Otsuka Pharmaceuticals UK Ltd Response to ERG Clarification Questions

Section A: Literature searching

A1. **Priority Question:** Please justify the rationale behind limiting all literature searches to 2004 onwards and English language only.

Response

As there are currently no licensed treatments for ADPKD, as supported by the final scope for this appraisal, a time horizon of 10 years was considered appropriate to identify any relevant literature. The systematic review by Myint et al (1) indicate that the earliest publication of a trial of a compound attempting to slow ADPKD progression was in 2005 (2). Studies were limited to the English language to identify the most pertinent evidence for England and Wales.

A2. **Priority Question**: Please clarify why different search terms were used for the cost facet for the autosomal dominant polycystic kidney disease (ADPKD) and end-stage renal disease (ESRD) searches (Section 7.5.3 Resource Identification, appendix 10.13).

Response

Separate cost facet search terms were used in the ADPKD and ESRD searches (Appendix 10.13) for two reasons. Firstly, broad search terms were used in the ADPKD search as this may in addition to identifying resource user and unit costs, have identified additional economic evaluations for section 7.1. Secondly, economic evaluations of ESRD were not required specifically, and as a result a more focused set of research terms could be employed. The focused set of terms was beneficial as there is a large volume of literature on ESRD.

A3. Please provide the search terms and details of resources used for congress abstract searches (appendix 10.2.5).

Response

Table 1 and Table 2 below summarise the congresses searched and the search terms used. All searches were performed on 11th August 2014, using the congress website and using the native website search functionality. The eligibility criteria for each of the searches were then applied to the identified abstracts. Search results were incorporated in the PRISMA flow diagrams in the submission.

Please note: Abstracts were not available for every year within the search data range. The congress meetings reported were the only meetings available.

Table 1: ISPOR Congress Abstract Search

Search terms	**ISPOR Europe 2012 – 15th Annual European Congress**	**ISPOR Europe 2013 – 16th Annual European Congress**	**ISPOR International 2012 – 17th Annual International Meeting**	**ISPOR International 2013 – 18th Annual International Meeting**	**ISPOR International 2014 – 19th Annual International Meeting**
ADPKD terms					
'polycystic kidney'	0	0	0	4	1
'ADPKD'	0	0	0	3	1
'PKD'	0	0	0	4	0
ESRD terms					
'end stage renal'	4	2	3	4	5
'end stage kidney'	0	0	0	1	0
'ESRD'	2	10	12	13	12
'ESKD'	0	0	0	0	0
'chronic kidney'	7	10	15	17	16
'chronic renal'	3	2	4	3	3
'renal failure'	9	3	17	9	4
'renal transplant'	7	6	7	3	3
'renal replacement'	2	4	1	1	0
After duplicates removed	**28**	**31**	**49**	**38**	**32**

Table 2: Other Congress Abstract Searches

Search terms	European Renal Association – European Dialysis and Transplant Association (ERA – EDTA) 2012	European Renal Association – European Dialysis and Transplant Association (ERA – EDTA) 2013	World Congress of Nephrology (WCN) 2013	American Society of Nephrology (ASN) – Kidney Week 2012	American Society of Nephrology (ASN) – Kidney Week 2013
ADPKD terms					
'polycystic kidney'	25	23	21	125	130
'ADPKD'	11	18	14	97	114
'PKD'	13	18	7	148	111
ESRD terms					
'end stage renal'	152	66	101	348	154
'end-stage renal'	101	89	104	348	216
'end stage kidney'	18	11	17	37	24
'end-stage kidney'	9	20	27	37	23
'ESRD'	140	138	165	462	769
'ESKD'	6	17	101	17	31
'chronic kidney'	338	345	421	748	829
'chronic renal'	71	52	68	88	84
'renal failure'	157	125	184	265	209
'renal transplant'	105	110	83	220	124
'renal replacement'	96	69	103	158	212
After duplicates removed	750	740	934	1841	2021

A4. Please provide the search terms used for, and results found from Cost Effectiveness Analysis (CEA) registry searches (appendix 10.2.5).

Response

Table 3 below summarises the search terms used and the results found on the CEA registry. The search was conducted on 11th August 2014 and identified one study only following the exclusion of duplicate studies.

Table 3: CEA Registry Search

Search Term(s)	Results	Results meeting the eligibility criteria
Tolvaptan	0	0
Polycystic kidney disease	1	0
PKD	1 (duplicate)	0
ADPKD	1 (duplicate)	0

The paper identified was:

Perovic, Sasa, Jankovic, Slobodan, Renal transplantation vs hemodialysis: cost-effectiveness analysis. Vojnosanit Pregl,2009-Aug; 66(8):639-44. (3)

A5. In section 7.4.5 Health Related Quality of Life (HRQoL) Studies (appendix 10.12.5): Please clarify what 'Internet' searches were conducted, providing details of sources used, search terms and results found.

Response

Table 4 below summarises the internet sources and search terms used to identify health related quality of Life (HRQoL) Studies. The searches were conducted on 11th August 2014.

Table 4: HRQoL internet searches

	Internet sources	
	Google	**Google Scholar**
Search terms	'ADPKD utilities'	
	'tolvaptan utilities'	
	'ADPKD HRQoL'	
	'tolvaptan HRQoL'	
	'ADPKD quality of life'	
	'tolvaptan quality of life'	

For the internet searches only the first 20 results of each search were review as these have the highest relevance (all/most of the search terms are in the retrieved results). The results of the internet searches were cross-referenced with the literature identified in the other searches. No new relevant publications were identified in the internet searches.

A6. In section 7.5.3 Resource Identification (appendix 10.13): What search dates were used for the ESRD searches? A range of January – August 2014 is given in the company's submission (CS) for all databases. Please provide specific dates for each database searched.

Response

The searches were conducted on 5th August 2014. The date spans of the searches were from January 2004 to the 5th August 2014.

Section B: Clarification on effectiveness data

B1. **Priority Question:** The primary endpoint in the main study (TEMPO 3:4) included in the section on clinical effectiveness was change in total kidney volume (TKV). However, TKV was not listed as an outcome of interest in the final scope. Please justify the use of TKV as the primary outcome in the submission.

Response

The role of TKV in ADPKD is well described as it is important to the submission, but is not the primary outcome.

TKV was pre-specified as the primary efficacy outcome of TEMPO 3:4. Accordingly, we believe it is natural to report the primary efficacy results of the pivotal trial as per protocol in our submission and outline the role of TKV as a surrogate measure of treatment efficacy in ADPKD. Further, TKV has been demonstrated to be an important prognostic indicator for ADPKD progression, which is a core feature of our economic model. Therefore it was important to describe and justify the role of TKV in predicting ADPKD progression in our submission, irrespective of whether TKV was listed as an outcome of interest in the final scope.

However, the economic evaluation does not utilise TKV as an outcome and is concerned primarily with decline in renal function to describe ADPKD patient health status, which is line with the final scope. Baseline TKV is one of the variables used to define modelled patients and TKV is assumed to be correlated with eGFR over time, however TKV plays no active role in describing patient health status and treatment effect is assessed directly on renal function in the economic model, as required by the final scope.

B2. **Priority Question:** Section 1.13 of the CS states that "Hepatotoxicity has been observed in some patients receiving tolvaptan for ADPKD, which was reversible following discontinuation. To mitigate this potential risk, monthly monitoring of liver function for the first 18 months, and every 3 months thereafter, will be required." Please provide a proposed treatment pathway for tolvaptan including monthly monitoring of the liver function and possible transplantation required.

Response

The proposed treatment pathway is in line with the requirements of the anticipated final SmPC:

- The physician measures liver function tests (LFTs) prior to the commencement of tolvaptan and will determine if the patient is able to commence treatment based on the licensed indication
    - At commencement of treatment, if the LFTs are abnormal then the physician should consider the advice of a hepatologist and monitor the patient at increased frequency
- The physician then commences the patient on tolvaptan, and will escalate the dose as per the titration schedule to the maximum dose or to a level that is tolerated by the patient.
- The physician will monitor LFTs every month to determine if the liver enzymes (specifically Alanine transaminase (ALT) rises to above three times the upper limit of normal after the commencement of treatment
- If the patient's LFTs do not show rises that require specific action and if the patient remains clinically well with no symptoms or signs of liver disease, then treatment with tolvaptan may continue
- If ALT rises to above three times upper limit of normal or other signs of liver injury are seen (as defined in the SmPC), then treatment with tolvaptan should be interrupted and the LFTs should be monitored more frequently
    - The physician should consider if the patient should be permanently discontinued PC

- LFT testing must continue until symptoms and/or signs and/or laboratory abnormalities stabilise or resolve, and then tolvaptan may be recommenced
    - A reduced dose may need to be considered, and more frequent LFT monitoring may be required
- After 18 months, LFT monitoring should be performed 3monthly
    - At any stage if abnormal LFTs are seen, the patient should be managed as described above.

In the TEMPO programme no patients had permanent liver injury, required liver transplantation or died, this was despite drug induced liver injury not being anticipated and monitoring of liver function tests only taking place every 4 months. Given this and the requirement for monthly liver function testing of all treated patients it is not anticipated that any patients will have significant enough liver injury (including the need to transplantation) therefore this has not been modelled.

B3. **Priority Question:** Tables B12 and B13 provide subgroup data by chronic kidney disease (CKD) stage for TKV and annualised rate of change in renal function respectively. Please provide similar subgroup data by CKD stage for all endpoints defined in the scope.

Key secondary composite end point of clinical disease progression

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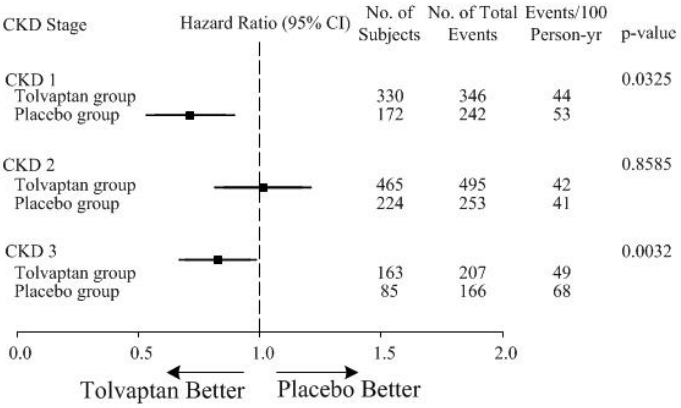

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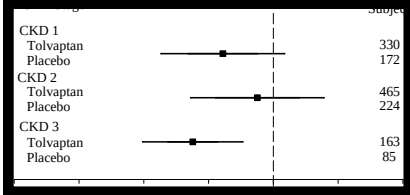

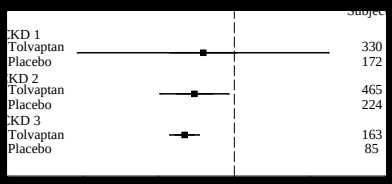

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- <u>mortality</u>

No mortality was recorded in either the placebo or tolvaptan arm of the TEMPO 3:4 trial.

- adverse effects of treatment

The adverse events of treatment were not analysed by CKD stage.

- health-related quality of life

Health-related quality of life was not assessed in the TEMPO 3:4 trial. However, quality adjusted life year were estimated as part of the economic evaluation and the results by TKV are presented in question c6

B4. **Priority Question:** Stopping rules are not considered in the CS (although the final scope states that these should be considered if evidence allows).

- What is the predictive value of a lower-than-average one-year increase of TKV of tolvaptan users for TKV increase in the next 2 years, correcting for baseline TKV (Tempo 3:4 data)?

- What is the predictive value of a lower-than-average two-year increase of TKV of tolvaptan users for TKV increase in the next 3 years, correcting for baseline TKV (Tempo 4:4 extension trial data)?

Response

Otsuka has attempted to identify patients where it could be determined that stopping rules based on treatment response would be appropriate, but overall no meaningful advice or recommendations can be given. For individual patients with ADPKD, the trajectory for the expected decline in renal function and expected increase in TKV cannot be predicted in a validated way due to the natural history of the disease. For example, a patient may have a renal cyst that contributes to that patient's overall TKV. Over this time the cyst may haemorrhage or become fibrotic, and this will have a particular effect on the TKV. Therefore a TKV in individual patients may sometimes increase, decrease or stay the same in relatively short time periods, such as one year. At a population level, patients with ADPKD as a group may have a TKV that increases with time, however for an individual ADPKD patient the expected change in TKV over short time periods cannot be accurately predicted even with the knowledge of their past growth rates. As a result of this it is not possible to create a predictive algorithm to identify which individual patient is responding to therapy or what their long term trajectory will be. In addition, the TEMPO 3:4 study did not have any specific stopping criteria for patients that would be relevant here. Therefore Otsuka is unable to recommend specific stopping rules based on the clinical trials and known disease experience.

The predictive value of the requested analysis would be very low.

B5. Please provide an overview of the reasons why 530 participants (figure B2 on page 93 of the CS) did not fulfil the inclusion criteria.

Response

The disposition of the TEMPO 3:4 patients is shown below in the **Table 7**

Table 7: TEMPO 3:4 Excluded Patient Disposition

Reason for exclusion between screening and randomisation	**Number of subjects**
Did not meet inclusion criteria	
• Did not provide informed consent:	7
• Did not have a diagnosis of ADPKD	2
• Had an estimated GFR of <60 mL/min within 31 days of randomization: 119	119
• Did not have a rapid estimated rate of renal volume increase based on total renal size >750 mL by MRI at randomisation	370
Met exclusion criteria	
• Subjects who in the opinion of the trial investigator and/or sponsor present a safety risk	4
• Subjects who are unlikely to adequately comply with the trial's procedures	2

• Subjects having contraindications to, or interference with MRI assessments	9
• Subjects taking medications or having concomitant illnesses likely to confound endpoint assessments	11
• Subjects taking other experimental (i.e., non marketed) therapies, or taking approved therapies for the purpose of affecting PKD cysts, or those taking or have a history of taking tolvaptan	1
Other reasons for exclusion	5
TOTAL	530

B6. Drug induced liver injury was one of the main reasons tolvaptan was not approved by the FDA for usage more than 30 days. However, tolvaptan is approved for the treatment of hyponatremia (in the USA) and volume overload in heart failure (in Japan).[4, 5]

- Please provide the post marketing surveillance data on drug induced liver injury for any other relevant tolvaptan trials, e.g. the EVEREST trial.

<u>Response</u>

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- Please provide the maximum frequency of drug induced liver injury reported in any of the tolvaptan trials or post marketing surveillances done in the past

Response

The maximum frequency of drug induced liver injury reported in any of the tolvaptan trials or post marketing surveillances done in the past was seen in the TEMPO3:4 trial. The frequencies are provided in the table below.

Table 8: frequency of drug induced liver injury

	Tolvaptan			**Placebo**		
Abnormality	**Subjects**	**Subjects Meeting Criteria**	**%**	**Subjects**	**Subjects Meeting Criteria**	**%**
ALT >3x ULN	958	42	4.4	484	5	1.0
ALT >3x ULN with Bili >2x, but ALP <2x ULN (Hy's Laboratory Criteria)	957	2	0.2	484	0	0
Death or Liver Failure		0	0		0	0

- What is the expected efficacy of this risk management program given post-marketing data on other potentially hepatotoxic drugs?

Response

In considering the appropriate risk management plan for tolvaptan in ADPKD, Otsuka considered which other programmes have taken in place for other medicines where there was a signal of liver injury. Otsuka therefore considered the experience of the use of bosentan, an endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension (PAH) (7, 8).

It was recognised in the bosentan clinical development programme that there was an association between its use and liver function test abnormalities. Although reversible, there was the possibility that the liver damage could be severe or permanent. As a consequence, the manufacturer instituted a programme where a physician could not prescribe bosentan unless they were appropriately educated regarding the risks. The physician would commit to undertaking appropriate monitoring of LFTs. Physicians were also encouraged to participate in the post-marketing surveillance programme. The manufacturer also instituted a tailored distribution system approved separately by each competent authority in Europe. When the programme was evaluated, it was determined that no new safety signals were discovered, and the rate of occurrence and severity of elevated LFTs observed in the bosentan post-marketing surveillance programme matched that originally seen in the clinical trial setting.

With the use of tolvaptan in ADPKD, the design of RMP is similar. The prescribing physician will have to be trained regarding the safety of tolvaptan in ADPKD and will undergo a post-training assessment. Once a prescription for tolvaptan has been written and sent to the pharmacist, the pharmacist is required to check that the prescribing physician has been authorised. Otsuka will provide a list of authorised prescribers to the pharmacist for this purpose. After this check has been made, the pharmacist may dispense tolvaptan.

Therefore Otsuka expects the risk management programme to be effective.

B7. The TEMPO 3:4 trial only includes patients between 18 to 50 years of age.[(4)] Please clarify whether the anticipated marketing authorisation will be for all adult patients, and not restricted to those between ages 18 and 50 (on treatment initiation).

Response

The draft SmPC for tolvaptan in ADPKD (enclosed) states that the indication is for all adult patients (aged 18+) and is not restricted to those between ages 18 and 50.

B8. Section 1.12 states that “With respect to evidence of rapidly progressing disease, no objective criteria are defined in the licensed indication meaning this

assessment will be more subjective according to specialist clinical judgement." Please provide further reasoning to clarify why no objective definition of rapidly progressing disease was used while definitions are available, for example in NICE clinical guideline 182[9].

Response

ADPKD is a disease defined by the presence and growth of cysts within the renal parenchyma. It has been demonstrated in independent research that the strongest predictor of renal outcomes in this disease is the size of the kidney and its rate of growth. This is clear from studies that have demonstrated that kidneys can become quite large prior to loss of renal function through the redundancy of renal capacity. Thus a loss of renal function measured by glomerular filtration rate marks a late stage in the natural history of this disease. Due to this the study population in TEMPO 3:4 was enriched with rapid progressors as defined by a renal volume of over 750ml and total kidney volume defined as the most appropriate outcome to demonstrate a disease modifying effect of tolvaptan. Therefore, if rapid progression is defined by loss of renal function or rate of decline in renal function the opportunity to treat patients who have rapidly progressing ADPKD but early in the disease may be missed.

[redacted]

An objective definition of rapidly progressing ADPKD has not been agreed within the clinical community.

B9. Section 2.6 of CS states that "Despite the majority of patients having a family history of ADPKD, the condition is often diagnosed relatively late and as an incidental finding during investigation of disease symptoms." However, in section 2.2 of the CS the estimated diagnosis rate was 90%, with diagnosed prevalence of 3.9/10,000 and total prevalence 4.3/10,000. Also, in section 2.6 of the CS, the undiagnosed prevalence was estimated to be 4.3/10,000.

- Please provide a definition for 'undiagnosed ADPKD'.

Response

Undiagnosed ADPKD refers to those individuals who are anticipated to have ADPKD but have not had any formal diagnosis.

- Please provide the correct prevalence for 1) undiagnosed but diagnosable (positive according to Pei criteria(10)), 2) undiagnosable (Pei-negative but will definitively develop ADPKD), 3) diagnosed and 4) total.

Response

Otsuka performed an analysis for the COMP in order to justify the designation of orphan drug status, and this analysis examined at the epidemiology of ADPKD (11). From this analysis Otsuka ascertained that the estimated diagnosed prevalence of ADPKD in the UK is 3.9 per 10,000. It further estimates that the current diagnosis rate is approximately 90%, the total prevalence (diagnosed and undiagnosed ADPKD) is estimated at 4.3 per 10,000. Therefore, the undiagnosed prevalence of ADPKD is estimated as 0.4 per 10,000. A figure for the undiagnosable ADPKD prevalence has not been estimated by Otsuka or other groups as a clear definition for this has not been identified. The figures provided here have been accepted by the COMP in order to grant orphan designation.

- Please provide a definition of a renal cyst (e.g. minimum size).

Response

The Pei criteria do not refer to a minimum size of renal cyst. The criteria use the numbers of cysts in one or both kidneys depending on age in order to make the diagnosis of ADPKD. Normally the renal cysts that can be seen on ultrasound scanning are of a size of 5mm or greater; however renal cyst size on ultrasound is not used in the determination of the diagnosis of ADPKD, rather it is the number of cysts.

Section C: Clarification on cost-effectiveness data

Stopping rule

C1. **Priority Question:** Please explore the use of stopping rules (in line with the response to question B4 above) in the economic evaluation. Please include the costs of any medical resources associated by applying the stopping rule, based on the data available regarding treatment response and tolerability.

Response

Please refer to the response to question B4.

Subgroup analyses

C2. **Priority Question:** Please perform subgroup analyses for the base case stratified by the rate of decline of renal function and by baseline total kidney volume (excluding and including PAS), as per the final scope issued by NICE. If not considered appropriate to undertake these subgroup analyses, please provide an explanation.

Response

As requested, the subgroup analyses stratified by baseline TKV are detailed below in Table 9. The TKV was divided into four groups 750-1249 ml; 1250-1749 ml; 1750-2249 ml; and 2250 ml and over for the analysis.

It is important to bear in mind that modelled patients are defined at baseline by age, gender, eGFR and TKV. Therefore for the purpose of these analyses we have held the other baseline variables constant as per the base case in our submission as we presume this is what the ERG has intended in its request. However, baseline age and eGFR will change in line with baseline TKV. We presented subgroup analyses based on the observed baseline values for TKV and age, by CKD stage, in the observational OVERTURE study (see Table B60 and 61 in original submission and Table 9 below). This analysis is likely to be more informative, being based on real-world age/TKV/eGFR combinations, than the requested analyses where TKV is arbitrarily changed holding the other baseline variables constant (See Table 9 below).

We have not performed the subgroup analyses by rate of renal function decline since this request would imply one of two potential methodological approaches, neither of which we believe to be appropriate or applicable.

Firstly, we could interpret this analysis as modelled patients being stratified at baseline by recent history of renal function decline. This analysis is not possible since the economic model uses baseline renal function, not rate of decline, to predict progression. In any event this analysis would be clinically inappropriate for similar reasons to the rationale outlined in the response to question B4. Recent rates of renal function decline, based on a small sample of eGFR values which can be volatile, may not reflect the true underlying rate of renal function decline. Application of such arbitrary cut-offs at the individual patient level would be associated with a high level of clinical uncertainty and would be difficult to meaningfully implement in clinical practice.

Secondly, it would be theoretically possible to retrospectively examine the individual patient simulations from the base case analysis and stratify the patients by their (lifetime or other) rate of renal function decline. We would regard this as a mining exercise solely for the purpose of reducing the ICER, which could not be supported clinically.

Table 9: Subgroup analyses for the base case by baseline total kidney volume [including PAS]

TKV	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
750 to 1249 (Mean = 999.5)	[redacted]	£153329	18.27	17.56	14.35	13.45	[redacted]	0.71	0.90	[redacted]
1250 to 1749 (Mean = 1499.5)	[redacted]	£174,437	17.73	16.91	13.71	12.78	[redacted]	0.82	0.93	[redacted]
1750 to 2249 (Mean = 1999.5)	[redacted]	£185,225	17.38	16.55	13.32	12.43	[redacted]	0.83	0.89	[redacted]
2250 and over (Mean = 2500)	[redacted]	£191,885	17.12	16.27	13.04	12.16	[redacted]	0.85	0.88	[redacted]

Estimation of treatment effect

C3. **Priority Question:** In the economic evaluation the treatment effect seen in TEMPO 3:4 is directly applied to renal expected Glomerular filtration rate (eGFR). This is justified (CS page 158-159) by the idea that the correlation between eGFR and TKV as observed in patients receiving no treatment may misrepresent the relationship in tolvaptan patients. Please perform a scenario analysis for the base case (excluding and including PAS) with the treatment effect directly applied to TKV (and not applied to eGFR).

The correlation between TKV and eGFR during the natural history of disease progression has been well studied in ADPKD patients in naturalistic settings/receiving no active treatment (see section 2.1of the submission). TKV as a surrogate outcome in ADPKD allows us to stratify progression in ADPKD and assist in characterizing the level of benefit in delaying disease progression in different patient sub groups. However, knowledge around the existence of the same relationship as well as its extent has not been studied or established for patients who have received tolvaptan, an intervention which modifies natural disease progression. To assume the same relationship in tolvaptan patients is likely to misrepresent the ultimate treatment effect on the principal outcome of interest, rate of renal function decline. Therefore, it is deemed most appropriate to directly apply the treatment effect seen in TEMPO 3:4 to change in renal function, rather than introduce TKV as an intermediate outcome for assessing treatment effect which may confound the results. Further, as the ERG notes in question B1 above, TKV was not listed as an outcome of interest in the final scope. As a result the scenario analysis below should be interpreted with extreme caution.

The analyses consider the application of a 49.2% constant reduction in TKV growth for tolvpatan compared to no active treatment, with the resultant impact on renal function determined by the underlying equations linking TKV and GFR as outlined in our submission. All other base case inputs assumptions are unchanged.

Table 10: Mean discounted base-case results per patient (probabilistic mean estimates, including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£178,610	16.75	12.63				
Tolvaptan	[redacted]	17.1	12.99	[redacted]	0.35	0.36	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Model code error

C4. **Priority Question:** The model code is not consistent with the company submission and/or information from the Excel sheet. For instance, in 'Private Sub Simulate_initialize()', a GAMMA distribution is used for some utility parameters while a BETA distribution is mentioned in Table B35 and in the Excel sheet. Moreover, the opposite is true for some cost parameters (that is, a BETA

distribution is used while a GAMMA distribution is mentioned in Table B35 and in the Excel sheet). These inconsistencies were observed by the ERG for multiple parameters including:

- uCKD1
- uCKD2
- uCKD3
- uCKD4
- uCKD5
- cPAIN
- cExtraVisits1
- cExtraVisits2
- cExtraVisitsSubs
- cMonitor1
- cMonitor2
- cMonitorSubs

Please correct all inconsistencies between the model code, the Excel sheets and the submission document, and, if necessary, provide an updated model file. Please also provide updated results of all analyses in the submission document, if necessary.

Response

The errors in the model code have been corrected and they now match the Excel sheet and the submission document. An updated Excel file is included with this response. The revised base case results are included below in Table 11. The revisions to the model resulted in a small reduction in the base case ICER from [redacted] to [redacted]

Table 11: Mean discounted base-case results per patient (probabilistic mean estimates, including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£179,056	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	[redacted]	0.83	0.92	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The cost-effectiveness acceptability curve is presented in [redacted] (including the PAS). Including the PAS the probability of cost-effectiveness at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was [redacted]%, [redacted]% and [redacted]%, respectively.

[redacted]

All sensitivity analyses and subgroup analysis have been revised and are presented in Table 12 and Table 13.

Table 12 : Summary of probabilistic mean per-patient results of structural sensitivity and scenario analyses performed in the economic evaluation of tolvaptan versus no active treatment [including PAS]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
Base-case analysis	[redacted]	£179,056	17.59	16.76	13.55	12.63	[redacted]	0.83	0.92	[redacted]
Structural sensitivity analyses										
Clinically significant pain excluded	[redacted]	£177,983	17.58	16.75	13.58	12.66	[redacted]	0.84	0.92	[redacted]
Scenario analyses										
ESRD therapy eGFR <6	[redacted]	£177,301	17.68	16.86	13.60	12.68	[redacted]	0.82	0.92	[redacted]
ESRD therapy eGFR <10	[redacted]	£180,338	17.57	16.7	13.54	12.6	[redacted]	0.87	0.94	[redacted]
Discount rates = 0%	[redacted]	£360,975	27.92	26.35	20.35	18.82	[redacted]	1.57	1.53	[redacted]
Discount rates = 1.5%	[redacted]	£264,007	22.5	21.31	16.82	15.59	[redacted]	1.19	1.23	[redacted]
Treatment effect CKD-EPI	[redacted]	£177,895	17.49	16.79	13.42	12.67	[redacted]	0.69	0.76	[redacted]
Treatment discontinuation year 4+ (0% SE 0%)	[redacted]	£179,418	17.61	16.75	13.57	12.63	[redacted]	0.86	0.94	[redacted]
Treatment discontinuation year 4+ (2.0% SE 0.8%)	[redacted]	£179,056	17.51	16.76	13.46	12.63	[redacted]	0.75	0.83	[redacted]
Disease progression	[redacted]	£183,513	17.46	16.61	13.39	12.48	[redacted]	0.84	0.92	[redacted]
Conservative care (5%)	[redacted]	£188,109	17.79	17.02	13.66	12.78	[redacted]	0.77	0.88	[redacted]
Conservative care (15%)	[redacted]	£170,049	17.39	16.50	13.44	12.48	[redacted]	0.89	0.95	[redacted]
CKD 3-4 HSUVs (Wu & Yang, 2014)	[redacted]	£179,056	17.59	16.76	13.71	12.77	[redacted]	0.83	0.94	[redacted]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
ESRD HSUVs decrements (Minimum Values)	[redacted]	£179,056	17.59	16.76	13.29	12.26	[redacted]	0.83	1.02	[redacted]
ESRD HSUVs decrements (Maximum Values)	[redacted]	£179,056	17.59	16.76	14.20	13.41	[redacted]	0.83	0.78	[redacted]
Disutility with treatment	[redacted]	£179,732	17.57	16.76	13.41	12.63	[redacted]	0.82	0.78	[redacted]
European population Subgroup	[redacted]	£174,420	17.74	16.90	13.74	12.80	[redacted]	0.84	0.94	[redacted]
HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year; SC, standard care (no active treatment)										

Table 13: Summary of the results of the subgroup analyses (probabilistic mean estimates, per-patient, including PAS)

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
Subgroup analyses based on TEMPO 3:4 baseline characteristics										
CKD stage 1	[redacted]	£140,729	18.61	17.86	14.82	13.89	[redacted]	0.74	0.93	[redacted]
CKD stage 2	[redacted]	£192,563	17.26	16.45	13.14	12.29	[redacted]	0.81	0.86	[redacted]
CKD stage 3a	[redacted]	£220,581	15.37	14.65	11.02	10.33	[redacted]	0.72	0.69	[redacted]
CKD stage 3b	[redacted]	£229,037	14.95	14.26	10.62	9.97	[redacted]	0.70	0.66	[redacted]
Subgroup analyses based on OVERTURE baseline characteristics										
CKD stage 1	[redacted]	£127,810	20.09	19.34	16.44	15.53	[redacted]	0.75	0.92	[redacted]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
CKD stage 2	[redacted]	£147,059	16.02	15.38	11.98	11.17	[redacted]	0.63	0.80	[redacted]
CKD stage 3a	[redacted]	£169,594	12.84	12.45	8.90	8.37	[redacted]	0.39	0.53	[redacted]
CKD stage 3b	[redacted]	£194,781	11.58	11.24	7.58	7.14	[redacted]	0.34	0.43	[redacted]

Model transparency

C5. **Priority Question:** The Markov trace and simulation is mainly coded in the Macro modules. The input parameters are presented and named in the Excel worksheets and referred to in the Macros. However, the parameters are often redirected/renamed, sometimes multiple times, in the Macro code (for example "pPatientState(i)") and parameters are introduced in the macro without clear description (for example "Patient_state(i)"). This severely hampers the model transparency. Please complete the table below for all parameters that are used in the Macro code (including all parameters that are redirected to each other). As an example the table has been completed for "PatientState(1)", "Patient_state (2)", "probPAIN_C(1, 2)", "probPAIN_C(1, 3)" and "probPAIN_C(2, 2)".

Parameters table

Parameter name VBA code	**Parameter name Excel sheet**	**Reference in Excel sheet**	**Value**	**Description**	**Source**
probPAIN_C(1, 2)	pPAIN_Ctrl	Control!$E$59	0.07	Annual probability of serious kidney pain for CKD stage 1 (control arm)	TEMPO 3:4 trial
probPAIN_C(1, 3)	-	Control!$F$59	0.004	Standard error of annual probability of serious kidney pain for CKD stage 1 (control arm)	TEMPO 3:4 trial
probPAIN_C(2, 2)	-	Control!$E$60	0.07	Annual probability of serious kidney pain for CKD stage 2 (control arm)	TEMPO 3:4 trial
Patient_state(1)	-	-	-	If this parameter is 1, then the patient is on hospital haemodialysis	-
Patient_state(2)	-	-	-	If this parameter is 1, then the patient is on satellite haemodialysis	-
…					

Response

Please see the accompanying Excel spreadsheet for the details requested.

Adverse events HRQoL

C6. **Priority Question:** In the base-case analysis of the economic model it was assumed that "… adverse events associated with tolvaptan treatment do not affect HRQL" (page 205) and therefore no adverse events (AEs) (besides kidney pain) were incorporated in the model. However, tables B18 and B19 in section 6.9.2 of the submission show that the numbers and the percentages of patients with serious treatment-emergent AEs as well as the most common AEs and serious adverse events are quite different for tolvaptan compared with placebo. This gives a reason to believe that the effect of AEs on HRQoL associated with tolvaptan is different compared with placebo.

a. Please fully justify why treatment dependent AEs and related disutilities are not incorporated in the model.

The ERG is correct to note that the data presented in tables B18 and B19 of the main submission highlight that the adverse event profile of tolvaptan treated patients is different to that of the placebo group in TEMPO 3:4. However these differences are not necessarily sufficient to justify more detailed modelling of adverse events in economic evaluation.

Currently the economic model assesses changes in patient HRQoL, including both ADPKD complications and adverse effects of treatment, in the following ways:

- Time-dependent rates of discontinuation from tolvaptan treatment as per those observed in TEMPO 3:4, returning the patient to the no active treatment rate of progression
- Option for disutility associated with tolvaptan treatment (set to zero in the base case, explored in scenario analysis)
- Risk of clinically significant renal pain event, with an associated utility decrement
- Health state utility decrements associated with advancing CKD stages, incorporating the impact of ADPKD complications

With this in mind, one should consider if these aspects of the model bias the analysis in favour of tolvaptan in order to judge whether more granular examination of adverse effects is required.

The overall proportion of patients that experienced any treatment-related adverse events (TAEs) was comparable in both the tolvaptan and placebo groups. Many of the TEAEs that were reported more frequently for tolvaptan than placebo, and for which the difference between groups was statistically significant, are plausibly related to a relative state of dehydration or to increased ingestion of fluids in response to signs and symptoms of dehydration. In general, these frequently reported TEAEs occurred early following initiation of treatment, were mild to moderate in severity, and were infrequently reported as serious. Symptoms of urination, while inconvenient, can be managed by appropriate timing and titration of dosing. Given tolvaptan's mechanism of action, thirst is both a common TEAE and a desired reminder to replenish body water lost as a result of tolvaptan treatment in subjects with ADPKD. The results of this analysis showed that the majority of new onset TEAEs associated with the aquaretic effects of tolvaptan occurred early in the trial (i.e., in the first 3 months of treatment) in both treatment groups.

Therefore given the relative frequency, severity and timing of these events, it is reasonable to assume their impact on patient HRQoL has been adequately captured by the ability to down-titrate the dose of tolvaptan and through the discontinuation rates applied to the model. Further, results from TEMPO 3:4 do not suggest any clinically significant withdrawal effects following discontinuation of tolvaptan treatment.

Consistent with efficacy results, tolvaptan treatment was associated with a reduction in the reporting of adverse events related to ADPKD conditions or complications. The proportion of subjects who experienced urinary tract infection was consistently higher in subjects on placebo than in subjects on tolvaptan throughout the duration of the trial. Similar results were observed with other ADPKD-related TAEs or medical concepts, such as renal pain, haematuria or anaemia.

Serious AEs were nominally higher in the placebo group (18.4% compared to 19.7%). Individual serious TAEs that occurred more frequently (> 0.5% difference) in tolvaptan subjects compared with placebo subjects included ALT Increased, AST Increased and headache. In comparison, serious TAEs that were reported more frequently (> 0.5% difference) in the placebo group included appendicitis, pyelonephritis, urinary tract infection, renal cyst haemorrhage, renal pain and hypertension.

Therefore, on balance, it is reasonable to conclude that more detailed consideration of these events in the economic model would add little value, would not greatly impact the overall results and in any event would be highly likely to favour tolvaptan. That is, the modelling approach in the base case is likely to be conservative with respect to this issue.

b. Please provide a scenario analysis for the base case (including and excluding the PAS) incorporating treatment dependent AEs and related effects on HRQoL.

Not applicable, please see above.

c. Please clarify the reference/source for the 0.05 value given in table B49 for the disutility with treatment and why this is different from the 0.0123 value mentioned on section 7.4.9, page 200. Please clarify and justify which of these two is used for the 'Disutility with treatment' scenario analysis.

Response

The value of 0.05 in table B49 is a typographical error. The value should be 0.0123 as cited on page 200 of section 7.4.9. The correct disutility value of 0.0123 was used in the 'disutility with treatment' scenario analysis.

It should be noted that we have no evidence that HRQL is reduced by tolvaptan-related aquaresis. The disutility of 0.0123 was explored in sensitivity analysis (Sullivan et al., 2011) and was applied for the duration of tolvaptan treatment. We expect this to be a highly conservative analysis as additive disutility is possibly not appropriate over patients' lifetime, as those unable to tolerate tolvaptan are likely to discontinue treatment in the early stages of treatment as seen in the TEMPO 3:4 study with year one discontinuation of 15.3%, year two discontinuation of 6.5% and year three discontinuation of 2.9%.

Adverse event costs

C7. **Priority Question:** No adverse events, other than kidney pain, were explicitly modelled in terms of costs in the economic model. Yet it is stated that "All patients incur the same health state costs while in a given health state, regardless of whether they are currently receiving tolvaptan" (page 215, CS). Tables B18 and B19 in section 6.9.2 of the submission show that the numbers and the percentages of patients with serious treatment-emergent AEs as well as

the most common AEs and serious adverse events are quite different for tolvaptan compared with placebo. Please fully justify why adverse event-related costs are not incorporated in the model. Please provide a scenario analysis for the base case where treatment dependent adverse events and related costs are incorporated in the model (excluding and including the PAS).

Please refer to the response to question C6 above. It is highly likely that the current modelling approach is conservative against tolvaptan with respect to the relative impact of treatment-related adverse effects and ADPKD complications. More detailed consideration of these events in the economic model would add little value, would not greatly impact the overall results and in any event would be highly likely to favour tolvaptan.

Impact of severe drug induced liver injury

C8. **Priority Question:** Hy's law is a prognostic indicator that the FDA follows to evaluate the potential for drug-induced severe liver injury and typically refers to significant elevations of liver enzymes with concomitantly elevated bilirubin where etiologies other than the drug have been ruled out. Finding two Hy's law cases is considered highly predictive that the drug has the potential to cause severe drug-induced liver injury (DILI) when given to a larger population.[5] In the pivotal trial 2 Hy's law cases were found. It is uncertain whether the proposed treatment pathway will prevent cases of Hy's law and DILI. Please provide a scenario analysis for the base case (excluding and including PAS) where the costs and quality of life impact of the occurrence of DILI is explored.

Within the tolvaptan ADPKD trials, liver injury was seen as described in the response to question B6. The frequency of drug induced liver injury reported the TEMPO 3:4 trial is provided in the table below.

Table 14: Frequency of drug induced liver injury reported the TEMPO 3:4 trial

	Tolvaptan			Placebo		
Abnormality	**Subjects**	**Subjects Meeting Criteria**	**%**	**Subjects**	**Subjects Meeting Criteria**	**%**
ALT >3x ULN	958	42	4.4	484	5	1.0
ALT >3x ULN with Bili >2x, but ALP <2x ULN (Hy's Laboratory Criteria)	957	2	0.2	484	0	0
Death or Liver Failure		0	0		0	0

Tolvaptan characteristically causes a hepatocellular injury with onset between 3 and 14 months of treatment. The injury typically progresses by biochemical criteria for weeks after discontinuation of treatment, and resolves slowly over one to several months. This typical

progression should in the future be useful in assisting the diagnosis of liver injury due to tolvaptan. However, it should be noted that drugs with characteristic signatures may produce injuries without all the characteristics of that signature. The risk of liver failure appears to be negligible during the first 3 months of treatment with tolvaptan.

As part of the risk management programme, patients will have LFTs monitored every month for the first 18 months and then will have LFTs monitored every 3 months. If LFT abnormalities are seen then treatment with tolvaptan will be interrupted. In addition, in the clinical trial programme and post-marketing experience, there have been no cases of fulminant hepatic failure nor patients who have required liver transplantation as a consequence.

Therefore it is very unlikely that a patient who may progress to severe LFT abnormalities or liver disease would not be identified and have treatment with tolvaptan interrupted while they are managed further.

As there have been no irreversible cases of liver damage in the tolvaptan study programme we have no data upon which to base a model with the occurrence of DILI.

Additional benefits not captured in the estimation of QALY gain

C9. Please clarify whether it is the company's belief that tolvaptan offers additional benefits that are not incorporated in the estimated QALYs. If so, please provide further details and supporting evidence.

Response

Yes, it is the company's belief that tolvaptan offers additional benefits that are not incorporated in the estimated QALYs. The unaccounted for benefits include:

- Our long-term disease modelling estimates that tolvaptan will delay ESRD and lead to a reduction in kidney transplants by approximate 20%. This reduction in the demand for kidney transplant would result in benefits for ESRD patients and the NHS. Patients on the waiting list for a kidney are more likely to receive a kidney transplant and more likely to receive it sooner resulting in improved quality of life for those patients, which is not captured in the current NICE QALY calculation.

  The NHS will benefit from reduced waiting times for transplant and subsequently dialysis as dialysis capacity increases due to appropriate patients progressing from dialysis to earlier transplant. Both valuable efficiency savings for a service that will soon undergo a change in commissioning route from NHS England to individual Clinical Commissioning Groups and Welsh Local Health Boards.
- The polycystic kidney disease (PKD) charity notes in their comments on the 'Draft remit and draft scope (pre-referral)' (12) that there is a substantial psychological burden associated with ADPKD. We believe that an improvement in the psychological impact suffered by ADPKD patients will be achieved with the availability of an active therapy; unfortunately the evidence is not yet available to quantify this benefit as part of the economic evaluation.
- In their response to the draft remit and scope for this evaluation the PKD charity noted factors they felt were not fully captured by the QALY included "employability (ability to gain and stay in employment), financial impact on

patients, families and carers (e.g. life/travel insurance, reduced working hours)" (p19,(12)).

- The QALY as applied in the reference case also fails to account for improved patient health resulting in a reduction in the impact on the lives of carers' of ADPKD patients.

Age-standardised mortality rate

C10. Table B39 states that mortality in ADPKD patients prior to CKD stage 5 is equal to mortality in the general population. No information was found on mortality for CKD stage 5.

a. Please clarify and justify how mortality for CKD stage 5 patients was incorporated in the model.

Response

Mortality in CKD 5 (prior to treatment) was modelled from life tables. Once the patient's eGFR declined to 8.5 survival was modelled according to treatment modality (conservative care, dialysis and transplant).

b. Please provide the methods and results of a scenario analysis for the base case using ADPKD-specific mortality risks.

Response

Although eight (13-20) studies considered the mortality of ADPKD patients were identified (page 35, section 2.1 of the submission) no data was identified that was considered appropriate to model ADPKD specific mortality.

The study by Florijn et al. (14) in the Netherlands provides some standardised mortality ratios (SMR) for ADPKD patients. However, there are a number of limitations to this data:

- The estimates are based on five large families with chromosome 16 linked ADPKD.
- There were only 83 deaths in the 10,279 person years.
- The time horizon for the mortalities, and the SMRs, spanned from 1889 to 1992. Substantial medical developments have been made in this period including antibiotics, antihypertensive therapy, dialysis and renal transplant (14). An analysis of 50-59 year olds over time revealed a continuous mortality decline, particularly after 1970.
- The mortality estimates do not distinguish between patients in end stage renal disease (ESRD) (and receiving treatment) and those not. As a result the mortality rates would be a double count of ESRD mortality for ESRD patients and overly pessimistic for patients in CKD stages one to four.

In light of the factors above we do not feel it is possible to include robust ADPKD specific mortality rates in the model and conduct the requested analysis.

Jacobi process

C11. To incorporate correlation between parameters in the probabilistic sensitivity analyses, a Jacobi process was used.

- Please justify why the Jacobi process was preferred above the more commonly used Cholesky decomposition for this purpose.

Response

The Cholesky decomposition of the covariance matrix is widely employed to generate random deviates from a multivariate normal distribution. Within health economics this method of decomposition is widely used; no doubt due to its description in the chapter for implementing probabilistic sensitivity analysis within the textbook "Decision Modelling for Health Economic Evaluation" by Briggs et al (21). It is not, however, the only method of decomposition available. We utilised another common decomposition method known as spectral (or Eigenvector) decomposition. Either method is appropriate in this context as a means of deriving sampled deviates from a set of correlated normally distributed variables. Despite its relative simplicity, the Cholesky matrix can be unstable due to the requirement for the variance-covariance matrix to be positive definite - preventing any two risk factors from being perfectly correlated. The eigenvalue decomposition method carried out using the Jacobi method is typically more stable and described by Press et al. (22) as fool-proof.

The important question for sampling correlated variables is that the correlated normal random deviates are sampled by the model correctly. The following illustration of the sampling of two variables shows that the method employed produces appropriately sampled deviates.

Variable A: mean (SD) = 4.47 (0.08); Variable B: mean (SD) = -0.060 (0.01); Covariance = -0.001

Summary statistics of 1,000 sampled deviate:
Variable A: mean (SD) = 4.47 (0.08); Variable B: mean (SD) = -0.060 (0.01); Covariance = -0.001

The Shapiro-Wilk test for normality confirmed the variables were normally distributed (Variable A: W = 0.9982, p-value = 0.3736; Variable B: W = 0.9977, p-value = 0.168; where the null hypothesis is that variables are normally distributed). The associated QQ-plot supports this finding as shown below:

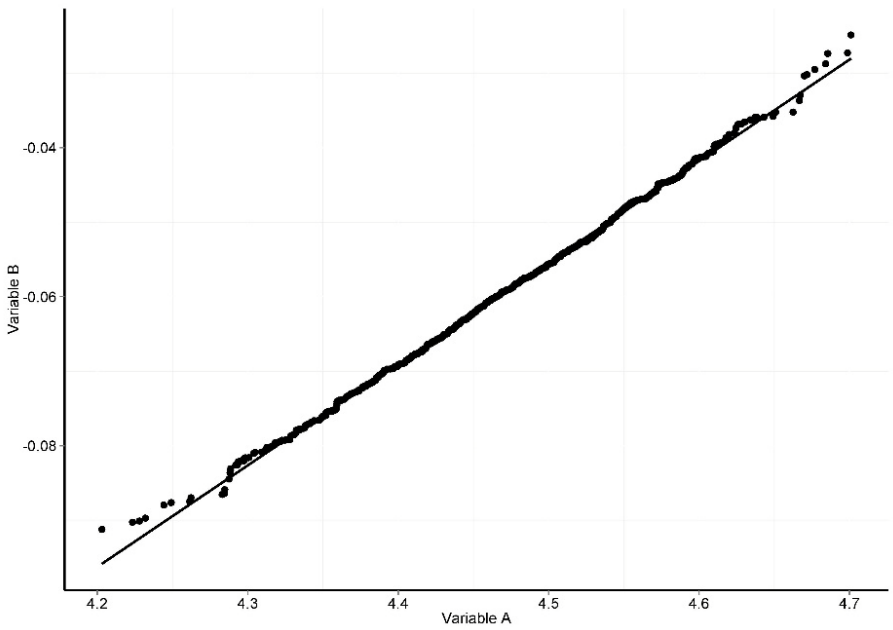


Figure 7: Treatment cost weighting

- Please provide the results of a scenario analyses for the base case that uses a Cholesky decomposition instead of a Jacobi process.

Response

Regrettably we were not possible to conduct a scenario analyses for the base case that uses a Cholesky decomposition instead of a Jacobi process within the available time.

Treatment cost weighting

C12. In addition to a half-cycle correction, weighting is applied to treatment costs, to reflect the timing of treatment discontinuations.

a. Please clarify that this weighting is necessary in addition to the half-cycle correction that is applied.

Response

The application of treatment costs among patients ending treatment due to discontinuation was handled differently to patients ending treatment due to ESRD or death. The half-cycle correction was applied to treatment costs when cessation of treatment occurs as a result of ESRD or death only.

Weighting parameters were applied to treatment costs when cessation of treatment occurs as a result of discontinuation, without any half-cycle correction to avoid double adjustment. Weightings are necessary to better represent the timing of discontinuation as seen in the trial (patients who discontinued typically did so earlier on). Applying weightings of 0.5 would be equivalent to applying a half-cycle correction, if no further information was known about the timing of discontinuation within each cycle.

b. Please provide updated results of the base case (including and excluding the PAS) excluding this weighting of treatment costs.

Response

Table 15 presents the results of sensitivity analysis run using the following weighting of treatment costs for all years: 0, 0.5, 1.

Table 15: Summary cost effectiveness results of sensitivity analysis varying weighting of treatment costs [including PAS]

Results per patient	Base case	Sensitivity analysis: Weighting value in all years		
		0	0.5	1
With PAS				
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	+0.92	+0.91	+0.91	+0.91
Incremental life years	+0.83	+0.82	+0.82	+0.82
ICER	[redacted]	[redacted]	[redacted]	[redacted]
Note that in this sensitivity analysis weighting values were fixed (i.e. SE=0) and thus estimated benefits also varied slightly from the base case due to randomness.				

Changes to the weighting parameter values did not change the estimated ICER substantially from the base case, with ICERs ranging from £[redacted] to £[redacted].

Time horizon

C13. The first 3 years change in TKV, eGFR and the relative reduction in eGFR decline (slope) are directly based on trial data. Afterwards, these parameters are extrapolated using regression functions (based on TEMPO 3:4 trial data). Please provide the results of scenario analyses for the base case which use a time horizon of 3 years (that is no extrapolation), 5 years, 10 years, 15 years, 20 years, and 25 years (all excluding and including PAS).

Response

The treatment effect of tolvaptan in ADPKD has been proven to persist for 5 years or more in an open label extension of the tempo 3:4 trial (23). There is no evidence to support efficacy decline within a specific time horizon. This is supported by the continued effect in the open label extension (23) and the consistency of maintaining effect in patients at different stages of disease in TEMPO 3:4 (24). The scenario analyses requested by the ERG should be interpreted with extreme caution as they underestimate the benefit of tolvapatan.

Table 16: Time horizon scenario analysis [including PAS]

	Time horizon					
	3 years	5 years	10 years	15 years	20 years	25 years
ICERs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The analysis clearly shows that tolvaptan is more cost-effective over the long term for the chronic condition of ADPKD.

Health state costs

C14. Please provide a one-way sensitivity analysis for all health state related costs (for example using the 95% confidence interval).

Response

Health state costs were varied by +/- 1.96*SE as shown in Table 17. Results of the sensitivity analysis are presented in Table 18.

Table 17: Cost inputs utilised in sensitivity analysis of health state costs

Cost parameter	Base case inputs		Sensitivity analysis inputs	
	Mean	SE	Lower	Upper
CKD 1	£171.89	£25.78	£121.35	£222.43
CKD 2	£171.89	£25.78	£121.35	£222.43
CKD 3	£1,436.16	£215.42	£1,013.93	£1,858.39
CKD 4	£3,357.65	£503.65	£2,370.50	£4,344.80
CKD 5 (prior to ESRD treatment)	£5,238.59	£785.79	£3,698.44	£6,778.74
ADPKD (Conservative care)	£5,238.59	£785.79	£3,698.44	£6,778.74
ADPKD (HD)	£5,238.59	£785.79	£3,698.44	£6,778.74
ADPKD (PD)	£5,238.59	£785.79	£3,698.44	£6,778.74
ADPKD (Transplant)	£5,238.59	£785.79	£3,698.44	£6,778.74
Conservative care	£5,238.59	£785.79	£3,698.44	£6,778.74
Hospital HD	£39,397.47	£1,627.90	£36,206.79	£42,588.15
Satellite HD	£36,749.45	£1,943.93	£32,939.35	£40,559.55
Home HD	£23,357.48	£943.92	£21,507.40	£25,207.56
APD	£24,359.77	£685.73	£23,015.74	£25,703.80
CAPD	£17,514.74	£672.59	£16,196.46	£18,833.02
Transplant maintenance year 1	£19,044.44	£2,856.67	£13,445.37	£24,643.51
Transplant maintenance year 2+	£7,876.52	£1,181.48	£5,560.82	£10,192.22

Table 18: Results of health state costs sensitivity analysis [including PAS]

Results per patient	Base case	Sensitivity analysis: Health state costs	
		Lower	Upper
With PAS			
Incremental costs	[redacted]	[redacted]	[redacted]

Incremental QALYs	+0.92	+0.83	+0.83
Incremental life years	+0.83	+0.92	+0.92
ICER	[redacted]	[redacted]	[redacted]

Lower health state costs were associated with lower total costs accumulated in both arms, smaller downstream cost offsets associated with Tolvaptan therapy and thus higher incremental costs overall. By contrast, higher health state costs led to higher absolute costs accumulated in both arms, greater downstream cost offsets and thus lower incremental costs associated with Tolvaptan. Application of lower health state costs increased the ICER from £[redacted] in the base case to £[redacted]. Increased health state costs were associated with improved cost-effectiveness compared to the base case, with an estimated ICER of £[redacted].

Extrapolation of treatment effect

C15. It is assumed that the treatment effect is time independent and will last while patients are on treatment. This is however uncertain. Please explore different assumptions regarding the extrapolation of the treatment effect: please provide scenario analyses for the base case in which the treatment effect after 3 years (the trial duration) is set at 0%, 10%, and 50% of the treatment effect observed in the pivotal trial.

Response

The treatment effect of tolvaptan in ADPKD has been proven to persist for 5 years or more in an open label extension of the tempo 3:4 trial (23). There is no evidence to support efficacy decline. This is borne out, not only in continued effect in the open label extension (23) but also in the consistency of maintaining effect in patients at different stages of disease (24). The scenario analyses requested by the ERG are outlined below and should be interpreted with caution.

Table 19: Scenario analyses 1 - treatment effect after 3 years is set at 50% of the treatment effect observed in the pivotal trial [including PAS].

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£179,056	16.76	12.63				
Tolvaptan	[redacted]	17.17	13.08	[redacted]	0.41	0.45	[redacted]

Table 20: Scenario analyses 1 - treatment effect after 3 years is set at 10% of the treatment effect observed in the pivotal trial [including PAS].

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£179,056	16.76	12.63				
Tolvaptan	[redacted]	16.93	12.82	[redacted]	0.17	0.19	[redacted]

Table 21: Scenario analyses 1 - treatment effect after 3 years is set at 0% of the treatment effect observed in the pivotal trial [including PAS].

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£179,056	16.76	12.63				
Tolvaptan	[redacted]	16.88	12.77	[redacted]	0.12	0.14	[redacted]

Table 22: Scenario analyses 1 - treatment effect after 3 years is set at 0% of the treatment effect observed in the pivotal trial (all patients discontinuing at the end of year 3) [including PAS].

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£179,418	16.75	12.63				
Tolvaptan	[redacted]	16.88	12.76	[redacted]	0.12	0.14	[redacted]

Internal validity

C16. Please clarify how the internal validity of the economic model was assessed.

Response

Activities undertaken to assess the internal validity of the model include:

- Testing that changes in model inputs have expected/explainable impact on modelled results e.g. extreme input values, utilities set to one/zero, life tables set to zero, discounting set to zero, 0 or 100% treatment effect, etc.
- Output of individual sampled values to test multivariate sampling of coefficients
- Output of patient level data (e.g. eGFR trajectories) during development process
- Stepping through model code and performing patient walk-through
- Comparison of estimated disease progression trajectories to predictions made by source equations outside of the model
- Comparison of deterministic results against PSA
- Comparison of interim/final results with pre-determined expectations from previous models/ logical/approximation calculations
- Review by secondary internal modeller
- Review by external modeller: spreadsheet calculations, VBA and data
- Review of model inputs against source material

Additionally, face validity was checked with clinical experts (problem, structure, data, assumptions and results). The approach taken is in line with the ISPOR guidelines for model transparency and validation and the NICE DSU TSD for patient-level simulation.

Section D: Textual clarifications and additional points

D1. Figure B12 on page 122 of the CS is difficult to read and interpret. Please provide this figure after correcting the formatting, adjusting the colouring if necessary.

Response

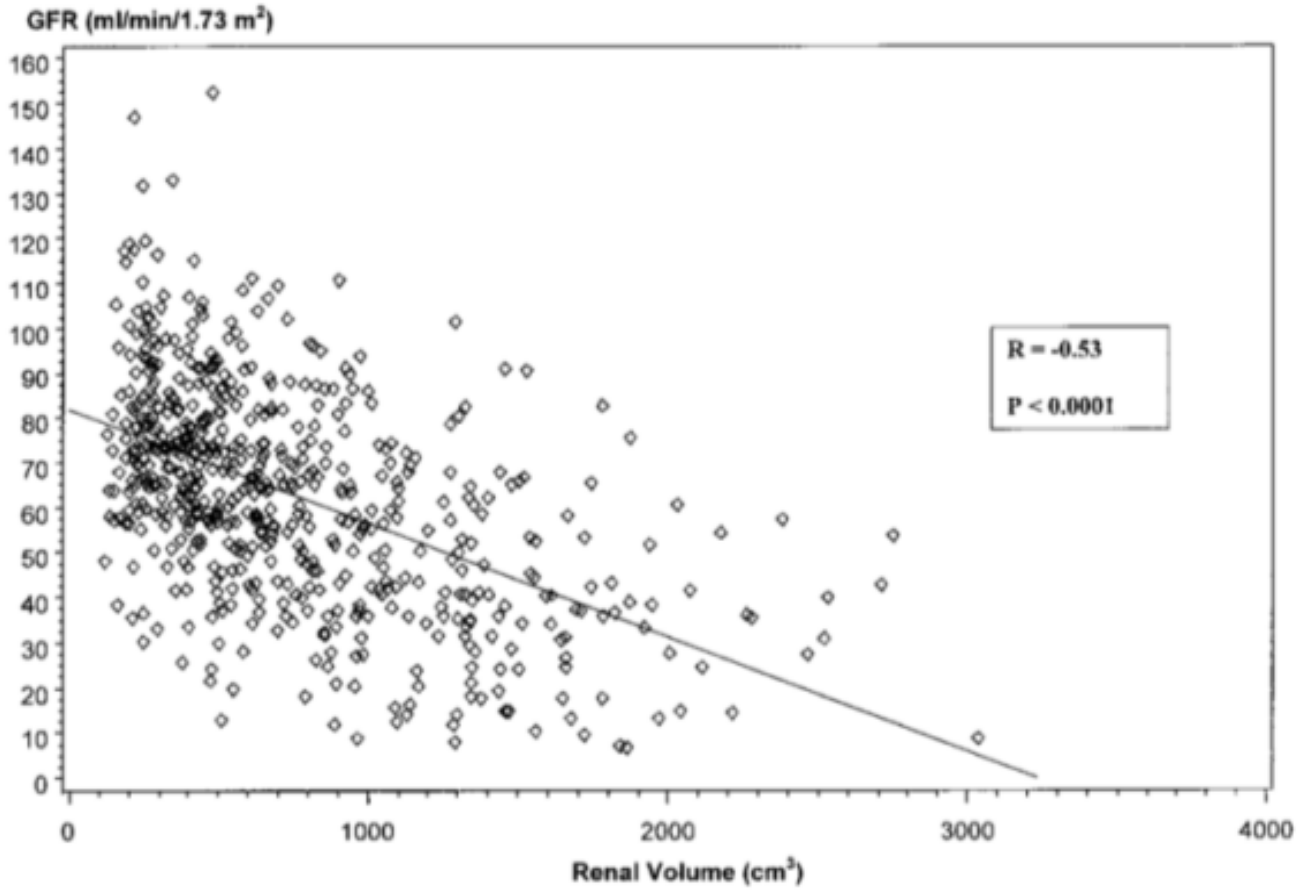
The clearest version of the figure available is to be found on page 254 of the TEMPO 3:4 CSR. The CSR is included with this response.

D2. The text in the following figures is difficult to read because of the small size. Please provide enlarged text. Figure A6, A7, B3, B4, B5, B6, B7, B8, B9, B10, B11.

Response

The enlarged figures and text are included below.

Figure A6: Relationship between GFR and renal volume in patients with ADPKD

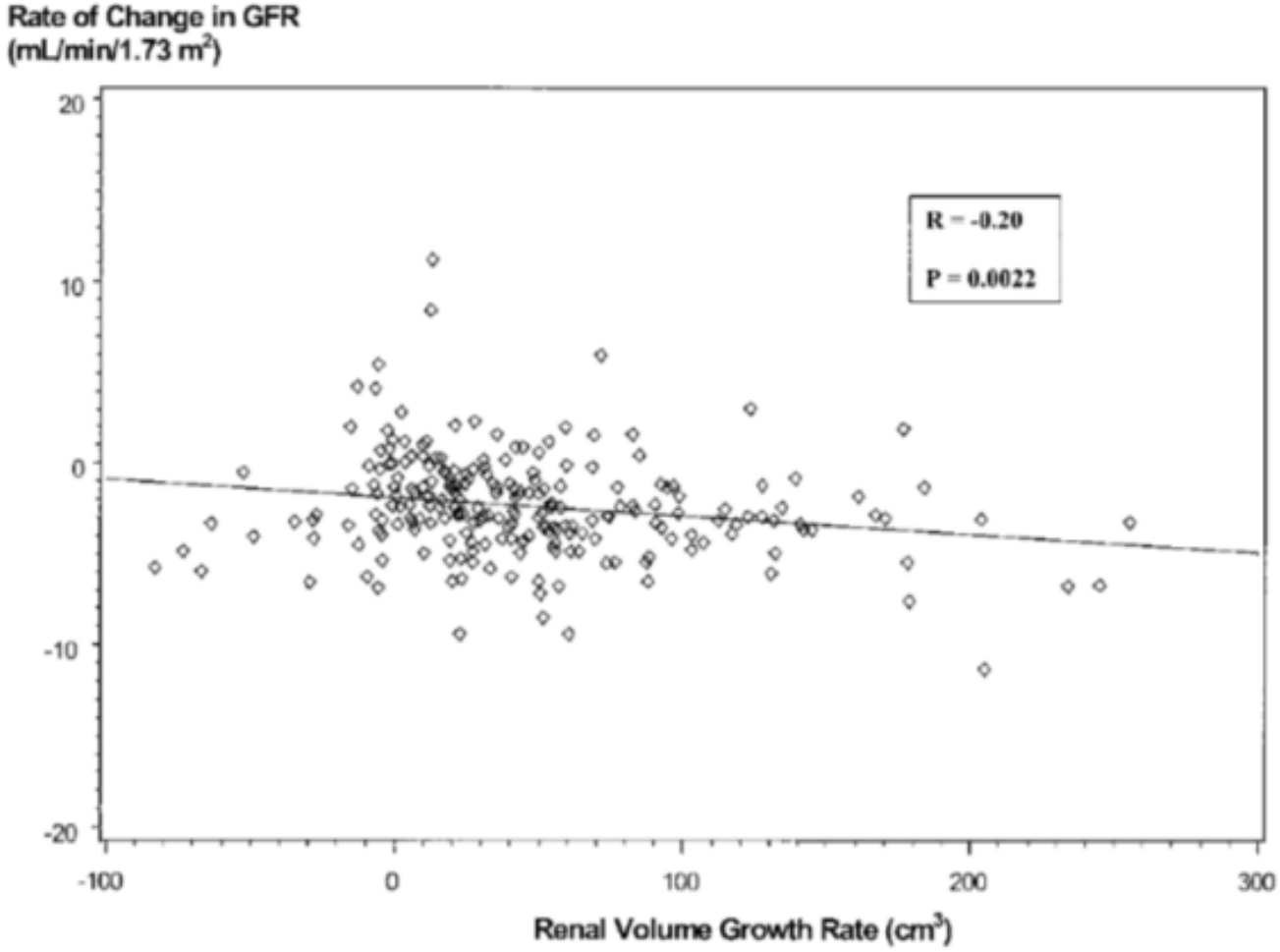


ADPKD = autosomal dominant polycystic kidney disease; GFR = glomerular filtration rate.

Note: N = 229; figure shows all data points for each subject.

Source: Fick-Brosnahan *et al*. (25)

Figure A7: Relationship between rate of change in GFR and renal volume growth rate in patients with ADPKD

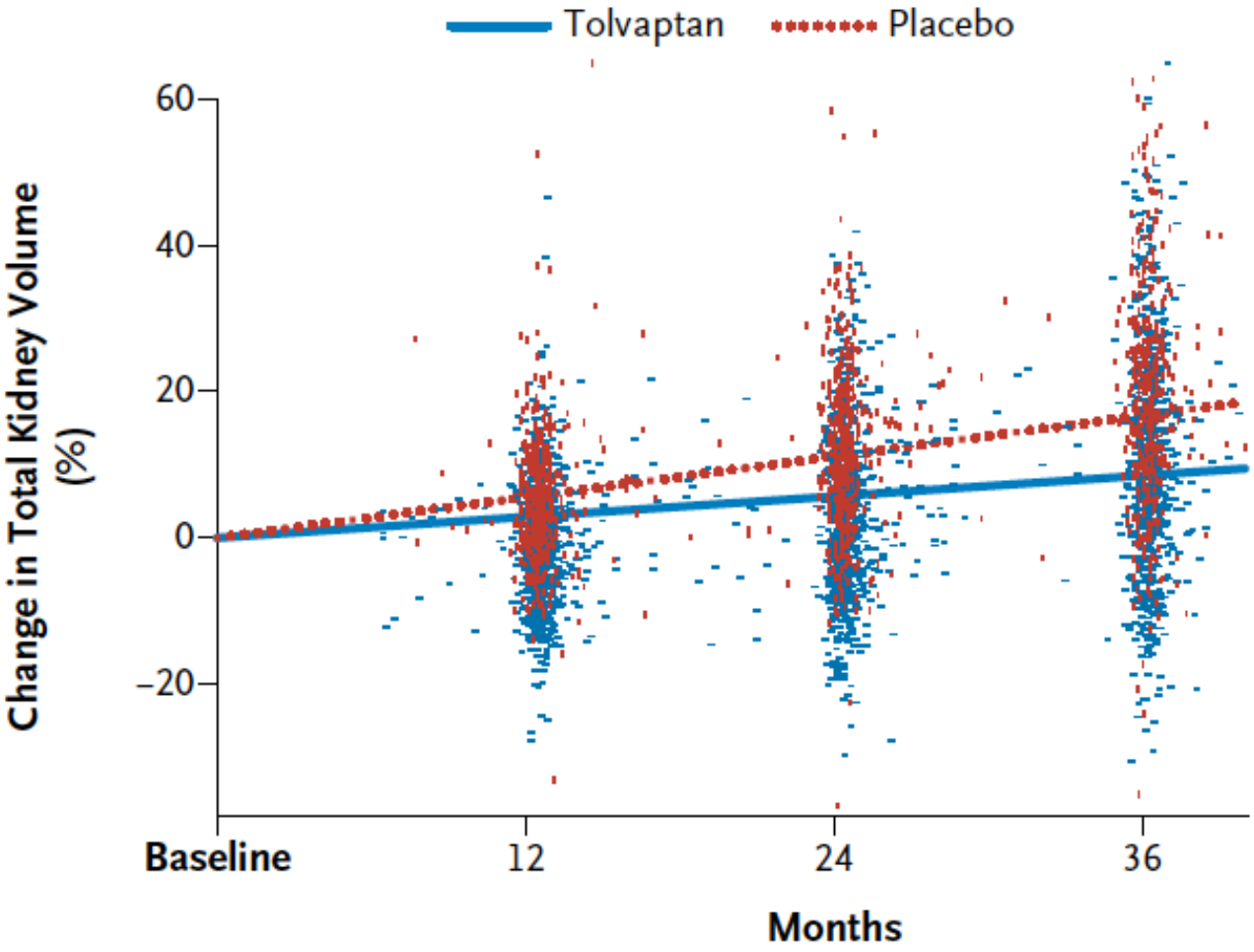


ADPKD = autosomal dominant polycystic kidney disease; GFR = glomerular filtration rate.

Note: N = 229.

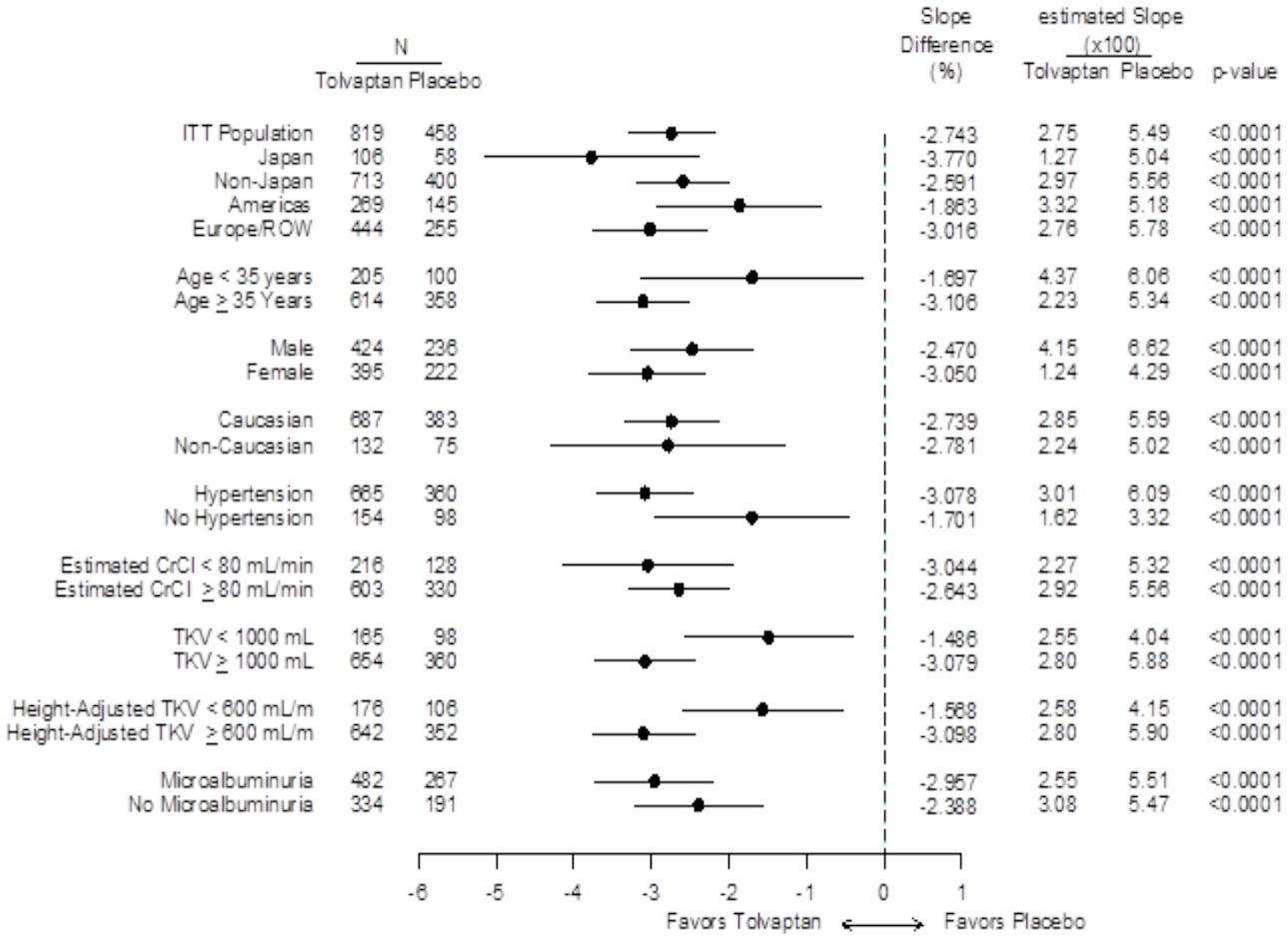
Source: Fick-Brosnahan *et al*. (25)

Figure B3: Rate of change in total kidney volume within the treatment period



Source: Figure 2A, Torres *et al*. (24).

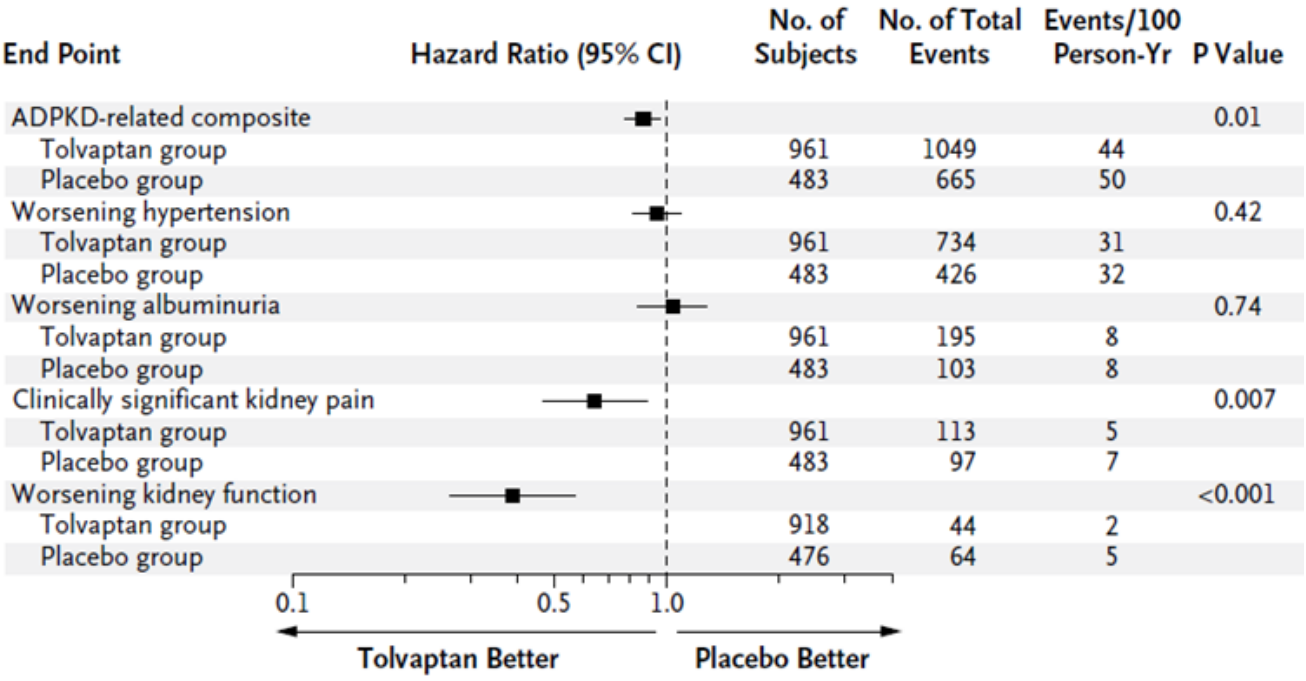
Figure B4: Subgroup analyses of TKV slope difference



CrCl = creatinine clearance; CSR = clinical study report; ITT = intention to treat; ROW = rest of world; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume.

Source: CSR TEMPO 3:4 Figure 9.3.3-1 (Otsuka, data on file, (26)); Figure 2B (Torres *et al*. (24)).

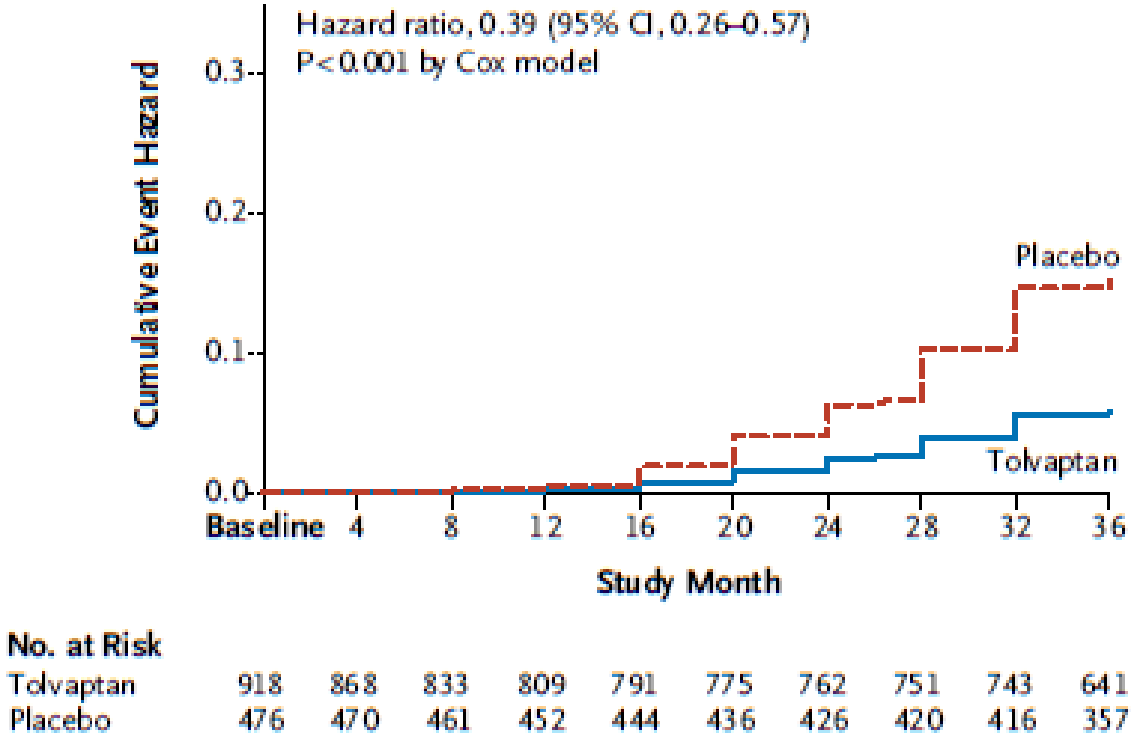
Figure B5: Forest plot of the treatment effect in the time to investigator-assessed multiple ADPKD progression



ADPKD = autosomal dominant polycystic kidney disease; CI = confidence interval; Yr = year.

Source: Figure 3A, Torres *et al*. (24).

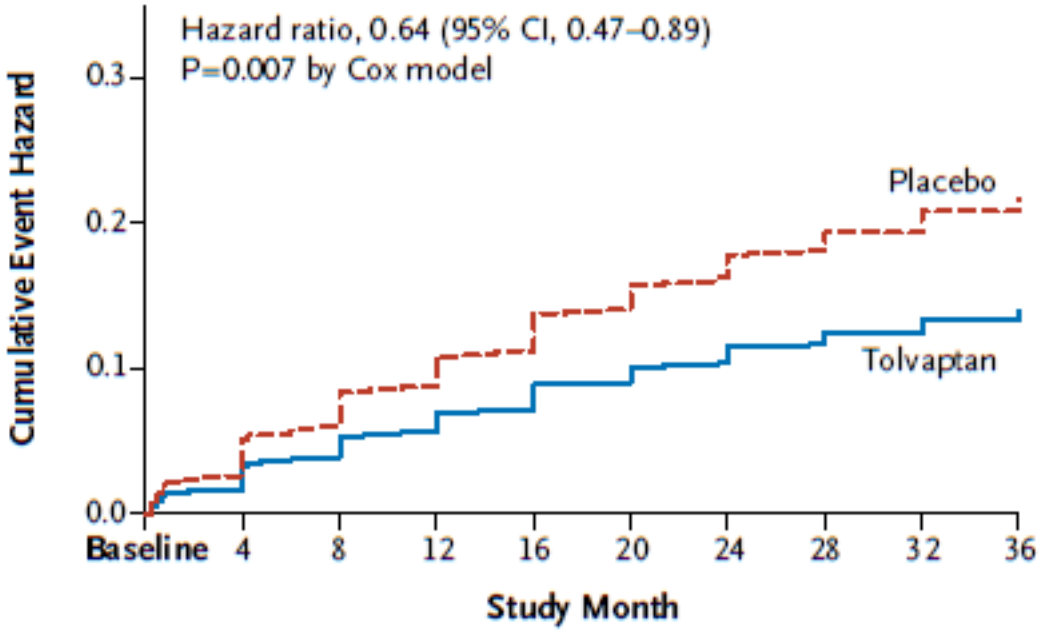
Figure B6: Cumulative hazard functions for the time to worsening renal function



CI = confidence interval.

Source: Figure 3C, Torres *et al*. (24).

Figure B7: Cumulative hazard functions of the time to clinically significant renal pain

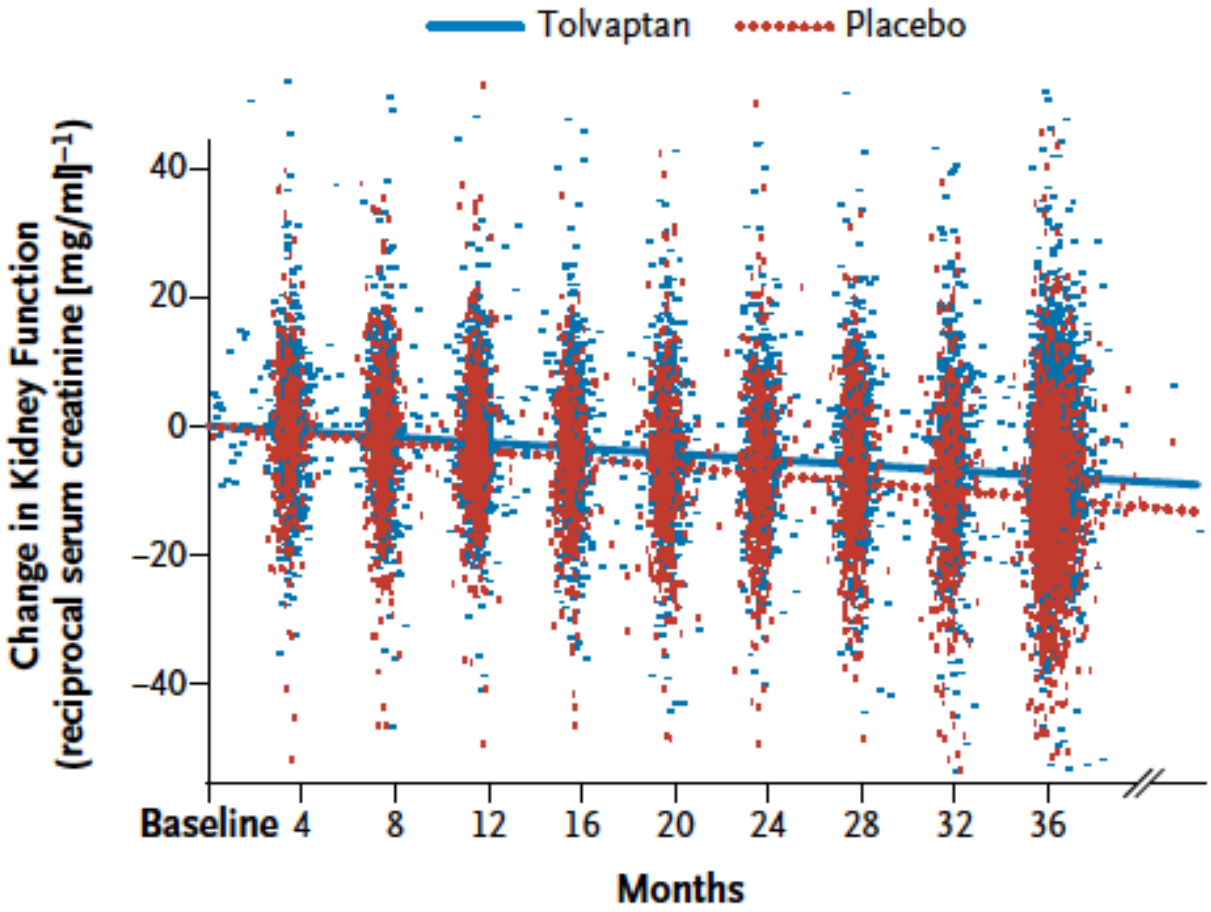


No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

CI = confidence interval.

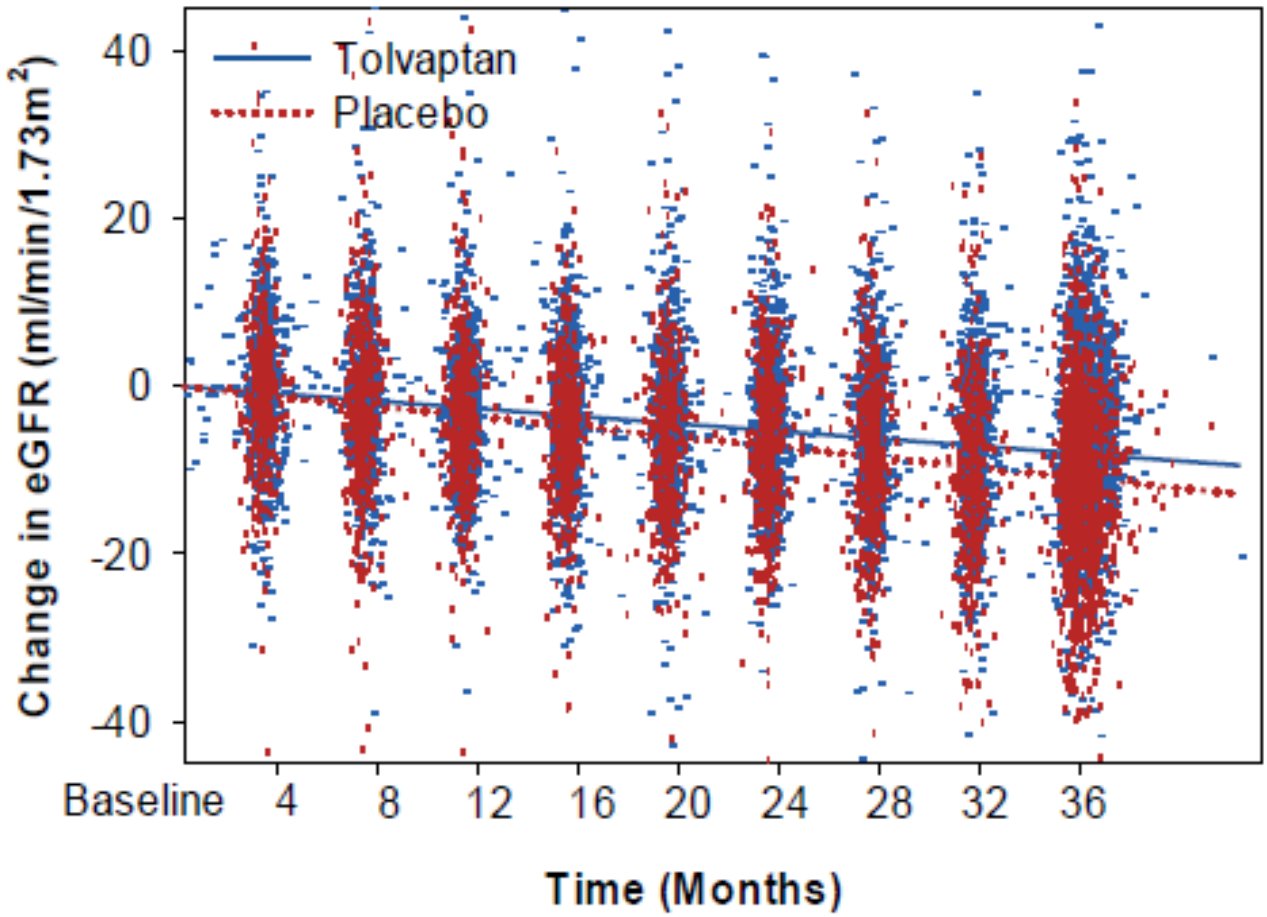
Source: Figure 3D, Torres *et al*. (24).

Figure B8: Rate of change in renal function (measured using reciprocal serum creatinine [mg/mL^{-1}])



Source: Adapted from Figure 2C, Torres *et al*. (24).

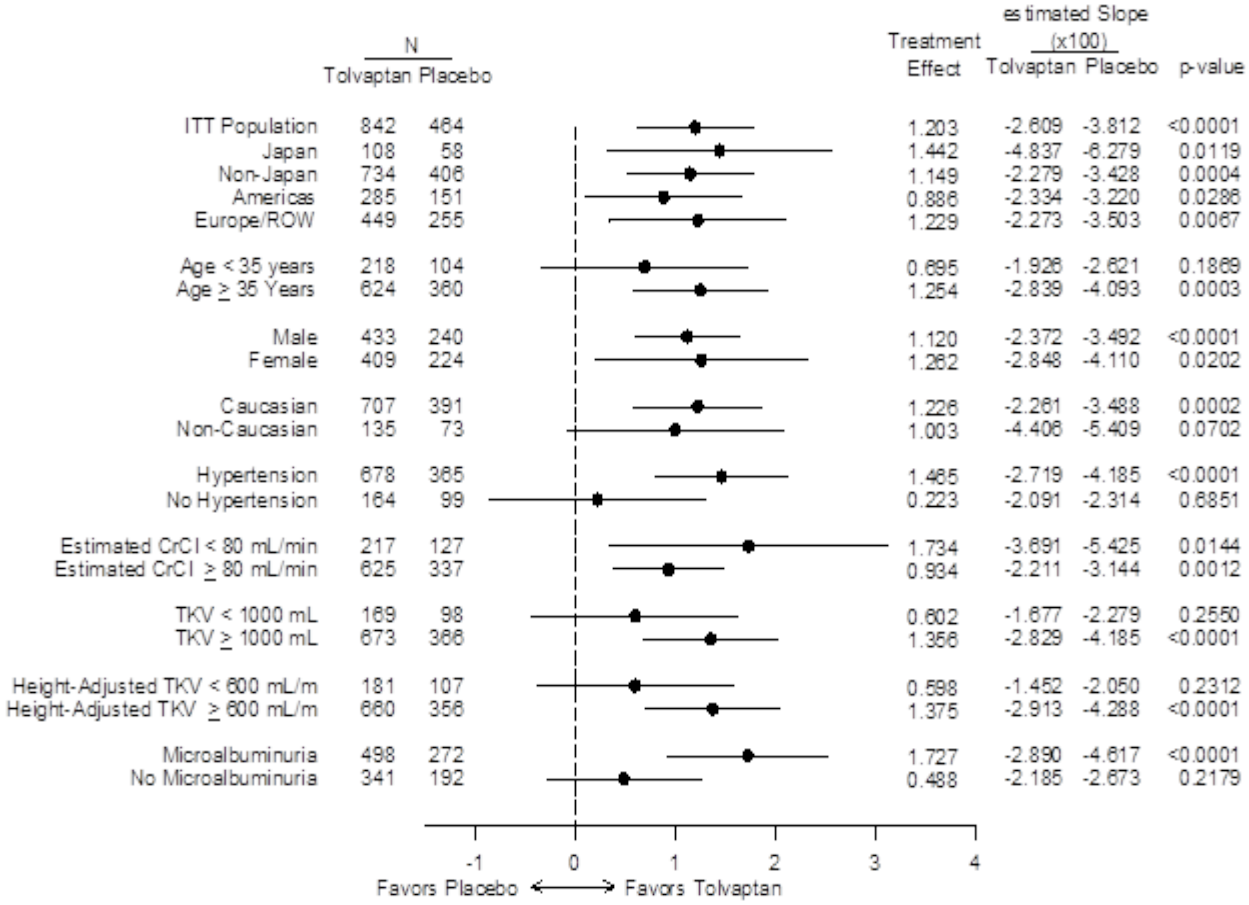
Figure B9: Rate of change in renal function (measured using $eGFR_{CKD\text{-}EPI}$ [mL/minute/1.73 m^2])



eGFR = estimated glomerular filtration rate; $eGFR_{CKD\text{-}EPI}$ = estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration.

Source: Adapted from Figure S3, Torres *et al*. (24).

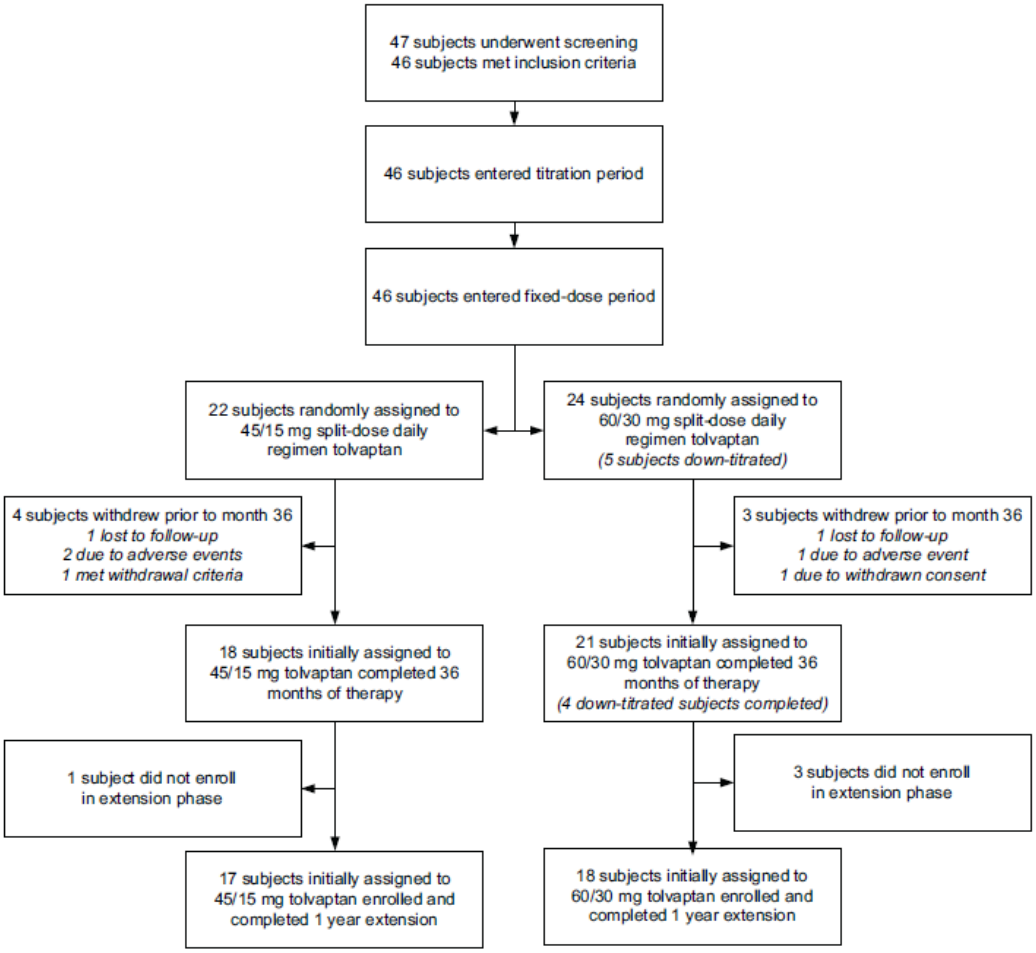
Figure B10: Subgroup analyses of annualised change in renal function (1/serum creatinine [mg/mL]$^{-1}$)



CrCl = creatine clearance; CSR = clinical study report; ITT = intention to treat; ROW = rest of world; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume.

Source: CSR TEMPO 3:4 Figure 9.5.1.3-1 (Otsuka data on file,(26)).

Figure B1. Figure B11: Patient disposition in TEMPO 2:4



TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

Source: Otsuka data on file (27).

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