimised subgroup tolvaptan represents a cost-effective use of NHS resources

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