Otsuka Pharmaceuticals (UK) Limited response to the Appraisal Consultation Document relating to tolvaptan for the treatment of autosomal dominant polycystic kidney disease [ID652]

Otsuka Pharmaceuticals (UK) Limited (OPUK) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) relating to tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD). We are disappointed in NICE's draft guidance that tolvaptan is not recommended within its licensed indication despite the committee concluding that tolvaptan is an innovative treatment and the first treatment shown to specifically impact on the progression of ADPKD.

We have identified a number of issues relating to accuracy, data relevance, interpretation and recommendations that we would like to draw to the attention of NICE and stakeholders to the appraisal. In addition, and in light of the draft guidance, we have provided in a separate document a revised cost-effectiveness analysis incorporating the revised patient access scheme (PAS) which has been submitted to the Department of Health.

1. Has all of the relevant evidence been taken into account?

Point 3.19 on page 13 incorrectly states that the results of the subgroup analysis by CKD stage were marked as commercial in confidence and could not be displayed. This is valuable information that should have been made available in the ACD to all commentators.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Otsuka does not agree with all of the interpretations of the clinical and cost-effectiveness evidence in the ACD. Below we outline the issues we will address in detail:

- <u>Clinical evidence</u>
    - Generalisability of TEMPO 3:4
    - Uncertainty regarding efficacy results from TEMPO 3:4
        - Handling of missing data
        - Effect size in renal function decline
    - Measurement of TKV
    - Committee conclusion on hepatotoxicity

- <u>Cost-effectiveness</u>
    - Uncertainty regarding the role of TKV and application of treatment effect
        - Role of TKV in ADPKD progression
        - Application of treatment effect directly to GFR
    - Uncertainty regarding EQ-5D data from OVERTURE
    - Uncertainty regarding utility data applied to model
    - Preferred base case modelling parameters
    - CKD-EPI rather than the reciprocal of serum creatinine
    - Treatment discontinuation
    - Increased mortality
    - Equal cost for CKD stage 3 and 4
    - Post-transplant costs
    - Relative effect of ADPKD complications and tolvaptan adverse effects on HRQoL
    - Hy's law cases

- Monitoring costs
- Most plausible ICER

Clinical evidence.

Generalisability of TEMPO 3:4.

We note with concern in section 4.9 of the ACD that, with respect to TEMPO 3:4:

"*The Committee concluded that the generalisability of the trial results may be limited because of differences in the trial population compared with people with ADPKD seen in routine clinical practice*."

We strongly disagree with this conclusion. The Committee considers two aspects of the study in reaching this judgment:

1) That a high number of patients were excluded from the study either due to restrictions in the inclusion criteria (namely TKV at least 750ml, age up to 50 years, creatinine clearance at least 60ml/min) or due to other reasons, who would otherwise be considered for treatment in practice
2) That a low proportion of patients in the study (~5%) were from the UK

In our view the ERG and Committee have not objectively considered the likely impact of these factors on the generalisability of the study to UK practice, and instead have adopted an unreasonably cautious position. In order to objectively assess the generalisability of the study, one should consider whether the efficacy results from the study can be applied to the decision problem in light of these concerns. Dealing with each of the issues in turn:

Patients excluded from the study

The ERG's assertion that a high number of patients that would be considered eligible for treatment in the UK were excluded from TEMPO 3:4 is highly likely to be incorrect.

Approximately 70% of patients considered screening failures did not meet the inclusion criteria for either renal function or TKV, which were intended to ensure a population with a high risk of rapid progression were studied. We acknowledge, given the subjective nature of "evidence of rapidly progressing disease" in the licensed indication, that a minority of these excluded patients may ultimately have been considered eligible for tolvaptan under the licensed indication. However it is also reasonable to assert that the vast majority of these patients would not in fact be classified as having evidence of rapidly progressing disease, would be ineligible for treatment, and are therefore properly excluded from the trial. This factor surely lends strength, not weakness, to the generalisability of the study to UK practice.

The exclusion of patients aged over 50 years from the study was also a pragmatic step to ensure that the study was enriched with patients at high risk of rapid progression. Again, we acknowledge that some patients aged over 50 years in UK practice may be considered eligible for treatment under the licensed indication. However these patients are highly likely to be a minority of the patients considered eligible in UK practice.

In totality, it can be reasonably assumed that the vast majority of patients likely to be considered eligible for tolvaptan treatment under the licensed indication would meet each of the age, TKV and renal function inclusion criteria for TEMPO 3:4. This conclusion can be regarded as strongly supportive of the study's generalizability to UK practice.

Low proportion of patients from UK

Whilst it is true that only a minority of patients randomised to TEMPO 3:4 were from the UK, this is not unusual in large, international clinical studies, and certainly not a reason in and of itself to question generalisability of the results to the UK. This would only be a genuine reason for concern if there is evidence of systematic confounders that could impact treatment effect across borders, such as significant differences in baseline demographics or local treatment patterns.

The included patients in TEMPO 3:4 were similar, in terms of ethnicity, as may be expected in UK practice:

- 84.3% Caucasian
- 1.3% Black
- 1.5% Hispanic
- 12.7% Asian
- 0.2% Other

Of the 1,445 patients enrolled, 690 (47.8%) were recruited into European sites including nine countries; UK enrolment was comparable to the overall European recruitment on a country by country basis. The pre-specified Europe/Rest of World subgroup in TEMPO 3:4 excluded patients from Americas and Japan, and this subgroup comprises 793 patients (n=527 tolvaptan; n=266 placebo) or approximately 55% of the full randomised population. Examination of the estimated tolvaptan treatment effect in this the Europe/ROW patient subgroup reveals that the relative reduction in the slope of renal function decline was 35.1%, as compared to 31.6% in the full trial population.

With the above points in mind, we can be confident that the treatment effect estimated for the full trial population is unlikely to be reduced in a UK-specific subgroup. On the contrary, based on the evidence above, it is more likely than not that this treatment effect would be increased rather than decreased.

It has also been shown that the rate of renal progression in ADPKD has not been meaningfully improved over several decades despite progress in symptom management (1)**.** This provides confidence that renal progression in ADPKD is highly unlikely to be impacted by local treatment patterns, leading us to the conclusion that lack of UK patients would not confound the generalisability of the study in this regard.

Overall, we find no evidence to support the ERG and Committee's conclusion regarding the generalisability of TEMPO 3:4 to UK practice and in light of the rationale provided above, we urge the ERG and Committee to reconsider their view on this issue.

Uncertainty regarding efficacy results from TEMPO 3:4

The Committee concluded that there were two potential issues (missing data and effect size) leading to uncertainty in the strength of the efficacy results from TEMPO 3:4. We would like to take the opportunity to reassure the ERG and Committee that the efficacy results from TEMPO 3:4 are robust in these respects.

Handling of missing data

Otsuka notes that in section 4.9 of the ACD the Committee was concerned about the effect of missing data possibly introducing uncertainty about the size of the treatment effect in real life. Otsuka believes that the missing data do not affect the conclusions of the TEMPO 3:4 study in any negative way, and that the following will help reinforce that the overall results and conclusions from the TEMPO 3:4 study still stand.

In the TEMPO 3:4 study, 80.1% of all subjects completed the study. It had been anticipated during the design of the trial that the overall data loss would be below 20%. At month 36, data was missing at a rate of 23.0% for tolvaptan and 13.8% for placebo (a difference of 9.2%). Some subjects in this group did elect to be followed up remotely, and this resulted in the subjects who withdrew completely being 15.8% in the tolvaptan group vs 9.9% in the placebo group.

To understand the possible impact of the missing data, two key analyses were performed on the efficacy data:

- First, it was assumed that for all patients who withdrew from the study, that there was 100% loss of efficacy of tolvaptan. This was called 'jump to placebo'.
- Second, the level of lost efficacy required was estimated before the statistical significance changed from significant to non-significant for the comparison. This was called the 'tipping point'

The results of these analyses are provided here:

Primary endpoint (TKV)

- The 'jump to placebo' approach (100% loss of efficacy) results in the efficacy for tolvaptan vs placebo to still be significant ($p<0.0001$)
- The tipping point analysis results in the p-value for the difference between tolvaptan and placebo only rising above 0.05 when 333% of the treatment effect at month 36 is subtracted from the data imputed for the tolvaptan subjects
- The reduction of treatment effect of 333% equates to a TKV growth at month 36 of 40.25%
    - This is over twice the observed placebo change of 18%
    - This is over four times the observed tolvaptan change of 9%
- Hence the primary endpoint results and conclusions from the overall TEMPO 3:4 study are still valid.

Key secondary composite endpoint

- The 'jump to placebo' approach results in the efficacy for tolvaptan vs placebo to still be significant ($p<0.0325$)
- The tipping point analysis results in the p-value for the difference between tolvaptan and placebo only rising above 0.05 when there is an assumed loss of 110% of the treatment effect
- If it is assumed that the time to the first composite event for the withdrawn tolvaptan patients followed the same Kaplan-Meier curve as seen for the time point to the first event seen in placebo patients, it is estimated that 50 events (23% of 221 withdrawn) may have been unobserved in the tolvaptan subjects and 8 events (12% of 67 withdrawn) may have been unobserved in the placebo subjects
    - Re-inserting these events in the analysis results in a significant p-value of 0.0410, and using the tipping point approach, it would have to be assumed

that 58 unobserved events would have to be assumed to have occurred in subject withdrawing from tolvaptan for the p-value to be above 0.05

- Therefore the key secondary composite endpoint results and conclusions from the overall TEMPO 3:4 study are still valid.

Secondary efficacy endpoint of eGFR

- The jump to placebo approach results in the efficacy for tolvaptan vs placebo to still be significant ($p<0.0001$)
- The tipping point analysis results in the p-value for the difference between tolvaptan and placebo only rising above 0.05 when there is an assumed loss of 267% of the treatment effect
    - A 267% reduction in treatment effect is equivalent to a reduction at 36 months of 16.19 mL/min/1.73m^2
    - This is an increase of over 60% of the observed placebo change of 10.41 mL/min/1.73m^2
- Therefore the results of the secondary efficacy endpoint of eGFR and the conclusions based on this in the overall TEMPO 3:4 study are still valid.

Based on the above analyses, Otsuka believes that that impact of missing data does not negatively affect the overall conclusions about the efficacy of tolvaptan in ADPKD made from the TEMPO 3:4 study.

Effect size in renal function decline.

We note the comment in section 4.6 of the ACD:

"*The Committee understood from the company representatives that rate of decline in renal function, as assessed by eGFR, was included as a secondary outcome, but that the trial was not powered to detect a statistically significant difference in this endpoint…"*

We have undertaken a *post-hoc* power calculation using the pre-specified analysis on eGFR slope using the CKD-EPI formula. The incremental difference in slope of renal function, based on CKD-EPI, was 0.977 (leading to the 26.4% relative treatment effect reported in our original submission), with analysis of variance of individual subject slope (6.1441) and variance of noise (30.9125). For a three year study with three equal spaced visits within each year, the sample size formula provided by Leffante (2) used. Since in this formula all subjects are assumed to have all visits, we instead used the number of subjects who had an actual month 36 eGFR observation (equal to 1,086) in this *post-hoc* power calculation. We maintain 2:1 randomization as per the original protocol.

Under these assumptions, with an alpha of 0.05, the 1,086 subjects would provide over 99% power to detect a difference of 0.977 in eGFR slope. Even with an alpha reduced to 0.01, which was used for the key secondary endpoint, the 1,086 subjects still provide 99% power to detect a difference of 0.977 in eGFR slope. This post-hoc power would be even higher when discontinued subjects were included in the analysis.

Accordingly, we are able to confidently rely on the power of the TEMPO 3:4 study to detect a statistically significant difference on eGFR.

In combination, the rational provided above on these two areas of concern should serve to reassure the ERG and Committee that the efficacy results from TEMPO 3:4 can be regarded as robust.

Measurement of TKV

In section 3.23 it is stated that:

"*The ERG also criticised the measurement of TKV by the ellipsoid method as potentially unreliable because in ADPKD the kidneys lose their predictable shape.*"

It is incorrect that the TEMPO 3:4 study measured TKV by the ellipsoid method. The TKV measurement used methodology adapted from that which was established in the National Institutes of Health Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) program. The ellipsoid equation was only applied in optional screening that took place prior to the trial commencing

Committee conclusion on hepatotoxicity

NICE has incorrectly accepted the view of the ERG in that all patients fulfilling Hy's law cases would have a liver transplant at year 1 and would die immediately afterwards. The manufacturer does not agree that this is the appropriate view to take.

The following points are discussed here:

- The theoretical risk of liver failure and transplantation in patients administered tolvaptan for ADPKD
- Real world data obtained from post-marketing experience in Japan
- The risk minimisation measures that are in place to reduce the likelihood of seeing Hy's law cases in real life when Jinarc is prescribed in the UK

The theoretical risk of liver failure and transplantation in patients administered tolvaptan for ADPKD

Drugs that cause serious liver injury tend to do so within the first year of treatment but also drugs capable of causing progressive hepatocellular liver injury generally do so with similar latency, causing elevations in serum ALT > 3 X ULN.

In the TEMPO 3:4 study, the incidence of new serum ALT elevations > 3 X ULN in the tolvaptan-treated arm was very low after 18 months and did not appear to be different from that observed in the placebo arm. Within TEMPO 3:4 and 4:4, during treatment with tolvaptan, three patients were identified fulfilling the laboratory criteria for Hy's law, so constituted the three Hy's Law cases. All three patients had resolution of their liver function abnormalities upon stopping treatment. In the TEMPO studies, no patients experienced liver failure, no patients required liver transplantation, and no patients died. Specifically for the Hy's law cases, all three patients had their liver function tests return to normal with no chronic liver injury reported following permanent discontinuation of tolvaptan. Subsequently a theoretical estimate of the risk of liver failure was calculated, and this assessment was performed by Professor Paul Watkins on behalf of Otsuka (Professor of Medicine, Pharmacy, and Public Health University of North Carolina - Chapel Hill Director, Hamner-UNC Institute for Drug Safety Sciences).

This estimation was based on the events seen in the studies, observations from registries and duration of exposure. There are three large registries of drug induced liver injury (DILI) and these indicate that 10% of patients with hepatocellular jaundice due to a drug (which fulfil Hy's law criteria) will develop liver failure (3). In order to calculate the risk of liver failure, the appropriate denominator for the calculation risk would be the number of patients treated during the time of greatest susceptibility.

It is difficult to precisely quantify the hepatic safety risk posed by tolvaptan for an individual ADPKD patient. In TEMPO 3:4, the incidence of de novo serum ALT elevations > 3 × ULN in tolvaptan treated subjects was no higher than those observed in the placebo arm after 18 months of treatment. Nevertheless, since it has been estimated that approximately 10% of patients with hepatocellular jaundice due to a drug may develop liver failure, an estimate of the risk of potential liver failure in ADPKD patients on tolvaptan is 3/838 × 0.10, or about 1:3000 patients (n=838 is the number of subjects in the clinical trials who were treated with tolvaptan for at least 18 months). This incidence was accepted by the FDA in their safety review of tolvaptan for use in ADPKD.

Following a recommendation from the TEMPO Steering Committee to increase the frequency of monitoring to monthly, no additional Hy's Law cases have been identified to date (n=1275 subjects exposed for ≥18 months) further lowering the incidence of potential liver failure to approximately 1:4000(4). It should be noted that liver biochemistry monitoring was relatively infrequent in TEMPO 3:4 and its open-label extension. More frequent monitoring in real world use is expected to further lower the risk of liver failure. In some cases, liver injury did progress for weeks after stopping drug treatment, followed by slow resolution, and it seems unlikely that the risk of serious liver injury could be eliminated solely by more frequent monitoring. While no additional Hy's law cases have been identified since implementation of a comprehensive monitoring program consisting of monthly liver enzyme testing went into effect, Otsuka recognises that the number of additional patients treated may not have sufficient power to eliminate the possibility of another Hy's case from occurring.

The assumption that all Hy's law cases would require a liver transplantation is not an appropriate one to make. A recent publication by Bernal and Wendon in the Lancet reviewed acute liver failure and provides useful information to assist in this assessment. Of cases with acute liver failure, less than 10% received liver transplants. However the authors go on to discuss data from the European Liver Transplant Registry from 2012 which lists 1-year post–transplant survival at 79% and 5-year survival at 72%. Deaths when they did occur were mostly due to infections, and these tended to occur in the first three months following the transplant.

Real world data obtained from post-marketing experience in Japan

Otsuka has some limited data from Japan on the post-marketing experience in patients prescribed tolvaptan for ADPKD. Since tolvaptan was made available for ADPKD in March 2014 and until the end of May 2015, over 680 ADPKD patients had received tolvaptan for this use.

Within this, 28 hepatic disorder SMQ adverse events were spontaneously reported, of which 12 were considered serious. Whilst acknowledging the difficulties in interpreting such post-marketing spontaneous adverse events, this is comparable to the clinical trial experience in TEMPO 3:4. In addition, monthly monitoring (similar to what will be done in Europe) enabled early detection of these liver enzyme elevations and subsequent interruption or discontinuation of treatment to prevent irreversible liver injury. In addition, there have been no confirmed Hy's Law cases in post-marketing surveillance of tolvaptan in ADPKD in Japan.

UK Risk Minimisation Plan for Jinarc use in patients with ADPKD

The risk minimisation plan for Jinarc, which has been agreed with the MHRA, will help ensure that abnormal liver function tests, when seen, are managed appropriately so that the risk of seeing Hy's law cases would be greatly reduced, and so that the theoretical risk of liver failure is reduced further.

All patients commenced on Jinarc will have a pre-treatment liver function tests (LFTs) measured and then LFT monitoring will continue on a monthly basis for the first 18 months of treatment. After this, LFT monitoring will be performed every three months. If abnormalities are seen, as per the SmPC, clinicians are given specific direction on whether Jinarc should be permanently discontinued or temporarily discontinued. Clinicians are also provided advice on how to monitor further.

In summarising the above:

- The risk of Hy's law occurrences as observed in the TEMPO studies will be minimised with a clear and practical risk management plan
- Where Hy's law cases did occur in TEMPO 3:4, no subsequent liver failure events were recorded
- Furthermore, the theoretical risk of death associated with any liver failure and liver transplant event has clearly been overestimated by the ERG

In conclusion, based on the above, the manufacturer does not agree with NICE and the ERG that it is appropriate to make an assumption that all Hy's law cases, if seen, would require a liver transplant at one year, and would die immediately afterwards. Therefore, Otsuka does not include these events in our revised base case.

Cost-effectiveness

Uncertainty regarding the role of TKV and application of treatment effect

We note the Committee's assertion in section 4.9 of the ACD:

"*The Committee did not agree with using regression equations for modelling the disease progression in the standard care arm and then using direct data from the clinical trial to model the treatment effect of tolvaptan, and therefore concluded it would have been preferable if the economic analyses considered only the eGFR results of the trial. The Committee further concluded that modelling eGFR using TKV as a surrogate endpoint introduced the potential for bias and therefore increased the uncertainty in the results of the model*."

We disagree strongly with the Committee's conclusion in this regard and would like to take the opportunity to re-emphasise why, in our view, it is: a) optimal to model underlying ADPKD progression according to the relationship between TKV and GFR, rather than by GFR alone; and b) most appropriate to apply the treatment effect of tolvaptan directly to underlying GFR decline.

Role of TKV in ADPKD progression

It is important to be clear the model on which our economic evaluation was based ("ADPKD Outcomes Model" (5) (6) (7)) was co-developed by Otsuka Europe with several European ADPKD clinical experts, as a disease model, and in response to a genuine area of clinical uncertainty. That is, ADPKD is a heterogeneous condition, with no universal consensus within the clinical community on how best to predict and measure ADPKD progression.

Our economic evaluation utilises an adaptation of the disease model which enables cost-effectiveness analysis to be conducted.

In developing the disease model it was clearly determined that constructing the model without ADPKD-specific features and/or prognostic indicators would fail to represent the full course of ADPKD. Based on the weight of published evidence, clinical expert opinion and the data available to inform the model, TKV clearly emerged as the most appropriate ADPKD-specific feature to incorporate, both as a measure of renal progression and key prognostic indicator. The rationale is well described in our original submission, but summarised below:

- ADPKD typically progresses significantly in terms of renal size prior to the decline in renal function (8, 9)
- TKV is a strong predictor of the rate of future renal decline (10)
- TKV growth is strongly correlated with renal function decline over the long term (11)
- TKV growth is linked to incidence of ADPKD complications, such as pain (12)

Once developed, the disease model underwent extensive validation against the best available external data sources, also described in our original submission.

As such, we believe it would be inappropriate to modify/simplify a robustly developed and validated disease model for the purposes of constructing an economic evaluation. On the contrary, it is our firm belief that using TKV as a prognostic indicator and surrogate outcome is the best available method for modelling underlying ADPKD progression, being in concert with the latest evidence and current clinical expert opinion. We find no justification for the Committee's assertion that this approach introduces bias; the use of such surrogate markers generally in disease models is commonplace, and is well justified in this particular instance

Application of treatment effect directly to GFR

As noted above, the disease model was not developed with the (disease-modifying) effect of a potential treatment intervention as the primary objective. The model was constructed on the principle of a well-established correlation between TKV and GFR in natural ADPKD progression. The hypothesis that this correlation between TKV and GFR remains identical in patients exposed to tolvaptan (a disease-modifying intervention) has not been tested, and would require understanding of the complex biological pathways of ADPKD and mechanisms of tolvaptan effect.

Indeed, examination of the data from TEMPO 3:4 would seem to indicate that the relationship between the effect of tolvaptan on TKV growth relative to that on renal function is not straightforward. This would indicate that using the natural history correlation between TKV and GFR to impute the effect of tolvaptan on renal function indirectly from TKV is likely to introduce unnecessary uncertainty and bias. This methodology would also ignore the specific direct evidence from TEMPO 3:4 on the effect of tolvaptan on renal function decline.

As such, and assuming that underlying ADPKD progression has been accurately modelled, the most appropriate (and unbiased) approach is to apply the treatment effect of tolvaptan on renal function directly.

In summary:

- Otsuka have developed and extensively validated a naturalistic ADPKD disease model, in which the well-established correlation between TKV and GFR is integral to accurately predicting disease progression
- The economic evaluation utilises an adaptation of the disease model which enables cost-effectiveness analysis to be conducted
- Applying an effect of tolvaptan on renal function indirectly from TKV is likely to introduce unnecessary uncertainty and bias
- Applying treatment effect of tolvaptan directly on renal function is the most appropriate approach in line with the evidence from the TEMPO 3:4 study

In light of these points, we would urge the ERG and Committee to reconsider their view on the appropriateness of our approach to modelling ADPKD progression and our efforts to minimise bias/uncertainty.

Uncertainty regarding EQ-5D data from OVERTURE.

We would like to take the opportunity to clarify the issue raised in section 4.12 of the ACD. It is stated that:

"*However the Committee was aware that one of the trials for tolvaptan, the OVERTURE trial (see section 3.2), had collected EQ-5D data. The Committee questioned the company on whether these data had been available for use in the economic model. It heard from the company that these data had not been made available for the submission and that only interim data were available. The Committee did not agree that ADPKD-specific HRQoL data should be disregarded because they are only available from an interim analysis and highlighted that the company could have used interim results for modelling HRQoL. The Committee concluded that it would have preferred to see ADPKD-specific health-state utility values used in the model and consequently, the results using the Gorodetskaya utility values were associated with a considerable degree of uncertainty*."

We can confirm that analysis of EQ-5D data collected in OVERTURE, interim or otherwise, have not yet been completed. We can reassure the Committee that no ADPKD-specific HRQoL have been disregarded in our economic analysis.

Uncertainty regarding utility data applied to model.

The Committee states in section 4.16 that the ERG preferred base case and worst case scenario do not account for uncertainty in the utility values. It should be noted that the utility values were:

- Identified from a systematic review.
- Selected due to studies by Miskulin *et al*. (13), Suwabe *et al*. (14), Ying and Krishnan (15), and Yusop *et al*. (16) finding that the quality of life (SF-36) of ADPKD and chronic kidney disease (CKD) patients were similar
- Assessed for face validity at an advisory board with nephrologists and health economists
- Assessed in sensitivity analysis
- Incorporated into the model stochastically to account for parameter uncertainty

We believe that the uncertainty in utility values has been addressed thoroughly in the submission.

Preferred base case modelling parameters.

The ERG identified six issues in in their preferred base case and an additional five in their exploratory worst case scenario analysis that differ to the Otsuka base case; see Table 1 below. The merits of the parameters are assessed below.

Table 1: NICE/ERG Preferred base case modelling parameters

ERG preferred case	ERG exploratory scenario
1. Correct model code	Correct model code
2. Disutility of HD & PD complications	CKD-EPI
3. Equal CKD 3 & CKD 4 costs	7.Pre-ESRD Increased mortality
4. CKD-EPI	8. Treatment discontinuation (6.5%)
5. Disutility of tolvaptan	9. Increased monitoring costs
6.Equal kidney pain	10. Decreased post-transplant costs
	11. HY's Law
ERG ICER = £64,500	ERG ICER = £72,700

Note: CKD = Chronic Kidney Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, ERG = Evidence review group, HD = haemodialysis, ICER = incremental cost-effectiveness ratio, PD = peritoneal dialysis.

Otsuka accept that there was a coding error, which disadvantaged tolvaptan, and that the disutility value for complications of haemodialysis and peritoneal dialysis should be 0.02. Dealing with each of the remaining issues in turn:

CKD-EPI rather than the reciprocal of serum creatinine.

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). Indeed, this view was reinforced by ADPKD clinical experts during the 1st Appraisal Meeting, who noted that there was not a clear cut correct measure for assessing change in renal function, although in UK practice CKD-EPI was frequently used for 'spot' measurements in the clinic.

It should also 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 preference can be regarded as conservative.

With that said we recognise that a choice is required and that CKD-EPI is named as the preferred GFR estimate 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.

Treatment discontinuation.

We welcome the Committee's acknowledgement that the ERG's exploratory assumption that an increase in discontinuation rate from 2.9% in year three to 6.9% in subsequent years is an overestimation, and that a continuation of a rate of 2.9% would be more plausible. Recently available data from the TEMPO 4:4 extension study on the long-term

discontinuation of patients receiving tolvaptan (> 3 years) suggests that annual discontinuation is estimated to be approximately 2.7%. As such the long-term rate of 2.9% will be applied in our revised base case.

Increased mortality.

In section 3.31 it is stated that the ERG account for ADPKD-specific mortality, prior to ESRD, by assuming a hazard ratio (HR) of 2.0. As was noted in the Otsuka response to the ERG clarification questions (question c10) there is a paucity of evidence on this topic. Of the eight papers (17-24) only one had hazard ratios for ADPKD patients, Florinj et al. (18). This paper was rejected on the grounds that it, amongst other things, failed to account for medical developments such as dialysis and renal transplants, and includes ESRD patients. It is important to note that the hazard ratio estimated by Florinj (18) was 1.6 (1.3 to 2.0) confirming that the ERG's estimate of 2.0 is far too conservative. As a compromise, we apply a hazard of 1.6 in our revised base case even though we regard this value as too high.

Equal cost for CKD stage 3 and 4.

In section 3.32 it is noted that the ERG did not agree with CKD 3 costs being an adjustment of CKD 4 cost using a medical record abstraction study (25, 26) on the grounds that the study may not be fully representative of the population in the UK. Whilst the study is based on a convenience sample the findings confirm clinical opinion that resource use and costs increase as renal function declines e.g. moving from CKD 3 to CKD 4. It should be noted that the finding of CKD 4 patients having greater resource use and costs than CKD 4 patients was also found in France and Spain.

As such, we disagree that this adjustment to the model is appropriate. Nevertheless, in our revised base case we have applied the adjustment given its low impact on the overall results.

Post-transplant costs.

The ERG suspect that including post-transplant maintenance costs in addition to background ADPKD management costs <u>may</u> lead to double counting. It should be noted that the ERG did not feel it was appropriate to include this potential for some double counting assumption in their preferred base case. Following kidney transplant, ADPKD patients remain at risk of ADPKD-specific complications requiring background treatment. Such issues may include cysts in the unremoved native kidney(s), requirement for subsequent nephrectomy of the native kidney(s), liver cysts related complications, diverticulitis and/ or colonic perforation, new-onset diabetes, intracranial aneurysms and cardiac events (27).

Nevertheless, in our revised base case we have applied the adjustment given its low impact on the overall results.

Relative effect of ADPKD complications and tolvaptan adverse effects on HRQoL.

We note with concern the Committee's conclusion in section 4.13 of the ACD:

"*The Committee concluded that it was appropriate to include a utility decrement for tolvaptan treatment and in the absence of any further evidence to suggest a different utility decrement, accepted the rate that had been used within the exploratory analyses performed by both the company and the ERG*."

Further we note with concern the Committee's related conclusion in section 4.14 of the ACD:

"The Committee was aware that the effect of this exploratory analysis [equalising the risk of significant kidney pain] by the ERG was very small, and recognising some of the uncertainty in this variable, it accepted the ERG's approach as conservative."
The Committee's conclusions on these issues are intrinsically linked given that they both directly relate to the relative impact of tolvaptan on patient HRQoL whilst the patient is on treatment. It is our firm view that the Committee has misinterpreted the intention of our scenario analysis on treatment disutility (included in our original submission) and the ERG's exploratory analyses on treatment disutility and kidney pain. The sum total of the Committee's position on these two issues leads to the conclusion that tolvaptan significantly reduces HRQoL for all treated patients for as long as they remain on treatment. This represents a disproportionate bias against tolvaptan that is contradictory to the available evidence.

Within the economic model, patient HRQoL can be materially impacted (during the potential treatment period prior to ESRD) by the following three factors directly related to tolvaptan treatment:

- Discontinuation from tolvaptan treatment due to AEs
- Significant kidney pain event
- Disutility associated with tolvaptan AEs

Dealing with each of these factors in turn:

Discontinuation from tolvaptan treatment due to AEs

In their assessment of the relative impact of tolvaptan treatment on HRQoL, the ERG and Committee have not accounted for the impact of discontinuation from tolvaptan treatment due to AEs. As clearly outlined in our original submission, evidence from TEMPO 3:4 robustly demonstrates that those patients unable to tolerate the aquaretic side effects of tolvaptan tended to discontinue treatment within 3-6 months of initiation.

In our economic model, we have incorporated the absolute patient discontinuation rates (due to any reason) observed in TEMPO 3:4 (15.3% in year 1, 6.5% in year 2 and 2.9% in year 3 onwards in our revised base case). Patients discontinuing treatment receive no further incremental treatment benefit and are returned to the placebo disease progression trajectory from the start of the cycle in which discontinuation occurs.

In this way, the vast majority of patients for whom aquaresis will be sufficiently problematic to significantly impact their HRQoL are removed from treatment, leading to poorer outcomes in the long-term. These patients are included in the tolvaptan group on an ITT basis, which we regard as appropriate. Nevertheless, it is a fact that this approach significantly reduces the overall HRQoL of the tolvaptan group, and therefore must be accounted for in any consideration of the net effect of tolvaptan on patient HRQoL.

Significant kidney pain events.

As noted in section 4.14 of the ACD:

"Regarding the probability of kidney pain, the Committee noted comments from clinical experts that kidney pain is not necessarily reflective of CKD stage and that reduction in pain could be seen as an effect of the drug because of the reduction in kidney size."

It is therefore concerning that the Committee has not recognised the clinical validity of this assumption in favour of a conservative assumption that has no evidence to support it. 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. This is supported by the results of TEMPO 3:4 and is biologically plausible, as per the expert opinion quoted above.

This assumption (equal risk of significant kidney pain) contradicts the findings of the TEMPO 3:4 trial (28), where tolvaptan was shown to reduce the risk of clinically significant kidney pain by 29% (absolute reduction: 2 events per 100 person-years) compared with placebo (5 events per 100 person-years vs 7 events per 100 person-years; HR 0.64; 95% CI: 0.47, 0.89; p=0.007) (28).

That this variable has a small impact on the ICER is irrelevant; it could be equally included or excluded by the same rationale. We would strongly oppose the removal, on non-clinical grounds, of this important patient benefit of tolvaptan treatment by the ERG and Committee. We urge the ERG and Committee to reconsider their view on this variable.

Disutility associated with tolvaptan AEs

It is important to be clear at the outset that there exists no evidence to suggest that tolvaptan treatment leads to significant and long-term reductions in patient HRQoL due to adverse effects. In our original submission we recognised that the Committee may have concerns regarding the explicit non-inclusion of tolvaptan adverse effects in our economic model. Accordingly, the functionality to apply a disutility of tolvaptan treatment was incorporated into the model, and as a responsible step, we included an exploratory scenario analysis utilising this functionality in order to demonstrate the potential sensitivity impact of cost-effectiveness. The disutility value applied was extreme, and in no way do we regard it as a true effect.

This scenario analysis was repeated by the ERG, again as exploratory, in their report. We were therefore surprised to note that the Committee had accepted this this exploratory scenario analysis as appropriate when it has no basis in evidence.

The inclusion of this exploratory scenario, being significant and long-term, has a disproportionately negative impact on the HRQoL of tolvaptan patients (see below). We acknowledge that there may be a minority of patients who persist with tolvaptan treatment in the face of side effects that significantly impact their HRQoL. However we do not accept the assertion that this is true of all patients and for as long as they remain on treatment.

Testimony from patient and clinical experts (as noted in the ACD, section 4.2) clearly outlines their perspective in this regard:

"*The patient experts stated that, given the lack of active treatments for ADPKD to date, the availability of tolvaptan gives patients hope, not just for themselves but also for future generations. The clinical experts stated that this is the first treatment to target the disease rather than manage complications. The Committee noted that the main adverse reaction of tolvaptan is extreme thirst, which significantly affects daily lifestyle, but the patient experts explained how it is possible to adapt to the need to drink a significantly increased volume of water and that it is important to give the body time to adjust to this change. In the patient experts' experience, taking the later dose sufficiently early before going to bed limits the impact on the quality of sleep. The Committee understood from the patients that on balance the advantages of tolvaptan and the hope that it brings in terms of slowing disease progression outweigh the disadvantages.*"

With this testimony in mind it is clear that the impact of tolvaptan-related aquaresis on patient HRQoL for those who persist on treatment will be, at very worst, variable according to individual adaptability and, at best, a manageable, transitory impact.

In addition, any potential negative impact of tolvaptan on patient HRQoL due to adverse effects must be balanced against the potential positive impact of tolvaptan on patient HRQoL due to reduction in ADPKD complications. Data from TEMPO 3:4 in our original submission clearly illustrates that rates of adverse events were well balanced between the tolvaptan and placebo groups, with tolvaptan patients experiencing more events related to aquaresis, and placebo patients experiencing more events due to ADPKD complications.

In TEMPO 3:4, 78% of tolvaptan-treated subjects reported an aquaretic AE and, although common, only accounted for 9% of discontinuations. Those who discontinued due to aquaretic AEs were younger, had better renal function, and higher baseline urine osmolality suggesting that aquaretic AEs are most prevalent and most disturbing to subjects in early stages of disease(29). The impact of this effect would appear to be self-correcting since subjects typically discontinued quickly (median time to discontinuation, 92 days(29)).

The benefits of tolvaptan treatment appear to at least balance aquaretic AEs for those who persist on treatment. In a *post-hoc* analysis of TEMPO 3:4 data by CKD stage(30), time to composite ADPKD-related events favoured tolvaptan [HR (95% CI), 0.83(0.70-0.98), $p<0.05$]. Disease related outcomes begin to manifest within the second and third decade of life, long before measurable declines in renal function occur. In TEMPO 3:4, tolvaptan significantly reduced the number of hospitalisations due to renal complications and renal pain, [HR (95% CI): 0.403 (0.238-0.677), p=0.0004; 0.232 (0.092-0.542), p=0.0004), respectively] which supports tolvaptan's early benefits on ADPKD-related complications(31).

Taking all these points into account, the evidence-based conclusion is that the net impact on patient HRQoL of tolvaptan AEs, relative to reduction in ADPKD complications, is no worse than neutral. In our revised base case we suggest a new value for tolvaptan treatment disutility which is in line with this conclusion. We urge the ERG and Committee to reconsider their view on this variable.

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 2 : 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.

Hy's law cases

Please see above for the clinical discussion of the appropriateness of modelling Hy's law. 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 (32), assuming 3 per 958 Hy's Law patients would experience liver injury, the figure should be approximately 1 per 3000 (3 Hy's Law ÷ 958 X 10% ≈ 1/3000) (32). As a result the numbers of liver failure patients have been over estimated by approximately a factor of nine.

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% (33).

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.

We do not believe it is appropriate to model Hy's law cases in the revised base case.

Monitoring costs

In section 3.38 the ACD outlines how the ERG modelled additional monitoring costs.

a) Patients with serum alanine aminotransferase higher than three (4.4%) received double the LFT monitoring of other patients for the duration of the model (up to 60 years).
b) All patients on tolvaptan received an additional consultant visit due to possible adverse events from year three until death or discontinuation.

In response to the inclusion of these additional costs, we have the following observations:

a) Both TEMPO 3:4 and TEMPO 4:4 (34) data show (see Figure 1) that the risk of alanine aminotransferase (ALT) elevation is not different to placebo after the first 18 months. Accordingly, doubling the monitoring frequency for patients with raised ALTs is plausible for the first 24 months following initiation (and is included in the revised base case); however there is no evidence to support double frequency of monitoring for the remainder of the model time horizon.

b) Otsuka disagrees 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 (28) 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]). Assuming no additional consultant visits for tolvaptan patients in the Otsuka base case was a conservative approach given that placebo patients have 2.15% more SAEs. It is not appropriate to include the ERG assumption of additional consultant visits for SAEs in the most plausible ICER.

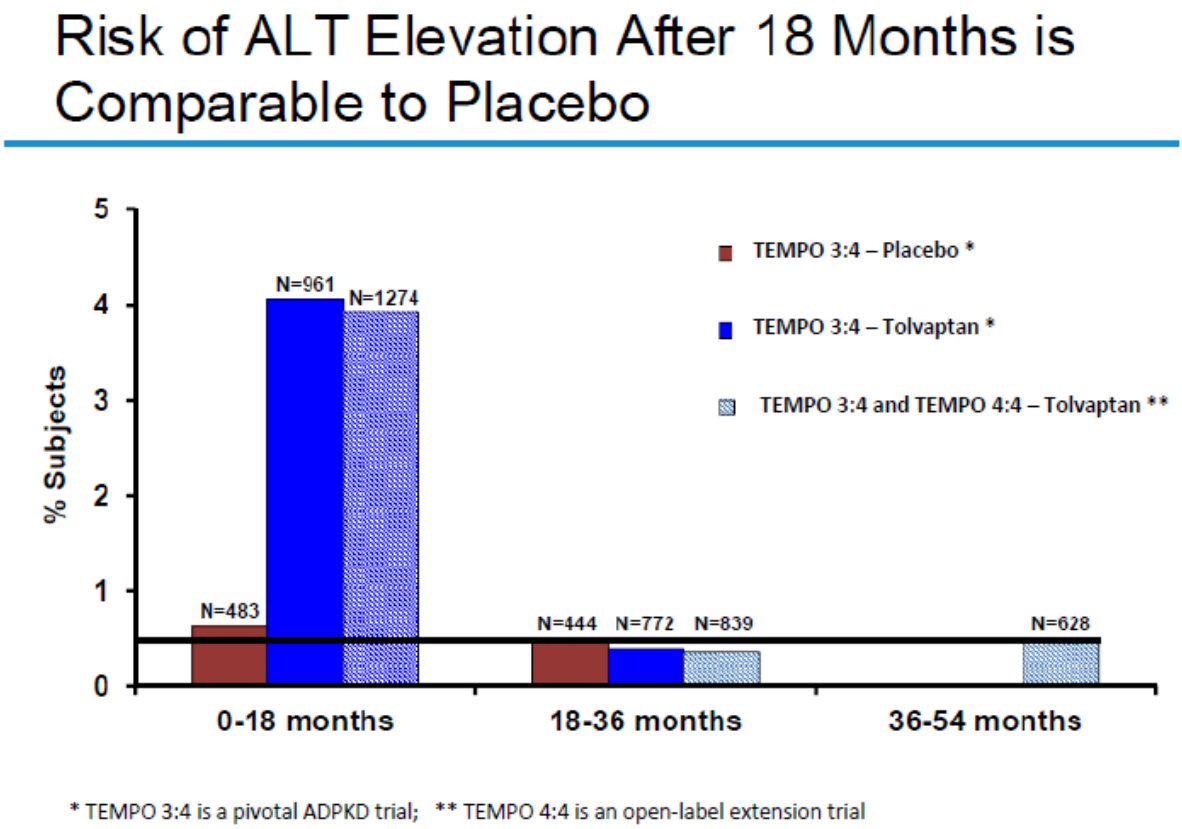

Figure 1: Risk of ALT elevation after 18 months is comparable to placebo (Adapted from Otsuka 2013)

Most plausible ICER

We were very surprised that, in section 4.15 the committee states that the ERG's worst case scenario analysis was plausible and should be considered when deciding on the most plausible ICER for tolvaptan. Otsuka firmly believes that this is inappropriate and the most plausible scenario should not comprise of extreme assumptions.

On the balance of the evidence presented by the ERG, the discussion at the NICE appraisal meeting on 1st April 2015, the challenges outlined in the ACD and Otsuka's own beliefs (as set out above), we are of the opinion that a base case incorporating the following factors is an appropriate compromise to arrive at the most plausible ICER:

- Corrected model code error
- Applying a disutility value of 0.02 for dialysis complications
- Differential risk of kidney pain
- Treatment disutility due to tolvaptan AEs of 0.0025
- A treatment discontinuation rate of 2.9% after 3 years

- Equal CKD 3 & CKD 4 costs
- Measurement of eGFR using the CKD-EPI equation
- Increased mortality with a hazard ratio of 1.6
- Increased monitoring costs for the first two years of treatment for elevated ALTs
- Decreased post-transplant costs

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. The provisional recommendations are not a suitable basis for guidance to the NHS. We disagree with some assumptions underlying the most plausible base case which are overly cautious, conservative or negative and do not reflect the true nature of the benefits of tolvaptan to patients and the NHS. In light of the ACD, Otsuka is providing new evidence and a revised cost-effectiveness analysis which we believe will result in tolvaptan being considered a cost-effective use of NHS resources and being recommended for use in suitable ADPKD patients. Tolvaptan is an innovative, “first of its kind” treatment that has been shown to significantly delay the progression of ADPKD

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