NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tolvaptan for treating autosomal dominant polycystic kidney disease

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Otsuka	***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	Comments noted. Section 4.6 of the FAD has been amended to state '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, but overall it was satisfied that TEMPO 3:4 was relevant to UK clinical practice.'

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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.	
Otsuka	***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	Comments noted. The Committee was satisfied with the handling of missing data therefore this has been removed as a consideration in the FAD.

Consultee	Comment [sic]	Response

	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	

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	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.	

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Otsuka	***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	Comment noted. The Committee was satisfied that the trial was likely adequately powered therefore this consideration has been removed from the FAD.

Consultee	Comment [sic]	Response
	should serve to reassure the ERG and Committee that the efficacy results from TEMPO 3:4 can be regarded as robust.	
Otsuka	***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	Comment noted. The FAD has been amended by removing the statement quoted by the company.
Otsuka	***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	Comment noted. The Committee understood hepatotoxicity issues can be avoided through increased monitoring, that there had been no cases of Hy's law since the frequency of monitoring had been increased, that liver biochemistry monitoring was relatively infrequent in the TEMPO studies, and that more frequent monitoring would be expected in real world use which would further lower the risk of liver failure. The Committee concluded that Hy's law cases were not included in the Committee's preferred modelled assumptions. Please see FAD section 4.15

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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–	

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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.	

Consultee	Comment [sic]	Response
Otsuka	***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.	Comment noted. The company's revised base case in the additional evidence submission used a different method of modelling disease progression (CKD-EPI) which has been discussed in section 3.47 of the FAD. The comments are therefore no longer relevant to Committee's consideration of the revised base case.
Otsuka	*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	Comment noted. The company's revised base case in the additional evidence submission used a different method of modelling disease progression (CKD-EPI) which has been discussed in section 3.47 of the FAD. The comments are therefore no longer relevant to Committee's consideration of the revised base case.

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	and our efforts to minimise bias/uncertainty.	
Otsuka	***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	Comments noted. Section 4.16 of the FAD states: "in a late submission that the ERG did not have the opportunity to critique, the company presented an analysis using EQ-5D data from patients with ADPKD from the OVERTURE trial" … "The Committee concluded that although the analyses presented had not yet been critiqued by the ERG, they provided confidence that the ADPKD-specific EQ-5D data from OVERTURE were unlikely to significantly alter the outcome of the revised base case analysis".

Consultee	Comment [sic]	Response
	We believe that the uncertainty in utility values has been addressed thoroughly in the submission.	
Otsuka	***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	Comments noted. The company's revised base case was in agreement with the ERG's revised case for the issues relating to the use of CKD-EPI for measuring disease progression, the preferred discontinuation rate (of 2.9%) after year 3 in the model, and the hazard ratio of 1.6 for mortality. The Committee considered each of the issues highlighted by the company in its revised base case in its additional evidence submission. Section 4.12 of the FAD states: "The Committee understood that there were several differences in the assumptions adopted by the company in its additional evidence submission compared with those preferred by the ERG in its critique of the company's additional evidence". The issues regarding the treatment-related utility decrement for tolvaptan are discussed in section 4.13 of the FAD. The issue regarding the probability of kidney pain for tolvaptan and placebo is discussed in section 4.14 of the FAD. The issue regarding Hy's law events is discussed in section 4.15 of the FAD.

Consultee	Comment [sic]	Response
	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 [redacted]. 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,	

Consultee	Comment [sic]	Response
	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-	

Consultee	Comment [sic]	Response
	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 <u>all</u> 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	

Consultee	Comment [sic]	Response
	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.*	

Consultee	Comment [sic]	Response
	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	

Consultee	Comment [sic]	Response
	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.	

Consultee	Comment [sic]	Response
	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*	

Consultee	Comment [sic]	Response
	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**

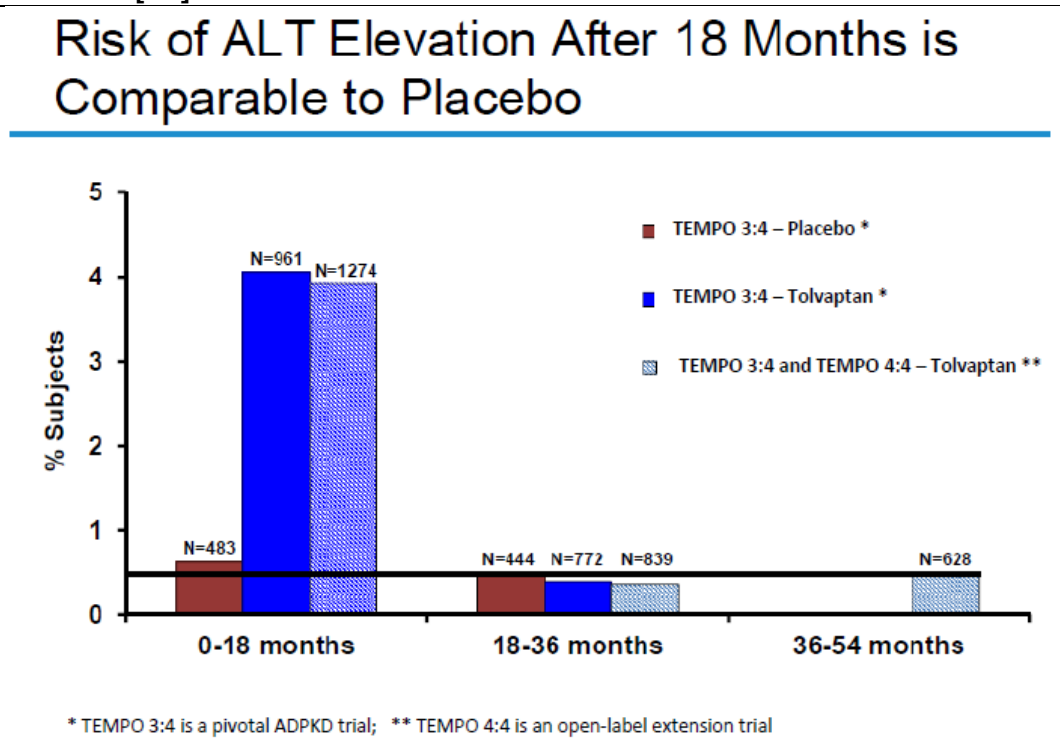
*Annual rates of discontinuation for reasons excluding AEs, are always included and were derived from data from TEMPO 3:4 as follows: 2.19 (±0.47)% in year 1, 4.30 (±0.717)% in year 2 and 2.23 (±0.54)% in year 3.

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.

Consultee	Comment [sic]	Response
	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.	
Otsuka	***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.	Comment noted. The Committee understood hepatotoxicity issues can be avoided through increased monitoring, that there had been no cases of Hy's law since the frequency of monitoring had been increased, that liver biochemistry monitoring was relatively infrequent in the TEMPO studies, and that more frequent monitoring would be expected in real world use which would further lower the risk of liver failure. The Committee concluded that Hy's law cases were not included in the Committee's preferred modelled assumptions. Please see FAD section 4.15.
Otsuka	***Monitoring costs*** In section 3.38 the ACD outlines how the ERG modelled additional monitoring costs.	Comment noted. Section 3.52 of the FAD states: "The ERG further noted that the company had agreed

Consultee	Comment [sic]	Response
	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.	with the increased monitoring costs applied except for the additional monitoring costs after the second year. The ERG commented that given the serum ALT elevation after 18 months for patients having tolvaptan compared with placebo, it was likely that the scenario proposed by the company was more plausible than the increased monitoring costs scenario proposed by the ERG in its exploratory analysis." Since both the company's revised base case, and that of the ERG were in agreement with the appropriate monitoring costs to include in the model, this was no longer an issue considered by the Committee.

Consultee	Comment [sic]	Response
	 **Figure 1: Risk of ALT elevation after 18 months is comparable to placebo (Adapted from Otsuka 2013)**	
Otsuka	***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.	Comment noted. Section 4.18 of the FAD states: "Committee therefore considered the most plausible ICER was likely to be most closely represented by that reflected in company base case of approximately £23,500 per QALY gained."

Consultee	Comment [sic]	Response
	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	
Otsuka	**1. 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	Comment noted.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Simone Goren – patient expert, nominated by PKD Charity	I would like to express my deep disappointment at the NICE committee's decision not to recommend Tolvaptan (JINARC). This has caused myself and my family deep distress. As this was the only treatment currently available for treating the incurable, genetic disease ADPKD. Whilst I understand the decision was a complex one when looking at the economic model. What I would like you to keep in mind is the human aspect to this decision. Having watched my father's health deteriorate as a result of this awful disease. Then watch him go through kidney transplant and all that entails both prior to the operation and seeing the ongoing struggles he faces. (Which included my mother having to donate her own kidney to allow him to have some quality of life). The alternative of taking medication which causes increased thirst seems an easy decision. Were it not for the fact that I am fortunate enough to be on the drug trial for Tolvaptan, then in reality I would be faced with my own health seriously declining within the next 10 years This would have not only a large impact on my own life, and family life, but also mine and my families' financial future. I am one of the lucky ones, I have been on this medication for the past 5 years and I believe as a direct result of this my kidney function and creatine has remained stable. Although I cannot know what it would have been without it I am sure my health would have been adversely affected. As far as I am aware there is no evidence to support the ERG's comment that "increased fluid intake …. May have an impact on decline in renal function'. Additionally I am confident that, the amount of fluid that we drink each and every day could not be replicated by someone not on this medication. For us drink is a necessity and much as someone would want to drink such large quantities I feel it would be impossible to sustain. We feel an undeniable thirst which must be quenched regardless of where or what else is happening. It wakes us in the night and means that we always have water	Comment noted.

Nominating organisation	Comment [sic]	Response
	available to us where ever we are. We will get off trains to get a drink, have to pull over to buy extra water if stuck in traffic even if this means we will be late for or miss meetings in order to quench our thirst. We panic if our water bottle goes missing or gets taken away at airports. I do not accept that someone would be able to tolerate this level of fluid intake without being on the drug. I believe I was on the placebo for the first two years of the trial and much as I wanted to drink a great deal I never drank more than 3-4 litres a day. Whereas now on the active drug I drink between 6-8 litres every day wherever and whatever I am doing. As a result of your decision, other members of my family and the wider ADPKD community do not have the option to receive this potentially life changing drug. The future of my children and their children seems to be very uncertain, with no other possible treatments in the pipeline. Whilst I accept that JINARC/Tolvaptan is far from perfect, I truly believe it is an excellent option for ADPKD patients and urge you to reconsider your decision.	
Theresa Williams– patient expert, nominated by PKD Charity	On 28th May 2015, the PKD charity sent out an alert to everyone connected with the charity that the European Medicines Agency had finally agreed to license Tolvaptan in Europe. It has been such a long time coming – the ONLY drug ever created with the capacity to safely slow down cyst development in PKD patients. We patients and our families were ecstatic. At 5pm on 28th May, 2015 as a patient expert at the 1 April 2015 Tolvaptan Appraisal Hearing, I received notification from NICE that they would NOT be approving Tolvaptan for NHS use – at least that was the recommendation of the preliminary Committee hearing. Euphoria turned to utter devastation. I honestly can't put into words the despair I felt when I read the judgement. Hope was ignited and extinguished in less than 8 hours - so near after all those years but yet so far. The following week, bound by the confidentiality clause I had signed for NICE, was the second longest week of my life. (The first was the week it took for my mother, skeletal like an Auschwitz inmate, to die from a failing kidney - slipping into a coma on 3 June 2000 aged 59, progressing to her	Comment noted.

Nominating organisation	Comment [sic]	Response
	death 7 days later with myself and my dad doing the palliative care at home – nothing prepares you for a body shutting down forever). My friends were congratulating me on reading the news that was being shared on Facebook and in which I had been tagged. Tolvaptan had been licensed so surely I was very happy given I trialled the drug and was so positive about the whole experience of being on it. (Everyone at work knows about my trial – I am the water bottle lady) Outwardly I was smiling and agreeing it was fantastic news – which it is – but inwardly I was a tortured soul because I knew something they didn't, we in the UK may actually be unable to use the only drug to give us years (approx. 1 year for every 3 years on the drug) of extra normal life. Before end stage renal failure means we are hooked up to a machine, when we mentally prepare ourselves for the donor kidney lottery and pray that whilst we wait – we don't die from kidney failure or suffer extensive injuries from strokes (which blinded my mother and paralysed her sister down the left side of her body) which means we are reliant on relatives and hospitals to give us the care we need to stay alive in a horrible twilight life. The drug is expensive – there is no getting away from that but for me there are so many economic considerations that were not addressed because there is no empirical data available but they do exist. Firstly – the benefit of continuing in gainful employment. It was given lip service in the decision document but let me explain what it translates into for me. At 50 years of age, I am currently at the peak of my career earning a very decent salary as an Associate Director of Tax at my Big 4 firm. They have told me I'm up for promotion next year. Despite being on the drug and having to adjust the way I work – I've been excelling in the workplace – That's because I'm still healthy. The drug is doing its job of slowing down the side effects of cyst development; -the pain of cysts pressing on nerves, the discomfort of carrying around heavy kidneys and liver will come because the drug is only slowing things down but we are not there yet. Yes my organs are big but so far I appear to have avoided those complications to the extent that they are debilitating. Not only am I contributing Tax and National Insurance to the Exchequer from my	

Nominating organisation	Comment [sic]	Response
	salary, there is the "multiplier effect" that comes with being able to continue longer in full time employment receiving significant net earnings which at my age and with my family history would soon be on the wane were it not for this drug. My earnings are currently helping my two children to cope with University living costs, I'm spending money in the wider economy on a variety of consumer durables, weekend breaks in the UK, putting more money into my pension for a retirement I hope actually takes place. I'm healthy. I not only work, I do voluntary work with young disadvantaged teenagers. I don't need anyone to look after me yet (My dad gave up work at 50 to look after my mother – so did my uncle with my aunt). I'm not on benefits (so there is a cost saving to the exchequer). I'm able to travel for work and for pleasure. The world is still my oyster. By now my mother and aunt were slowly finding out that their homes were turning into their prisons. This is just one person's testimony to what the drug is doing for me when I compare it to my PKD relatives. We are a family who have a cluster of the females with PKD arriving at end stage renal failure at an average age of 58 (my mother died at 59, aunt at 58, second aunt successfully transplanted as she turned 58, grandad died at 62). As with most PKD patients – those ages are embedded in my brain. Secondly, the psychological impact of knowing my normal life is being extended because I've been on Tolvaptan for so long, means I'm positive not negative about my future! This positive state of mental well-being is important for me personally and for my family (for my two kids to see me happy and positive so that they don't worry about me such that it impacts on their mental health) but is equally important in the workplace as a depressed team member pulls down the performance of an entire team. Positive mental health is now so important in our workplace that my firm runs regular Mental Health First Aid courses to help people with mental health issues and create Mental Health First aiders because the impact of negative mental health issues on team performance as well as individual performance is costing the firm a LOT of money. Big employers across the nation are doing likewise. PKD sufferers do suffer	

Nominating organisation	Comment [sic]	Response
	disproportionately from poor mental health (see the PKD Charity's survey) because of their feelings of helplessness – if there is nothing out there to slow things down and you are told to just wait until you need dialysis or transplant – you are not going to be Mr Positive at work when those cysts start paining you etc. Poor mental health usually accelerates poor physical health issues. This drug breaks that mould. It really is that important – physically and psychologically to PKD sufferers. It gives hope. It boosts our mental health whilst keeping our physical health better for longer. Given I've been on the drug nearly 7 years –and I'm now 50, if I could continue on it, given our family does have a cluster age for death of 58/59, I could buy myself an extra 5 years of "normal life" before I hit end stage renal failure. My death age would move from 59 to 64! Five years is a long time to benefit from "normal life". I did an undergraduate degree and post graduate qualification in 5 years (as I'm sure many of you on the committee did), as a kid I learned to walk, talk, read, sing, learn Irish dancing and win a few medals even. Between 1964 – the year of my birth to 1969 – the Americans had managed to come up with the technology to put a man on the moon! Five extra years of a quality life and maybe longer before that new death age of 64 kicks in. Given its 14 years from now – scientists could even discover how to stop the cysts from getting bigger and destroying our kidneys not just slow it down? I could end up working to that new ripe old age for retirement of 67! Reference was made in the Committee meeting by Professor Mc Veigh and reference again in the NICE Appraisal Consultation document that drinking large amounts of water could possibly come up with the same result. I drink 6-8 litres of water in the day and 2, sometimes 3 litres at night. I love my water – it's the sweetest nectar on the planet when you are on Tolvaptan. The drug gives you dry mouth and you so desperately want to drink water that you will stop immediately whatever you are doing to drink it. Nothing is more important than the water. The drug makes you do that. Without the drug you don't get to that level of desperation to drink water without even realising you are drinking it. I was off the drug for a few weeks	

Nominating organisation	Comment [sic]	Response
	between Tempo ¾ and Tempo 4/4 and despite leaving pints of water all around the house, beside my computer, on the bathroom shelf above the sink, in the kitchen, beside the sofa in the living room, on my bedroom locker - at best I drank 2 litres in the day and half a litre at night (I simply didn't wake up – the drug makes you thirsty in your sleep so you have to wake up no matter how exhausted you are). Without the drug I drank almost a quarter of what I drink in a normal day whilst on Tolvaptan. That is the reality of what a human body will and will not do without this drug. I knew how important drinking the water was to me and I couldn't do it. The placebo results prove this. To get the results that Tolvaptan gets – you need to be on the drug because it is what makes you want to drink such a large volume of water. This drug works. It's side effects are not a problem. Yes you adjust your life to live with the drug and yes -you have to be prepared when you go out travelling, shopping etc. that you have sufficient liquid with you and you know where there are toilets available. Yes your sleep is broken at night but I liken it to the massive changes in my life when I had two very young children. My sleep was broken but unlike with Tolvaptan I was not guaranteed to get back to sleep so quickly. I had to plan my trips out of the house ensuring I had nappies, SMA, bananas, LIGA, water for the babies in case they got hungry. I had to know where there were toilets for my two year old potty training son and changing rooms for the 2 month old's nappy and oh yes – a discreet place to breastfeed. Millions of people adjust to sleep deprivation and leaving the house with two young children is done with military precision carrying a bag that contains everything but the kitchen sink (not just 2 litres of water) and nobody blinks an eyelid….We are just a variation on an old theme but this drug despite its life style side effects, actually gives us the chance for a longer normal life. I'm sorry I've taken up so much of your time but this drug – the only drug out there to give us a normal life for longer, is really important to us PKD patients. We have so much more to give our families and the greater community and we just need to be given the chance of	

Nominating organisation	Comment [sic]	Response
	getting those extra years of life. Three generations of my family have waited for this drug to be developed, people in other countries will be given it. This is a significant medical breakthrough and I beg you to reconsider your decision so that PKD sufferers in the UK can join others around the globe for the very first time in living longer normal lives.	
Professor Albert Ong – clinical expert, nominated by Renal Association	Thank you for giving me the opportunity to comment. I wish to point to some inaccuracies in 3.20 and 3.23 referring to work done by the ERG. 3.20 It is true that standard care as currently practiced in the UK has not been defined and mirrors that for CKD. Consensus guidelines have not been published. The issue of aggresive blood pressure managament has been addressed in the HALT studies recently published in the NEJM (Schrier et al, NEJM 2014; Torres et al, NEJM 2014). In the first study (HALT A) which investigated patients with preserved kidney function (eGFR>60ml/min), the lower blood pressure group (<110/75) was associated with a slower increase in total kidney volume (TKV) compared to standard blood pressure control (p=0.05) but no change in eGFR slope was detectable. This data contrasts with that for tolvaptan where both improvements in TKV and eGFR were observed. I have summarised these comparisons in a recent review for the Lancet (Ong et al, Figure 3A). There is therefore no basis to recommend more aggressive blood pressure reduction beyond standard levels (<130/80). The benefits of increasing fluid intake have not been rigorously tested and remain unproven. In the TEMPO3/4 study, all patients including the control group were encouraged to maintain adequate hydration (drinking at least 3-4L/d). This is likely to have reduced the true differential effect between controls and treated groups by suppressing vasopressin and could be reflected by the lower rate of %change in TKV (5.5%) in the placebo group compared to previous studies (6.8-11.8%). Increasing fluid intake is not part of current	Comments noted. NICE considered the comments in the response and the paragraphs referred to in the ERG's comments and agreed it was appropriate to remove reference to these comments in the FAD (the use of aggressive blood pressure reduction and increased fluid intake, as well as the reference to the use of the ellipsoid method for measuring TKV changes).

Nominating organisation	Comment [sic]	Response
	standard care. 3.23 In the TEMPO3/4 study, TKV was initially accepted by the FDA as a primary end-point and therefore the study was powered for this outcome. It is important to point out that changes in TKV from MRI scans were measured by sterology (gold standard), not by the ellipsoid method, which would not be accurate enough to detect changes in TKV and lack precision for measuring TKV.	
The Polycystic Kidney Disease (PKD) Charity	The Polycystic Kidney Disease (PKD) Charity is **deeply disappointed** that the National Institute for Health and Care Excellence (NICE) **has not recommended tolvaptan** within its European marketing authorisation for treating autosomal dominant polycystic kidney disease (ADPKD)[i]. Tolvaptan is acknowledged by NICE as an **'innovative treatment[ii]'** and the '**first shown to specifically impact on ADPKD progression[iii]**', targeting the disease and not just managing the symptoms and complications. The Committee further noted that the '**availability of Tolvaptan gives hope[iv]'** for people with ADPKD, their children and families. The PKD Charity recognises that the Appraisal Consultation Document or ACD (issued May 2015) is not the final guidance on tolvaptan. We understand the challenges in modelling the economic cost-benefit associated with this long-term incurable disease. We urge the Committee to re-consider their initial considerations and recommend tolvaptan to address the significant unmet need and continuing disease burden in the cohort of patients who would derive most value from this important new treatment. **Our argument for access** We do not feel that the NICE Committee has taken all relevant evidence into account, for example the direct healthcare costs of treating both kidney and liver cyst ruptures, surgical interventions on the kidneys and other organs, infections and pain throughout a patient's lifetime and especially in the years prior to kidney failure. In addition, we do not feel that the Committee has acknowledged the full impact of living with ADPKD – the psychosocial and emotional	Comments noted. During the Appraisal Committee meeting the Committee was presented with the results of the PKD Charity survey as described in the response. The Committee considered the points raised in the response and considered the raised points that not all direct healthcare costs treating kidney / liver cyst ruptures, surgical interventions, infections and pain had been captured, or the indirect costs such as lost employment, productivity etc. on individuals and families. The Committee was mindful however that technology appraisals are assessed from the perspective of the NHS and PSS. The Committee considered the points raised about not considering the full impact (psychosocial and emotional) of living with ADPKD, and addressed these concerns in its conclusions regarding the fact that tolvaptan was considered an innovative treatment (see section 4.19 of the FAD).

Nominating organisation	Comment [sic]	Response
	effects of a long-term inherited condition, and the indirect cost burden of lost employment, productivity and earnings on individuals and their families. *The current situation for someone with ADPKD* • ADPKD is uniquely different from other chronic kidney diseases. It is a complex, progressive, systemic condition affecting many parts of the body, and the **most commonly inherited kidney disease**. First reported in the 16th century, ADPKD is incurable, with those affected enduring a relentless progression towards end-stage renal disease (ESRD), accompanied by a plethora of renal and extra-renal complications. • Global prevalence rates range from 1 in 500 to 1 in 4000[v], with a large number of individuals being undiagnosed during life. ADPKD can, however, be diagnosed at any time, in adulthood or in children (sometimes in utero). Being dominantly inherited, the risk of passing on ADPKD to children is 1 in 2. Many patients with ADPKD will know similarly affected family members; many will have lost loved ones from ADPKD. • ADPKD is characterised by the formation, growth and multiplication of fluid-filled cysts in the kidney and other organs. The bulging cysts **profoundly enlarge the kidneys** replacing healthy tissue. A normal kidney weighs approximately 150g; an ADPKD kidney can grow 80 to 120 times as big. In one extreme case, two ADPKD kidneys together weighed 22kg or approximately one fifth of the patient's body weight. Individual cysts themselves can expand to 9 or 10cm in length – which is the size of an average, normal human kidney. • Symptoms such as burst kidney and liver cysts, bleeding and infections are common. These recurring incidents cause both chronic and acute pain. In the PKD Charity's **survey of UK**	

Nominating organisation	Comment [sic]	Response
	Patients' and Carers' Experiences of ADPKD[vi], nearly half of all patients (250 individuals) - reported suffering acute severe pain at least once a month, 1 in 10 on a daily basis. Most said that pain interfered with normal daily life 'extremely'. Over 4 in 10 reported inadequate pain relief. *"I don't think my drugs deal adequately with the type of pain that I have… the pain that interferes with my sleep."* *"Had to wait a long time to get treatment for pain. Ended up in casualty for pain relief."* • Kidney failure occurs in most ADPKD patients, on average before the age of 60 years[vii]. Not all patients will reach ESRD, but when that occurs, dialysis and/or transplantation are the only **life-saving treatments**. • An epidemiological study of patients on the UK Renal Registry in England and Wales with ADPKD and ESRD was carried out for the period 1 January 2000 and 31 December 2011[viii]. A total of 52,608 individuals started renal replacement therapy (RRT) during the study period, of which 3,598 (6.8%) had ADPKD. **The median age of commencing RRT was 55 years in the ADPKD group** compared with 62 and 66 years in those with diabetes or other kidney disease. This young age of starting RRT had not changed within the ADPKD group over the 10-year period. • It is common knowledge that treating chronic kidney disease patients consumes a substantial amount (nearly £1.5bn or 3%) of the NHS budget for a relatively small number of the overall population. Half of this sum is on RRT. ADPKD patients, though few in number, are therefore costly to treat. Moreover, many are living longer owing to lower cardiovascular risk through better blood pressure control[ix], which can mean they may need more than one transplant or	

Nominating organisation	Comment [sic]	Response
	several periods on dialysis. • The NICE Committee does not seem to have taken account of other healthcare costs associated with treating ADPKD. • Some patients may require removal of their native kidneys (by surgical nephrectomy), before and/or after RRT, to enable transplant to go ahead or deal with complications such as pain and infections from massive cystic kidneys. Some patients will need cyst aspiration or de-roofing. These nephrectomies and other interventions carry surgical risk and are costly procedures. • Nearly 8 out of 10 patients in the PKD Charity survey were taking a range of prescription medicines as a result of their ADPKD. As well as painkillers and antibiotics, drugs typical in managing CKD may be needed, eg allopurinol to prevent gout, statins, EPO, vitamin D and phosphate binders. • Additional complications include: increased risk of brain aneurysms needing major brain surgery (such as coiling) and leading to strokes or death; increased frequency of kidney stones; and highly debilitating polycystic liver disease, which sometimes necessitates costly liver transplantation. • In addition – also not considered by the NICE Committee – are the non-healthcare costs associated with long-term, debilitating conditions. • Aside from the clinical manifestations, people with ADPKD are frequently **profoundly affected by the psychological, emotional and social side-effects** of this inherited, long-term condition. The PKD Charity survey found that over 9 in 10 people admitted to feelings of anxiety, sadness, guilt, loss of self-confidence and hopelessness. Over two-thirds reported impact on overall family life, nearly half reported impact on their sex life and 1 in 3 had made career sacrifices due to pain and general debility. *"Failure of marriage, lack of earning potential and constant guilt for being a burden when unwell and*	

Nominating organisation	Comment [sic]	Response
	passing it to children." • Patients complain about being viewed as 'obese', having a 'beer belly' or looking perpetually 'pregnant' - resulting in body dysmorphia and sometimes desperate attempts to 'lose weight' with malnutrition consequences. • The NICE Committee noted the absence of HRQoL assessment in the TEMPO 3:4 trial. However, there are no specific ADPKD patient-reported outcome measures which capture the impact of symptom. Studies employing widely-used measures such as SF-36 QoL have had mixed results; researchers consider them too generic and insensitive to measure the diversity and slowly progressive effects of ADPKD[x]. • In severe cases of ADPKD, people will experience kidney failure at the peak of their earning potential and in the prime of their personal and family lives – resulting in sometimes cataclysmic loss of jobs and future earnings/pensions/tax contributions. • In the PKD Charity survey, people reported loss of personal and family earnings of between £10,000 and £100,000. Costs fall on carers as well as patients: 1 in 5 carers in the PKD survey said they had left their employment to take care of affected family members (spouses and children). Most people diagnosed with ADPKD will also experience increased travel insurance premiums and the majority will be denied life and health insurance. Many will need welfare benefits. • All this can have significant consequences on parenthood decisions. In the PKD Charity survey, some respondents said they had chosen not to have children. • When many family members are affected or may have died prematurely - whether parents, siblings or children – "**ADPKD can feel like a death sentence"**. *"On the balance of probability you face death in*	

Nominating organisation	Comment [sic]	Response
	your later 50s early 60s if there is no intervention. I fear for my future and the fact that I could die prematurely and as a single parent not be there for my children." *Hopes were raised by first-ever licensed therapy* • Until recently, there were no licensed therapies available to slow progression of ADPKD. The successful global clinical trial by Otsuka Pharmaceuticals (TEMPO 3:4[xi]) has resulted in the first-ever drug JINARC® to receive marketing authorisation in Europe on 28 May 2015. • The active ingredient, tolvaptan, was shown to affect the rate of kidney cyst growth and modify the progression in trial participants. JINARC® has been licensed in the EU, Japan and Canada, and represents a significant step forward for thousands of people with ADPKD, their families and carers, and future generations. • There was a hope among the many thousands of people with ADPKD that tolvaptan could give a "better quality of life". From the PKD Charity survey: *"I hope Tolvaptan to be successful so that my son will never reach end stage renal failure. I hope for him to live his life to the full without ADPKD impacting his life as much as it has mine and my sister."* • Whilst not all respondents in the PKD survey were certain about taking tolvaptan, all welcomed a drug that could potentially delay dialysis and transplantation. • Additional benefits, as seen in the trial, include fewer infections and less pain from slower cyst and kidney growth. *Are there other commissioning options?* • We recognise that tolvaptan is not suited to every ADPKD	

Nominating organisation	Comment [sic]	Response
	patient at CKD stages 1 to 3 (the indicated use). This is a very broad group but within this cohort are the faster progressing, typically younger patients, with young families, struggling to cope with their jobs and daily lives, who are living with the fear of early ESRD and premature death. Could NICE consider some form of restricted commissioning for such patients? • Could 'Commissioning through Evaluation' for these fast-progressing patients be an option to enable new data to be collected within a formal evaluation programme? • These fast-progressing patients, historically, were challenging to identify owing to genotype and phenotype variability but this will change with the availability of new academic-led models, eg from Irazabal et al[xii], which promise more accurate stratification of ADPKD patients by total kidney volume (TKV). • With the support of the UK Renal Registry, an ADPKD Registry is feasible within 6 to 9 months. This will capture more data on ADPKD patients at earlier CKD stages, in particular biomarkers such as TKV, to aid patient identification. *The future without access to tolvaptan* • We asked patients how they rated current healthcare approaches and one in 2 described them as fair, poor or very poor in managing their ADPKD. • Without a recommended therapy, 'standard care' based on symptom management until ESRD is the only option. There is therefore no motivation to change this unstructured approach to managing ADPKD patients. • At present, standard care can vary considerably as there are no agreed best practice guidelines. There are no dedicated NHS specialised services (aside from standard CKD and RRT care). Very few hospitals have specialist clinics for ADPKD patients.	

Nominating organisation	Comment [sic]	Response
	• Many patients still report that their doctors have little understanding of what it's like to live with ADPKD and have an attitude of 'sit back and wait for inevitable kidney failure'. • Regrettably, the NICE Committee commented that '**aggressive blood pressure management and increased fluid intake may have an impact on decline**[xiii]'. There is no evidence to support these comments. Whilst patients with other forms of chronic kidney disease (CKD) such as diabetes have benefited from approaches to slow the decline of kidney function, these have not worked in ADPKD[xiv]. • In conclusion, the PKD Charity reiterates its deep disappointment that people living with incurable, inherited, life-threatening and debilitating ADPKD are denied access to a licensed therapy which has the potential to improve the quality of their lives, and the lives of their family members and future generations. We ask NICE and the manufacturer to work together to develop an economic model that takes account of the latest clinical developments and is scientifically robust to identify the patients that will benefit most from this treatment.	
National Kidney Federation	The NKF is the largest kidney patient charity in the UK, forms part of Kidney Charities Together (an alliance containing Kidney Research UK, British Kidney Patient Association, Polycystic Kidney Disease (PKD) Charity and the Kids Kidney Charity), has support of the All Party Parliamentary Kidney Group and works in close partnership with various NHS organisations (including NHS England and the Clinical Reference Groups for Renal Dialysis & Transplantation) and Associated Renal Industry to improve the quality, provision and equity of access of services/treatments for kidney patients. The NKF supports the interests of all kidney patients (and their carers/family) with Chronic Kidney Disease (CKD), those being treated with renal replacement therapy (RRT) or those conservatively	Comments noted. Please see responses to comments raised above.

Nominating organisation	Comment [sic]	Response
	managed. This response directly supports the evidence presented by the PKD Charity in their submission and is intended to compliment insight from other kidney charities including the BKPA and KRUK. The NKF is saddened and deeply frustrated both with the disappointing decision by the National Institute for Health and Care Excellence (NICE) not to recommend Tolvaptan for treating Autosomal Dominant Polycystic Kidney Disease (ADPKD) but also for the many patients, carers and family members for whom this drug promises such hope of a better quality of life and potentially improved life expectancy. The ability to slow the rate of progression of ADPKD for patients and family members is priceless; keeping well for longer will enable the ability to plan, prepare, educate, gain support and emotionally accept future treatment. Keeping well for longer will reduce the burden on the NHS financially and enable individuals to participate and contribute fully to life being engaged citizens. Each year of dialysis is estimated to cost between Â£25-30,000, while transplantation in year one has estimates ranging from Â£16-41,000. The potential to have less dialysis, drug burden, inpatient stays, reliance on patient transport and multi-disciplinary input through Tolvaptan will bring savings to the NHS. Staying in employment is widely regarded as both beneficial for physical as well as mental health and the NKF is acutely aware from reports to our Advocacy Service and attendees at our Annual Patient Conferences that once out of work financial support and a route back into employment is minimal with an ever decreasing cuts in benefits and support and variable access to counsellors, psychologists and	

Nominating organisation	Comment [sic]	Response
	renal social workers within Secondary Care and delays in accessing referrals to psychological therapy in Primary Care. Working age individuals with ADPKD have the potential with Tolvaptan to sustain their time in employment and make future preparations around work. This provides the potential to stay in work after starting RRT having which gives a health benefit, but importantly offers a financial and contributory benefit to the state. Preparation allows individuals to engage and understand key educational messages which in turn enable decisions and choices around future health care to be made in a timely rather than rushed manner. For many this means treatment options that meet ones needs that have been discussed with family members and health care professionals, which importantly allow space to discuss living donation. For individuals with a potentially long pathway of many decades, time and space at the beginning of the journey is the foundation to living well and keeping well for longer. The NKF note from the PKD Charity â€˜that Tolvaptan is not suited to every ADPKD patient at CKD stages 1 to 3 (itsâ€™ indicated use). This is a very broad group but within this cohort are the faster progressing, typically younger patients, with young families, struggling to cope with their jobs and daily lives, who live with fear of early ESRD and premature death. Such patients should, we feel, be considered for early access to Tolvaptan, as soon as possible.â€™ The NKF supports in particular the above stance and we add with authority and insight that this younger cohort often faces some of the greatest challenges in managing the physical demands of RRT; inherent complications, diet restrictions, drug burden; and associated risk burden from infection, cancer and steroid induced diabetes. We also note the significant burden and destructive effect on families where more than one individual is identified with ADPKD and	

Nominating organisation	Comment [sic]	Response
	requires treatment. Kidney patients, their carers and families rightly demand the best in access to health care treatment and services from the NHS in the UK today. In terms of progressive kidney disease that results in end stage kidney disease we know there is no cure, only treatment. The potential to stave off treatment is a massive advance for any kidney disease; in the case of ADKPD this is huge - Tolvaptan is acknowledged by NICE as an â€˜innovative treatmentâ€™ and the â€˜first shown to specifically impact on ADPKD progressionâ€™, targeting the disease and not just managing the symptoms and complications. Tolvaptan not only brings the obvious health benefits but the myriad of psychological, social, financial and personal. Therefore the proposed decision not to approve Tolvaptan is of major significance for the ADPKD community and we believe will have a potentially devastating impact for their care, quality of life and length of life. Whilst the NKF is mindful that the final guidance on whether to use Tolvaptan has not been made we strongly and respectfully urge the committee to reconsider their initial considerations and recommend Tolvaptan to address a recognised high unmet need and continuing disease burden.	
British Kidney Patient Association (BKPA)	The British Kidney Patient Association (BKPA) notes the feedback from the NICE Evidence Review Group and kidney patients with ADPKD in making these comments to NICE for further consideration in its review of tolvaptan. While NICE has concluded that a) this is a drug with some utility for people with ADPKD but that b) the evidence it has seen has not given it sufficient confidence to justify its authorization the BKPA would like to ask it to consider approval of the drug under some well-defined conditions.	Comments noted. Please see responses to comments raised above.

Nominating organisation	Comment [sic]	Response
	This would enable the collection of further evidence in a UK population whilst also enabling people with ADPKD to choose to undergo tolvaptan treatment with full support from their healthcare professionals. There is an excellent example of innovative commissioning and enabling choice in the NHS decision to commission TAVI devices for aortic valve replacement http://www.england.nhs.uk/wp-content/uploads/2013/04/a09-p-a.pdf We should like to ask whether NICE would consider making such an approach. Furthermore we would like to ask whether NICE has given full consideration to the social, health and economic gains to be made by delaying development of Chronic Kidney Disease versus the quality of life, increased mortality and economic burden of dialysis? Dialysis costs are estimated as about Â£33,000 pa by NHSBT and there is evidence that people with ADPKD will live longer on dialysis, thereby increasing the lifetime costs of this treatment vs the cost of a disease-modifying drug. While transplantation is a good option it is a scarce resource with a long waiting list and about 1 kidney patient a day dies whilst they wait. For two thirds of those on dialysis their further complications will mean that they are unable to move to the transplant waiting list anyway.	
Kidney Research UK	Kidney Research UK was concerned to learn that NICE has not recommended Tolvaptan (Jinarc) within its European marketing authorisation for treating ADPKD. Kidney Research UK supported the original submission made to NICE by the PKD Charity, who went to great lengths to gather patient experiences of ADPKD. We were also fully supportive of their	Comments noted. Please see responses to comments raised above.

Nominating organisation	Comment [sic]	Response
	nomination, and subsequent NICE acceptance of, our eminent colleague, Professor Albert Ong, as the clinical expert. We have reviewed the response made by the PKD Charity to your decision. We fully endorse their view. We were pleased to read that NICE have acknowledged the clinical benefits of the drug and that this technology is unique and first in class; there is no other current treatment which slows the progression of the disease. However, we are deeply disappointed that NICE have not fully appreciated the wider quality of life and economic benefits which would accrue from the deployment of the treatment. This decision denies hope to the families affected now and to future generations. However, we note that Otsuka have agreed a patient access scheme (PAS) with the Department of Health. In light of the response to this decision, surely now you should embark upon a renegotiation of the discount to get this technology into routine clinical use?	

Comments received from commentators

Commentator	Comment [sic]	Response
	No comments received	

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Housewife/ Carer		I am very disappointment in the decision to reject tolvaptan. My family have been devastated by this disease. My mother in law died at 43, my sister in law died at 52 and my husband had kidney failure at 43 followed by 2 years of dialysis and transplant. I have 2 children with the disease and this drug is the only light at the end of the tunnel for them. There are no other treatments and as they are now over 30 they are facing the inevitability of kidney failure. They have both made the decision not to have children because of this disease. To tell them that a treatment our family has awaited for years is not cost effective is heartbreaking to us. Also it surely must be better to prevent the progression of this disease and save money on dialysis, transplant etc not to mention the loss of earnings when kidney failure ensues	Comment noted. The Committee heard from the patient experts that tolvaptan may have a positive psychological benefit for people with ADPKD. The Committee understood the importance of such benefits, which may be difficult to capture in measures of health-related quality of life in addition to those already included in the QALY calculations. The Committee concluded that tolvaptan is an innovative treatment and it is the first treatment that has been shown to specifically impact on the progression of ADPKD.
Patient 1		I am concerned that the committee has not fully understood the impact of ADPKD on patients and families in terms of daily life and effects of deteriorating renal function to the point of dialysis. There is no treatment for delaying the onset of dialysis and all that it entails, the limitations, diet restrictions, disabilities, effects on family life and reduced work capabilities. Tolvaptan has been shown to delay total kidney volume and cyst progression, where water intake and BP management have not. Tolvaptan has been licensed in Canada and Japan. In not recommending it as a treatment for ADPKD NICE has denied many patients not just hope but actual benefits of the treatment. This should not be a blanket decision, but one available to the nephrologists to make on an individual patient basis. That NICE conclude by supporting BP management and increased water intake is insulting - the majority of ADPKD patients are doing this to the best of their ability anyway.	Comment noted. The Committee heard from the patient experts that tolvaptan may have a positive psychological benefit for people with ADPKD. The Committee understood the importance of such benefits, which may be difficult to capture in measures of health-releated quality of life in addition toover those already included in the QALY calculations. The Committee concluded that tolvaptan is an innovative treatment and it is the first treatment that has been shown to specifically impact on the progression of ADPKD.
Patient 2		I can't understand how you can say this drug is beneficial to sufferes with PKD and then say it's too costly. My understanding is that this drug would stop patients being on dialsysis because it is aimed for stages 1-3 so surely the NHS would rather spend money on this drug than spend money on dialysis?	Comment noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
Patient 3		This was the thing keeping me and my family going through this hell we have to endure. I live everyday seeing my two children who I have passed this life sentence to. I have gone through all the stages and have now had a transplant so have to think of all the pain and suffering I have endured which they will have to go through. I have lost my house, career and my mind over this and to think someone is stopping my children from having a treatment that will postpone their suffering is a disgrace. I am so so sorry and hurt you can't see past the cost or fact it can't work for everyone	Comment noted. The Committee considered the points raised about not considering the full impact (psychosocial and emotional) of living with ADPKD, and addressed these concerns in its conclusions regarding the fact that tolvaptan was considered an innovative treatment (see section 4.19 of the FAD).
Patient 4		Very disappointing that you have not considered the full effect of Tolvaptan on ADPKD and have looked at on kidney failure in general. This appears to be the first drug that does work for ADPKD and this should be taken into account.	Comment noted. See points raised in responses above
Patient 5		After years of waiting and hoping for a treatment for one of the most common renal diseases Tolvaptan was developed. I am deeply disappointed that myself and every other person living with this incurable, inherited, life-threatening and debilitating kidney disease may be denied access to a licensed therapy which has the potential to improve the quality of our lives, and the lives of our family members and future generations. Regrettably, the NICE Committee have commented that aggressive blood pressure management and increased fluid intake may have an impact on declineâ€™. There is no evidence to support these statements. Whilst patients with other forms of chronic kidney disease (CKD) such as diabetes have benefited from approaches to slow the decline of kidney function, these have not worked in ADPKD[vi]. This is the first drug that has promised any relief from the unrelenting symptoms of renal failure, constant discomfort and severe pain. We are being denied the opportunity to be able to continue a productive life. On the balance of probability we face death in our later 50s early 60s if there is no intervention. I urge you to reconsider your decision and give us all a chance at a normal life.	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
Carer 2		I believe that the committee hasn't fully taken into account the affect ADPKD has on patients and carers. Everybody deserves the access to preventive and slow progression drugs. I believe that this committee haven't fully taken all relevant evidence into account, including current cost implications the NHS is experiencing with renal conditions. The active ingredient, tolvaptan, was shown to affect the rate of kidney cyst growth and modify progression; this would lead to less of a cost implication over time for the NHS.	Comment noted. See points raised in responses above
Patient 6		I am deeply disappointed with this decision which does not seem to take into account the ongoing medical and psychological issues of living with PKD on a day by day basis and the prospect that kidney failure will strike before 60. I am 37 and have been on blood pressure medication every day since the age of 27. I have two children who may have inherited this. My father had to have a kidney transplant at the age of 55 and has been unemployed since then - this is what is currently facing me without Tolvaptan which, in the recent TEMPO 3:4 showed that Tolvaptan demonstrated a significant relative reduction of 49.2% on total kidney volume growth over 3 years when compared with placebo. I would urge NICE to review this for me and the thousands of others like me who without Tolvaptan will be condemned to slow and often painful decline of kidney function until transplant is the only hope.	Comment noted. See points raised in responses above
Patient 7		As a ADPKD patient, with 2 young children with a 50/ 50 chance of inheritance, I am deeply saddened by this decision. This disease affects all of my life greatly, I am anxious, suffer depression regarding it. I also have no hope for my children that a treatment is there, and this decision is likely to thwart any interest of other drug companies to develop similar drugs. I now have no chance of . fathering more children as I do not want the heartache of potentially affecting another child.	Comment noted. See points raised in responses above
Patient 8		I am a 26 year old female with PKD and I was diagnosed nine years ago at the age of 17. Until that point, and a couple of years after, I had suffered very few ill side effects from this condition. This changed at the age of 19. I began to suffer with pain, infections, and urate kidney stones. It was however, only a couple of times a year and I felt as though I could deal with it. It did affect my day to day life, but only for a couple of times a week, and a couple of times a year. This all changed a few years ago. I	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		was studying a degree in BSc Midwifery. The pain and stones I experienced during this time was so severe that I struggled with the workload and fell behind. I failed my first year and had to leave the course. This was the first time having PKD and what comes with it had affected me and my life. It had ruined my dreams of a career and I felt lost. With my physical health being in such bad condition, my mental health also began to deteriorate (I have since been diagnosed with BPD.) Despite all of this, I managed to get myself a job as a Support Worker in a hospital. After beginning this job, my kidneys and condition drastically worsened. Due to the long hours and heavy work, I found that the pain which was minimal before quickly became daily. The infections which were only once or twice a year became constant. I had and still have to have a lot of days off sick and I struggled with the workload. My Bradford score was in the thousands and I couldnâ€™t reduce it because of the constant pain I was in. I have been hospitalised more times than I can count, and the future looks bleak. If I am in this much pain and my kidneys are still fully functional, how will the pain be when their function begins to reduce? How will I cope then, and how will I work? I am in pain every day, and the only way I can work most days is to dose up on painkillers, which cannot be good for my system. I am almost certain my job does not help my condition; however, I feel I am now stuck. Because of my condition, and it being a condition which will only get worse, not better, I have been told I am basically unemployable. A job I was offered was since withdrawn after they found out about my Kidney Disease and Bradford score. Tolvaptan gave me hope; I knew it wouldnâ€™t solve the issue of what was already there but the thought that it could prolong my kidney function for a good 5-10 years excited me. I do not know when my kidneys will begin to fail and how quickly it will progress. What I do know is that I have family members who have not suffered much in comparison and they have now been told they need a transplant while they are still in their 50â€™s. This frightens me. I donâ€™t want to have a transplant while I am still so young. The pain, and the amount I suffer with my PKD and the effect it has on my life has made me take the decision that when I am ready to have children,	

Role*	Section	Comment [sic]	Response
		I am going to do it using IVF, and eggs which do not hold the gene for PKD. I would never want my children to suffer like me; in fact, I would never want even my worst enemy to suffer like this. Even carrying a child frightens me, as I am worried about how this may affect my body and my condition. I am aware that it made my nana quite ill. I find it sad that cost is a big factor in choosing to not fund Tolvaptan. It could help many people and bring hope where there was previously none. I have a granddad who has dementia and is on more tablets every day than what seems can be counted. It seems silly that a dying man of 86 who cannot even self-medicate is given more help and medication, than a young woman of 26 who still has a lot of her life ahead. I just hope your decision can be changed by mine and others stories. It is hard to know how bad it can be unless you are actually in a position like mine, and I feel the bigger picture should be looked at more than the smaller one.	
Patient 9		Polycystic kidney disease has dominated four generations of our family. Tolvaptan is the first ever drug developed to reduce cysts within the kidney. Progress and hope for patients with this life threatening disease rather than waiting for the inevitable failure of the kidneys. The studies showed benefits to patients and the administrating of Tolvaptan per annum, compared to dialysis, must be cost effective to the NHS. It is not reasonable within the NHS organisation to have NO investment for kidney patients where their are benefits of cyst reduction when taking the drug. PKD impacts family, career and well being. Patients are being discriminated on the grounds of disability where no hope or drug is currently being offered. This compares with millions spent on cancer related drugs and advancement. We urge you to determine that this drug should be available within the NHS.	Comment noted. See points raised in responses above
Patient 10		I think that the panel should take into account the potentially very long term psychological aspects of this disease (30/40 years), especially when at present there is NO OTHER treatment available. Hope is a very poweful medicine.	Comment noted. See points raised in responses above
Patient 11		I would like to say how disappointed I was to find it has not been approved. I have been on the trial for over 5 years and I have not had anywhere near the deterioration of kidney function that could have been expected. This will mean that I will be able to work for longer and pay more	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		taxes and not be a drain on public funds. I suggest that NICE have not taken all these extra factors into account! It is to late for me, but the fact that there was no real treatment available with this inherited disease has meant I have had to make the difficult decision not to have any children as I did not want to pass on this dreadful disease, however this has had difficult effects on my relationship. If treatments like this drug are more available in the future then it would provide hope for people like me in the future and would completely change my family circumstances! Please, please reconsider the funding for this drug as the effects of not being treated will be huge. Surely the price of thee drug will come down in the future. There are many, many kidney patients that could benefit from this!	
Patient 12		I'm an ADPKD patient. My maternal grandmother died from ADPKD aged 50, my mother died at the age of 48 from ADPKD. My son has inherited ADPKD and Tolvaptan represents the only viable option to delay the inevitable failure of his kidneys and the expensive progression to dialysis. Dialysis affects so many aspects of the lives of both the patient and their family. Given the progression of the disease in my family my son is likely to be unable to work when he is in the prime of his life thereby being unable to contribute to society and fulfil his talent and aspirations. My son's story will be matched by many others who are also denied access to Tolvaptan. I understand Tolvaptan may not be suitable for all ADPKD patients but to deny access to it for the many who will benefit is short sighted and completely at odds with the decisions taken by other countries in recent times to authorise the drug, most notably Canada. I urge you, please reconsider your decision.	Comment noted. See points raised in responses above
Carer 3		I have cared for my husband who has ADPKD, which was diagnosed in l989, through to end stage renal failure in 2009. He then continued life on dialysis for three and a half years until he received a kidney transplant in 2013. This illness drastically restricted both our lives and those of our children. Our daughter has inherited ADPKD and is now in continuous pain from the cysts on her kidneys. As she is only 40 years of age she has many more years of pain and suffering ahead of her. I understand she	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		is not alone in this suffering as many more people are being diagnosed with this horrible, debilitating disease. I urge the Committee to re-consider allowing the use of Tolvaptan in Britain as it is the only hope of relief for these patients.	
Patient 13		I am a patient who has suffered from ADPKD for over 50 years, culminating in dialysis and eventually a kidney transplant. Sadly, my daughter who is now aged 40 years, has inherited ADPKD,and is in continuous pain from cysts on her kidneys. I am disappointed that the Committee appears to have not understood the suffering this disease has on patients and lives of family members. I urge you to reconsider permitting the use of Tolvaptan in Britain as it is the only hope of bringing some relief to patients.	Comment noted. See points raised in responses above
Patient 14		I have PKD myself, my mother and father have it. My mother is asymptomatic but my father had 2 years of dialysis and then a successful transplant. My older sister also has it and is feeling the effects, she's currently being tested for a match with her husband and friend. I also have it, apart from reduction to my function levels I'm not noticing any effects yet but I am in a steady decline. This wouldn't just change my life, it could change my family and my world.	Comment noted. See points raised in responses above
Spouse of person with PKD		My husband has pkd and has in the past been given the hope that he could be an ideal candidate for this medication. He is young and healthy but we live in the knowledge that his health is borrowed time and the inevitable future will be years of struggle. A drug that can help him in anyway needs to be considered on more than just cost.. You need to look at the people whose lives could be changed immensely. You need to look at the families in need of some hope.	Comment noted. See points raised in responses above
Patient 15		Thank you for your careful investigation of the merits of tolvpatan for delaying symptoms of autosomal dominant polycystic kidney disease. However, some aspects of the disease seem to have been given too little consideration. PKD is a disease of the poor. Not because poverty causes PKD but because PKD impoverishes families. This is a disease which affects 50% of the members of a family, debilitating many of those of working age to the extent that not only are they unable to earn money or perform any substantial share of the household chores but that they also affect the earning power of other family members by needing additional care.	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		Families like this cannot build up resources to help smooth out the bumps of ordinary living. Famously, many young people today get help from "the Bank of Mum and Dad", but not if the parents' income disappeared prematurely and there are several other relatives of varying generations in need of extra help. The loss from the work force of older and more experienced workers is unfortunate for the families, and unfortunate for the country. Buying more years of a useful working life would be valuable. It is easy to find a list of the special tailored support that people with PKD receive from the NHS. For almost all of us, any blank sheet of paper will do. We receive a service designed for everybody else with chronic kidney disease, and it often seems to be given begrudgingly. Why bother about people for whom there is no effective treatment? (Unfortunately, that attitude seems to hold even when we are seeking available relief from extremely unpleasant symptoms. Our GPs often do not have the experience to be of much help, and the doctors who do have that experience appear to feel that people with an untreatable disease do not merit their time.) Many people with PKD believe it is our lack of economic clout that has left us so unsupported. Individually, we usually do not have the money, time or energy for attention-getting campaigns. That 50% chance imposes a great cost on families. Our lack of visibility is compounded by the fact that people with PKD may not be able to work long enough to reach senior decision-making positions, and even our unaffected siblings can have been hampered in their careers by an upbringing with less available money and more necessary responsibilities than their peers. We would all have preferred that people with PKD mattered enough for there to have been accurate statistics for you to have worked from. There is another pernicious effect of the age at which PKD first makes its effects felt. This is a disease of people who have children still living at home. The quality of life of those children can be badly impacted by the illness of a parent, and not just by the financial aspect. Pain and fatigue can limit the interactions between parent and child, whether it is a crying toddler who needs to be picked up and cuddled, a primary school child with energy that needs wearing off with a ball game, or a troubled teenager who might bring themselves to talk more easily if they could go for a long walk with a parent. These things need doing now -- they can't	

Role*	Section	Comment [sic]	Response
		wait until another day when the parent might be feeling better. Every bad day is a day lost forever. Family evenings are less fun if one parent is too exhausted to talk and the other parent is busy seeing all the chores are completed. And all too often the strains have broken the family unit and there is just a single parent who is both exhausted and having to try and hold everything together. Of course a child in a family with PKD is likely to be making a larger-than-usual contribution to the household chores, and may explicitly be a carer for their parent. The children of a parent with PKD will learn that it is a hereditary disease, and one that they may have. It is very difficult to see a parent in pain and distress which you cannot alleviate. To know that it is possible that you will be in the same situation later is a terrible burden to bear. If tolvaptan can buy families a few more years of normal family life, that is hugely valuable. The children of parents with PKD deserve to have their quality of life preserved as much as possible. Many of these children were only born because their parents believed that effective medications for PKD would appear on the scene shortly -- to allow a parent to have the health to care for the child in the way that they would like to do, and to help the child live a more normal life when they are an adult. We hope that tolvaptan is only the first step along the road to major improvements for the life of people with PKD, but it is a very important symbol of that better future.	
Patient 16		I have ADPKD and have always hoped Tolvaptan would be a lifeline for sufferers. There are no other drugs available. I hoped the drug would help my daughter who has early signs of the disease and maybe my grandchildren. Surely sufferers of ADPKD should be given hope as the drug may delay kidney failure. Canada and Europe have approved the drug please give sufferers in the UK the chance to be given this drug. My late son, A PhD. Biochemist was so excited when research was being done on this drug. Please, please give further consideration to approving Tolvaptan.	Comment noted. See points raised in responses above
Patient 17		I would like to repond to the recent decision on the use of TOLVAPTAN, I was rencently diagnosed with ADPKD. and think that Tolvaptan may help to slow down the deterioration of my kidneys, allowing me to keep working and contributing to society eg my taxes etc. instead of me being a drain on	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		the NHS and social security. I therefore urge you to reconsider this decision & allow me and others to lead a relatively normal life.	
Patient 18		I am having problems trying to submit a comment for the Tolvaptan appraisal for poly cystic kidney disease. Please can this be forwarded to the correct department. I have APKD and I am currently lucky with good functioning kidneys and would hope to prolong this for as long as possible, I am fit and healthy, do not smoke, exercise regularly, I am not overweight and would like this to remain so and avoid the need for dialysis should I run into problems in the future as my disease progresses. Surely the cost of Tolvaptan would be more cost effective than dialysis 3 times a week and all the other cost any other complications will incur. I would like to support approval of Tolvaptan by NICE.	Comment noted. See points raised in responses above
Patient 19		Having been unable to leave comment on your website (I am registered) I hope this email response for the Tolvaptan Appraisal Committee will be put forward for consideration. As a patient suffering from ADPKD and a suitable candidate for the new drug Tolvaptan I am extremely disappointed to hear that the NICE are not to recommend Tolvaptan to treat the condition. This drug would give hope to people like myself and their families who deal with the incurable condition on a daily basis. My kidney function is OK, but I have chronic pain which at times is acute - I recently suffered burst cysts from which the fluid went into my pancreatic cavity. This was debilitating for a number of days and took several weeks to recover from. The only 'treatment' was pain relief - most are inadequate and so to be pain free I used strong prescribed medication, which have its own side effects. I also have the additional complications of hypertension an increased risk of brain aneurysms (my grandfather died from one) and polycystic liver disease. I used to be very active - 6 years ago I competed in a mini triathlon - but now find it difficult to participate in any activity as I become very breathless. This concerns me on an emotional level as I have an active family and can no longer join them, but I am also worried that it will have a financial impact if I am unable to continue working (I am already denied life	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
		insurance and was unable to get a mortgage which places a great burden on my husband). Surely the cost associated with long term dialysis that I am likely to face (my mother was on dialysis for 17 years and my brother is on dialysis after having both kidneys removed) must be worth an alternative treatment being sought? I am extremely disappointed that I, and many other like myself, are to be denied access to a licensed therapy which has the potential to improve the quality of our lives, but also the lives of our family members and those of future generations.	
Partner of an ADPKD patient		As the partner of an ADPKD patient, I am disappointed to see that that NICE have not recommended that Tolvaptan be used to treat this condition. Over the last three years, my wife's lifestyle has been greatly affected through weight gain (approximately 15KG), breathlessness and general severe abdominal discomfort and she is no longer the active person she used to be (she competed in a triathlon 6 years ago). Until her kidney function is sufficiently reduced that she requires dialysis, there is currently little effective treatment available to ease her discomfort. Transplant, apparently, is not an option while her kidneys have sufficient function. She has read that she might be a candidate for the trialling of this drug given her current kidney function. To have this option removed before the drug has even been trialled is a grave disappointment. Her mother was on dialysis for 17 years due to the same condition. Her younger brother recently had both kidneys removed, has been on dialysis since and is awaiting a transplant with little sign of one forthcoming. Surely the costs associated with long term dialysis that both he and my wife potentially face must be worth an alternative treatment being sought? I trust that these thoughts will be taken into consideration before the final recommendation is made.	Comment noted. See points raised in responses above

Role*	Section	Comment [sic]	Response
Patient		With polycystic kidneys the doctors plotted its development but could only control my blood pressure and diet for several years before failure and dialysis to stay alive. I have had very successful transplant and realise how ill I was before this. My daughter has inherited the disease as I did from my father and this new drug would hopefully make a better life for her as it develops.	
Carer		I am very disappointed by the initial decision to reject the use of Tolvaptan in England and Wales. My son has PKD despite the fact that there is no history of the disease in the family. The condition seriously affects his life both in terms of his physical and mental wellbeing. He will almost certainly need a kidney transplant before the age of 40 unless the progression of the disease can be slowed. Tolvaptan offers some hope to patients who at the moment have no effective treatment available. The cost to the NHS of drugs to alleviate symptoms provide dialysis and carry out transplants is considerable to say nothing of the cost to individuals in their physical and mental wellbeing . I believe Tolvaptan is authorised for use in Canana and Japan and would respectfully ask that the Committee reconsider their original decision and permit its use here.	Comment noted. Please see points raised in comments above.

Role	Patient
Comments	540 With polycystic kidneys the doctors plotted its development but could only control my blood pressure and diet for several years before failure and dialysis to stay alive. I have had very successful transplant and realise how ill I was before this. My daughter has inherited the disease as I did from my father and this new drug would hopefully make a better life for her as it develops.

Role	Carer
Comments	541 I am very disappointed by the initial decision to reject the use of Tolvaptan in England and Wales. My son has PKD despite the fact that there is no history of the disease in the family. The condition seriously affects his life both in terms of his physical

Comments noted. Please see points raised in comments above.

Role*	Section	Comment [sic]	Response
		and mental wellbeing. He will almost certainly need a kidney transplant before the age of 40 unless the progression of the disease can be slowed. Tolvaptan offers some hope to patients who at the moment have no effective treatment available. The cost to the NHS of drugs to alleviate symptoms provide dialysis and carry out transplants is considerable to say nothing of the cost to individuals in their physical and mental wellbeing . I believe Tolvaptan is authorised for use in Canana and Japan and would respectfully ask that the Committee reconsider their original decision and permit its use here.	

Role	Patient
Comments	543 Hello, Having read through much of the research to do with Tolvaptan - it appears to me that there is a correlation between the drug and a slowing down of this most unpleasant degenerative disease. I have known that I am a sufferer since the age of 21, I am now 38, I inherited it from my Father who was on dialysis/had a kidney transplant and lived for 17 years without his original kidneys functioning. The emotional aspect of peoples lives slowly being drained away by this disease is obviously not something that is particularly important in this study. Obviously overall cost with NHS funding as it is is supremely important. But the fact that most of the rest of the civilised world have taken this drug on as a successful slower down of PKD should surely surely be something NICE should listen to. Canada for example are NOT a silly country that wastes money. They see a drug that HUGELY INCREASES the good quality and relative value of PKD sufferes lives.. I could not even begin to tell you how much difference and extra 5 or ten years of functional

Role*	Section	Comment [sic]	Response
		kidneys would mean to me. It literally brings tears to my eyes to think about it. The stress and strain that is caused by certainty of future kidney failure is one of the bleakest feelings you can imagine. The HOPE that this drug and its successful intergration into other countries PKD treatment brings, is only equal to the despair that NICEs deeply short sighted response to Tolvaptan has caused. Why do we have to be the country that simply cannot see hope, value of life and frankly, very positive medical results over burocracy and accounting. The result saddened me deeply. I can only hope that when the board reconvene they can try to see that people living for longer without there kidneys failing IS an important thing. Even down to the simple fact that if I can work until I am 60 rather than 50 I can put at least an extra Â£100 thousand of tax into the country... I would beg the board to reconsider their verdict. As for the side effects issue.. I do not know a single human being who would prefer to be on dialysis over the side effects of a drug. And it is truly truly idiotic to think that is even a possibility. Thirsty and still functioning kidneys? I would take that EVERY SINGLE TIME and I cannot think of a human beaing who would not.	
Role	NHS Professional		
Comments	544 My mum was diagnosed with ADPKD. She has cysts on her liver and kidneys. Sometimes the pain she suffers from the size of the cysts, or from a cyst bursting is that severe that she can hardly move. She is in constant pain in her day to day life. This drug would dramatically improve her quality of life. I think it is disgusting that it has been deemed as not cost effective when it will reduce the need for dialysis in the latter stages of the disease.		
Role	Patient		

Role*	Section	Comment [sic]	Response
Comments		545 As a PKD patient, it has been 11 years since the disease was diagnosed at age 28. As well as the hypertension as a result of the disease getting progressively worse since diagnosis, I have now begun to experience discomfort when I sit, lie down or move into different positions due to the enlarged nature of my cystic kidneys. I am also exhausted continuously which means I can't work. I walk and swim to stay fit, but when I walk too much, or it is too hot outside, my ankles swell up and my feel become extremely uncomfortable, making longer walks of 10,000 steps and up unmanageable. This doesn't help in managing my weight, as you can imagine. I have been prescribed antidepressants for the feelings of hopelessness and fear of developing renal failure. I witnessed my father going through the process of dialysis and infections to his kidneys and various stays in hospital - which I do not think I could bear to endure myself. I had been given hope by the Tolvaptan trials, and by the fact that the drug has been found to help stem the progression of the disease. I could bear living as I am but the thought of the disease getting worse, and ruining my quality of life further is very distressing. I have many dreams and ideas of things I would like to achieve - but more and more I can see these slipping away, as time brings me closer to a life of dialysis, followed, if I am lucky, with the trauma of a transplant, and the rest of my life on the great number of anti-rejection drugs which my father was on after his transplant. The cost of all this to the NHS plus the cost of people becoming unable to work, with the associated costs to the exchequer and the welfare bill are surely critical in considering the whole picture of the cost of Tolvaptan. In my case, I am a housewife, and not in receipt of benefits - however, my husband is in the top 1% of earners, and our son is currently predicted a stellar		

Role*	Section	Comment [sic]	Response
		academic career. But, we are going to have to leave the UK and move to a nation where Tolavptan is available - thus reducing tax income to the nation of Â£75k per annum as of now, with the prospect in the near future of very much greater earnings. This is a sad day for us as we love the UK, I have been contributing as a charity volunteer and we can see our son going far as he continues in education - but this is simply not workable. Our experience of hospital stays in the NHS have not been favourable - with dirt, unhelpful staff and frightening patients all helping us in our decision that without treatment to prevent my having to end up in hospital with renal failure, we cannot afford to remain in this country. The NHS has a monopoly on care in the UK, and as such private insurers do not take people like me on - unlike the system in France, where my father received first class care till his death. We will have to take away our great contributions to the UK and move to a country which will not only value us but also look after us properly. I clearly hope you will reconsider your decision to reject this important drug - and that you consider the greater cost to the economy of this disease, left untreated, but also the cost to the individual and their families of the emotional burden of getting progressively sicker, and possibly dying - since the UK has been an abject failure at ensuring people opt out of organ donation it is likely more and more people will die of this disease - this will also be on your conscience.	

Role	Patient
Comments	546 I am saddened to hear that NICE has initially rejected Tolvaptan. I was diagnosed with ADPKD ten years ago (at 38) and I have been learning more about my disease and regularly attending renal clinic for results, ever since. My kidneys are

Role*	Section	Comment [sic]	Response
		growing steadily and significantly, as my kidney function gradually decreases. I have two young daughters and I hope that they will have an effective drug to treat them, in future, if they are found to have inherited ADPKD from me. Knowing that I have ADPKD, and that there is no drug treatment currently available, has significantly affected my outlook on life and my hope for a 'normal' middle/old age. It would make a tremendous difference to me to know that I could slow this progression to end stage renal disease by taking a drug on a daily basis. From what I have read and heard about Tolvaptan, I have good reason to believe that it is indeed an effective treatment, and I am aware of its availability on prescription in Canada. Therefore, I am dismayed to learn about this initial rejection in England and Wales and I wonder whether the immediate cost of introducing the drug has taken precedence over the long term benefit of having fewer patients to treat for dialysis/transplant in the future. I urge NIC to reconsider.	
Role		Public	
Comments		547 My husband has advanced polysystic kidney disease and we are in the process of donation. I do not want my 2 young daughters to have to go through this nightmare. PLEASE reconsider your position very carefully. You can and should do all you can to try help people like us. Give it a chance.	
Role		Patient	
Comments		548 I suffer from ADPKD as do other members of my family. Please think twice about your decision not to authorise tolvaptan. My	

Role*	Section	Comment [sic]	Response
		consultant at Kings is very keen on it and has mentioned it to me as a possible ray of hope. Please reconsider even if it is only suitable for a small number of sufferers, Its a horrible thing to live with and effects not just only the patient but their friends family and work colleagues.	
Role		Public	
Comments		549 Although too late for my husband, who is already in end stage kidney failure and on dialysis, I urge you to reconsider allowing doctors to prescribe tolvaptan to patients who suffer with PKD. If a drug had been available which slowed cyst growth this would have meant a reduced number of drugs needing to be prescribed . For instance, before ESRF my husband needed numerous blood pressure medications, EPO, iron infusions, aspirin (to reduce the repeat TIA risk). He is now on dialysis aged 51 and is unable to work as effectively as he did before ESRF. If a drug had been made available sooner, then it might have reduced the need for some or all of his inpatient stays when he got a UTI or other associated complications. Finally, I do not work for Otsuka, and have no connection with them, I have, however, worked in the pharmaceutical industry so am aware of the cost of discovering new drugs and bringing them to the market. With such short patenting periods, the drug companies need to recover some of these costs in order to fund research into further innovative drugs. Please take all these other costs into account, rather than just rejecting Tolvaptan straight away. Thank you for your consideration.	
Role		Patient	

Role*	Section	Comment [sic]	Response
Comments	550 Please don't reject Tolvatpan. We know it isn't a cute for all but this is a significant step forward after years of no government funding. My family has been substantially affected by polycystic kidney disease and our children deserve a chance to delay the onset. The continuous physical pain is made all the worse by the lack of any drugs to combat the disease and provide the all important hope.		

Role	Carer
Comments	551 We are truly disappointed to hear that tolvaptan has been rejected. This could not only make a huge difference to my husbands life, but also the life's of my two young children.

Role	Patient
Comments	552 For years my family has watched and waited for this drug to be approved. After a life time of being told there was no cure or treatment for this debilitating disease there was finally hope. When it was approved for use across Europe, we rejoiced. I had participated in an 18 month trial to support the drug trials and it was finally paying off! Only to be told a week later that it had been rejected due to cost! We were devastated. How can you put a coat on quality of life? I lost my grandfather, Aunty and Dad to this disease. I watched my dad die slowly over four months and sat with him the night he passed away.

Role*	Section	Comment [sic]	Response
		My sister and I are both suffering from the effects of this disease and my son was diagnosed at the age of ten. He's 13 now and I had hoped that his quality of life would not be impaired by this disease, or at least that the effects could be postponed for many years. To deny people access to the only treatment is cruel and short sighted. I cannot believe that years of medication to treat the effects of this disease, along with the cost of dialysis, transplants, associated drugs, surgery costs and staff , as well as benefits when people are unable to work,can be less expensive than a drug that has been proven to slow down the progression of this disease. Please stop thinking short term	
Role		Patient	
Comments		553 As a person who suffers from PKD and has seen many family members suffer and die from this dreadful disease I plead with you to please find this treatment. I have been waiting for many years for this breakthrough treatment. PKD affects my life every day both emotionally and physically. My kidneys are still functioning ok and I have been pinning my hope on something helping to prolong my kidney life. Something that can help me live a better, more productive and healthy life and ultimately those of my children who have no doubt inherited this disease as well. Please reconsider your decision, you will be saving lives.	
Role		Public	

Role*	Section	Comment [sic]	Response
Comments		554 PKD affects my girlfriend and several of her family. This research, and medication gave them hope that they may live longer, healthier, and avoid the difficult life relying on dialysis. Please review this decision on behalf of my family and the many other sufferers.	
Role		Patient	
Comments		555 I am health professional who also suffers from ADPKD as does my mother, aunt, cousin and my daughters are yet to be tested. ADPKD impacts on my life and that of family members . My mother is currently waiting for dialysis. If there is a drug available that can slow the progress of this disease then I wholeheartedly support it. I worry about my children as I am aware of the 50:50 chance that my 3 daughters have of having this disease. ADPKD is a disease that does not only affect the physical health of sufferers but their mental health also....I worry about my future and hope NICE reconsiders it's rejection and on line with Canada and the alEuropean commission approves JINARC as the first licensed drug to treat adults with ADPKD . This will not only give myself hope that the deterioration of my condition will be delayed but that there will be hope for my daughters. Please license this drug .	

Role*	Section	Comment [sic]	Response
Role	Parent		
Comments	556 As a parent of a child diagnosed with ADPKD I would like to express how deeply disappointed I am that you have not recommended the use of Jinarc for the treatment of this disease. My daughter is a 3rd year dental student at Bristol University and her studying and daily life is very difficult due to the symptons of this disease. She is often in agony due to infections and this has an adverse effect and a massive impact on her life. People with ADPKD have been waiting for a lifeline from this deadly disease and when Tolvaptan came along it seems their prayers were answered but this hope has been taken away by the decision of NICE. I cannot understand how NICE have decided that this drug does not deliver a cost effective benefit to a person with ADPKD and I urge NICE to rethink their decision to reject this drug.		
Role	Patient		
Comments	557 I have the condition ADPKD which I inherited from my father. Having seen everything that he has had to go through since his diagnosis is horrific, leading to a full Kidney transplant of which my mother donated her kidney to him! This disease has affected our whole family with the stress and strain of living with this horrendous infliction - I really feel that you should please reconsider your verdict to license this drug for use in ADPKD treatment. I personally do not want to have to go through everything I've seen my poor dad go through		
Role	Patient		

Role*	Section	Comment [sic]	Response
Comments		558 I am a patient with APKD; my father had end stage renal failure from APKD and needed dialysis in his early 60s. I am also a GP working in inner city practice. I believe that this disease places a significant burden of symptoms on WORKING AGE adults,and therefore your calculations of QALY for tolvaptan should reflect this, including time off work, medications and health contacts that others of a similar age do not require. As retirement age is INCREASING, to enable the country to pay pensions for everyone, surely there is a cost benefit that has not been fully explored by enabling people, such as myself, to reduce cyst size and progression, and to end up with a longer healthy working lifespan to contribute to the UK (and in my case, disappearing species of inner city GPs!) economy? For these reasons the appraisal of cost effectiveness of Tolvaptan needs to be reviewed.	
Role		Partner of PKD sufferer	
Comments		559 I am due to be married this coming October- my partner has been diagnosed with pkd and is in good health at the moment. However his mother and his granny who also suffer both have received kidney transplants- his granny's now failing after 6 years. My partners uncle also suffers from the disease- he unfortunately has suffered bleeds in the brain. Now we are getting married we are thinking about starting a family in the near future- currently going through genetic counselling , the future is unknown for my partner and also my future children. At a recent hospital consultation we were told of this drug being on	

Role*	Section	Comment [sic]	Response
		the horizon , now to be told it may not be available is heartbreaking. I look at my family's future, and as a nurse Myself see patients suffering from this and beg that you reconsider this decision. Too many generationd have suffered I pray that it won't go on. Please please see the dramatic change this could make to thousands of families.	
Role		Public	
Comments		560 Please could you reconsider your decision. My two sisters and two nephews suffer with this. You could could prolong their lives, save their pain and let them have a better way of life!	
Role		Patient	
Comments		561 Polycystic Kidney Disease has a big impact on the lives of patients and their families, knowing that the patient's condition may deteriorate dramatically. The uncertainty is a constant worry in our lives. Tolvapton was greeted with great excitement within the community of medical staff and patients, followed by immense disappointment by the decision not to recommend the drug for use in APKD. We feel that a lifeline that was in our reach has been snatched from us and implore that the decision be reconsidered.	
Role		Patient	
Comments		562 I have pkd and this drug would have saved my family from stress and heartache whilst caring for me. It may have helped me avoid having 2 heart attacks and costing the NHS money to	

Role*	Section	Comment [sic]	Response
		trear those conditions. I may also have been able to contrubute to the economy longer by delaying my need for dialysis. Please reconsider and approve this drug.	

Role	Public
Comments	563 This is very upsetting and worrying. My two sisters and nephew have this disease. This treatment will prolong their lives, improve their health too. I think it is a huge mistake and the decision needs to be looked into again.

Role	Patient
Comments	564 I watched my father die of PKD related illness. I saw him endure dialysis where he would frequently bleed out. I saw his suffering. Since my diagnosis, I have been doing everything I can to stop getting end stage failure, from monitoring my blood pressure to drinking 4 litres of water a day as this was the only thing my nephrologist could recommend. I understand that the NHS, which kept my father alive for 10 years, is financially stretched but the financial cost of dialysis and all the associated medication that goes with PKD is surely a huge cost too, not to mention the economic cost and the emotional suffering. I chose not to have a family based purely on my PKD. I could not forgive myself if I gave it to my child too knowing there is nothing to help them. Please reconsider your appraisal. Please look at the wider costs of this ticking time-bomb of a disease. Please help me and others like me.

Role	Patient

Role*	Section	Comment [sic]	Response
Comments		565 This was the only hope available for my family and other pkd patients and desperately needs to be reviewed and approved to save and improve lives. This new drug could help so many people suffering this disease and I desperately urge you to reconsider tolvaptan and please accept for administration in UK	
Role		Patient	
Comments		566 This drug could change the lives of many patients. By postponign the need for dialysis I may be able to work long enough to enure financial security for my family. As the major wage earner I need to keep working. Whilst possible to remain at work during dialysis it is nto going to be easy, will require more time off, will affect my performance on a daily basis and all in all I will be dependent on having a considerate employer. Failing this I will be dependant on State aid. Whatever this drug costs it must pay for itself compared with the costs of treatment for kidney failure and the loss of economically productive years for patients. I understand that there could be liver consequences, but not all patients experience them and nothing is lost if you have to stop, but there is a lot ot gain. This isn't a cure but it prolongs the healthy, independant and contributing years of patients lives. Even if I stay healthy for just a few more years then that time that I can be providing for my family and not needing external support.	
Role		Patient	
Comments		567 I wanted to add my support for approval of Tolvaptan. As a retired GP, I suffer from ADPKD, and have been the recipient of a kidney transplant from my wife. My daughter has now been	

Role*	Section	Comment [sic]	Response
		diagnosed with the condition. I want her to have the benefit of a medication that will improve her chances of preventing chronic renal failure in the future.	

Role	NHS Professional
Comments	568 SInce being made aware I have this condition I am constantly worried about my future. I have taken all the steps in my power to improve my health . I am at the stage 3A where I believe this drug could be of great help to me live a normal life. My father died at 62 . I am now 48. I constantly worry about dying so young. I employ people and worry about who will take over when I am not able to work, I feel isolated and alone with this condition. I wish in a way I had never been informed about it as the knowlesge I have this relentless condition I can do nothing about makes me feel tearful and hopeless. I was really happy when I thought there may be something that could slow down the disease process as this gave me some hope whch has now been taken away again by your decision not to fund on a not being cost effective basis

Role	Patient
Comments	569 Why is Tolvaptan not being used ? PKD is a life long disease , my family is suffering this terminal disease ... I can't work because of this !! my father and his sister died because of this !!! my daughter is suffering now and only just 16 years old , has missed 50% of her schooling the last 2 years ... her outlook is poor as she suffers kidney pain 24/7 ... this new drug could help her enjoy life while she is young ... Cancer !!!!! well they get all the funding all the drugs .. yet PKD .. has to fundraise to help pay for the research that has bought TOLVAPTAN to this stage

Role*	Section	Comment [sic]	Response
		... other countries have start this drug to help people who suffer with this ..... if you had this !!! wouldn't you want to be able to have this drug ???? thanks for reading this	

Role	Patient
Comments	570 Please reconsider approving Tolvapan to slow down the process of kidney failure in APKD. For myself it is probably too late, but for my 2 sons it can make a huge difference. I have known about my condition for nearly 30years, it is like living with a time-bomb, if my sons who know they have inherited the disease, knew there was a drug that could help them live a normal life for longer, they may not live the same time-bomb life that I have, please give them the opportunity, thank you.

Role	Carer
Comments	571 Tolvaptan is the first real hope that our family has that may delay the need for dialysis, which will cost so much more than the pills. Please do take away our hopes unless you have another more effective treatment that is proving that it will be better. I have a husband. Two daughters and one granddaughter so far (3 undiagnosed yet). A brother in law, a niece and 2 nephews. This is such a big deal for our family.

Role	Carer
Comments	572 Whatever the draw backs of this new treatment it is far far preferable to Dialysis which is a really difficult treatment and which creates depression sexual dysfunction isolation and dependency issues for all its patients. The issue of thrist is

Role*	Section	Comment [sic]	Response
		paradoxical as on dialysis the patient cannot drink... or eat what he likes... and the body suffers in many ways... and with transplants the poison of the rejection drugs and steroids are far worse than the Billirubin fears... AS far as the expense is concerned... unless the drug is used it cannot be developed and refined through time - so it should be allowed to be used in specific cases to begin with. To dismiss is very short sighted.	

Role	Carer
Comments	573 My 18 year old daughter has PKD, her kidneys are enlarged and covered in cysts, she has frequent infections. Her father has the condition, her grandfather died aged 47 of the condition. Please give her some hope. The trials show some success with Tolvaptan..what other hope or help does anyone with PKD have?

Role	Patient
Comments	574 I believe tolvaptan should be available in the uk for all patients with PKD

Role	Patient
Comments	575 I think Tovaptan should be available to patients in the UK as it is in Canada.

Role*	Section	Comment [sic]	Response

Role	Patient
Comments	576 I am very disappointed that NICE do not believe this drug will deliver a cost-effective benefit. We as a family believe there are major benefits, particularly for our children wo are at risk of developing ADPKD. We feel they should have the best medicines available for treatment of the early stages of the disease. Also, anything that has the chance of limiting the development of this disease should be considered especially given the costs of long term care and transplant treatment. Please will you reconsider?

Role	Patient
Comments	577 As an ADPKD patient, the possibility of treatment, for me, for my family, for any child I may one day have, brought a lot of hope. Tolvaptan may not be the perfect treatment but it is a start. Even if it only helps in certain cases it is worth authorising.

Role	Patient
Comments	578 As a patient I find it disgraceful that you have decided to not allow the use of tolvaptan which would increase the my amount of "active" time before I need to start worrying about kidney dialysis/transplant and delay my eventual death to PKD. Why do I pay taxes?

Role	Patient

Role*	Section	Comment [sic]	Response
Comments		579 By not recommending Tolvaptan for the treatment of ADPKD NICE has removed any hope of a delaying treatment for this disease for thousands of people currently suffering with the associated symptoms of this disease. There does not seem to be a logical medical based reason for denial of this potential delaying treatment which therefore means the decision seems to be taken for financial reasons rather than benefits to patients. This is not right and will not improve the QOL for many patients. Currently there is no SOC for ADPKD and no treatment of the underlying disease. If Tolvaptan was to delay the need for dialysis or transplant surely that would be a good thing.	
Role		Patient	
Comments		580 As a Pkd sufferer, I was extremely disappointed when I heard that nice were not going to approve tolvaptan due to financial matters. My grandad had it who had go on dialysis for the remainder of his shortened life, my mother has it who was at a similar age to when he died, I have it and it's a strong possibility my kids may have it. It would mean so much to me as I worry about all our futures. Thanking you, please reconsider!	
Role		Public	
Comments		581 I have been closely following the Tolvaptan trials over the last few years, and was hopeful that NICE would endorse the product in the UK, thereby giving hope to current and future sufferers of ADPKD. As a sufferer myself, one who is nearing the end lifespan what such drugs as Ramipril, etc can do for me, and as an imminently expectant father to a child with	

Role*	Section	Comment [sic]	Response
		potential ADPKD, it is a great disappointment that NICE has turned down Tolvaptan. I urge NICE to please reconsider their decision, and help those of us afflicted to have a better chance at achieving our hopes and dreams.	

Role	Patient
Comments	582 I am a recently retired GP, having had to give up work on health grounds. I have ADPKD, and have considerable personal knowledge of the effects of this disease, as my father and uncle were killed by the disease, and my brother and my two sons have the condition. The TOPIC 3:4 trial would suggest that tolvaptan has a marked benefit in reducing cyst development and slowing the decline in eGFR. This could mean many who now face a prospect of renal replacement therapy in later life might now never require dialysis. I worry about the signal you are sending out if you reject tolvaptan, as it would surely act as a disincentive to the pharmaceutical industry to invest further funds in the development of treatment for ADPKD. When statins were first developed, they were extremely expensive and I remember reading journal articles saying that these drugs should be rejected as they could bankrupt the NHS. However, the clinical case for them rapidly became overwhelming, and far from bankrupting the NHS, they have played a significant rÃ´le in reducing NHS spending on cardiac care, and the drugs are now a fraction of their initial cost. It is too late for me to benefit from tolvaptan, but it would offer my sons the possibility of a dialysis-free future.

Role	Public

Role*	Section	Comment [sic]	Response
Comments		583 The impact on family and close friends is significant as prime earner`s income stops and lifestyle changes significantly as well as partner having to be main earner plus carer and mother to teenagers .	

Role	Carer
Comments	584 Hi, I am the parent of a 12 year old girl, who has multiple cysts on both kidneys. She is monitored every 4 months at alder hey. BP and Blood tets and urine checked. Throughout her short life she had dealt with wetting issues, water infections, headaches dry skin, itchy skin but on the whole has been ok. We know however she is a ticking bomb and there isn't a day goes by where i dont question myself through guilt, worry about her future, worry about our familys future and the strain and struggle ahead. The constant news that there is no cure, no support, no medicines to slow cyst growth or help with pain relief is heartbreaking and really makes you feel helpless. So when tolvaptan was released this was the first bit of positive news i had heard since finding out about PKD. I was hopeful that at the very least this would slow cyst growth down and prolong my daughters kidney health. We are aware that she will need to undergo transplant at some point so my own life and close people tend to hold back socially to hopefully day be a donar and a healthy one at that. when required. The news that you have rejected this drug is another massive Kidney blow... and although you have your reasons, expense shouldn't be one of them. I hope you revisit your decision and maybe one day that one bit of positive news PKD patients seek will actually happen.

Role*	Section	Comment [sic]	Response

Role	Public
Comments	585 I am aware of the severe difficulties this disease has to those who suffer it, including persistent, increasing, chronic pain, and low life-expectancy. The impact on quality of life is significant and longstanding, particularly as this can develop at a young age. Tolvaptan is the only treatment available for this disease, it is treatable and there are no alternatives, as such, it is cruel and unjust to make it unavailable on the NHS. As this disease has a high chance of being passed on, surely younger generations to come are at an increasing risk of exposure to this disease - in which case we should be encouraging investment and research in to this area, rather than removing the incentive by deeming these sufferers as unworthy of treatment. This is precisely what NICE will be doing by removing access to the only treatment available.

Role	Parent of a PKD Sufferer
Comments	586 Please reconsider recommending Tolvaptan. I lost a beautiful sister to PKD my daughter also has this dreadful disease, I want my daughter to live a full and happy life with her son and any other children she may have in the future, we need some hope, Tolvaptan could possibly bring this hope. Please reconsider.

Role	Public

Role*	Section	Comment [sic]	Response
Comments		587 I have advanced stage PKD and this drug would not benefit me in an way. However, my youngest son also has the disease And I would very much like that he had the opportunity to have a drug that can slow down the growth of cysts. He would then hopefully not have to have dialysis or a transplant. Therefore, please give this serious thought and think of the potential benefits of providing a better quality of life for this with this disease. Kind regards Ken.	
Role		Patient	
Comments		588 I am a sufferer of PKD which was passed down to me through my mother. My son has been confirmed with it and has 3 children who may have inherited this disease. They are too young to be tested yet. It is the most common kidney disease but has no treatment whatsoever at present. Please give families like us a chance to at least slow down the progression of this disease. It is too late to benefit me but could benefit my son and my grandchildren. I do not want them to suffer as my mother did and I am now. Please listen to us - we feel forgotten. Cancer gets all the headlines and treatment but there are a significant number of us too.	
Role		Patient	

Role*	Section	Comment [sic]	Response
Comments		589 PKD has affected me with very large kidneys, severe and chronic flank pain which has now cost me my job. This treatment was a last hope to keep my existing function for as long as possible. If it reduced the pain as well this would have been an added bonus. I'm only 35 and shouldn't be considered for medical retirement.	
Role		Patient	
Comments		590 As a PKD sufferer there is currently no drug for us to slow down this horrible disease which affects us in many ways and limits lifestyle. Please support it to ease the suffering	
Role		Patient	
Comments		591 As an ADPKD patient, I was dismayed that NICE has rejected Tolvaptan. I watched my mother and two of my aunts die from this disease, and nothing has radically changed in the treatment of it in 40 years. Tolvaptan is the light at the end of the tunnel for many sufferers who, like me, face the prospect of life on dialysis. Waiting for your kidneys to fail completely is living with a death sentence. It is stressful and depressing. Tolvaptan offers some hope to sufferers. Surely, savings would be made on not having so many dialysis patients, fewer transplants needed, and less frequent visits to clinics. I would urge you strongly to reconsider your decision and give hope to the thousands of patients whose quality of life could be improved.	
Role		Patient	

Role*	Section	Comment [sic]	Response
Comments		592 I would like to ask you to carefully reconsider the decision not to recommend tolvaptan to treat ADPKD at the second appraisal meeting on 7 July in Manchester.	
Role		Patient	
Comments		593 I was devastated to read that NICE had initially rejected the drug Tolvaptan. Can you imagine that having know from an early age that my kidneys were deteriorating, following in my fathers footsteps onto a life of dialysis, that because of your decision my daughter is condemned to the same life? We knew that she had PKD before she was born as we saw the cysts on the untrasound. We also knew that like my father and myself, there was no drug or treatment that could stop or slow the growth of cysts until we heard of the successful trials or Tolvaptan. For a time we believed that maybe there was something that could halt the expectation of a life of dialysis and now that hope is removed by NICE's decision. Dialysis is cruel, it is not a treatment as there is no chance of getting better, it is a slow death sentence and there is no life while on dialysis. It is just a painful existence that many more will be condemned to unless the decision is reversed. Please go and see a dialysis unit before you reconsider on Tolvaptan and keep as many people off dialysis for as long as possible. Remember that the tablets are cheaper than dialysis and all the associated drugs	
Role		Patient	

Role*	Section	Comment [sic]	Response
Comments		594 I come from a large family who is extensively affected by PKD. My Father is one of 12 siblings - 6 of whom are affected and have all undergone kidney transplants as a result. This genetic condition has been passed down to many more family members, myself included who are all preparing to undergo transplants at some point in our lives as no other treatment is currently available. From the studies and trials that have taken place, this drug could help in delaying or even removing the need for a transplant for many people, greatly decreasing the strain on the NHS for treatment such as appointments, scans, blood tests, dialysis, surgery and a lifetime of aftercare following a transplant. To not authorise the use of this drug would be a shameful waste of years of research into the causes and treatments for this disease and could prevent thousands of people living relatively healthy lives without the need for transplants which are so few and far between. I hope and wish you will reconsider your decision. Kind regards	
Role		Patient	
Comments		595 This disease had blighted my family for several generations. Any drug that can slow down the symptoms in my eyes is essential and NICE souls approve use of this drug immediately and across the board .	
Organisation		Patient	
Comments		596 PKD and its treatment by dialysis often causes difficulties for people in their working lives. I feel that the opportunity to start	

Role*	Section	Comment [sic]	Response
		treatment which would slow the advance of the condition and hence delay the need to start dialysis till later in life would be beneficial. I would urge you to consider this appeal sympathetically. Thank you for your attention.	

Role	Patient
Comments	597 As a APKD patient I have been at stage 3 for the last ten years, however generally I have seen a massive decline in my health and my ability to manage everyday life over the last three years. I am a nurse and continue to work full time but this is at a cost of things I can do at home due to tiredness. I get very tired, I feel like I am carrying twins all the time, which affects my breathing and ability to eat a meal. I have had to give up exercising and am only just managing to continue walks. If I had been given Tolvaptan ten years ago things might be different for me now. I have lost a parent and one sister to APKD, my sister being only sixty. My brother has APKD as does one of my children, the other not yet scanned. Tolvaptan gives up hope to slow down a disease that hangs like a chain around patients necks. I note , forgive me if I missed this in your calculations you do not include costs of pain relief medications, vitamin D supplements (which are costly) and other medications which increase as symptoms of kidney failure progress. The cost to society should also be considered, in treating patients with a drug that may keep them living a decent life for a while you are also keeping us at work and contributing to everyday life including paying taxes. Tolvaptan provides a hope to keep up living normally for a while longer.

Role	Patient

Role*	Section	Comment [sic]	Response
Comments		598 I am writing on behalf of myself and my two daughters, Ellie Collins and Isabel Bradshaw. My daughters have, unfortunately inherited Polycystic Kidney Disease with combined liver cysts, which I inherited from my father, who in turn, inherited this from my grandfather. Both of the latter died in their early 60s and the prognosis for myself seems to be following a similar route. I have been on blood pressure medication for over 20 years because of the associated hypertensive condition caused by poor kidney function. One of my daughters has already started along this route. It is disheartening to hear over and over again from all the experts in the field, that there is no cure - only transplant if you are lucky and it is successful, or dialysis, which is costly, life changing and shortens lifespan. I am told that the cut-off for transplant is 70 years and I am half hoping that my kidneys fail before this in the hope that I might qualify for a transplant. That is all with respect to my own future but needless to say, what concerns me far more is that the future should look brighter for my children and grandchildren. We come from a long line of teachers and have much to contribute therefore to future generations. Tolvaptan offered us some hope that the growth of the cysts could be halted or slowed so that our condition would not affect our longevity. I am sure you will have heard from the bodies (charities and research organisations) of the potential for Tolvaptan to change the prognosis for PKD sufferers and to provide a more economical alternative to the interventions currently available for us. It is a not inconsiderable proportion of the population who suffer from this disease and it seems shocking that there is currently no cure available in this country. I do hope that this personal account of living with PKD will go some way to ensuring that Tolvaptan is now made available for us.	
Role		Public	

Role*	Section	Comment [sic]	Response
Comments		599 I have watched my wife decline from full of energy, always on the go and helping others to someone who is in constant pain and incredibly tired all the time. Making these drugs available on NHS would perhaps go a great way in helping this condition.	
Role		Patient	
Comments		600 I am a patient with ADPKD, which has caused a chronic pain condition. I wondered if it would be helpful to describe some of the symptoms I suffer from so that you are provided with a picture of the impact it has on my day to day life. And also to give you an idea of why the possibility of the success of tolvaptan is so important. Symptoms: - Daily back pain, constant dull ache, infrequent stabbing pain - Inability to stand or walk for more than 20 mins - Frequent bouts of insomnia - Frequent need to urinate which is uncomfortable (like cystitis symptoms) caused by burst cysts - Frequent bouts of vomiting (sometimes 7 times a day) probably caused by the size of my kidneys - For info, my kidneys have excellent function and they measure 17cm, the biggest cyst measures 6cm	

Role*	Section	Comment [sic]	Response

Role	Close Friend
Comments	601 Please will your reconsider your decision on the above treatment. I have a dear friend who is only 45 years of age and who suffers from this debilitating illness. It could make a huge difference to her life and let her plan for a longer and hopefully improved future.

Role	Public
Comments	602 My father suffered from ADPKD although it was not diagnosed until he suffered kidney failure. His health and quality of life deteriorated significantly; he had to have dialysis in a hospital 3 times a week, and he was unable to play with his grandchildren as he would have liked. The combination of renal and heart problems meant he spent a lot of his last years in and out of hospital. Fortunately I have not inherited this disease but my sister has. NICE's decision not to recommend tolvaptan to treat ADPKD means that she loses the possibility of her kidney disease not getting worse, and avoiding end stage failure. If there's a chance that my sister, or anyone else with AKPKD, could avoid the experience of my father, I think it should be taken. I urge NICE to reconsider its decision. I am deeply disappointed that people living with this incurable, inherited, life-threatening and debilitating kidney disease may be denied access to a licensed therapy which has the potential to improve the quality of their lives, and the lives of their family members and future generations.

Role	Patient

Role*	Section	Comment [sic]	Response
Comments		603 As a patient of pkd and a carer or my child who also is a pkd patient I belive tolvaptan is a break though achievement for pkd suffers. Why would this not be recognised and allowed on the NH'S? My son was diagnosed when I was pregnant and it has been a horrendous 7 years with his health and myself in my late 30s this drug would help and aid pkd suffers throughout uk and reduce the rate of cysts growing on kidneys as seen in trials. Please reconsider ur desicion u would be helping the young and old with this new drug	
Role		Patient	
Comments		605 Dear NICE, I am a PKD patient and have been living with the disease for 20 years. I do not understand why Tolvaptan is not being considered for usage in the UK, when it is available in other regions such as Canada. Surely a drug which can stop the growth of kidney cysts is a better solution than dialysis and transplatation and would be more cost effective in the long run? My mother died from kidney disease after transplantation and dialysis, which she endured for over 20 years. If a pill is available to replace all those hospital stays and consultant visits, then it has to be worth a trial?	
Role		Patient	
Comments		606 As a sufferer of PKD (all family and my children have also inherited it) there is nothing that can be done except to accept it	

Role*	Section	Comment [sic]	Response
		and put up with it knowing your life will be shorter than the average. Surely if there is anything that can alleviate suffering and possibly lengthen life expectancy, then we should be allowed it. Knowing there is nothing that can be done is one of the hardest things to accept with PKD.	

Role	Patient
Comments	607 As there is currently no treatment for ADPKD sufferers this drug is an important first step in finding an appropriate treatment Please re consider your descision.

Role	Patient
Comments	608 From a patients view I am so upset that the hope of treatment for this condition has gone. My father died from it 14 years ago, I then found out that I have it, and now both my children have it. My daughter is only 15 and has high blood pressure and huge cysts with poor kidney function and my son is only 11 and has high blood pressure already. This treatment would have helped them to lead a better "more normal" life and they cannot have it. It is a very disapointing result

Role	Patient
Comments	609 I am so disappointed by the rejection of the use of Tolvaptan. Disappointed for the grandmother, uncle and mother I have lost to this wretched disease, disappointed for my 3 year old daughter Ellen and disappointed for myself. Having been diagnosed at Christmas 2014 at the age of 33, the small

Role*	Section	Comment [sic]	Response
		window of hope provided by the research that is underway and by trials such as those involving Tolvaptan were the things that kept me going. Please rethink. My mother spent several years on expensive dialysis and her last 2 years were predominantly as an inpatient at QA hospital Portsmouth. What life? What expense? Please reconsider the economics and the lives.	
Role	Carer		
Comments	611 Having watched my husband die of ADPKD dialysis (10 years) and my two adult children have inherited the disease. How can I sit back and let this happen. As you are aware it costs the national health Â£30k a year to keep a patient on dyalisis. What is the point of keeping someone alive on a machine if and when a drug comes along you are to prepared to give it a chance. Please reconsider your disicion on Toluaptan for the future of the next generation.		
Role	Patient		
Comments	612 I am a PKD patient, female aged 38. I suffer frequently with pain but my blood tests are currently normal. The family prognosis, what limited information I have, seems reasonable with members living into their 60s without the need for medical intervention. I seem to suffer more than family members and I would have liked have been able to make the decision to use Tolvaptan on the NHS. I understand that the increased water intake patients need to take with Tolvaptan could be throwing a false positive, but even this shows Tolvaptan, by making a patient drink more, has benefits to people like me. I urge to you reconsider. Don't cut my life short. I live a full and healthy one		

Role*	Section	Comment [sic]	Response
		currently and I am not a burden on the NHS. If I suffer from renal failure later, surely I will cost much more.	

Role	Patient
Comments	615 I would urge NICE to seriously consider making Tolvaptan available to PKD sufferers. As a PKD sufferer myself, I have had to watch my grandfather's quality of life slowly deteriorate as his kidney function decreased. There is not enough research done in this area and, now that a treatment has become available (Tolvaptan) it should be made available to sufferers. It is a glimmer of hope for sufferers who face life with an untreatable disease.

Role	Public
Comments	616 The drug could be in reach if we where to build the NHS up, as a posed to the constant erosion by cuts, I would pay more tax for a better service.

Role	Patient
Comments	618 Dear Recipient/s I am 43 year old man who was diagnosed with AKPKD around 6 years ago and have had many symptoms associated with the disease for a number of years, which were not attributed to the disease until it was finally diagnosed, these being high blood pressure (which was picked up in a free heath check at my workplace) and gastric reflux (diagnosed by my GP around 10 years ago). I was only made aware of AKPKD by a family member, who suggested that I should ask my GP to investigate

Role*	Section	Comment [sic]	Response
		my symptoms further. I have always kept myself as fit as possible and my high blood pressure was initially put down to 'stress', even though I had repeatedly told my GP that I was not under any significant stress at all. Since being diagnosed, my life has somewhat been put on hold. I am lucky enough to have a good job and salary at present, but I am reluctant to progress my career and I have expressed to my wife that I we most likely will not move house again as I am very concerned that if my AKPKD progresses further, I will leave her with a high debt burden (due to me posssibly not being able to work) and I am unwilling to put my family in this situation. Although I have a daughter, I have also put on hold the possibility of having further children, due to the reasons given above. I have also found it a challenge to get certain insurances (e.g. life insurance) due to the inhibitive cost, when I declare my condition. The physical and emotional burden of living with AKPKD is significant, as it feels like living with a 'ticking time bomb', given that the chances of end stage renal failure are high. From a purely economic standpoint, I am a higher rate tax payer and in fact, the cost of providing this drug would be far less than the tax I pay every month on my income. In other words, if the drug allows me to continue to work and lead a relatively normal life, my net contribution would significantly outweigh the cost of the treatment. I recognise that this is not the case for all AKPKD patients though. I am somewhat surprised at the initial rejection of approval for JINARC, given that EMA approval was granted and approval granted in Canada too. I am certain that the economic cost to the NHS for treatment of patients with end stage renal failure is much higher than the cost of prescribing JINARC and the impact to patients, families and lives far higher too. I would urge you to reconsider the initial appraisal outcome and grant approval for JINARC as the positive impact of such a drug is huge, with delay to kidney failure and the ability for AKPKD patients to have 'hope' in living relatively normal lives again.	

Role*	Section	Comment [sic]	Response
		Thank you & kind regards	

Role	Patient
Comments	619 I was devastated to read that NICE has not recommended tolvaptan to treat ADPKD. For nearly 13 years, I have followed the progress of tolvaptan through the early research to trials. I was unable to take part in the clinical trial owing to low kidney function but the promise it offered of a delay to dialysis and early death has made living with ADPKD more bearable. Although the drug comes too late to delay my journey to kidney failure and possible early death, it gave hope to a better life for my niece and nephew, and 2 great-nephews, who inherited ADPKD from my affected sisters. My father died at 57 of ADPKD and one of my sisters died 3 years ago at 59 of ADPKD. A younger sister has already had a transplant. I have lost 75% of my kidney function and am almost certain to need dialysis or a transplant, which will cut short my career and, as Iâ€™m self-employed, critically affect my finances. I have actually considered opting for no dialysis or transplant, ie death, rather than trying to live on minimal money and the daily burden of needles, pills and unhappiness. I know that the NHS has budgetary constraints but there is NOTHING else that can slow the invidious progression of ADPKD. The trial showed a significant reduction in the rate of kidney function decline. In the years leading up to complete kidney failure, patients suffer considerably and cost the NHS a lot of money - in pain relief, emergency admissions and antibiotics for cyst infections, and frequent hospital appointments. Then thereâ€™s the knock on cost impact on my

Role*	Section	Comment [sic]	Response
		working life - lost earnings, career impairment, higher insurance premiums or being denied any insurance. The psychological burden can be immense - genetic guilt and a form of grief, waking up each day knowing that I will never be free of ADPKD and each day is a day nearer dialysis or transplant. 'Standard care' for ADPKD patients in the NHS is around symptom management of kidney related problems. But ADPKD is more than a kidney disease; it is not amenable to traditional CKD care and it carries with it higher risk of aneurysms, hugely cystic livers (that sometimes need transplanting as well as kidneys), acute and chronic pain from infections as well as CVD from hypertension. Tolvaptan is the first therapy shown to slow down this rotten disease and I urge NICE to authorise this drug.	

Role	Patient
Comments	620 It is essential that Tolvaptan is given as an option for PKD patients. I have had a grandfather and father that have died of this disease. I have a brother and sister and we have all spent time on dialysis. I looked after myself as well as possible following all the guidelines and being monitored by the NHS for some 35 years and still I succumbed to the disease. It must have cost a lot to monitor me for such a period then I believe about Â£25-30k pa to dialyse plush the cost of all the drugs. I have been in intense pain for about 8 years through the cysts. I lost my business with a turnover of Â£1.5m and the jobs of 20 people because I was unfit to work. I now live off the State rather than pay in to it. I also lost my wife who couldn't cope with my illness. I have twin boys and my sister also has twins. We feel that a drug that prevents the cysts forming provides them with a greater chance of a full life and it must therefore

Role*	Section	Comment [sic]	Response
		cost the UK less in the long run. Please reconsider this application and prevent this suffering.	

Role	Patient
Comments	621 As a patient suffering from ADPKD and a suitable candidate for the new drug Tolvaptan I am extremely disappointed to hear that the NICE are not to recommend Tolvaptan to treat the condition. This drug would give hope to people like myself and their families who deal with the incurable condition on a daily basis. My kidney function is OK, but I have chronic pain which at times is acute - I recently suffered burst cysts from which the fluid went into my pancreatic cavity. This was debilitating for a number of days and took several weeks to recover from. The only 'treatment' was pain relief - most are inadequate and so to be pain free I used strong prescribed medication, which have its own side effects. I also have the additional complications of hypertension an increased risk of brain aneurysms (my grandfather died from one) and polycystic liver disease. I used to be very active - 6 years ago I competed in a mini triathlon - but now find it difficult to participate in any activity as I become very breathless. This concerns me on an emotional level as I have an active family and can no longer join them, but I am also worried that it will have a financial impact if I am unable to continue working (I am already denied life insurance and was unable to get a mortgage which places a great burden on my husband). Surely the cost associated with long term dialysis that I am

Role*	Section	Comment [sic]	Response
		likely to face (my mother was on dialysis for 17 years and my brother is on dialysis after having both kidneys removed) must be worth an alternative treatment being sought? I am extremely disappointed that I, and many other like myself, are to be denied access to a licensed therapy which has the potential to improve the quality of our lives, but also the lives of our family members and those of future generations.	

Role	Carer
Comments	623 My wife suffers from ADPKD. Her father died of PKD related illness and was in great pain for the last 5 years of his life. I do not want to see this happen to my wife. ADPKD is not a lifestyle related disease but in my wife's case, hereditary. She is doing everything she can do keep herself healthy, from eating, exercise, keeping her blood pressure under control and drinking 4 litres of water a day. We both feel powerless over this disease. Tolvaptan is the only medication available - it's not as if patients have a choice of which to take - and NICE's decision to reject it is removing her only hope of not getting to end stage kidney failure. She is lucky that she is not in pain but she is exhausted and is unable to work. We have ruled out having a family because of this disease. If this drug were made available we may have a second chance of having children. She gets depressed and tearful, especially when she remembers how her father struggled. I strongly urge NICE to reconsider urgently - it really is a case of life or death.

Role	Public

Role*	Section	Comment [sic]	Response
Comments	624 ADPKD does not currently have any standard treatment. There are many symptoms that could be delayed if there was an approved treatment available to delay the onset of symptoms. Tolvaptan, as proposed, does not seem to have any significant medical drawbacks to prevent its approval. Therefore denial of its approval seems to be based on short-term financial reasons rather than potential improvements of QOL for thousands of patients currently suffering. In my view the use of Tolvaptan would be more cost effective, reducing the need for as much costly dialysis and transplants ultimately combined with a reduced need for costly subsequent post-transplant associated medication.		
Role	Local government professional		
Comments	625 This is so important and should be made legal and available for PKD sufferers!!		
Role	Carer		
Comments	626 As the partner of an ADPKD patient, I am disappointed to see that that NICE have not recommended that Tolvaptan be used to treat this condition. Over the last three years, my wife's lifestyle has been greatly affected through weight gain (approximately 15KG), breathlessness and general severe abdominal discomfort and she is no longer the active person she used to be (she competed in a triathlon 6 years ago). Until her kidney function is sufficiently reduced that she requires dialysis, there is currently little effective treatment available to ease her discomfort.		

Role*	Section	Comment [sic]	Response
		Transplant, apparently, is not an option while her kidneys have sufficient function. She has read that she might be a candidate for the trialling of this drug given her current kidney function. To have this option removed before the drug has even been trialled is a grave disappointment. Her mother was on dialysis for 17 years due to the same condition. Her younger brother recently had both kidneys removed, has been on dialysis since and is awaiting a transplant with little sign of one forthcoming. Surely the costs associated with long term dialysis that both he and my wife potentially face must be worth an alternative treatment being sought? I trust that these thoughts will be taken into consideration before the final recommendation is made.	

Role	Public
Comments	To whom it may concern (nice@nice.org.uk) :- I am imploring you to recommend TOLVAPTAN to treat ADPKD. My daughter age 45 has suffered for many years with this disease. She has already had a liver transplant because of it and now her kidneys are only working at 40%. She has 4 children, 3 of whom are also confirmed sufferers of ADPKD. Transplants are inevitable for all of them at some point in their lives, but surely if that process can be delayed for as long as possible, then what is a traumatic experience for them and extremely expensive procedure for the NHS, must be the sensible way to go.

Role*	Section	Comment [sic]	Response
		My point is that surely this drug could save the NHS money! I hope and pray you will listen to my concerns and the concerns of many others whose lives are blighted by this dreadful disease. Many thanks,	

Role	Patient
Comments	628 I wish for NICE to consider approving Tolvaptan. PKD is a disease that affects whole families . I have the genetic disease, as did my father and his mother, my grandmother, before him. One of my children has also inherited the disease and it is my son for whom I hope for a cure or, at least a slower progression of cysts that cause the kidney failure. Please do not take that hope away.

Role	
Comments	629 Sirs/Madams, I understand that your appraisal has concluded in you thinking that Tolvaptan is not costly effective in UK. Please I would like you to consider that for every person who can delay his/her dialisys treatment it is a huge saving for the tax payer. People with ADPKD start dialisy before they reach 60. When we go to dialisy we can't work full time, so we need benefits. If Tolvaptan delays the start of dialisy for patiens because the cysts are better controlled, many patients may start dialisy by the time they have to retire, so no extra benefits will be given to them.

Role*	Section	Comment [sic]	Response
		Can I also suggest to try it for, let's say 5 to 10 years and then revise again the results. Also, I would like to say that, I think, many particularindividuals give personal donations to continue investigate this terrible medical condition we have without having done anything wrong in our lifestyle, as it is inheritated. I think it is only fair to give us some hope after all our efforts. I have not sais anything for myself, as I am afraid it would be too late for me. I don't think they would give me the treatment at the advanced stage I am now, but please consider all those points.	

Role	Public
Comments	630 I am deeply disappointed that this drug has not been approved. My sister is very ill with this disease and I was hoping for anything that might help in anyway towards a cure. Please can this be reconsidered?

Summary of comments received from members of the public

Theme	Response
Committee has not acknowledged the full impact of living with ADPKD – the psychosocial and emotional effects of a long-term inherited condition	The Committee heard from the patient experts that tolvaptan may have a positive psychological benefit for people with ADPKD. The Committee considered the points raised about not considering the full impact (psychosocial and emotional) of living with ADPKD. The Committee understood the importance of benefits such as the hope that tolvaptan provides, which may be difficult to capture in measures of health-related quality of life in addition to those already included in the QALY calculations. The Committee concluded that tolvaptan is an innovative treatment and it is the first treatment that has been shown to specifically impact on the progression of ADPKD.
Committee has not taken all relevant evidence into account, for example the direct healthcare costs of treating both kidney and liver cyst ruptures, surgical interventions on the kidneys and other organs, infections and pain throughout a patient's lifetime and especially in the years prior to kidney failure. And the indirect cost burden of lost employment, productivity and earnings on individuals and their families.	The Committee considered the raised points that not all direct healthcare costs treating kidney / liver cyst ruptures, surgical interventions, infections and pain had been captured, or the indirect costs such as lost employment, productivity etc. on individuals and families. The Committee was mindful however that technology appraisals are assessed from the perspective of the NHS and PSS.

[i] NICE Appraisal Consultation Document or ACD (issued 5 June 2015) http://www.nice.org.uk/guidance/indevelopment/GID-TAG447/consultation
[ii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.17
[iii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.17
[iv] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 4.3
[v] Ong et al. Lancet 2015; 385: 1993-2002
[vi] During November and December 2014, the PKD Charity ran a specially-designed survey amongst UK adults with ADPKD, plus their relatives and carers, on the impact of the condition on overall health, wellbeing and quality of life. A total of 651 individuals responded, of whom 513 were ADPKD patients, and 138 relatives/carers. Whilst recognising the limitation of patient-led research, we believe this survey highlighted and reinforced what we know from years of listening to patients and family experience stories.
[vii] Spithoven EM, et al. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival-an analysis of data from the ERA-EDTA Registry.
Nephrol Dial Transplant 2014;29 (Suppl 4):iv15-iv25
[viii] Shaw C, et al. Nephrol Dial Transplant 2014;29:1910–8
[ix] Patch C, et al. Use of antihypertensive medications and mortality of patients with autosomal dominant polycystic kidney disease: a population-based study. Am J Kidney Dis 2011;57:856–62

[x] Chapman AB, et al. Autosomal dominant polycystic kidney disease (ADPKD): Executive Summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference (with Online
Appendix). Kidney Int Mar 18. doi: 10.1038/ki.2015.59
[xi] Torres VE, Harris PC et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England Journal of Medicine. 2012;367 (25): 2407-2418
[xii] Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. Irazabal et al. J Am Soc Nephrol. 2015 January; 26(1): 160–172. Published online 2014 June 5. doi: 10.1681/ASN.2013101138
[xiii] NICE Appraisal Consultation Document or ACD (issued 5 June 2015), item 3.20
[xiv] Spithoven EM, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in
autosomal dominant polycystic kidney disease. Kidney Int 2014; 86:1244–52