in collaboration with:

Tolvaptan for treating autosomal dominant polycystic kidney disease

Produced by Kleijnen Systematic Reviews Ltd (UK) in collaboration with Erasmus University Rotterdam and Maastricht University (The Netherlands)

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Abbreviations

ADPKD	Autosomal Dominant Polycystic Kidney Disease
AE	Adverse Events
AiC	Academic in Confidence
ALT	Alanine transaminase
AMP	Adenosine monophosphate
ANCOVA	Analysis of covariance
APD	Automated PD
ASN	American Society of Nephrology
AST	Aspartate transaminase
AUC	Area under the curve
AVP	Arginine vasopressin
BP	Blood pressure
cAMP	cyclic AMP
CAPD	Continuous ambulatory PD
CEA	Cost-effectiveness Analysis
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Registry of Controlled Trial
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in Confidence
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMR	Cochrane Methodology Register
COMP	Committee for Orphan Medicinal Products
CrCl	Creatinine clearance
CRISP	Consortium for Radiological Imaging Studies of Polycystic Kidney Disease
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
DAPS	Direct Access: Pathology Services
DARE	Database of Abstracts of Reviews of Effects
dBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DTPA	Diethylene triamine pentaacetic acid
$eCrCl_{CG}$	Estimated creatinine clearance by means of the Cockcroft-Gault formula
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated GFR
$eGFR_{CKD\ EPI}$	Estimated GFR by Chronic Kidney Disease Epidemiology Collaboration
$eGFR_{MDRD}$	Estimated glomerular filtration rate calculated using Modification of Diet in Renal Disease formula
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERA–EDTA	European Renal Association–European Dialysis and Transplant Association
ERG	Evidence Review Group
ESRD	End-Stage Renal Disease
ET	Early termination

EU	European Union
EUR	Erasmus University Rotterdam
FDA	U.S. Food and Drug Administration
FOI	Freedom of information
GGT	Gamma-glutamyl transpeptidase
GFR	Glomerular filtration rate
HD	Haemodialysis
HR	Hazard ratio
HRG	Healthcare Resource Groups
HRQoL	Health-related Quality of Life
HSUV	Health state utility values
HTA	Health Technology Assessment
HTN	Hypertension
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
ITT	Intention to Treat
IU	International unit
IVRS	Interactive voice response system
KSR	Kleijnen Systematic Reviews
LFT	Liver function tests
LS	Least squares
LYG	Life year(s)
MAP	Mean atrial pressure
MDRD	Modification of Diet in Renal Disease
mg	Milligram
mGFR	Measured GFR
MMRM	Mixed-model repeated measure
MRI	Magnetic resonance imaging
N/A	Not applicable
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc
PAS	Patient access scheme
PCS	Physical component summary score
PD	Peritoneal dialysis
PD	Pharmacodynamic
PK	Pharmacokinetic
PKD	Polycystic kidney disease
PPS	Personal Social Service
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
RMP	Risk Management Plan
RRT	Renal replacement therapy

SAE	Serious Adverse Events
SAP	Statistical analysis plan
sBP	Systolic blood pressure
SC	Standard care
SD	Standard deviation
SE	Standard error
SF-12	Short Form (12) Health Survey
SF-36	Short Form (36) Health Survey
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SOC	System organ class
STA	Single Technology Appraisal
TEMPO	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes
THIN	The Health Improvement Network
TKV	Total kidney volume
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
Uosm	Urine osmolality
U.S.	United States (of America)
US	Ultrasound
USA	United States of America
V2RA	Vasopressin V2 Receptor Antagonist
VBA	Visual Basic for Applications
WCN	World Congress of Nephrology
Wk	Week

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope is as follows: "*People with autosomal dominant polycystic kidney disease*" (ADPKD). This is in line with the patient population included in the company's submission.

The intervention described in the company's submission ("*tolvaptan*") matches the intervention described in the final scope.

The comparator defined in the NICE scope was, "*Standard care, including routine surveillance without tolvaptan*". According to the company's submission, the standard care does not involve any active treatment for ADPKD. This is in line with the ERG's understanding of the topic area.

The outcomes defined in the final scope are reflected in the decision problem in the company's submission.

The ERG is aware that the company has offered a patient access scheme (PAS). End of life criteria are not relevant for this project.

1.2 Summary of clinical effectiveness evidence submitted by the company

Tolvaptan is a disease-modifying therapy for ADPKD aiming to delay renal progression in ADPKD, by reducing kidney growth and slowing renal function decline.

In TEMPO 3:4 (n > 1,400), tolvaptan demonstrated a significant relative reduction of 49.2% in total kidney volume (TKV) growth over three years when compared with placebo (absolute reduction of -2.71% per year; 95% confidence interval (CI): -3.27, -2.15; p<0.0001). In parallel with the effects on TKV growth, tolvaptan was associated with a significant relative reduction of 31.6% in the rate of renal function decline over three years, compared with placebo (absolute reduction of 1.20mg/ml^{-1} serum creatinine, 95% CI: 0.62, 1.78; p<0.001). Treatment with tolvaptan was associated with a significant 61% relative reduction (absolute reduction: three events per 100 person-years) in the risk of worsening renal function over three years, compared with placebo (two events per 100 person-years versus five events per 100 person-years; hazard ratio (HR) 0.39; 95% CI: 0.26, 0.57; p<0.001).

Tolvaptan reduced the risk of clinically significant kidney pain by 29% (absolute reduction: two events per 100 person-years) compared with placebo (five events per 100 person-years versus seven events per 100 person-years; HR 0.64; 95% CI: 0.47, 0.89; p=0.007). Evidence of efficacy was observed in all subgroups analysed.

For the primary endpoint (TKV), tolvaptan showed a consistent and significant effect favouring tolvaptan across all studied chronic kidney disease (CKD) stages. Within CKD stage 1 patients only, the difference between treatment groups showed no significant difference for renal function decline. In patients with CKD 2 and 3 tolvaptan improved both the rate of TKV growth and GFR decline. Tolvaptan also demonstrated continued efficacy

over longer periods of exposure, as observed from the interim results from TEMPO 4:4 (five years).

During the follow-up of TEMPO 3:4 (three years), 15.4% of patients assigned to the tolvaptan arm (versus 5% in the placebo arm) discontinued due to adverse events (AEs). Hepatotoxicity has been observed in some ADPKD receiving tolvaptan, including three cases meeting Hy's Law criteria. To mitigate this risk, measures are described in the European Union Risk Management Plan to ensure that patients receive monthly liver function tests for the first 18 months of treatment with tolvaptan, and three-monthly thereafter.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The inclusion criteria of the TEMPO 3:4 trial are broadly in line with the final scope. Both, treatment and placebo, were given alongside *"best standard care"*. As the term was not defined, there is some uncertainty on what measures comprised best standard care and how this could have influenced the overall findings. The trial did not provide results for one of the outcomes defined in the final scope, i.e. health-related quality of life. Following the inclusion criteria (e.g. TKV ≥ 750 ml creatinine clearance ≥ 60 ml per minute), 530 patients were excluded. Generalisability of the trial is further limited as only 73 out of the 1,445 patients (5%) included in TEMPO 3:4 came from the UK. There is limited evidence for CKD stage 3 patients (17% of the included participants). Furthermore, the trial only included patients aged 18 to 50 years.

Sample size calculation for the TEMPO 3:4 trial was based on an endpoint which is outside the scope which might mean that the outcomes relevant for this submission are underpowered.

The ERG agrees with a previous FDA assessment stating that the finding of two or more Hy's Law cases (indicating drug-induced liver injury) in a clinical trial safety database is a strong predictor of a drug capable of causing such injury. Other adverse events, such as thirst and polyuria may affect the ability of patients of patients to take effective doses of tolvaptan. More people in the tolvaptan group (n=148, 15.4%) than in the placebo group (n=24, 5.0%) discontinued treatment due to adverse events in the TEMPO 3:4 trial but no deaths were reported in either group.

The company presented results for TKV, the primary endpoint of the TEMPO 3:4 trial. This outcome is outside the final scope and the ERG has some concerns regarding the value of this surrogate endpoint and questions whether the measurement of TKV in patients with ADPKD is reliable.

The ERG was able to obtain a publication cited in the CS which was not sent as part of the company's submission. The two randomised studies described in the publication provide additional results on safety (discontinuation and adverse events) which are in line with the findings of the TEMPO 3:4 trial.

Overall, the ERG has a number of concerns regarding how well the evidence presented in the company's submission reflects the final scope and is generalisable to the UK population. Applicability of the findings might be further limited by the length of follow-up as well as the

measurement of outcomes (glomerular filtration rate (GFR), TKV). There are some concerns regarding the safety of tolvaptan, especially regarding the potential of inducing liver injuries.

1.4 Summary of cost-effectiveness submitted evidence by the company

In the systematic review the company did not identify any cost-effectiveness studies relevant to this submission. Therefore a *de novo* economic evaluation was performed.

The model is a patient level state transition model, which the ERG believes is appropriate to model this decision problem. The population in the analysis is consistent with the scope, although it should be noted that the TEMPO 3:4 trial (primary source for the economic model) included only patients aged 18-50 years while no age restriction was included in the final scope and the proposed licensed indication. Moreover, only a small proportion of the TEMPO 3:4 trial population was from the UK (5%; 73 out of 1445). The comparators are standard care with and without tolvaptan, which is in line with the scope. The base case amounted to £34,769 including PAS and to £[redacted] excluding PAS. Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be [redacted] a threshold of £30,000 to £40,000 per quality-adjusted life year (QALY) [redacted] a PAS.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG questioned a number of assumptions underlying the economic evaluation of tolvaptan, and addressed several of these issues in the ERG base case. The ERG base case ICER amounts to £43,280, including PAS. This ICER is higher than the company's base case (£34,769 including PAS). Including the PAS the probability of cost-effectiveness, according to the ERG base case, at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 24%, 31% and 42%, respectively. The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS. However, not all uncertainty is incorporated in these probability estimates; most notably the uncertainty of the extrapolation of the treatment effect. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a strong increase compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

In general the submission was well presented and it should be noted that the company aimed to answer the points raised in the clarification letter. The company searched all required databases specified by NICE. The company's submission provided sufficient detail for the ERG to appraise the searches, which were well documented and easily reproducible. Additional searches of conference abstracts and other resources were undertaken by the company for all sections. The searches were well translated amongst the different resources used. The model structure and approach is appropriate.

Replaced by erratum

1.6.2 Weaknesses and areas of uncertainty

The ERG is concerned about the language bias of restricting the searches to English language only; this is not in line with current best practice.

Generalisability of the only identified randomised, controlled trial, TEMPO 3:4, is limited by a) the relatively strict inclusion criteria based on which many patients were excluded; b) the restriction to patient aged 18 to 50 years; c) the low number of UK patients and d) patients in CKD stage 3. There is some uncertainty regarding measurement of GFR and TKV. As best standard care which was provided in both groups (tolvaptan and placebo) was not clearly defined, there is some uncertainty surrounding the potential effect of measures forming best supportive care.

The main weakness of the cost effectiveness analysis presented in this submission is a number of assumptions that potentially favour tolvaptan and are, in the ERG's opinion, unjustified. Most notably, the extrapolation of the treatment effect over the lifetime of the population. Other assumptions and/or model inputs the ERG questioned are:

- Exclusion of adverse events (other than kidney pain)
- Kidney pain being treatment dependent and CKD-stage independent
- The CKD-stage 3 costs
- The disutility for HD and PD complications
- The use of general population mortality (instead of ADPKD-specific mortality)
- The extrapolation of the treatment discontinuation probability
- Monitoring costs

The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed additional scenario analyses exploring the impact of 1) incorporating liver complications based on Hy's Law cases; 2) incorporating ADPKD-specific mortality risks for CKD stage; 3) incorporating more conservative treatment discontinuation probabilities; 4) incorporating increased monitoring costs and; 5) lower transplant costs. The ICERs of these scenario analyses ranged between £34,754 and £42,893 with PAS. Moreover, the ERG constructed an alternative base case wherein 1) a model code error was corrected; 2) the kidney pain probability was assumed equal for both arms; 3) the costs for CKD-stage 3 were corrected; 4) a disutility was applied for being on Tolvaptan treatment and; 5) the disutility HD and PD complications was decreased. This resulted in a base case ICER of £43,280 with PAS.

Replaced by erratum

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

Autosomal dominant polycystic kidney disease (ADPKD)

The final scope stated that *"polycystic kidney disease (PKD) is a genetic disorder that causes the growth of multiple cysts on the kidneys. PKD occurs in two forms - autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD)"*.[1]

According to page 26 of the company's submission (CS)[2], *"Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a serious, inherited, progressive cystic renal disease. ADPKD is primarily characterised by the development and expansion of fluid-filled cysts in the kidney. Over time, the expanding cysts physically displace and obstruct renal tubules, blood vessels and lymphatics, as well as promote apoptosis, atrophy and fibrosis of the renal parenchyma, leading to an increase in kidney volume, progressive loss of function, and renal failure"*.[3, 4]

ADPKD is a genetic disorder with a highly variable disease course. The majority of patients with ADPKD eventually develop end-stage renal disease (ESRD), with mean age of approximately 58 years.[2, 5, 6] However, the disease presentation, severity and the rate of progression may vary substantially which make establishing a prognosis of ADPKD difficult.[2]

"ADPKD is caused by a mutation in one of two polycystin genes: PKD1 (chromosome region 16p13.3), which accounts for the majority (approximately 85%) of cases, and PKD2 (chromosome region 4q21), which accounts for approximately 15% of cases.[6]*"*

ADPKD being an autosomal dominant disease implies that the patients inherit the disease by receiving an abnormal gene from one parent. Each patient possesses a 50% probability of passing this autosomal dominant gene to their offspring.

"Clinical features in ADPKD consist of renal manifestations (those related to the kidneys) and extra-renal manifestations (those unrelated to the kidneys)" (see Table 2.1).

Table 2.1: Renal and extrarenal manifestations of ADPKD
(Based on table A4 of the CS[2])

Renal manifestations	Extrarenal manifestations
Renal cysts Enlarged, palpable, distorted kidneys Hypertension Cyst haemorrhage Cyst infection Recurrent urinary tract infections Nephrolithiasis (kidney stones) Macroscopic haematuria Pain (e.g. abdominal and flank) Renal failure Proteinuria Microalbuminuria	Polycystic liver disease Pancreatic cysts Subarachnoid cysts Seminal vesicle cysts Sperm abnormalities leading to male infertility Vascular abnormalities such as intracranial aneurysms, thoracic aortic artery dissection, and coronary artery aneurysms Valvular heart disease Colonic diverticulosis and diverticulitis
ADPKD = autosomal dominant polycystic kidney disease; CS = company's submission Sources: Halvorson 2010[7]; Patel 2009[4]; Takiar 2011[3]	

ERG Comment: The prognosis of autosomal dominant polycystic kidney disease (ADPKD) is complicated due to the heterogeneity of the disease. ADPKD is often diagnosed in the later stage of life. Disease progression is highly variable and usually becomes symptomatic between ages of 30 and 60 years.[1] Therefore, many patients pass on the disease to their offspring unknowingly before being diagnosed with ADPKD. The kidney is the most important organ involved; however, other organs could be affected by cysts as well (see Table 2.1).

Prevalence of ADPKD

Section 2.1 of the CS states that *"in England and Wales, the diagnosed prevalence of ADPKD is estimated as 3.9 per 10,000, and the undiagnosed prevalence is estimated as 4.3 per 10,000"*.[8]

As per company's response to the clarification letter, "*undiagnosed ADPKD refers to those individuals who are anticipated to have ADPKD but have not had any formal diagnosis.*"[9] In their response, the company has further estimated the current diagnosis rate as 90%. Hence, the total prevalence (diagnosed and undiagnosed ADPKD) was estimated to be 4.3 per 10,000 and the undiagnosed prevalence was estimated as 0.4 per 10,000.[9] The company also states in their response that *"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"*.[9]

ERG Comment: The ERG spotted a discrepancy in Section 2.1 of the CS which reports the estimated *undiagnosed* prevalence as 4.3 per 10,000. However, in Section 2.2 of the CS, the *total* prevalence was estimated as 4.3 per 10,000. Following the response to the clarification letter the ERG is now convinced that the estimated prevalence of 4.3 per 10,000 for ADPKD in Section 2.1 is the total prevalence and not the undiagnosed prevalence.

The ERG notes that these prevalence figures provided by the company have been accepted by the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) in order to grant orphan designation.[9] The ERG suspects that the estimated prevalence of undiagnosed patients could be much higher than the figures submitted by the company. In the past, high risk group (e.g. children of ADPKD patients) might have chosen not to know their disease status due to lack of therapeutic options and remained undiagnosed. However, if tolvaptan is introduced as a therapeutic option for ADPKD in the UK a proportion of these patients who are at risk might seek a diagnostic test and subsequent therapy. As a result, the total prevalence of ADPKD might increase considerably.

Disease burden and mortality

According to page 36 of the CS[2], despite being rare, *"ADPKD is the fourth leading cause of end-stage renal disease (ESRD) in adults"*[10] and *"is associated with substantial burden on the healthcare services due to increasingly frequent hospital visits, management of complications and renal replacement therapy (dialysis and kidney transplantation)"*

"By a mean age of 56 to 60 years, patients with ADPKD reach ESRD and require interventions such as dialysis and transplantation, which have a substantial clinical and economic impact".[2] *"In particular, dialysis can have a negative impact on patient HRQL - on*

average, patients in ESRD would be willing to give up 10 years of life on dialysis in exchange for 4 years with normal renal function".[11]

According to page 35 of the CS, *"the age-standardised mortality rate in patients with ADPKD is 60% higher than in the general population.*[12] *Data from a UK cohort study reports that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years)*[13]*, as compared to the current UK life expectancy of 81.5 years.*[14] *However, the life expectancy in a faster progressing patient population considered in this submission is likely to be even lower."*[2]

ERG comment: ADPKD is associated with a significant reduction in patient health-related quality of life (HRQoL) and life expectancy. Overall, the evidence presented in the CS on this section was in line with the background information given in the final scope[1] and is also consistent with the ERG's understanding of the problem.

2.2 Critique of manufacturer's overview of current service provision

"Tolvaptan does not currently have a UK marketing authorisation for the indication detailed in this submission. A submission for marketing authorisation in the European Union (EU) was made in December 2013 through the European Medicines Agency (EMA) centralised procedure. CHMP positive opinion is anticipated in February 2015".[2]

Tolvaptan was granted orphan designation for the treatment of ADPKD by the European commission on 5 August 2013 but does not currently have a UK marketing authorisation for the population under consideration for this submission.[2] On 26 February 2015, the European Medicines Agency (EMA) has recommended granting a marketing authorisation to tolvaptan.[15]

On 5 August 2013 the Food and Drug Administration (FDA) did not approve tolvaptan for the treatment of ADPKD due to risk of liver injury, with patients potentially requiring liver transplant or leading to death.[16] However, the drug was approved for the treatment of ADPKD in Japan on 24 March 2014.

"No licensed treatment for ADPKD is currently available that has been demonstrated to delays [sic!] *ADPKD progression; a disease-modifying therapy that delays ADPKD progression is needed to provide a step-change in ADPKD management. Current standard of care is limited to management of the other signs and symptoms of the disease; control of hypertension, and interventions to manage patients as they approach or reach ESRD.*[17, 18] *ESRD is treated by renal replacement therapy (dialysis or transplant), which has substantial health care resource use and economic implications, as well as diminishing patient HRQL".*[19-22]

"The proposed licensed indication states that patients with ADPKD may be initiated on tolvaptan if in CKD stage 1-3 with evidence of rapidly progressing disease. In order to identify patients in CKD stage 1-3, a measure of renal function (in terms of estimated GFR) will be required. This is routinely assessed in ADPKD patients. 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.

Replaced by erratum

Clinicians may consider the frequency and severity of ADPKD complications (such as hypertension, haematuria and pain) and an assessment of renal size obtained by ultrasound, CT or MRI when deciding whether to initiate treatment with tolvaptan. Ultrasound is recommended in NICE Clinical Guideline 182[17] *for all PKD patients over 20 years of age".*[2]

"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 three months thereafter, will be required."[2]

ERG comment: ADPKD can be asymptomatic until about age 40 years and is often diagnosed relatively late. Currently, there is no strategy in place for routine screening of patients at-risk for ADPKD in the early stages of the disease. There is no clear classification system for disease progression; different information such as renal size, renal function, family history, genetics, history of complications etc. has been used by clinicians to predict future progression rates. Hence, the risk of fast progression is currently determined by individual clinical judgement.[2]

According to the recent NICE clinical guideline on chronic kidney disease (CKD) (CG 182), accelerated progression of CKD is defined as; *"a sustained decrease in glomerular filtration rate (GFR) of 25% or more and a change in GFR category within 12 months or a sustained decrease in GFR of 15 ml/min/1.73 m^2 per year".*[17] The ERG also notes the company's reply to the clarification letter that, *"an objective definition of rapidly progressing ADPKD has not been agreed within the clinical community".*[9]

It should be noted that other management options, such as increased fluid intake or aggressive blood pressure management, might be able to modify the cause of disease in early ADPKD. Results of a recently published RCT of 558 hypertensive participants with ADPKD concluded that *"compared with standard blood-pressure control, rigorous blood-pressure control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion".*[23]

Association of hepatotoxicity with tolvaptan remains a major concern for the ERG. Therefore, the ERG requested to provide a proposed treatment pathway for tolvaptan including monthly monitoring of the liver function and possible transplantation required.

In reply to this request[9], the company provided a proposed treatment pathway which *"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".*

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)
(Table on page 62 of the CS[2])

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with ADPKD	As defined by scope	N/A
Intervention	Standard care in combination with tolvaptan	As defined by scope	N/A
Comparator(s)	Standard care, including routine surveillance without tolvaptan	Standard care, including routine surveillance without Tolvaptan (No active treatment)	Currently, there are no pharmacological treatments indicated for ADPKD. Patients with ADPKD receive best supportive care or standard care to control symptoms and complications associated with the disease, irrespective of the choice to initiate tolvaptan. Patients receiving tolvaptan will continue to receive best supportive care, as necessary.
Outcomes	The outcome measures to be considered include rate of decline of renal function, symptoms of CKD (including pain), mortality, adverse effects of treatment, and HRQoL	Rate of decline of renal function (including percentage change in TKV)[a] Symptoms of chronic disease [b] (including pain) Mortality Adverse effects of treatment HRQoL	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes	NICE reference case	N/A

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	between the technologies being compared. Costs will be considered from a National Health Service and Personal Social Services perspective.		
Subgroups to be considered	If evidence allows, subgroups stratified by the rate of decline of renal function and by baseline TKV should be considered in the manufacturer's submission	Subgroups stratified by CKD stage, including stage 1, 2, 3a and 3b	N/A
Special considerations, including issues related to equity or equality	If evidence allows, the use of different stopping rules based on treatment response also will be considered	No clinical stopping rules have been proposed as part of the draft SmPC and therefore these are not explored further in the economic evaluation. Treatment is to be continued long-term and discontinued only in case of tolerability issues, at onset of ESRD, or by clinical judgement.	N/A

ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; HRQoL = health-related quality of life; N/A = not applicable; NICE = National Institute for Health and Care Excellence; SmPC = summary of product characteristics; TKV = total kidney volume.

[a] Includes annual rate of percentage change in TKV, time to investigator-assessed clinical progression (worsening kidney function, clinically significant kidney pain, worsening hypertension, and worsening albuminuria), and change in the slope of kidney function.

[b] Clinically significant kidney pain, worsening hypertension, and worsening albuminuria (change from baseline in kidney pain, change from baseline in mean arterial pressure in non-hypertensive patients; hypertensive progression events in non-hypertensive patients; change in antihypertensive therapy in hypertensive patients).

3.1 Population

The patient population described in the final scope is as follows: *"People with autosomal dominant polycystic kidney disease"*.[1] This is in line with the patient population included in the CS[2] and in the main trial for this submission, the TEMPO 3:4.[24]

ERG comment: The table above seems to be based on the draft scope issued by NICE. Overall, the ERG is convinced that the population is in line with the final scope. However, the available evidence from the TEMPO 3:4 trial only includes participants up to 50 years of age (see Section 4.2.1 of the ERG report).

3.2 Intervention

The intervention described in the CS ('tolvaptan') matches the intervention described in the final scope. According to page 23 in the CS, *"The initial dosage of tolvaptan in ADPKD is 60 mg per day (split-dose 45 mg and 15 mg). This is to be titrated upward to 90 mg per day (split-dose 60 mg and 30 mg), then to a target of 120 mg per day (split-dose 90 mg and 30 mg) if tolerated, with at least weekly intervals between titrations. Patients may down-titrate to lower doses, based on tolerability"*.

Tolvaptan (brand name Jinarc®) is a selective vasopressin antagonist, which specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron. Tolvaptan tablets are to be taken twice daily as a split dose titrated upward from 60 mg to a maximum tolerated daily dose of 120 mg. Patients continue to have a long-term treatment and are withdrawn at the onset of the end-stage renal disease (ESRD).[2]

ERG comment: The intervention in the CS matches the intervention described in the final scope.

3.3 Comparators

The comparator defined in the NICE scope was, *"Standard care, including routine surveillance without tolvaptan"*. Standard care was not fully defined in the final scope.[1] According to the CS, the standard care does not involve any active treatment for ADPKD.

The justification given by the CS in Section 5 was that *"currently, there are no pharmacological treatments indicated for ADPKD. Patients with ADPKD receive best supportive care or standard care to control symptoms and complications associated with the disease, irrespective of the choice to initiate tolvaptan. Patients receiving tolvaptan will continue to receive best supportive care, as necessary"*.[2]

ERG comment: Overall, the ERG was satisfied with the justification provided by the company. However, it should be noted that given that *"standard care"* was not clearly defined, some variation in treatments received is possible.

In addition, as noted in Section 7 of the ERG report, other management options, such as increased fluid intake and aggressive blood pressure management, might be able to modify the cause of disease in early ADPKD.

3.4 Outcomes

ERG comment: All outcomes defined in the final scope are reflected in the decision problem defined in Section 5 of the company's submission. However, as discussed in Section 4.1.2 of the ERG report HRQoL has not been included in Section 6.5 of the CS.

Replaced by erratum

3.5 Other relevant factors

In response to the clarification letter[9] the company stated it *"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"*.

ERG comment: The company has offered a patient access scheme (PAS). End of life criteria are not relevant for this project.

During the scoping workshop, clinicians expressed that a stopping rule would be essential. With that in mind, it is unfortunate that the company was unable to determine a stopping rule based on treatment response.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan et al. was used to inform this critique.[25] The submission was checked against the Single Technology Appraisal (STA) specification for company submission of evidence.[26] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness/identification of studies

Searches were reported for all databases required by NICE guidance: MEDLINE, Embase and Cochrane Library.[27] Searches were not specified for MEDLINE in Process, but as this database was included within the MEDLINE search for all other sections of the report, the ERG assumed that this was the case for the clinical effectiveness search. The database hosts for each database were listed; the date spans of the databases searched were provided, and the specific date the searches were run was made available on request. The company additionally searched conference proceedings for specific conferences and specific years, providing on request full details of the search terms and resources used.

The company translated the research question into appropriate search strategies and the ERG considered the searches to be adequate. Searches were clearly structured and divided into population and intervention facets. The searches were well reported and reproducible. No study design limits were applied and the company stated that the search strategies for clinical effectiveness (6.1) were used for the non-RCT evidence (6.8), adverse event (6.9) and cost-effectiveness (7.1) sections of the submission.[2]

The ERG was concerned that searches were limited to English language only. Current best practice states that *"Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"*.[28] In its response to the clarification letter[9], the company stated that *"studies were limited to the English language to identify the most pertinent evidence for England and Wales"*, however the ERG is concerned that potentially relevant studies may have been missed in this way.

Searches were limited to studies published from 2004 onwards. Following clarification, the company stated that *"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"*.[9] The ERG considers this justification sufficient for applying the date limit to the searches.

Non-RCT evidence

The same search strategies and databases were used as in Section 6.1 of the CS. As in Section 6.1, additional searches were undertaken for specific conferences for specific years. The same limitations already discussed for Section 6.1 therefore also apply to searches for this section.

Adverse events

The same search strategies and databases were used as in Section 6.1 of the CS. As in Section 6.1, additional searches were undertaken for specific conferences for specific years. The same limitations already discussed for Section 6.1 therefore also apply to searches for this section.

Cost-effectiveness

The same search strategies and databases were used as in Section 6.1 of the CS. As in Section 6.1, additional searches were undertaken for specific conferences for specific years, and the Cost-effectiveness Analysis (CEA) Registry was also searched. The same limitations already discussed for Section 6.1 therefore also apply to searches for this section.

Measurement and valuation of health effects

Searches were carried out for all the databases required by NICE. In addition, the Cochrane Library databases were also searched. The hosts for each database were listed; the date spans of the databases searched were provided, and the specific date the searches were run was made available on request. The searches were well reported and reproducible.

Additional conference searches were conducted and full details of search terms and resources used were made available on request. Internet searches were also conducted by the company, and full details of these were also provided on request.

Resource identification, measurement and valuation studies

Searches were carried out on all the databases required by NICE. In addition, the Cochrane Library databases were also searched. The hosts for each database were listed, the date spans of the databases searched were provided, and the specific date the searches were run was made available on request. Searches were well reported and reproducible.

Additional conference searches were conducted, and full details of search terms and resources used were made available on request.

Two separate sets of literature searches were conducted to identify cost and resource use in patients with ADPKD and ESRD. The cost/resource use facet for ESRD was narrower and more focussed than the ADPKD search. This was queried by the ERG, and the company response was that *"separate cost facet search terms were used in the ADPKD and ESRD searches 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"*. The ERG considers this response to adequately justify the difference between the literature searches.

Summary of searching

The searches in the CS were well documented and easily reproducible, and a good range of resources was used. The ERG has some concerns over the limits applied to the searches to restrict results to English language only.

4.1.2 Inclusion criteria

According to page 67 of the CS[2], *"the objective of the review was to identify available clinical and cost-effectiveness evidence relating to tolvaptan in patients with ADPKD. To be included in this systematic review, clinical references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table B1"* (see Table 4.1).

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence (Table B1 of the CS[2])

	Inclusion	Exclusion
Population	Patients with ADPKD	Animal or in vitro studies Human studies in healthy individuals
Interventions	Tolvaptan	Any other interventions
Study design	Any interventional clinical study RCT or non-RCT	N/A
Outcomes	All trial primary outcomes All stated trial secondary outcomes Renal size including total kidney volume (absolute or relative changes in volumes) Time to clinical progression Renal function Including glomerular filtration rate Cyst volume ADPKD complications such as hypertension and pain Adverse events Serious adverse events	Pharmacodynamic assessments Changes in laboratory parameters
Publication	English language Human study Published 2004 or later	Non-English language Editorial Review Letter
ADPKD = Autosomal Dominant Polycystic Kidney Disease; N/A = not applicable; RCT = randomised controlled trial		

ERG comment:

- The population (*"Patients with ADPKD"*) is in line with the final scope.[1]
- The intervention is defined to be *"Tolvaptan"* which does not reflect the final scope which defines the intervention as *"Standard care in combination with tolvaptan"*.[1] However, according to the clinical study report (CSR) of the only included study (TEMPO 3:4), *"treatments in this trial were tolvaptan or placebo in addition to the best standard of care therapy available in each region"*.[29] The term "best standard care" was not clearly defined as discussed in Section 7.

  It should be noted that the inclusion criteria would not be sufficient to inform an indirect comparison or a mixed treatment comparison as studies relevant for comparisons other than tolvaptan would not have been included. However, given that

tolvaptan is the *"first treatment licensed specifically to treat ADPKD"*[2] the approach used in the company's submission seems justified and is in line with the final scope.[1]

- Relevant study designs included *"Any interventional clinical study RCT or non-RCT"*. This was not specified in the final scope but seems justified.
- There are some concerns regarding the outcomes:
  - Specified in the final scope[1] but not included in Section 6.5 of the CS:
    - Health-related quality of life (HRQoL)
  - Not specified in the final scope[1] but included in the CS:
    - All trial primary outcomes
    - All stated trial secondary outcomes
    - Renal size including total kidney volume (absolute or relative changes in volumes)
    - Time to clinical progression
    - Cyst volume
  - Specified in the protocol for TEMPO 3:4[30] but not included in the CS:
    - ADPKD outcomes and medical resource utilisation. Analysis of additional events attributed to ADPKD for tolvaptan-treated patients as compared to placebo, including their health-economic outcomes
- Publications were limited to include "English language" studies published 2004 or later which were conducted in humans, see Section 4.1.1 for further details.

4.1.3 Critique of data extraction

The company's submission listed a total of 17 identified tolvaptan clinical studies (see Table 4.2).

One RCT was included, the TEMPO 3:4 study (156-04-251). As detailed in Table 4.3, various data sources were available for TEMPO 3:4. The only full journal publication was authored by Torres et al.[24]

Furthermore, three non-RCTs were included as detailed in Table 4.4.

Table 4.2: Identified tolvaptan clinical studies
(based on Table B2 (page 70) of the CS[2])

Study number	Tolvaptan studied?	RCT?	Complete?	Identified publications from systematic review	Presented in submission?	Comments
156-04-001	Yes	No	Yes		No	19 patients, Japan only, dose-finding trial
156-05-002	Yes	No	Yes	Higashihara 2011[31]	No	17 patients, Japan only, single arm extension of 156-04-001
156-09-003	Yes	No	Ongoing		No	13 patients, Japan only, single arm extension of 156-05-002, ongoing study
156-10-003	Yes	No	Ongoing		No	Single arm extension of 156-04-251 in Japan only, ongoing study
156-13-210	Yes	Yes	Ongoing		No	Ongoing study, no results available
156-13-211	Yes	No	Ongoing		No	Single arm extension of patients from various completed studies, ongoing study, no results available
156-04-248	Yes	Yes	Yes	Chapman 2005[32]	No	Small, short-term pilot dose-finding trials (n=11 and n=37)
156-04-249	Yes	Yes	Yes		No	
156-04-250 (TEMPO 2:4)	Yes	No	Yes	Higashihara 2011[31] Torres 2007[33]	Yes. Limited presentation.	Open-label extension of studies 156-04-248 and 156-04-249, dose-finding for pivotal study
156-04-251 (TEMPO 3:4)	Yes	Yes	Yes	Torres 2012[24, 34] Czerwiec 2013[35] Horie 2013[36] Devuyst 2014[37] Gansevoort 2013[38] Perrone 2013[39]	Yes. Full presentation.	Pivotal phase 3 study (n > 1400)
156-06-260	Yes	No	Yes	Irazabal 2011[40]	No	20 patients, 1 week study, phase 1b
156-08-271 (TEMPO 4:4)	Yes	No	Ongoing	Torres 2014[41]	Yes. Limited presentation.	Open-label extension study of several completed trials. Interim analysis only as it is an ongoing study.

Study number	Tolvaptan studied?	RCT?	Complete?	Identified publications from systematic review	Presented in submission?	Comments
156-09-283	Yes	No	Yes		Yes. Limited presentation	Case matched analysis of studies 156-05-002 and 156-04-250 with naturalistic CRISP and MDRD studies
156-09-284	Yes	No	Yes	Boertien 2012[42, 43], 2013[44]	No	27 patients, short-term exposure (3 weeks)
156-09-285	Yes	No	Yes		No	25 patients, PK/PD/tolerability study, placebo-masked
156-09-290 (NOCTURNE)	Yes	Yes	Yes		No	Short-term trial (8 weeks), complete but study report not yet available
156-10-291 (OVERTURE)	No	No	Ongoing		No	Observational study, ongoing

Table 4.3: Data sources for TEMPO 3:4
(based on Table B2 (page 70) of the CS[2])

Publication	Description
Czerwiec 2013[35]	Abstract
Devuyst 2014[37]	Abstract
Gansevoort 2013[38]	Abstract
Horie 2013[36]	Abstract
Otsuka Pharmaceuticals 2013[29]	Clinical study report (CSR)
Perrone 2013[36]	Abstract
Torres 2012[24]	Full journal article. Main publication of the trial
CSR = clinical study report	

Page 71 of the CS states that:

- The primary report was Torres 2012[24]
- Three publications report post-hoc analyses
  - Devuyst 2014[37] reported a post-hoc subgroup analysis of urine osmolality (Uosm) of participants in the global TEMPO 3:4 trial.
  - Gansevoort 2013[38] reported a post-hoc subgroup analysis on the effect of tolvaptan on albuminuria in the global TEMPO 3:4 trial.
  - Perrone 2013[36] correlated TKV and eGFR results from patients in the TEMPO 3:4 trial. Results support baseline height-adjusted TKV as a predictor of eGFR decline.
- A further two secondary publications are available:
  - Czerwiec 2013[35] reported an analysis of clinical outcomes from the global TEMPO 3:4 trial which are in line with the respective results reported in Section 4.2.3 of the ERG report.
  - Horie 2013[36] described a subgroup analysis of the global TEMPO 3:4 trial to determine the efficacy and safety of tolvaptan in Japanese patients.

Table 4.4: List of included non-RCTs
(based on Table B3 of the CS[2])

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
156-04-250 **NCT00413777** **(TEMPO 2:4)**	Titration phase 15/15 mg 30/15 mg 45/15 mg 60/30 mg 90/30 mg Fixed-dose phase and optional extension 45/15 mg 60/30 mg	46 ADPKD patients who previously participated in trial number 156-04-248 or 156-04-249	Open-label, dose-finding study to evaluate the safety, tolerability, and pilot efficacy of split-dose regimens	24, 31, 45	This study supports dosing regimen
156-08-271 **NCT01214421** **(TEMPO 4:4)**	Tolvaptan split-dose (AM/PM, titrated) 45/15 mg 60/30 mg 90/30 mg	976 ADPKD patients who had completed a phase 1, 2, or 3 tolvaptan trial, including TEMPO 3:4, and $eGFR_{MDRD}$ $\geq$ 30 mL/min/1.73 m^2	Non-randomised, parallel group, open-label extension study to investigate whether tolvaptan modifies ADPKD progression	41, 46	This study supports evidence that tolvaptan modifies ADPKD progression
159-09-283	As per 156-04-250/ 156-05-002 trials	Subjects who completed 36 months of trial assessments in the 156-04-250/156-05-002 trials and their case-matches from CRISP and MDRD studies.	Compare the rate of total kidney volume (TKV) change between tolvaptan-treated subjects and matched-control subjects receiving standard of care	N/A	Comparison of tolvaptan at proposed licensed dosing versus case-matched naturalistic "controls"

ADPKD = autosomal dominant polycystic kidney disease; $eGFR_{MDRD}$ = estimated glomerular filtration rate calculated using Modification of Diet in Renal Disease formula; RCT = randomised, controlled trial; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

ERG comment: It should be noted that the CS presents two tables labelled as "Table B2":

1. Table *"Identified tolvaptan clinical studies"* (page 70)
2. Table *"List of relevant RCTs"* (page 72)

Tables 4.2 and 4.3 of the ERG report are based on Table B2 presented on page 70 of the CS while Table 4.7 is based on Table B2 on page 72 of the CS.

The CS presented 17 identified tolvaptan clinical studies (see Table 4.2):

- 156-04-251 (TEMPO 3:4) is the only RCT presented in the CS and has been reported in seven publications (see Table 4.3 above). The quality assessment of this trial is presented and discussed in Section 4.1.4 of the ERG report while study characteristics and results are presented in Sections 4.2.1 to 4.2.3.
- Three non-RCTs have been identified (156-04-250 (TEMPO 2:4), 156-08-271 (TEMPO 4:4), 156-09-283) for which the CS included a *"limited presentation"*.[2] These studies are discussed in Section 4.2.4.
- The other 13 studies have not been presented in the CS. The ERG checked further sources, including a report by the FDA[47] in order to check if it was justified not presenting these studies. It seems reasonable to exclude ten of the studies due to comparison of various doses of tolvaptan (n=4), single arm design (n=4) or because there are ongoing (n=2). However, for three of the studies the reasons are less clear.

    1. 156-04-248: Described in the CS as *"small, short-term pilot dose-finding trial (n=11)"*. According to page 170 of the FDA report[47], the study used a *"randomized, double-blind, placebo-controlled, ascending dose"* study design.
    2. 156-04-249: Described in the CS as *"small, short-term pilot dose-finding trial (n=37)"*. According to page 170 of the FDA report[47], the study used a *"randomized, double-blind, parallel-arm"* study design.
    3. 156-09-290 (NOCTURNE): Described as *"short-term trial (8 weeks), complete but study report not yet available"*. No further information is given on the status of this trial. The aforementioned FDA report[47] also lists this study as ongoing as of 01 February 2013.

Based on the information in the CS, it is unclear why the two trials 156-04-248 and 156-04-249 were excluded. The publication cited by the company for both studies[32] was not included in the submission. However, the ERG obtained and examined the publication which included results for both studies and reported laboratory values (urine volumes, serum electrolyte concentrations, serum and urine osmolality) alongside results on safety (adverse events, treatment discontinuation). Therefore, results of the two studies provide additional information relevant to the company's submission and are discussed in the adverse events (Section 4.2.3). A third study (156-09-290 (NOCTURNE)) for which the *"study report* [is] *not yet available"* could provide further relevant information. As done for another ongoing trial (TEMPO 4:4, 156-08-271), it might be possible to present interim results for this study.

4.1.4 Quality assessment

The quality assessment of the TEMPO 3:4 trial was reported in Table B9 of the CS (see Table 4.5).

Table 4.5: Quality assessment of TEMPO 3:4
(based on Table B9 of the CS[2])

	How is this question addressed in the study?	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Randomisation was performed centrally, with stratification according to hypertension status, creatinine clearance, TKV, and geographic area Randomisation utilised IVRS to ensure appropriate stratification in the main regions (the Americas, Japan, and Europe plus the rest of the world)	Yes
Was the concealment of treatment allocation adequate?	The treatment allocation was by IVRS	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	The baseline characteristics between the 2 groups were similar	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Patients and investigators were blinded	Yes
Were there any unexpected imbalances in drop-outs between groups?	Percentage of patients who discontinued was 23% in the tolvaptan group and 14% in the placebo group	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All patients underwent randomisation, and those who received at least 1 dose of the study drug were included in the efficacy and safety analyses	Yes

IVRS = Interactive voice response system; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume
Adapted from: Centre for Reviews and Dissemination 2008[48]

ERG comment: The ERG agrees with the company's assessment of most items. Additions to the company's assessment of the study quality of TEMPO 3:4 are as follows:

- The study was described as *"double blind"*. According to page 127 of the CSR[2], *"while maintaining subject, investigator, and trial-personnel blinding, the bioanalytical laboratory staff was unblinded to treatment and the OPDC bioanalytical representative of the PK/PD* [pharmacokinetic/ pharmacodynamic] *and clinical pharmacology department was unblinded after the last subject's last visit following completion of all clinical assessments, but prior to database lock"*.
- As stated in Table B9 in the CS (see Table 4.5 above), the percentage of patients who discontinued was 23% in the tolvaptan group and 14% in the placebo group. Table 4.6 details the reasons for discontinuation.

Table 4.6: Reasons for treatment discontinuation in TEMPO 3:4
(based on figure B2 of the CS[2])

	Tolvaptan	Placebo
Randomised	n=961	n=484*
Discontinued the study	n=221 (23.0%)	n=67 (13.8%)
Had adverse event	n=148 (15.4%)	n=24 (5.0%)
Withdrew consent	n=50 (5.2%)	n=30 (6.2%)
Were lost to follow-up	n=15 (1.6%)	n=8 (1.7%)
Met withdrawal criteria	n=4 (0.4%)	n=0 (0%)
Were withdrawn by the investigator	n=3 (0.3%)	n=4 (0.8%)
Had a protocol deviation	n=1 (0.1%)	n=1 (0.2%)
* = 1 patient declined participation after randomisation		

4.1.5 Evidence synthesis

Page 112 of the CS states that *"No meta-analysis was undertaken because the relevant clinical evidence for tolvaptan comes from a single study"*.[2]

ERG comment: As only a single study, the TEMPO 3:4 trial[24], was identified, it is justified that no meta-analysis was undertaken.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Study characteristics of the TEMPO 3:4 trial

In this section we present the results from the only identified RCT, the TEMPO 3:4 trial (156-04-251). Study characteristics are presented in Table 4.7 while a summary of the study methodology can be found in Table 4.8.

Table 4.7: Overview of the TEMPO 3:4 trial
(based on Table B2 (page 72) of the CS[2])

Trial no. (acronym)	Intervention	Comparator	Population	Primary study reference
156-04-251 (TEMPO 3:4)	Tolvaptan split-dose regimens (AM/PM): 45/15 mg, 60/30 mg, or 90/30 mg for 36 months	Placebo oral tablet split-dose regimens (AM/PM): 45/15 mg, 60/30 mg, or 90/30 mg	Patients with ADPKD	Torres 2012[24]
ADPKD = Autosomal Dominant Polycystic Kidney Disease; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes				

According to page 134 of the CS, *"In TEMPO 3:4, tolvaptan was administered at the same dose as the proposed licensed dose that is anticipated to be used in clinical practice. In the trial, however, the titration was forced at weekly intervals to maximum tolerated dose. In the anticipated licensed indication, titration takes place at a minimum of weekly intervals (in order to allow for realistic scheduling of appointments in routine clinical practice), and 90+30mg is the target dose. The majority of patients treated with tolvaptan and placebo were up-titrated to the maximum daily dose of 120mg/day by the end of the titration period. It is anticipated that the ultimate real-world (maintenance) dose will be similar to that seen in TEMPO 3:4"*.

ERG comment: The intervention and comparator in TEMPO 3:4 are in line with the final scope.[1] The titration schedule corresponds with the titration schedule expected to be included in the licensed indication.

Both groups also received standard care. The company acknowledged that *"differences in clinical care existed in different regions (including a more intensive visit schedule in Japan)"*.[2]

Table 4.8: Summary of methodology of the TEMPO 3:4 trial
(based on Table B2 of the CS[2])

Trial no. (acronym)	156-04-251; NCT00428948 (TEMPO 3:4)
Study sites: Location (number of sites)	United States (29), Canada (3), Argentina (5), Australia (8), Belgium (3), Denmark (2), France (9), Germany (5), Italy (5), Netherlands (2), Poland (9), Romania (3), Russia (5), United Kingdom (11), and Japan (30)
Design	Randomised, phase 3, multicentre, double-blind, placebo-controlled, parallel-arm
Duration of study	36 months
Method of randomisation	Randomisation was performed centrally, with patients randomly assigned in a 2:1 ratio to receive tolvaptan or placebo and with stratification according to hypertension status, creatinine clearance, TKV, and geographic area. Randomisation utilised IVRS to ensure appropriate stratification in the main regions (the Americas, Japan, and Europe plus the rest of the world).
Method of blinding (care provider, patient and outcome assessor)	Tolvaptan and placebo tablets were identical in appearance Group assignment was concealed from investigators and participants Dose assignment was by IVRS

Intervention(s) (n =) and comparator(s) (n =)	Tolvaptan (961) Placebo (484)
Primary outcomes (including scoring methods and timings of assessments)	Annual rate of change in TKV from baseline assessed via an MRI at months 12, 24, and 36 or ET, with a window of ± 2 weeks
Secondary outcomes (including scoring methods and timings of assessments)	Key composite secondary endpoints • Time to multiple[a] investigator-reported ADPKD clinical progression events, including Onset or progression of HTN (BP measurement, need for treatment) Clinically significant renal pain (requiring medical intervention)[b] Worsening albuminuria (by category) Worsening renal function (25% decrease in 1/serum creatinine as a measure of GFR from steady-state post-titration baseline value[c]) Other secondary endpoints • Rate of change in renal function (from steady-state post-titration baseline value to last on-drug trial visit)[d] • Rate of change in MAP[e] • Change from baseline in patient-reported renal pain[f] • Time to hypertensive event[g] • Percentage of patients with clinically sustained decreases of BP[h]
Duration of follow-up	6 weeks Patients were followed by follow-up visit 1 (conducted 7 to 21 days after the month 36 visit) and follow-up visit 2 (conducted 7 to 21 days after follow-up visit 1).

ADPKD = autosomal dominant polycystic kidney disease; BP = blood pressure; dBP = diastolic blood pressure; $eGFR_{CKD\text{-}EPI}$ = estimated GFR by Chronic Kidney Disease Epidemiology Collaboration ; $eGFR_{MDRD}$ = estimated GFR by Modification of Diet in Renal Disease; ET = early termination; GFR = glomerular filtration rate; HTN = hypertension; IVRS = Interactive voice response system; MAP = mean arterial pressure; MRI = magnetic resonance imaging; sBP = systolic blood pressure; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

[a] All the clinical ADPKD progression events occurring during the double-blind treatment period from (1) the date of the first dose of trial medication (for HTN, proteinuria, and renal pain) or (2) the completion of the titration phase (for renal function) to the date of trial completion or ET were included in the analysis for all intention to treat.

[b] This included (in decreasing order of significance): a prescribed surgical or invasive radiological procedure to alleviate/reduce the renal pain (including epidural placement of medication); the introduction of, or increased dose of, narcotic or antinociceptive (e.g., tricyclic antidepressants) medication to alleviate/reduce the renal pain; a prescribed medical leave or activity restriction due to the pain or the prescription of relatively contraindicated, that is, “last resort” non-narcotic (including over-the-counter) analgesics .

[c] Administration of tolvaptan leads to a haemodynamic response in patients with ADPKD, which is associated with an initial decline in eGFR that is reversible upon treatment cessation.[44] Due to the reversible haemodynamic effects on the kidney, the baseline chosen for renal function endpoints (composite and non-composite) in the TEMPO 3:4 trial was a post-treatment initiation baseline, defined as the value obtained at the end of week 3 (end of tolvaptan titration phase) (Torres 2012[24]).

[d] The primary measure was 1/serum creatinine. Additional exploratory measures were based on estimates using demographic and/or anthropomorphic variables, i.e., $eCrCl_{CG}$, or $eGFR_{MDRD}$ or $eGFR_{CKD\text{-}EPI}$. Post-treatment initiation (end of titration period) creatinine was used as the baseline measure, to take into account the known tolvaptan-specific acute and reversible haemodynamic effect on eGFR.

[e] For patients who were non-hypertensive at baseline, change from baseline for resting MAP at scheduled clinic visits up to the point of exposure to antihypertensive therapy for any reason.

[f] Assessed by a 0-to-10 pain scale as average area under the concentration-time curve between baseline and the last trial visit or the last visit prior to initiating medical (e.g., narcotic or antinociceptive) or surgical therapy for pain. The question asked was: "*On a scale of 0 to 10, with zero representing no pain at all and 10 representing the worst pain you've ever experienced, what was the worst kidney pain you've experienced in the last 4 months?*"

[g] For patients who were non-hypertensive at baseline, time to progress to (1) high pre-HTN (sBP > 129 mmHg and/or dBP > 84 mmHg), (2) HTN (sBP > 139 mmHg and/or dBP > 89 mmHg), or (3) requiring antihypertensive therapy.

[h] For patients who were taking antihypertensive therapy at baseline, percentage with clinically sustained decreases of BP leading to a sustained reduction in antihypertensive therapy compared with baseline (while taking investigational medicinal product) at visit on months 12, 24, and 36 for hypertensive patients.

ERG comment: The TEMPO 3:4 trial was conducted in a variety of countries. Most of the 1445 included patients came from the USA (n=379), Japan (n=177) and Germany (n=157); only 73 patients came from the UK.

The primary outcome of the trial (*"Annual rate of change in TKV from baseline assessed via an MRI at months 12, 24, and 36 or ET, with a window of ± 2 weeks"*) was outside the final scope.[1] For completeness, results for this outcome are presented and discussed in Section 4.2.3 of the ERG report.

Length of follow-up

ERG comment: Results for the TEMPO 3:4 are available for a follow-up of up to 3 years. The CS also presents interim results after five years from the TEMPO 4:4 trial which is an open-label, non-randomised extension study. Results for longer follow-up periods, regarding e.g. late onset of adverse events or treatment effects, are not available. Therefore, any assumptions on later effects should be read with some caution (see Section 5.2.6).

Statistical analysis

Table 4.9 gives an overview of the statistical analysis in TEMPO 3:4.

Table 4.9: Statistical analyses in the TEMPO 3:4 trial
(based on Table B8 of the CS[2])

Trial no. (acronym)	156-04-251; NCT00428948 (TEMPO 3:4)
Hypothesis objective	**Primary objective:** The study was designed to test the null hypothesis that there would be no significant differences in the rate of TKV change (normalised as percentage) from baseline.
Statistical analysis	**Analysis of primary endpoint:** Individual slopes for TKV were compared between the groups by fitting the $\log_{10}$-transformed data on TKV to a linear mixed-effects Laird–Ware model. Antilog (with a base of 10) of the treatment effect and 95% confidence intervals derived from the model (in a $\log_{10}$ scale) provide a ratio of geometric means of the slope of TKV (i.e., 100% plus annual percentage change). A mixed-model repeated-measures analysis was applied to the repeated measures of change from baseline in $\log_{10}$-transformed data on TKV as a sensitivity analysis. **Key secondary composite efficacy analyses:** The analysis of the composite secondary endpoint was performed with the use of the Andersen–Gill approach for the extended Cox model, for analysis of time to multiple events. The *P* value was provided by the Wald test with the use of a sandwich estimate of the covariance matrix. Treatment was the sole variable in the model. Data were censored when patients withdrew from the trial. **Renal function slope analysis:** The analysis of the slope of renal function decline was similar to the analysis of the slope of the TKV.
Sample size, power calculation	**Primary endpoint:** Kidney growth rates per year in placebo and tolvaptan groups were assumed to be 7% and 5.6% (or 20% reduction), respectively. It was furthered assumed (in $\log_{10}$ scale) that the total noise SD and the SD of the slope across patients were approximately 0.017 and 0.0184, respectively, which were provided (0.017) or derived (0.0184) from the information provided by the HALT-PKD website. Using the sample size calculation formula for longitudinal trials provided by Lefante, with 85% power and 2:1 randomisation, the sample size was 504 for an alpha of 0.049. After an assumption of a 20% withdrawal rate for the trial, about 600 patients were to be enrolled to the trial. By doubling this number, a power equivalent to two independent studies was attained, while optimizing the operational management and enhancing the ability to evaluate the key secondary composite endpoint that would require a higher number of patients to achieve reasonable power. **Secondary endpoint:** The sample size needed for the key secondary composite endpoint was unknown at the planning stage of this trial. Since no reliable information on the event rate of the key secondary composite endpoint, or its components, was available in the scientific literature, this provided a rationale for the planned, blinded sample size recalculation. Blinded sample size recalculation was prospectively defined in the protocol to occur after either 1,000 patients had been enrolled or

	at least 200 patients had completed their month 12 visit, whichever came first. Assuming a 20% reduction in the key secondary composite endpoint, and with the frequency of the endpoint observed at the blinded sample size calculation, it is expected that this trial would have at least 85% power.
Data management, patient withdrawals	A total of 102/961 (10.6%) tolvaptan patients and 27/484 (5.6%) placebo patients agreed to further follow-up of PKD outcomes via telephone. For patients who discontinued the investigational medicinal product early, 70 patients in the tolvaptan group and 19 patients in the placebo group were followed until month 36. To assess the primary endpoint, subjects had MRI assessments at baseline and at months 12, 24, and 36 or early termination. For those who terminated early, MRI was performed only if the early termination visit was at least 6 months after the last MRI, as this was believed to be a reasonable timeframe in which a change in TKV could be detected.
MRI = magnetic resonance imaging; PKD = polycystic kidney disease; SD = standard deviation; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume.	

ERG comment: The TEMPO 3:4 trial was powered for the primary outcome which is outside the final scope.[1] However, as detailed below (see sample size, power calculation), a blinded sample size recalculation was conducted.

Subgroup analyses

According to Section 6.3.7 of the CS, pre-specified subgroup analyses were carried out for the primary and secondary endpoints in TEMPO 3:4:

- *Sex (male vs. female)*
- *Age (< 35 years vs. ≥ 35 years)*
- *Hypertension (yes vs. no)*
- *Estimated creatinine clearance (< 80 mL/min vs. ≥ 80 mL/min)*
- *Total kidney volume (< 1,000 mL vs. ≥ 1,000 mL)*
- *Height-adjusted total kidney volume (< 600 mL/m vs. ≥ 600 mL/m)*
- *Microalbuminuria (yes vs. no)*
- *Geographic region (Japan vs. non-Japan vs. Americas vs. Europe and the rest of the world)*
- *Race (Caucasian vs. non-Caucasian)*
- *CKD stage (1, 2, or 3 at baseline)*

ERG comment: The ERG agrees with the selection of pre-specified subgroup analyses presented in the company's submission.

Sample size, power calculation

The clinical study report (Sections 6.1 and 6.2) for the TEMPO 3:4 trial details how the sample size was calculated[29]:

"Kidney growth rates per year in placebo and tolvaptan groups were assumed to be 7% and 5.6% (or 20% reduction), respectively. It was furthered assumed (in log10 scale) that the total noise standard deviation (SD) and the SD of the slope across subjects were approximately 0.017 and 0.0184, respectively, which were provided (0.017) or derived (0.0184) from the information provided by the HALT PKD web site.[Reference 50[1]] *Using the sample size calculation formula for longitudinal trials provided by Lefante*[49]*, with 85% power and 2:1 randomization, the sample size was 504 for an alpha of 0.049. After an assumption of a 20% withdrawal rate for the trial, about 600 subjects were to be enrolled to the trial. By doubling this number, a power equivalent to 2 independent studies was attained, while optimizing the operational management and enhancing the ability to evaluate the key secondary composite endpoint that would require a higher number of subjects to achieve*

[1] Cited on page 158 of the CSR for TEMPO 3:4. Reference: National Institute of Diabetes and Digestive and Kidney Diseases [homepage on the Internet]. Bethesda: National Institutes of Health; [updated 2006 Jan 11; cited 2012 May 30] HALT PKD: A Clinical Research Study to HALT Progression of Polycystic Kidney Disease. Available from: www.niddk.nih.gov/fund/divisions/kuh/kdcsi/haltpkd.pdf

ERG comment: On 26 February 2015, the reference was no longer available online.

reasonable power. The sample size needed for the key secondary composite endpoint was unknown at the planning stage of this trial".

"Power projection of the key secondary composite endpoint[2] *against an alpha of 0.01 was performed in response to guidance received from the US FDA (10 Jun 2009 and 15 Nov 2005) that highlighted that the power needed for the approval of an application based upon a single clinical trial would need to be significantly greater than the typical 0.05 standard alpha. Originally, the IDMC* [Independent Data Monitoring Committee] *and sponsor's statistical plans for this endpoint relied on having 2 unrelated endpoints that each met a level of significance of 0.05 for a single trial approval. These meetings with the FDA clarified that the primary endpoint (TKV) was of uncertain clinical relevance meaning the key secondary composite endpoint would need to reach this high level of significance for approval with a single clinical trial. Assuming a 20% reduction in the key secondary composite endpoint, and with the frequency of the endpoint observed at the blinded sample size calculation, it is expected that this trial would have at least 85% power. Additional details are provided in Section 4.2 of the SAP, which is appended to this report".*

ERG comment: According to Table B8 of the CS (see Table 4.9 above), TEMPO 3:4 *"was designed to test the null hypothesis that there would be no significant differences in the rate of TKV change (normalised as percentage) from baseline"*. It should be noted that this outcome is not part of the final scope.[1] As detailed above, following FDA guidance a blinded sample size recalculation was conducted. This was based on the secondary composite endpoint2 which is also outside the final scope. Therefore, it is possible that the relevant outcomes defined in the final scope are underpowered.

Discontinuation and censoring

The percentage of patients who discontinued was 23% in the tolvaptan group and 14% in the placebo group. Table 4.6 (above) details the reasons for discontinuation.

According to page 132 of the CS, the statistical analysis plan (SAP) *"pre-specified mixed model repeated measures (MMRM) analyses to account for missing data; upon unblinding, analyses to account for data missing not at random were performed. Some of the randomised patients did not contribute efficacy endpoints for the trial analyses; other patients contributed information for only a limited period of time. There is no fully satisfactory way to account for these missing data and the pre-specified primary analysis of the composite secondary endpoint may not have adequately addressed the problem.*[50] *However, the missing data sensitivity analysis on renal function slope incorporating a non-parametric rank-sum test and 'tipping point' approach showed that the missing data do not impact on the statistically significant findings in the study.*[51]*"*

[2]Time to multiple investigator-reported ADPKD clinical progression events, including a) Onset or progression of HTN (BP measurement, need for treatment), b) Clinically significant renal pain (requiring medical intervention), c) Worsening albuminuria (by category), d) Worsening renal function (25% decrease in 1/serum creatinine as a measure of GFR from steady-state post-titration baseline value)

ERG comment: The ERG agrees with this approach to account for missing data.

Eligibility criteria

The full inclusion and exclusion criteria for the TEMPO 3:4 trial are presented in Table 4.10 below.

Table 4.10: Eligibility criteria of the TEMPO 3:4 trial
(based on Table B5 of the CS[2])

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
156-04-251 **NCT00428948** **(TEMPO 3:4)**	Patients aged 18-50 years Patients with ADPKD[a] Women capable of becoming pregnant[b] must be willing to comply with required reproductive precautions: remain abstinent or comply with approved birth control from 2 weeks before until 60 days after treatment Note: breastfeeding was not permitted while taking tolvaptan Patients with an $eCrCl_{CG} \geq 60$ mL/min ≥ 31 days before randomisation Patients with a TKV of ≥ 750 mL ≥ 14 days before randomisation (as measured by MRI)	Patients who, in the opinion of the trial investigator and/or sponsor, presented a safety risk[c] Patients who are unlikely to adequately comply with the trial's procedures Patients having contraindications to, or interference with, MRI assessments Patients who are taking medications or have concomitant illnesses likely to confound endpoint assessments Patients taking other experimental (i.e., non-marketed) therapies or taking approved therapies for the purpose of affecting PKD cysts Patients taking or with a history of taking tolvaptan

ADPKD = autosomal dominant polycystic kidney disease; CT = computed tomography; $eCrCl_{CG}$ = estimated creatinine clearance by means of the Cockcroft-Gault formula (with correction for sex and race where possible); MRI = magnetic resonance imaging; PKD = polycystic kidney disease; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume.

[a] Diagnosis of ADPKD (age 18-50 years) required several cysts in each kidney (3 if by sonography, 5 if by CT or MRI) in those with a family history of ADPKD, and 10 cysts (by any radiologic method) in each kidney and exclusion of other cystic kidney diseases if there was no family history. Excluded conditions included multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney, and acquired cystic disease of the kidney.

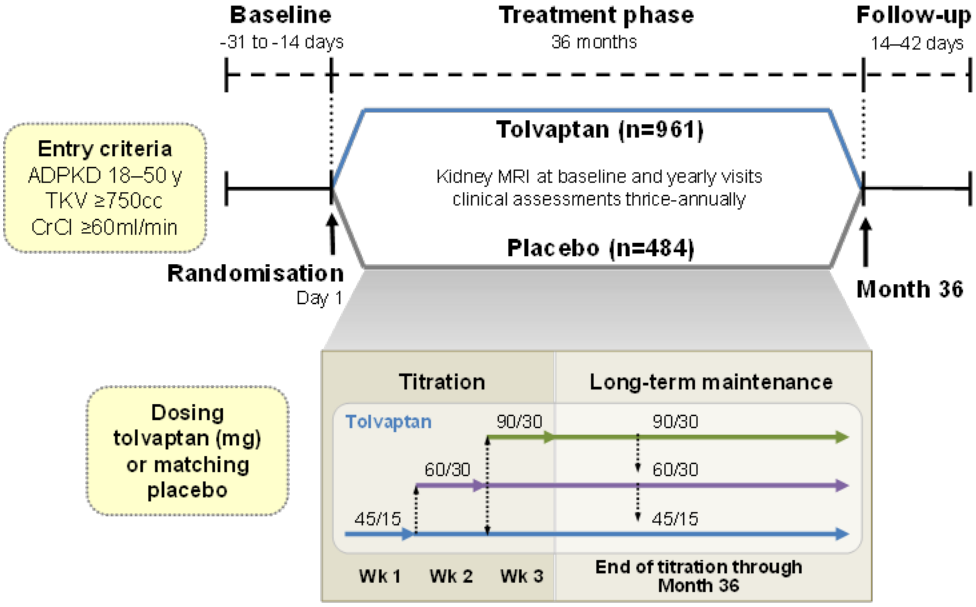
[b] Included women who were not abstinent, not surgically sterile (by hysterectomy or bilateral oophorectomy), and not postmenopausal for at least 12 consecutive months.

[c] Those patents excluded would either be contraindicated in routine practice, such as pregnant women or allergy to active substance, or would not affect the generalisability of the results such as disorders in thirst recognition or inability to access fluids.

Source: CSR TEMPO 3:4[29] Tables 5.2.1-1 and 5.2.2-1; Table 3.4.2-1 and 3.4.3-1 of the Torres 2012 protocol supplement[34]

The flow of patients through the study is presented in Figure 4.1.

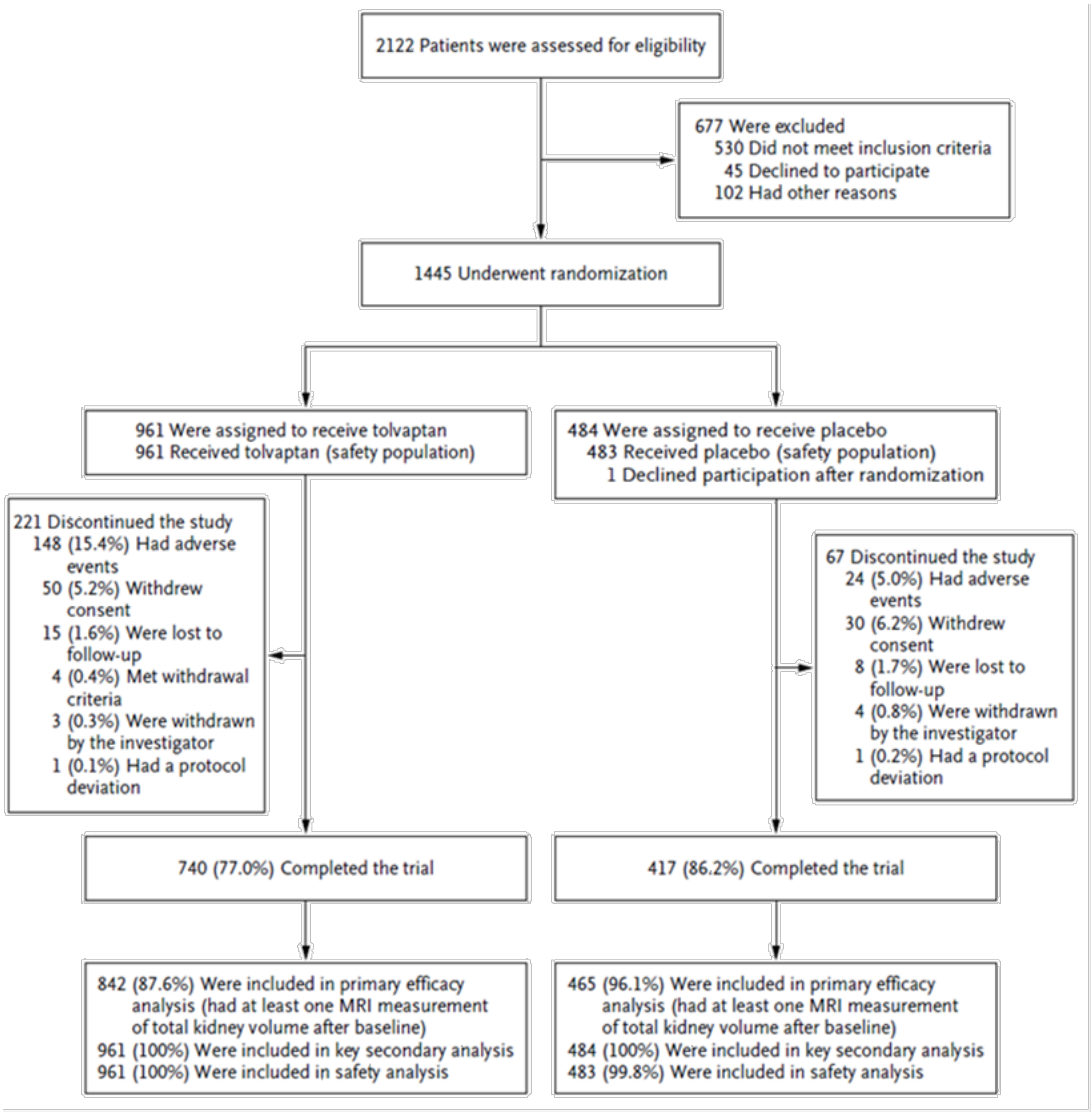
Figure 4.1: TEMPO 3:4 study patient flow diagram
(based on figure B1 of the CS[2] and figure 1 of Torres 2012[24])



ADPKD = autosomal dominant polycystic kidney disease; CrCl = creatinine clearance; MRI = magnetic resonance imagery; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume; Wk = week

Figure 4.2 shows the flow diagram for the TEMPO 3:4 trial.

Figure 4.2: TEMPO 3:4 flow diagram
(based on figure B1 of the CS[2])



ERG comment: It should be noted that that the TEMPO 3:4 trial only includes patients aged 18-50 years. As stated in the final scope[1], *"approximately 50% of people with ADPKD have established renal failure by 60 years of age, but one third will reach 70 years of age with some preservation of renal function"*. This patient group as well as children and adolescents are not covered by the TEMPO 3:4 trial.

In addition, 530 patients were excluded because they did not meet inclusion criteria for the trial (a total kidney volume of 750 ml or more as measured with the use of magnetic resonance imaging and a creatinine clearance of 60 ml per minute or more as estimated by means of the Cockcroft–Gault formula). That also means results are not generalisable to all ADPKD patients. The response to the clarification letter[9] stated that 370 patients were excluded for as they *"did not have a rapid estimated rate of renal volume increase based on total renal size >750 mL by MRI at randomisation"* while another 119 patients were excluded for having *"an estimated GFR of <60 mL/min within 31 days of randomization"*.

4.2.2 Patient characteristics in the TEMPO 3:4 trial

The demographics, baseline disease characteristics and medical history of patients in both treatment arms are presented in Table 4.11.

Table 4.11: Characteristics of participants in the TEMPO 3:4 trial
(based on Table B6 of the CS[2])

Trial no. (acronym) **Baseline characteristic**	**Tolvaptan**	**Placebo**
156-04-251; NCT00428948 (TEMPO 3:4)	**(n = 961)**	**(n = 484)**
Male sex, n (%)	495 (51.5)	251 (51.9)
Age: years, median	39 ± 7	39 ± 7
Race, n (%)[a]		
Caucasian	810 (84.3)	408 (84.3)
Asian	121 (12.6)	62 (12.8)
Other	30 (3.1)	14 (2.9)
Stratification factor, n (%)		
Hypertension	765 (79.6)	382 (78.9)
Estimated creatinine clearance < 80 ml/min	242 (25.2)	130 (26.9)
Total kidney volume < 1,000 ml	197 (20.5)	101 (20.9)
Medical history, n (%)		
Haematuria	338 (35.2)	164 (33.9)
Renal pain	496 (51.6)	239 (49.4)
Nephrolithiasis	187 (19.5)	109 (22.5)
Urinary tract infection	290 (30.2)	164 (33.9)
Anaemia	105 (10.9)	48 (9.9)
Proteinuria	233 (24.2)	116 (24.0)
CKD classification, n (%)[b]		
Stage 1	330 (34.5)	173 (35.9)
Stage 2	465 (48.5)	224 (46.5)
Stage 3	163 (17.0)	84 (17.4)
Current medication, n (%)		
Angiotensin-converting enzyme inhibitor	419 (43.6)	199 (41.1)
Angiotensin-receptor blocker	307 (31.9)	165 (34.1)
Angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, or both	683 (71.1)	350 (72.3)
Beta-blocker	171 (17.8)	94 (19.4)
Calcium-channel blocker	180 (18.7)	104 (21.5)
Diuretic	32 (3.3)	14 (2.9)
Height, cm	173.5 ± 10.4	173.6 ± 7.8
Weight, kg	79 ± 18	79 ± 18

Trial no. (acronym) Baseline characteristic	Tolvaptan	Placebo
Blood pressure, mmHg		
Systolic	128.6 ± 13.5	128.3 ± 13.5
Diastolic	82.5 ± 9.9	82.5 ± 9.3
Total kidney volume, ml[c]	1705 ± 921	1668 ± 873
Height-adjusted total kidney volume, ml/m	979 ± 515	958 ± 483
Serum creatinine, mg/dl[d]	1.05 ± 0.30	1.04 ± 0.32
Reciprocal of serum creatinine, mg/ml^{-1}	102.27 ± 27.21	104.30 ± 35.60
Estimated creatinine clearance, ml/min[e]	104.08 ± 32.76	103.80 ± 35.60
eGFR, ml/min/1.73 m^2[f]	81.35 ± 21.02	82.14 ± 22.73
Urinary albumin-to-creatinine ratio[g]	7.2 ± 14.3	8.6 ± 21.7

CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CSR = clinical study report; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; MRI = magnetic resonance imaging; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

[a] Race was self-reported.

[b] CKD classifications based on renal function estimated by CKD-EPI formula. CKD stage 1: GFR ≥ 90; stage 2: 60 ≤ GFR < 90; stage 3: 30 ≤ GFR < 60.

[c] Combined kidney volume of both kidneys assessed by an MRI.

[d] To convert values for creatinine to micromoles per litre, multiply by 88.4.

[e] The estimated creatinine clearance was measured with the use of the Cockcroft–Gault formula.

[f] The eGFR was measured with the use of the CKD-EPI equation adjusted for race.

[g] For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams per decilitre and creatinine in millimoles per decilitre.

Source: Table 1, Torres 2012[24]; Table 8.2-1, CSR TEMPO 3:4[29]

ERG comment: Overall, both treatment arms appear well balanced. However, it should be noted that most patients in the trial were CKD stage 1 (35%) and 2 (48%). Therefore, there is limited evidence for CKD stage 3 patients (17%).

4.2.3 Results

The final scope[1] lists the following outcome measures:

- rate of decline of renal function
- symptoms of chronic kidney disease (including pain)
- mortality
- adverse effects of treatment
- health related quality of life.

Results for these outcomes presented in the CS are discussed below. In addition, the ERG recognises that total kidney volume was the primary outcome in the only RCT presented in the CS, i.e. the TEMPO 3:4 trial. Therefore, this outcome is also discussed.

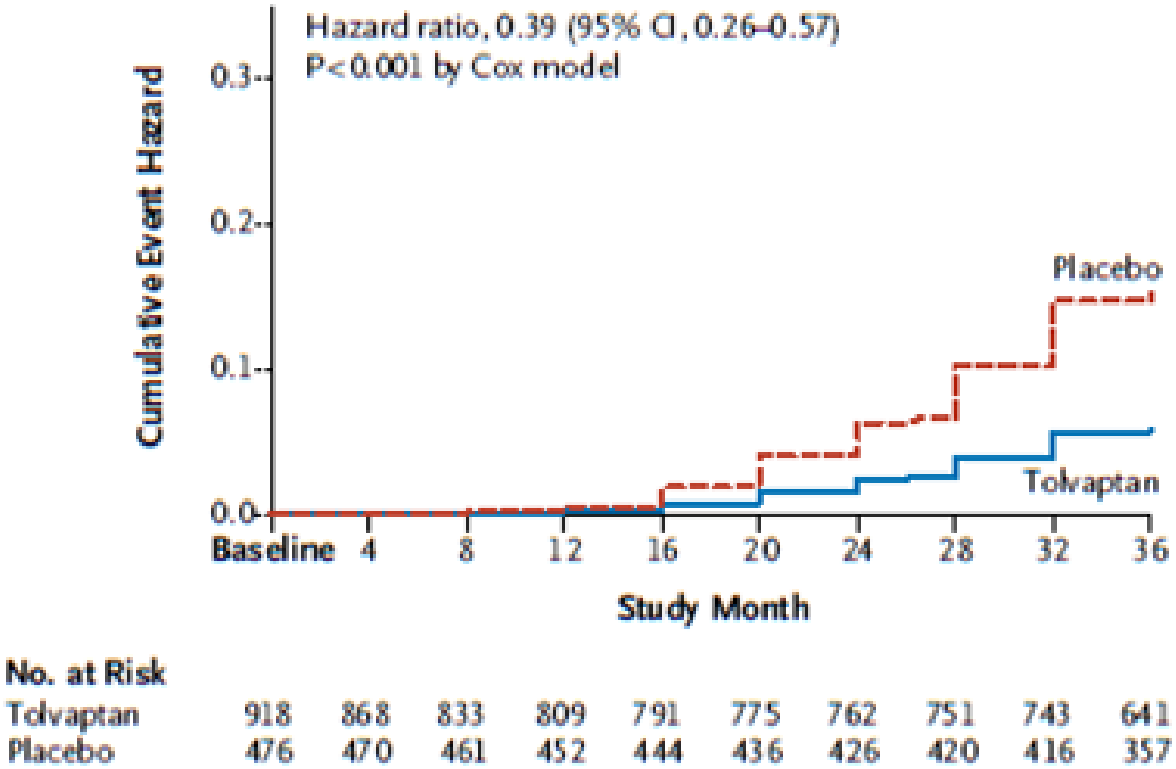
The ERG was able to obtain a publication cited in the CS which was not sent as part of the company's submission.[32] Results for the two studies included in this publication are reported where relevant.

Rate of decline of renal function in TEMPO 3:4

According to page 102 of the CS, *"treatment with tolvaptan was associated with a significant 61% relative reduction (absolute reduction: 3 events per 100 person-years) in the risk of worsening renal function over 3 years compared with placebo (2 events per 100 person-years vs. 5 events per 100 person-years; HR, 0.39; 95% CI, 0.26-0.57; P < 0.001)".*[2] Figure 4.3 shows the cumulative hazard functions for tolvaptan compared to placebo for the time to worsening renal function.

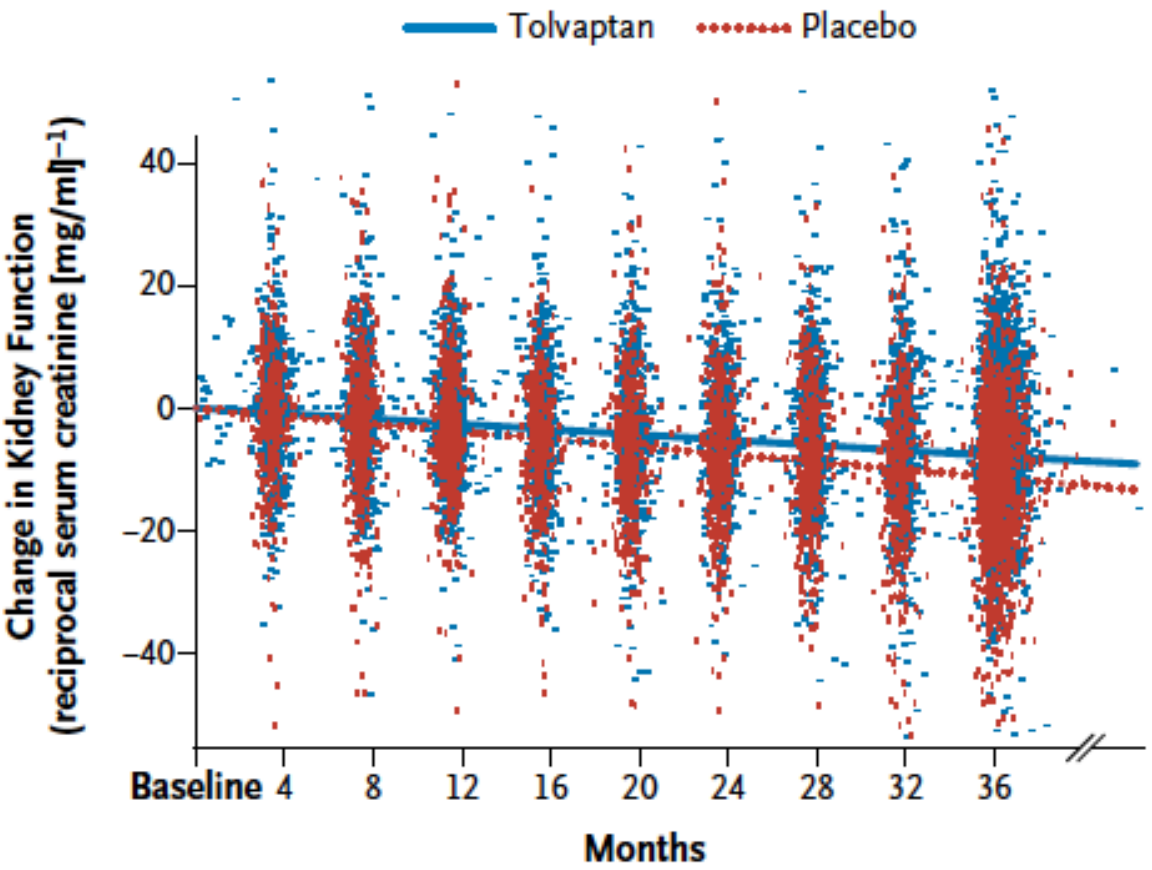
Figure 4.3: Cumulative hazard functions for the time to worsening renal function in TEMPO 3:4

(based on figure B6 of the CS[2] and figure 3c of Torres 2012[24], better quality unavailable)



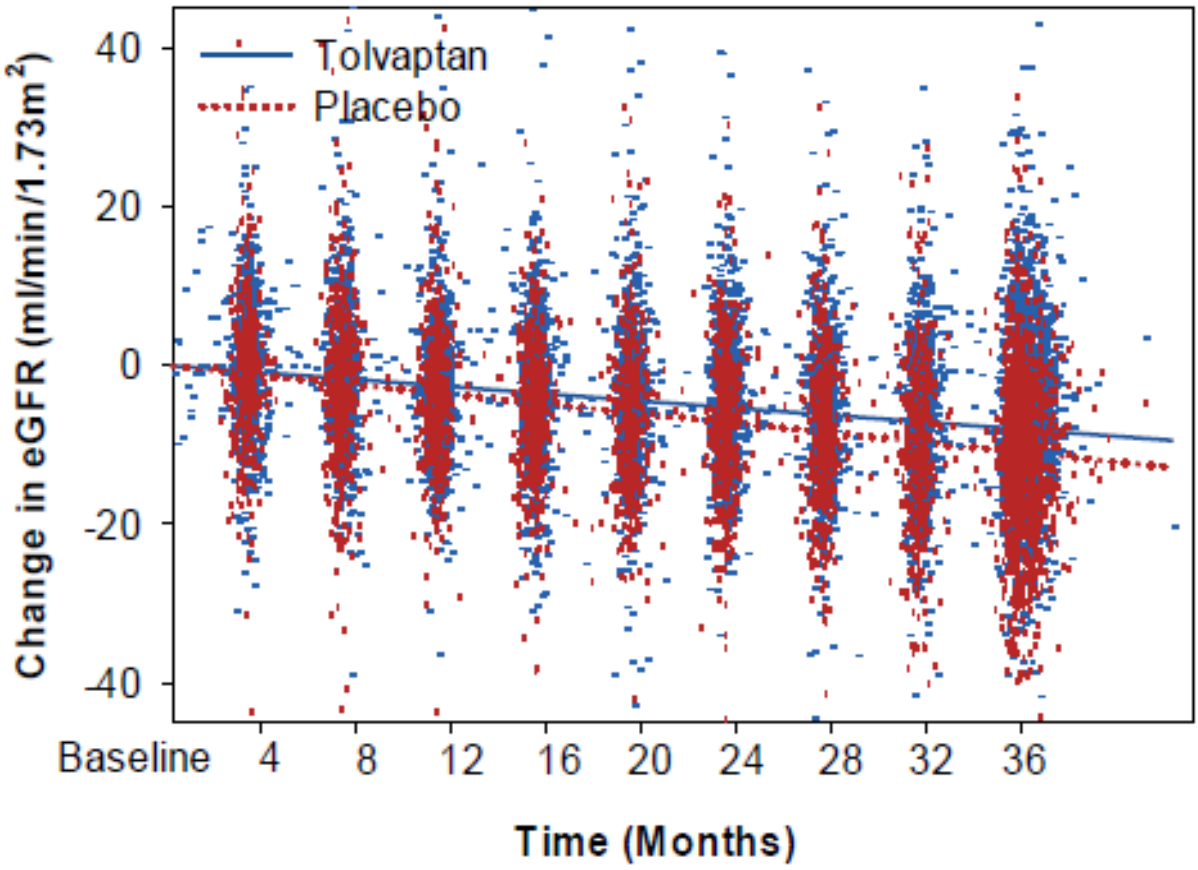
According to page 104 of the CS, *"the rate of change in renal function from the end of dose titration to month 36 was assessed by means of the slope of the reciprocal of the serum creatinine level as a measure of change in GFR. Patients treated with tolvaptan experienced significantly reduced decline in renal function, compared with those treated with placebo (estimated slope of −2.61 mg/mL^{-1} per year -1 vs. −3.81 mg/mL^{-1} per year-1, respectively; P < 0.001).*[29] *Tolvaptan was associated with a significant 31.6% relative reduction in the annual rate of renal function decline, compared with placebo (absolute reduction of 1.20 mg/mL-1 serum creatinine; 95% CI, 0.62-1.78; P < 0.001)*[24]*".*[2] Figure 4.4 shows the change in renal function (measured using reciprocal serum creatinine [mg/ml^{-1}]).

Figure 4.4: Change in renal function (measured using reciprocal serum creatinine [mg/ml^{-1}] in TEMPO 3:4
(based on Figure B8 of the CS[2] and Figure 2c of Torres 2012[24])



According to page 104 of the CS, *"reductions in renal function decline in the tolvaptan treatment arm compared with placebo were further supported by other methods of estimating renal function. In a subsequent analysis of the data to calculate the annual eGFR$_{CKD\text{-}EPI}$, the absolute treatment difference between the tolvaptan and placebo treatment arms was -2.72 mL/min/1.73 m^2 per year over 3 years (95% CI, 0.60-1.36; P < 0.001)[24]."*[2] Figure 4.5 shows the rate of change in renal function (measured using eGFR$_{CKD\text{-}EPI}$ [ml/minute/1.73 m^2]).

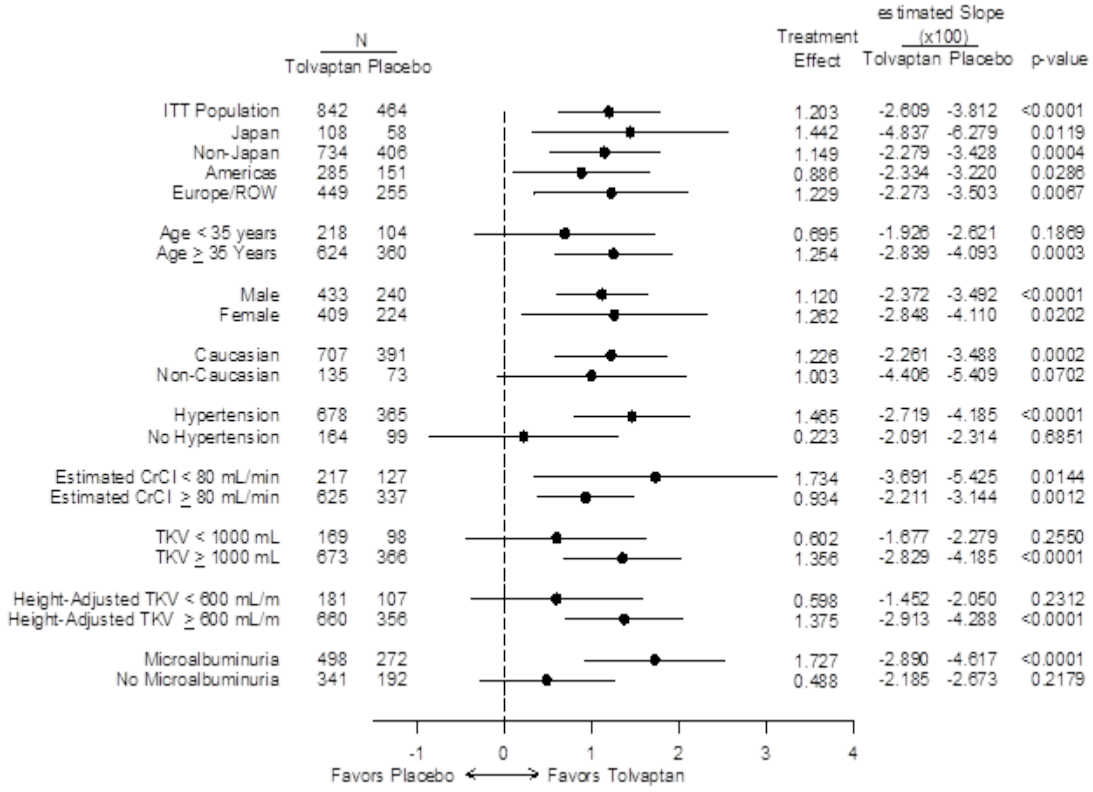
Figure 4.5: rate of change in renal function (measured using $eGFR_{CKD-EPI}$ [ml/minute/1.73 m^2]) in TEMPO 3:4
(based on figure B9 of the CS[2] and figure S3 of Torres 2012[24])



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

According to page 106 of the CS, *"treatment effect on renal function appeared to be consistent across the subgroups studied. In all subgroups, tolvaptan had a beneficial effect on renal function decline, compared with placebo. The effect was numerically greater than placebo (but not statistically significant) among patients < 35 years of age, those with no hypertension, those with no microalbuminuria, and those with a TKV of < 1,000 mL, or a height-adjusted TKV < 600 mL/m; these results are not surprising given that these subgroups are earlier in the disease where renal function decline is less pronounced. The effect was statistically significant in the other subgroups analysed".*[2] Figure 4.6 shows subgroup analyses of annualised change in renal function (1/serum creatinine $[mg/ml]^{-1}$).

Figure 4.6: Subgroup analyses of annualised change in renal function (1/serum creatinine [mg/ml]$^{-1}$) in TEMPO 3:4
(based on figure B10 of the CS[2] and figure 9.5.1.3-1 of the CSR[29])



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

The CS states that *"As some of the subgroups were relatively small (e.g., 218 patients < 35 years of age vs. 624 patients ≥ 35 years of age; 164 patients with no hypertension vs. 678 with hypertension), it is difficult to draw meaningful conclusions on the efficacy of tolvaptan in reducing the rate of renal function decline. The apparently differential effect of tolvaptan in patients with TKV under or over 1,500 mL (n = 427 vs. n = 415 in the tolvaptan arm) may be due to a slower rate of renal function decline in patients with < 1,500 mL, although data to support this assertion are lacking. Post-hoc analysis of renal function decline in subgroups of patients at each CKD stage (1, 2, and 3 at baseline) showed that tolvaptan significantly reduced the slope of renal function decline in CKD stages 2 and 3.*[24, 51] *The lack of significance in CKD stage 1 is not surprising given that this subgroup is earlier in the disease where renal function decline is much less pronounced during the trial, making detection of an effect more problematic."*[2] Table 4.12 shows the effect of tolvaptan on annualised rate of change in renal function (measured using reciprocal serum creatinine [mg/ml^{-1}]) from baseline by CKD stage.

Table 4.12: Effect of tolvaptan on annualised rate of change in renal function (measured using reciprocal serum creatinine [mg/ml^{-1}]) from baseline by CKD stage in TEMPO 3:4
(based on Table B13 of the CS[2])

Baseline CKD stage by $eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	N	Estimated slope (annualised)	[redacted]	[redacted]	P
Stage 1 (≥90)					
Tolvaptan	277	-1.831	[redacted]	[redacted]	0.4662
Placebo	162	-2.146			
Stage 2 (89-60)					
Tolvaptan	411	-2.683	[redacted]	[redacted]	0.0004
Placebo	216	-3.886			
Stage 3 (<60)					
Tolvaptan	151	-3.873	[redacted]	[redacted]	0.0068
Placebo	84	-6.506			

CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; SD = standard deviation
Sources: OPEL responses to EMA Day 120 list of questions 2014[52]: Table 3.2.3.7-3 Table 3.2.3.7-7 and Table 3.2.3.6-11[51]; Torres 2014[24]

Page 133 of the CS states that *"the primary outcome of clinical interest is renal function decline and therefore, ultimately, onset of ESRD. However, in a life-long disease with an extended period of disease progression such as ADPKD, measurement of ESRD can pose challenges in the clinical trial setting. There is a need for reliable and robust interim outcome measures to enable clinical studies to reliably detect efficacious treatment strategies over relatively shorter time scales and at earlier disease stages. Further, measurement of eGFR as primary endpoint in clinical trials in ADPKD poses challenges because deterioration of GFR occurs relatively late in the disease course and is highly variable among patients.*[10, 53, 54] *This outcome was measured robustly as a key secondary endpoint via four separate measures. How these results translate into longer-term benefits through modelling is explored in Section 7"*.

ERG comment: The ERG would like to highlight two points.

Firstly, as detailed in Table 4.11 (above), relatively few patients (17%) were included for CKD stage 3 (163 in the tolvaptan group, 84 in the placebo group). Therefore, the evidence presented for this subgroup (Table 4.12) is limited.

Secondly, there seems to be some uncertainty surrounding how to best assess the GFR. *"Accurate assessment of GFR is essential for interpreting the symptoms, signs, and laboratory abnormalities that may indicate kidney disease; for drug dosing; and for detecting and managing chronic kidney disease and assessing the prognosis"*.[55] *"Although there are divergent opinions regarding the best GFR estimation equation to use for the staging of CKD and the dosing of medications, most current data support CKD–EPI as the most accurate*

method for diagnosis and staging of CKD and CG for drug-dosing decisions".[56, 57] Combining different methods have been suggested.[55]

The CS presented an overview of renal function evaluations (see Table 4.13).

Table 4.13: Overview of renal function evaluations
(based on Table A5 of the CS[2])

Type of renal function evaluation	Details
Measured GFR (mGFR)	• Measured as the urinary or plasma clearance of exogenous markers, for example inulin, radio-labelled iothalamate, EDTA or DTPA, or iohexol • However, use of exogenous marker to measure GFR is complex, high-cost and difficult to do in routine clinical practice • Measurement errors of 5% to 20% have been reported. Such variation can occur within a single clearance measurement or between clearance measurements on different days
Estimated GFR (eGFR) or creatinine clearance (CrCl)	<u>Reciprocal of the serum creatinine or cystatin C level</u> • Estimated by measuring the serum level of an endogenous marker (e.g. creatinine or cystatin C) and, by use of an equation, calculating the estimated GFR. In the steady state, the serum level of an endogenous marker is related to the reciprocal of the level of GFR and can be used to estimate the GFR without a urine collection • In the pivotal TEMPO 3:4 trial, the primary measure of renal function was eGFR based on the reciprocal of the serum creatinine level • The most extensively studied and widely applied equations to calculate creatinine clearance or eGFR are the: - Cockcroft-Gault equation - Modification of Diet in Renal Disease (MDRD) study equation - Chronic Kidney Disease Epidemiology (CKD-EPI) equation
	<u>By urinary creatinine clearance</u> • Can also be estimated by evaluating urinary clearance of endogenous creatinine (i.e. creatinine clearance). This requires timed urine collections and blood sampling, and is therefore not used routinely in clinical practice to estimate renal function
CKD-EPI = Chronic Kidney Disease Epidemiology; DTPA = diethylene triamine pentaacetic acid; EDTA = ethylenediaminetetraacetic acid; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease. Sources: Lamb 2014[58], Stevens 200[59]	

Uncertainties regarding the estimation of the glomerular filtration rate, especially for early stages of ADPKD, are also acknowledged in the company's submission[2]: *"Estimated GFR (eGFR) by itself does not always reflect early kidney damage in ADPKD, due to compensatory hyperfiltration by undamaged nephrons, and may not be an accurate marker of*

disease progression until the later stages of ADPKD. Also, serum creatinine concentrations are naturally variable in individual patients depending on patient age, gender, muscle mass, diet, medication use, chronic illness and geographic, ethnic or racial group.[59] *Therefore, cross-sectional measurement may be confounded and lack sensitivity in early stages of ADPKD. The optimal choice of estimation technique is individualised based on patient characteristics and the objective of the assessment (i.e. diagnosis or evaluation of change)".*

Symptoms of chronic kidney disease (including pain) in TEMPO 3:4

According to page 109 of the CS, *"the analysis of change from baseline in renal pain (assessed by a 0 to 10 pain scale) did not yield any trends or statistically significant results.*[29] *The question asked was: 'On a scale of 0 to 10, with zero representing no pain at all and 10 representing the worst pain you've ever experienced, what was the worst kidney pain you've experienced in the last 4 months?'".* Table 4.14 shows time average area under the curve (AUC) of change from baseline in renal pain scale (0-10).

Table 4.14: Time average AUC of change from baseline in renal pain scale (0-10) in TEMPO 3:4

(based on Table B15 of the CS[2])

Treatment group	N	Mean	LS mean	Difference[a]	95% CI	*P* Value[a]
Tolvaptan	926	0.06	0.00	−0.08	−0.20, 0.03	0.1604
Placebo	467	0.09	0.08			

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; CSR = clinical study report; LS = least squares; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes

[a] Derived from ANCOVA with factors of treatment and baseline stratification factor interaction and covariate renal pain baseline.

Source: CSR TEMPO 3:4 Table 9.5.2-1[29]; Table S1, Torres 2012[24]

The CS (page 109) concluded that [redacted] In their response to the clarification letter[9], the company provided a [redacted] (figure 4.7).

Figure 4.7: Time to Multiple Renal Pain Events by CKD stage in TEMPO 3:4
(based on Figure 2 of the response to the clarification letter[9], better quality unavailable)

[redacted]

ERG comment: The ERG does not have any specific comments on this section.

Mortality in TEMPO 3:4, 156-04-248 and 156-04-249
According to page 127 of the CS, *"no patient died during trial participation.*[29]*"*.[2]

ERG comment: The ERG was able to obtain a publication cited in the CS which was not send as part of the company's submission.[32] None of the patients included in the two randomised studies (n=48) reported in the publication died.

Adverse events of treatment in TEMPO 3:4, 156-04-248 and 156-04-249
According to page 127 of the CS, *"observed risks based on the tolvaptan mechanism of action included those arising from aquaresis (e.g., polyuria, pollakiuria, nocturia, thirst and dry mouth), dehydration, hypernatremia, and hyperuricemia/gout. Over three years of study in the pivotal placebo-controlled trial (TEMPO 3:4), these events represented the adverse reactions most likely to limit a patient's ability to continue therapy.*[51] *Aquaresis-related symptoms led to the discontinuation of tolvaptan in 8.3% of participants, mostly within the first month.*[24] *Other less frequently reported, but predictable, adverse events attributable to tolvaptan use included hyperuricemia/gout and hypernatremia, which is also considered a class effect of vasopressin antagonists. The increased reporting of events of hyperuricemia/gout was expected due to decreased uric acid clearance by the kidney caused by tolvaptan treatment.*[29]

Among the subgroups of patients examined in the pivotal trial (e.g. age, sex, race, baseline stratification factors), none appeared to be more or less susceptible to frequently reported treatment-emergent adverse events.[51]".

The potential for hepatotoxicity of tolvaptan was noted on page 128 of the CS: *"The most notable safety issue associated with tolvaptan use, which was newly identified in the pivotal trial TEMPO 3:4, was the potential for hepatotoxicity. Transaminase elevations were seen in*

46 subjects (35/961, 3.6%, tolvaptan and 11/483, 2.3%, placebo) and emerged during the initial 14 month period after treatment initiation.[29]

Two of the 957 patients on tolvaptan in TEMPO 3:4 (0.2%) and 0 of 484 on placebo met the definition of a Hy's Law case (hepatocellular injury, serum ALT or AST > 3 × upper limit of normal [ULN], total bilirubin > 2 × ULN), an event likely due to tolvaptan treatment. One additional Hy's Law case was identified in a TEMPO 4:4 patient who had received placebo in TEMPO 3:4. In all cases, the abnormalities either resolved during treatment or returned toward baseline values with drug interruption or withdrawal. No reports of persistent sequelae were received.

A signature pattern for the rare hepatic events was identified as the acute onset of a hepatocellular injury between 3 to 18 months after starting tolvaptan therapy with gradual resolution over the subsequent 1 to 4 months. These events were not associated with fulminant liver failure, permanent liver injury or dysfunction, and no subjects required a liver transplant. No imbalance in hepatic events was observed between the tolvaptan and placebo groups in non-ADPKD clinical trials of patients with hyponatremia, heart failure or cirrhosis.

Appropriate patient monitoring and management should be implemented to mitigate this potential risk in the ADPKD population.[51] *These are described in the proposed EU Risk Management Plan (RMP) to ensure that patients receive monthly liver function tests for the first 18 months of treatment with tolvaptan, and three-monthly thereafter. These measures will include the mandatory provision of training material, checklists, etc., for the treating physician to ensure tolvaptan treatment is initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy, including hepatic toxicity and monitoring requirements. In addition, patient educational brochures and other items, such as alert cards, will be provided. Studies will be conducted to ensure the effectiveness of these measures".*

In their response to the clarification letter the company provided additional information on the issue.[9]

[redacted]

[redacted]

[redacted]

Table 4.15 presents serious treatment-emergent adverse events by system organ class in TEMPO 3:4 while Table 4.16 shows the most common adverse events and serious adverse events occurring in the TEMPO 3:4 trial.

In response to the clarification letter[9] the company clarified that *"adverse events of treatment were not analysed by CKD stage"*.

Table 4.15: Serious treatment-emergent adverse events by system organ class in TEMPO 3:4
(based on Table B18 of the CS[2])

Serious adverse event	Tolvaptan (n = 961) n (%)	Placebo (n = 483) n (%)	Relative risk: tolvaptan vs. placebo (95% CI)	Risk differences
Total[a]	177 (18.4)	95 (19.7)	0.94	-0.01
Blood and lymphatic system disorders	0	1 (0.2)	0.17	0.00
Cardiac disorders	14 (1.5)	5 (1.0)	1.41	0.00
Congenital, familial, and genetic disorders	0	1 (0.2)	0.17	0.00
Ear and labyrinth disorders	3 (0.3)	0	3.52	0.00
Eye disorders	3 (0.3)	1 (0.2)	1.51	0.00
Gastrointestinal disorders	20 (2.1)	12 (2.5)	0.84	0.00
General disorders and administration site conditions	13 (1.4)	4 (0.8)	1.63	0.01
Hepatobiliary disorders	8 (0.8)	4 (0.8)	1.01	0.00
Immune system disorders	1 (0.1)	0	1.51	0.00
Infections and infestations	32 (3.3)	23 (4.8)	0.70	-0.01

Serious adverse event	Tolvaptan (n = 961) n (%)	Placebo (n = 483) n (%)	Relative risk: tolvaptan vs. placebo (95% CI)	Risk differences
Injury, poisoning, and procedural complications	14 (1.5)	7 (1.4)	1.01	0.00
Investigations	15 (1.6)	4 (0.8)	1.88	0.01
Metabolism and nutrition disorders	6 (0.6)	5 (1.0)	0.60	0.00
Musculoskeletal and connective tissue disorders	11 (1.1)	8 (1.7)	0.69	-0.01
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	10 (1.0)	5 (1.0)	1.01	0.00
Nervous system disorders	20 (2.1)	5 (1.0)	2.01	0.01
Psychiatric disorders	3 (0.3)	3 (0.6)	0.50	0.00
Renal and urinary disorders	17 (1.8)	20 (4.1)	0.43	-0.02
Reproductive system and breast disorders	12 (1.2)	5 (1.0)	1.21	0.00
Respiratory, thoracic, and mediastinal disorders	7 (0.7)	1 (0.2)	3.52	0.01
Skin and subcutaneous tissue disorders	3 (0.3)	0	3.52	0.00
Vascular disorders	8 (0.8)	5 (1.0)	0.80	0.00

CI = confidence interval; CSR = clinical study report; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes

[a] Patients with serious treatment-emergent adverse events in multiple system organ classes were counted only once towards the total.

Source: CSR TEMPO 3:4 Table 9.5.5-1[29]

Table 4.16: Most common adverse events and serious adverse events in TEMPO 3:4 (based on Table B19 of the CS[2])

Adverse event	Tolvaptan (n = 961) n (%)	Placebo (n = 483) n (%)	Relative risk: tolvaptan vs. placebo (95% CI)	Risk differences
Adverse events more common in tolvaptan group				
Thirst	531 (55.3)[a]	99 (20.5)	2.70	0.35
Polyuria	368 (38.3)[a]	83 (17.2)	2.23	0.21
Nocturia	280 (29.1)[a]	63 (13.0)	2.23	0.16
Headache	240 (25.0)	120 (24.8)	1.01	0.00
Pollakiuria	223 (23.2)[a]	26 (5.4)	4.31	0.18
Dry mouth	154 (16.0)	59 (12.2)	1.31	0.04
Diarrhoea	128 (13.3)	53 (11.0)	1.21	0.02

Adverse event	Tolvaptan (n = 961) n (%)	Placebo (n = 483) n (%)	Relative risk: tolvaptan vs. placebo (95% CI)	Risk differences
Fatigue	131 (13.6)	47 (9.7)	1.40	0.04
Dizziness	109 (11.3)	42 (8.7)	1.30	0.03
Polydipsia	100 (10.4)[a]	17 (3.5)	2.96	0.07
Adverse events more common in placebo group				
Hypertension	309 (32.2)	174 (36.0)	0.89	-0.04
Renal pain	259 (27.0)[b]	169 (35.0)	0.77	-0.08
Nasopharyngitis	210 (21.9)	111 (23.0)	0.95	-0.01
Back pain	132 (13.7)	88 (18.2)	0.75	-0.04
Increased creatinine level	135 (14.0)	71 (14.7)	0.96	-0.01
Haematuria	75 (7.8)[a]	68 (14.1)	0.55	-0.06
Urinary tract infection	80 (8.3)[b]	61 (12.6)	0.66	-0.04
Nausea	98 (10.2)	57 (11.8)	0.86	-0.02
Serious adverse events more common in tolvaptan group				
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)	2.26	0.01
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)	2.26	0.01
Chest pain	8 (0.8)	2 (0.4)	2.01	0.00
Headache	5 (0.5)	0	5.53	0.01
Serious adverse events more common in placebo group				
Pyelonephritis	5 (0.5)	5 (1.0)	0.50	-0.01
Renal-cyst infection	6 (0.6)	4 (0.8)	0.75	0.00
Renal-cyst haemorrhage	3 (0.3)	4 (0.8)	0.38	-0.01
Renal pain	1 (0.1)	4 (0.8)	0.13	-0.01
Appendicitis	1 (0.1)	4 (0.8)	0.13	-0.01
Nephrolithiasis	2 (0.2)	3 (0.6)	0.34	0.00
Urinary tract infection	1 (0.1)	3 (0.6)	0.17	-0.01
Hypertension	1 (0.1)	3 (0.6)	0.17	-0.01

Note: Adverse events were categorised according to the Medical Dictionary for Regulatory Activities.
[a] $P < 0.001$ by Fisher's exact test, as compared with the placebo group.
[b] $P < 0.05$ by Fisher's exact test, as compared with the placebo group.
Source: Table 2, Torres 2012[24]

ERG comment: The ERG has a number of comments on this section.

1. Risk of drug-induced liver injury

The FDA found that *"tolvaptan's safety profile was not reassuring. Tolvaptan caused liver injury in patients with ADPKD. There were three subjects with hepatocellular liver injury judged to be at least probably due to tolvaptan ("Hy's Law" cases) out of ~860 subjects with ADPKD treated over a 14-month treatment period. These subjects did not progress to liver*

failure leading to transplantation or death, but the finding of two or more Hy's Law cases in a clinical trial safety database is a strong predictor of a drug capable of causing such injury".[16]

The ERG agrees with the view of the FDA. The potential effects on liver-enzyme levels and plasma levels of sodium and uric acid should be considered.

2. Other adverse events

Thirst (55.3% in tolvaptan group versus 20.5% in placebo group), polyuria (38.3% versus 17.2%), and related adverse events may affect the ability of some patients to take effective doses of tolvaptan. Although mentioned in the main text, no detailed results were reported for dehydration.

3. 95% confidence intervals not reported

It should be noted that Tables B18 of the CS (Table 4.15) and B19 of the CS (Table 4.16) did not report 95% confidence intervals to support the reported relative risks. Therefore, it is not possible to scrutinise the results in more detail.

4. High treatment discontinuation due to adverse events

As detailed in Section 4.1.4, more people in the tolvaptan group (n=148, 15.4%) than in the placebo group (n=24, 5.0%) discontinued treatment due to adverse events in the TEMPO 3:4 trial.

5. Additional information from 156-04-248 and 156-04-249

The ERG was able to obtain a publication cited in the CS which was not sent as part of the company's submission.[32] Study A (156-04-248) included 11 patients while study B (156-04-249) included 37 patients: *"In Study A, 21 mild and 3 moderate level side effects were reported in the tolvaptan and 4 mild and 1 moderate level side effect in the placebo group. Dry mouth (5/8) somnolence (3/8) headache (3/8) were most commonly reported independent of dose level. In Study B 35 mild to moderate side effects were reported in 21/37 subjects. Dry mouth occurred most often (11/37). Tolvaptan, a V2RA is well tolerated throughout a range of doses and when administered once or twice a day in ADPKD individuals with near-normal renal function"*.

Health-related quality of life

In response to the clarification letter[9] the company clarified that *"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"*.

ERG comment: Although HRQoL was an outcome of interest in the final scope[1] no results were reported in the section on clinical evidence. This is in line with the CSR for TEMPO 3:4 which did not present any results for HRQoL.[29]

As detailed in Section 7.4.5 of the CS, a *"systematic review of the literature was conducted to identify health state utility values (HSUVs) for patients with ADPKD or ESRD"*. This search is discussed in Section 4.1.1 of the ERG report.

Total Kidney Volume (TKV)

According to page 97 of the CS, the primary endpoint of the TEMPO 3:4 *"was rate of TKV change (normalised as percentage) from baseline for tolvaptan (combining all doses) relative to placebo, as measured by MRI. The rate of TKV change over the 3-year treatment period was significantly lower for the tolvaptan treatment arm (2.8% per year; 95% confidence interval [CI], 2.5-3.1) compared with the placebo arm (5.6% per year; 95% CI, 5.1-6.0.[29]"*.[2] Table 4.17 presents the rate of change in total kidney volume within the treatment period of TEMPO 3:4.

Table 4.17: Rate of change in total kidney volume within the treatment period of TEMPO 3:4

(based on Table B10 of the CS[2])

Treatment group	N	Mean rate of % growth/year (SD)[a]	Slope reduction (%)	Treatment difference (%) (95% CI)[b]	*P* Value[c]
Tolvaptan	819	2.78 (5.66)	49.2	−2.708 (−3.27, −2.15)	< 0.0001
Placebo	458	5.61 (5.33)			

CI = confidence interval; CSR = clinical study report; MRI = magnetic resonance imaging; SD = standard deviation

[a] Summary statistics were derived by regressing logarithm-transformed kidney volume data against time, then displaying regression-slope exponentials (random effect intercept). Time variable used in the regression was equal to (MRI date − baseline MRI date) / 365.25.

[b] Derived from delta method assuming independence between the estimates of the slope between the two treatments. Differences in slope were produced post hoc to facilitate clinical interpretation.

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

Source: CSR TEMPO 3:4 Table 9.3.1-1[29]

The CS also presents results for each individual year of the trial using a mixed-model repeated measure (MMRM) analysis.[2] (Table 4.18)

Table 4.18: Rate of change in total kidney volume within the treatment period of TEMPO 3:4

(based on Table B10 of the CS[2])

Visit	Treatment arm	N	Mean (%)	SD (%)	LS mean (%)	Treatment effect (%) (95% CI)	P Value
Year 1	Tolvaptan	818	−1.16	8.43	−1.65	−6.27 (−7.26, −5.28)	< 0.0001
	Placebo	457	5.05	9.35	4.62		
Year 2	Tolvaptan	767	3.27	11.52	2.93	−8.17 (−9.50, −6.84)	< 0.0001
	Placebo	425	11.49	11.30	11.10		
Year 3	Tolvaptan	698	9.65	15.38	9.56	−9.19 (−11.1, −7.32)	< 0.0001
	Placebo	380	18.85	16.29	18.75		

CI = confidence interval; LS = least square; MMRM = mixed-model repeated-measures; SD = standard deviation; TKV = total kidney volume

Source: CSR TEMPO 3:4 Table 9.3.2.1-1[1]; Figure S1 of Torres 2012[24]

ERG comment: The ERG has a number of comments on this section.

1. TKV is a surrogate endpoint

The ERG does consider TKV as a surrogate endpoint with very limited value. This is in line with the final scope which does not include TKV as an outcome of interest.[1] At the scoping workshop clinical experts commented that TKV is not generally measured in the UK (or anywhere else). TKV is a good measure of extent of disease as it predicts future decline of renal function. However due to natural variation between patients and unreliability of measurement TKV is not a reliable measure of treatment effect.

The results on TKV are part of the ERG report as it was the primary endpoint in the only RCT included in the CS, namely TEMPO 3:4.

2. Measurement of TKV

Page 40 of the CS states that "*TKV measured by ellipsoid method correlates well with TKV measured by the stereology method, and this has been validated using data from the CRISP cohort.*[60]*"*.

The ERG doubts whether TKV measurement by the ellipsoid method is a reliable approximation of the gold standard: the stereology method for ADPKD patients. The formula given in the CS would yield the exact volume if the kidney were an ellipsoid (=elongated/flattened sphere). It would still give a fair correlation if the kidney had a fixed shape (however elongated or flattened). However, in ADPKD the kidneys lose their predictable shape and become distorted. The cited work by Breau et al 2013[60] validated the method in 28 patients *"without congenital, cystic or neoplastic abnormalities"*, i.e. patients with predictable kidney shapes. If TKV change would be used as a measure of progression of disease, this potential unreliability might have serious consequences, e.g. a single cyst rapidly growing at the pole of a kidney (or rupturing and disappearing) would change the estimated kidney volume considerably.

3. Discrepancy in response to clarification letter

In their response to the clarification letter[9], the company explained that TKV was included as it *"was pre-specified as the primary efficacy outcome of TEMPO 3:4 (...) 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"*.

The ERG noted that despite this response, TKV was utilised in the economic model (see Section 5.2.6).

4.2.4 Included non-RCTs

Table 4.4 above gives basic information on the three non-RCTs presented in the CS:

- TEMPO 2:4

- Study 156-09-283
- TEMPO 4:4

Section 6.8 of the CS gives further information on these trials.[2]

TEMPO 2:4 was a *"phase 2, multicentre, open-label, parallel-group, dose-finding study evaluating the long-term safety and pilot efficacy of split-dose regimens. This was a 36-month trial with a 12-month extension period*[51]*"* which included 46 patients (22 in the tolvaptan 45+15 mg group and 24 in the tolvaptan 60+30 mg group).

"39 patients (84.8%) completed the trial through the month 36 visit, with similar percentages of patients in the two treatment groups completing the trial. Among the patients who discontinued, the most frequent reasons for discontinuation were adverse events (AEs) (3/46 patients, 6.5%) and being lost to follow up (2/46 patients, 4.3%)[45]*"*. No further details on AEs were reported in the CS.

"Safety was assessed by regular monitoring of AEs, directed physical examinations, vital signs, clinical laboratory, and electrocardiogram (ECG) measurements.[45] *Efficacy was assessed using the following endpoints:*

- *Urine osmolality at steady state*
- *Total kidney volume*
- *Renal function by eGFR estimated using the Modification of Diet in Renal Disease (MDRD) formula, the Cockcroft-Gault formula, and the reciprocal of serum creatinine*
- *Hypertension assessment (presence/absence, sBP, dBP, mean arterial pressure [MAP], therapy dosage, and medical resource utilisation)*
- *Renal pain assessment (patient self-assessed using a scale from 0 to 10, therapy dosage, and medical resource utilisation)*
- *Abdominal girth assessment (girth measured at regularly scheduled physical assessment, patient self-assessment, and medical resource utilisation)*
- *Polycystic Kidney Disease Outcomes Survey"*

"The annualised percent growth rate (mean [SD]) in TKV over the first 3 years was numerically higher in the tolvaptan 45+15 mg group (2.220 [9.567] percentage per year) than in tolvaptan 60+30 mg group (2.209 [11.560] percentage per year).[45] *The mean (SD) negative renal volume growth of −0.96% (5.17%) in the tolvaptan 45+15 mg group and −1.26% (5.31%) in the tolvaptan 60+30 mg group after 2 months of dosing suggests an acute effect of tolvaptan on this disease parameter.*[45]*"*

"Estimated glomerular filtration rate calculated using Modification of Diet in Renal Disease formula ($eGFR_{MDRD}$) (MMRM analysis) tended to decrease from baseline in both groups at each visit, with mean (SD) decreases seen at month 36 in the tolvaptan 45+15 mg group (−4.43 [8.50] mL/min/1.73 m^2) and the tolvaptan 60+30 mg group (−2.90 [11.37] mL/min/1.73 m^2). Estimated renal function using estimated creatinine clearance by means of the Cockcroft-Gault formula ($eCrCl_{CG}$) and reciprocal of serum creatinine showed similar results.[45]*"*

Study 159-09-283 aimed *"to compare TKV change and other clinical markers of ADPKD progression over a 3-year period between tolvaptan-treated subjects and matched-control subjects receiving standard of care"*.

"This study evaluated tolvaptan-treated subjects from phase 2 trials 156-04-250 and 156-05-002 versus subjects selected from the Consortium for Radiological Imaging Studies of Polycystic Kidney Disease [CRISP] longitudinal study and from the subset of ADPKD subjects evaluated by Klahr et al. (J Am Soc Nephrol 1995;5:2037-47) as part of the Modification of Diet in Renal Disease [MDRD] study matched by gender, hypertension status, age, and baseline TKV or eGFR. Assessment comparison time points for rate of change in TKV, eGFR, and presence of hypertension were Baseline, Year 1, Year 2, and Year 3. (...) Matching proceeded in a randomly selected order for tolvaptan-treated subjects, which was then reversed, until all had two matches (51 tolvaptan completers and 102 case-matched subjects were included in the primary analysis)."

"Primary Outcome Variable:

- *Rate of change (%) in TKV*

Secondary Outcome Variables:

- *Rate of change in eGFR (i.e., 100/serum creatinine, Cockcroft-Gault, MDRD, Japan MDRD)*
- *The change in systolic and diastolic blood pressure*
- *The time to onset of hypertension therapy in non-hypertensive subject"*

"Tolvaptan subjects and matched-controls had similar baseline TKV (1422 and 1635 mL) and eGFR (both 62 mL/min/1.73 m^2 using MDRD formula). The annual TKV growth averaged 1.7% per year for tolvaptan versus 5.8% for CRISP matched-controls ($p < 0.0001$, estimated ratio of geometric mean 0.96 [95% confidence interval [CI] 0.95 to 0.97]). Corresponding annualised eGFR declines (tolvaptan versus control) were -0.71 versus -2.1 mL/min/1.73 m^2/year ($p = 0.01$, LMM Group Difference 1.1 mL/min/1.73m2/year [95% CI 0.24 to 1.9]). Sensitivity analyses including withdrawn subjects were similar, while MMRM analyses were significant at each year for TKV and non-significant for eGFR. The slopes for TKV and eGFR were significantly and negatively correlated. Greater increases in TKV were correlated with greater declines in eGFR, with lesser changes for both occurring in the tolvaptan-treated subjects ($r = -0.21$, $p < 0.01$)".

TEMPO 4:4 is *"an ongoing study; with limited interim results" which is "a non-randomised, parallel group, open-label, multicentre extension for patients who have completed various other tolvaptan ADPKD studies, including TEMPO 3:4. The study aims to determine whether tolvaptan modifies the progression of ADPKD and if the effects of tolvaptan are sustained over time.*[41]*"*

"A total of 871 patients were enrolled" and *"assigned to a tolvaptan-split dose regimen of 45 mg + 15 mg, 60 mg + 30 mg, or 90 mg + 30 mg for a minimum of 2 years"*.

"The primary endpoint was the rate of change in TKV over the 2-year treatment period, and the secondary endpoint was the rate of change in eGFR (from the post-treatment initiation baseline).[41]*"*

"An interim analysis was conducted to investigate the persistence of tolvaptan's effect on eGFR. An intra-patient comparison of 304 delayed-treatment patients (i.e., those who received placebo in the TEMPO 3:4 trial), showed a significant improvement in the eGFR slope after switching from placebo to tolvaptan (from −3.59 to −2.85 mL/min/1.73 m^2 per year; treatment effect, 21%; P = 0.048).[41]*"*

"Patients receiving tolvaptan in TEMPO 3:4 (early-treatment patients) demonstrated a sustained and significant preservation of renal function during the TEMPO 4:4 two-year, open-label extension, compared with those patients who were receiving placebo in TEMPO 3:4 (delayed treatment) (P < 0.05 for 11/12 time points).[41]*"*

"A third analysis indicated that the 5-year slope for patients receiving tolvaptan in TEMPO 3:4 and TEMPO 4:4 combined (including the 3-month treatment gap between trials) remained significantly different from the patients who received placebo in the TEMPO 3:4 trial (slope TEMPO 3:4 = −2.92 vs. −3.63 mL/min/1.73 m^2 per year; treatment effect, 20%; P < 0.0001).[41]*"*

ERG comment: The results presented in this section are broadly in line with the results reported for the TEMPO 3:4 trial.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Page 113 of the CS states that *"No indirect or mixed-treatment comparisons were undertaken because the comparator of interest (no active treatment) was included in the pivotal clinical trial reported in Section 6.5"*.[2]

ERG comment: The ERG agrees with the decision not to conduct indirect or mixed-treatment comparisons.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The TEMPO 3:4 study is *"a phase 3, multicentre, double-blind, placebo-controlled, parallel-arm trial. Patients were randomised in a 2:1 ratio to tolvaptan (n = 961) administered twice daily in a split-dose, or placebo (n = 484) over three years"* (CS Page 65).[2]

ERG comment: Given that only one RCT was identified, the ERG agrees with the decision not to conduct an indirect or mixed treatment comparison.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG was able to obtain a publication cited in the CS which was not send as part of the company's submission.[32] As detailed in Section 4.1.3, the two randomised studies described in the publication provide additional results on safety (discontinuation and adverse events). The ERG presents these results in Section 4.2.3.

4.6 Conclusions of the clinical effectiveness section

The CS identified one RCT, the TEMPO 3:4 trial, as well as three non-RCTs relevant to the submission. However, the ERG has some concerns regarding the searches being restricted to English language only.

The inclusion criteria of TEMPO 3:4 are broadly in line with the final scope.[1] Both, treatment and placebo, were given alongside *"best standard care"*. As the term was not defined, there is some uncertainty on what measures comprised best standard care and how this could have influenced the overall findings. The trial did not provide results for one of the outcomes defined in the final scope[1], i.e. health-related quality of life. Following the inclusion criteria (e.g. TKV≥ 750 ml creatinine clearance≥ 60 ml per minute), 530 patients were excluded. Generalisability of the trial is further limited as only 73 out of the 1,445 patients (5%) included in TEMPO 3:4 came from the UK. There is limited evidence for CKD stage 3 patients (17% of the included participants). Furthermore, the trial only included patients 18 to 50 years old.

Sample size calculation for the TEMPO 3:4 trial was based on an endpoint which is outside the scope which might mean that the outcomes relevant for this submission are underpowered. The trial had a follow-up of three years.

[redacted] It should be noted that there is some uncertainty surrounding how to best measure the GFR.

The CS found that [redacted]

The ERG agrees with a previous FDA assessment stating that the finding of two or more Hy's Law cases (indicating drug-induced liver injury) in a clinical trial safety database is a strong predictor of a drug capable of causing such injury. Other adverse events, such as thirst and polyuria may affect the ability of patients of patients to take effective doses of tolvaptan. More people in the tolvaptan group (n=148, 15.4%) than in the placebo group (n=24, 5.0%) discontinued treatment due to adverse events in the TEMPO 3:4 trial but no deaths were reported in either group.

The CS also presented results for total kidney volume (TKV) which was outside the final scope[1] but the primary endpoint of the TEMPO 3:4 trial. The ERG has some concerns regarding the value of this surrogate endpoint and questions whether the measurement of TKV in patients with ADPKD is reliable.

Overall, the ERG has a number of concerns regarding how well the evidence presented in the CS reflects the final scope and is generalisable to the UK population. Applicability of the

findings might be further limited by the length of follow-up as well as the measurement of outcomes. There are some concerns regarding the safety of tolvaptan, especially regarding the potential of inducing liver injuries.

5 COST-EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective of cost-effectiveness review

The objective of cost-effectiveness review was to identify clinical and cost-effectiveness evidence relating to tolvaptan for the treatment of ADPKD. The following electronic databases were selected:

- Ovid MEDLINE and MEDLINE In-Process and Other Non-indexed Citations
- Embase
- Cochrane Library, including
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Registry of Controlled Trial (CENTRAL)
    - Cochrane Methodology Register (CMR)
    - NHS Economic Evaluations Database (NHS EED)

Searches were conducted in Ovid and were limited to studies in humans published in English from 01 January 2004 to 28 July 2014. Supplementary searching for clinical studies included review of congress abstracts for the following meetings from January 2012 to August 2014:

- European Renal Association–European Dialysis and Transplant Association (ERA–EDTA)
- World Congress of Nephrology (WCN)
- American Society of Nephrology (ASN)

Otsuka's own internal database of clinical studies was also searched.

ERG comment: The ERG considers the objective of the cost effectiveness review as appropriate. The quality of the search strategy is discussed in Section 4.1.1 of this report.

5.1.2 Inclusion/exclusion criteria used in the study selection

To be included in this systematic review, clinical references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in the Table 5.1 below.

Table 5.1: Eligibility criteria used in search strategy for cost-effectiveness studies
(based on Table B20 of the CS[2])

	Inclusion	Exclusion
Population	Patients (hypothetical simulated cohort or real) with ADPKD	Animal population
Interventions	Tolvaptan	Any other interventions
Study design	Any form of economic evaluation, including: Cost-effectiveness Cost-utility Cost-consequence Cost-benefit	Cost minimization Resource use

	Inclusion	Exclusion
	Cost per outcome	
Outcomes	ICERs Cost per QALY Cost per outcome Total costs (simulated) Clinical outcomes (simulated) Sensitivity analysis results	Clinical studies PRO/HRQoL
Publication	English language No year limit	Non-English language Editorial Review Letter
HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PRO = patient-reported outcome; QALY = quality-adjusted life year		

ERG comment: The ERG considers the inclusion/exclusion criteria of the cost-effectiveness review as appropriate. The quality of the search strategy is discussed in Section 4.1.1 of this report.

5.1.3 Included/excluded studies in the cost-effectiveness review

The search strategy identified one relevant cost-effectiveness study, which was the study from Erickson at al 2013.[61] The study aimed to determine how the benefits of tolvaptan seen in TEMPO 3:4 trial may relate to longer-term health outcomes, such as progression to end-stage renal disease (ESRD) and death, and to evaluate the cost-effectiveness of tolvaptan therapy compared with standard care (no active treatment) across different ADPKD populations in the United States. The study employed a Markov model, which was populated with aggregated clinical data from the TEMPO 3:4 trial.

A delay in the median time to onset of ESRD with tolvaptan of 6.5 years and an increase in life expectancy of 2.6 years were estimated in the base case results of the study. The base case incremental cost-effectiveness ratio (ICER) was $744,100 per quality-adjusted life year (QALY). A summary of the study is presented in Table 4.7.

The study was deemed as not relevant to decision-making in England and Wales given that: (i) the cost of tolvaptan applied are higher than the actual cost of tolvaptan to the NHS in England and Wales; (ii) resource use and unit costs in the United States are unlikely to be generalisable to the NHS in England and Wales; (iii) the analysis took the societal perspective (despite the fact that the model inputs were consistent with a third party payer perspective) and (iv) costs and outcomes were discounted at a rate of 3% per annum.

The economic model in the Erickson study used aggregated results from TEMPO 3:4 on renal function decline to define fixed relative rates of disease progression (based on eGFR scores). Patient baseline characteristics consisted in 40 year-old men and women with early ADPKD, defined by an eGFR of 80 ml/min/1.73 m^2 (additional cohorts of men and women who might be prescribed tolvaptan in clinical practice were explored in sensitivity analyses). Health states were defined by CKD stage (2, 3a, 3b, 4 and 5) and the model simulated patients over their lifetimes in three month intervals. Costs, quality of life and mortality rates were varied

by health state. Once patients progressed to CKD stage 5, it was assumed they experience costs equal to the averages of similarly-aged US patients with ESRD.

Mortality rates for patients in each CKD stage were calculated by multiplying CKD stage-specific mortality hazard ratios (derived from studies of the general CKD population) by age- and sex-specific US life table mortality rates. Mortality rates in stage 5 CKD were equal to those of similarly-aged US patients with ESRD adjusted to account for lower mortality in ESRD among patients with ADPKD. In the base case it was assumed that tolvaptan adverse events and ADPKD complications not directly related to renal function decline offset each-other in terms of cost and HRQoL impact and that the only effect that tolvaptan had on HRQoL was through attenuating eGFR decline.

The Company argues that the limitations in the study Erickson 2013[61] made it necessary to construct a de novo model that would be capable of accounting for patient heterogeneity in ADPKD progression, permitting the exploration of clinically-relevant subgroups, examination of ESRD pathways in more detail (the argument given here is that ESRD state was simplified to a single cost and utility value) and assessing the relative impact of tolvaptan tolerability and ADPKD complications.

ERG comment: The ERG agrees that the identified study Erickson 2013[61] has limited relevance for decision-making in England and Wales given that it uses: (i) the aggregated results from TEMPO 3:4 trial, (ii) United States specific costs and resource use, (iii) a different perspective taken as well as (iv) different discount rates. For this reason the company has provided a de novo analysis. The ERG agrees that this is the appropriate approach.

Table 5.2: Summary list of other cost-effectiveness evaluations
(based on Table B21 of the CS[2])

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Erickson 2013[61]	2013	USA	A Markov model of CKD was developed to evaluate tolvaptan therapy for slowing the rate of loss of kidney function	Patients aged 40 years with early ADPKD (eGFR: 80 ml/min/1.73 m^2) as the base case, with additional analyses in cohorts who may be prescribed tolvaptan in clinical practice (defined by age, eGFR at initiation of tolvaptan, and rate of eGFR decline without tolvaptan).	Tolvaptan: 15.3 Standard care: 14.2	Tolvaptan: $1,231,400 Standard care: $387,200 (all costs in 2010 US dollars)	$744,100

ADPKD = Autosomal Dominant Polycystic Kidney Disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; QALY(s) = quality-adjusted life year(s); US = United States (of America); USA = United States of America

5.1.4 Conclusions of the cost-effectiveness review

The search strategy developed by the company was able to identify only one cost-effective study on the topic. However the study was not deemed relevant given the higher cost of tolvaptan in the United States context, that the resource use and unit costs were not generalisable to the UK setting, the societal perspective taken and the discount rate. The company argued that the limitations of the study made it necessary to construct a de novo model that would be capable of accounting for patient heterogeneity in ADPKD progression, permitting the exploration of clinically-relevant subgroups, examination of ESRD pathways in more detail and assessing the relative impact of tolvaptan tolerability and ADPKD complications.

ERG comment: The ERG agrees that the identified study by Erickson et al[61] is not relevant to decision-making in England and Wales, a de novo model was needed in order for costs and outcomes relevant for decision-making in England and Wales.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

An overall summary of the *de novo* economic model developed by the company is given in Table 5.3.

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	Individual-patient state-transition model		Not available, see Section 5.2.2 of this report
States and events	Autosomal Dominant Polycystic Kidney Disease (ADPKD) stages 1-4, End-Stage Renal Disease (ESRD), Death		7.2.2
Comparators	Best supportive care without active treatment		2.7
Natural History	Different attributes (age, sex, eGFR, TKV and CKD stage) are assigned to individual patients in each of the three health states of the model which are updated at the end of each cycle (i.e. each year). The age and CKD stage attributes are used to incorporate age-specific and CKD stage specific input parameters		
Treatment effectiveness	Relative difference in decline of eGFR.	The effectiveness of tolvaptan was modelled by directly adjusting annual eGFR decline, as observed in the placebo arm TEMPO 3:4 over the	7.3.2

	Approach	Source / Justification	Signpost (location in CS)
		3-year trial period, and not by introducing TKV as an inter-mediate outcome (TKV was the primary outcome of TEMPO 3:4). This was done by calculating the decrease in absolute annual decline of eGFR for tolvaptan as a percentage of that for SC.	
Adverse events	The only AE included in the model was significant kidney pain.	The company justified this giving the argument that adverse events more common in patients receiving tolvaptan treatment are already common in ADPKD patients not receiving treatment and there is lack of evidence supporting a difference in effect on these outcomes due to tolvaptan. Moreover, it was argued that patients who cannot tolerate the adverse effects discontinue treatment in the model.	7.4.8
Health related QoL	Disutility vs. general population value applied. Utility estimates were based on a mix of EQ-5D with UK sample and value set and other EQ-5D measured in other populations and estimates elicited using TTO methods.	The systematic review identified no estimates for CKD stages 1 to 4 which were measured using EQ-5D in a UK ADPKD population and valued using the UK general population value set.	7.4.9
Resource utilisation and costs	Categories were: costs of intervention and comparators, as well as costs for CKD stages and ESRD.		7.5.1 - 7.5.8
Discount rates	3.5 % for utilities and costs	According to NICE reference case	7.3.6
Sub groups	Subgroup analyses were performed for patients in each CKD stage at		7.9.1

	Approach	Source / Justification	Signpost (location in CS)
	treatment initiation (stage 1, stage 2, stage 3a and stage 3b)		
Sensitivity analysis	The Company did not perform one-way sensitivity analyses. Several scenario analyses were performed.	The lack of one-way sensitivity analyses was justified by arguing that *"The stochastic individual patient simulation (with sampling of baseline characteristics) and probabilistic sensitivity analysis were programmed to run simultaneously..."*	7.7.7; 7.7.9
ADPKD = Autosomal Dominant Polycystic Kidney Disease; AE = Adverse event; CKD = chronic kidney disease; CS = company's submission; eGFR = estimated glomerular filtration rate; EQ-5D = European Quality of Life-5 Dimensions; ESRD = End-Stage Renal Disease; NICE = National Institute for Health and Care Excellence; SC = standard care; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume; TTO = Time trade-off; UK = United Kingdom			

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

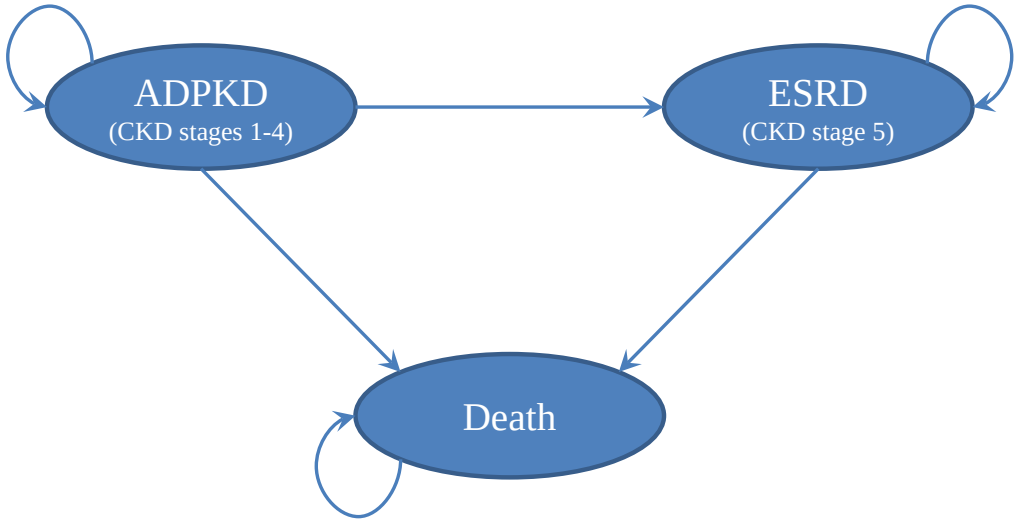
Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	The comparator defined in the NICE scope was, *"Standard care, including routine surveillance without tolvaptan"*. Standard care was not fully defined in the final scope.[1] According to the CS, the standard care does not involve any active treatment for ADPKD.
Patient group	As per NICE scope	Yes.
Perspective costs	NHS and Personal Social Services (PSS)	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	The key sources for clinical effectiveness of tolvaptan in the company's economic analysis are obtained from the patient level data from the pivotal TEMPO 3:4 study.
Outcome measure	Quality adjusted life years (QALYs)	Yes

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Health states for QALY	Described using a standardised and validated instrument	Utility estimates were based on a mix of EQ-5D with UK sample and value set and other EQ-5D measured in other populations (elicited using TTO methods).
Benefit valuation	Time-trade off or standard gamble	Yes. Where data was available (see above)
Source of preference data for valuation of changes in HRQL	Representative sample of the public	(See above)
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		Partially. One-way sensitivity analyses were not performed. Several scenario analyses were performed.
ADPKD = Autosomal Dominant Polycystic Kidney Disease; CS = company's submission; EQ-5D = European Quality of Life-5 Dimensions; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume; TTO = Time trade-off; UK = United Kingdom		

5.2.2 Model structure

The company submitted a de novo individual-patient state-transition model consisting of three health states (Figure 5.1). The TEMPO 3:4 trial is used primary source to inform the input parameters of the economic model.

Figure 5.1: Model structure
(adjusted version of the flow diagrams, Figures B13 and B14 presented in the CS[2])



ADPKD = autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; ESRD = end-stage renal disease

At the start of the model simulation, individual patient characteristics (age, gender, TKV and eGFR) are sampled from pre-defined distributions (Table 5.5). The eGFR value is subsequently used to update patients' CKD stage (Table 5.6). Patients' characteristics and CKD stage are updated at the end of each cycle. In case of CKD stage 5 (eGFR < 15 ml/min/1.73 m^2), patients transit from ADPKD to ESRD. Clinically significant kidney pain was the only complication explicitly incorporated and occurred in all CKD stages (except after kidney transplantation). The annual probability of significant kidney pain was independent on CKD stage and dependent on treatment (0.05 for Tolvaptan while it is 0.07 without Tolvaptan). The Company justified the exclusion of other complications given the lack of evidence supporting a difference in effect on these outcomes.

Table 5.5: Distributions to sample baseline patient characteristics

	Mean	Standard error	Distribution	Source
Current age (years)	38.70	0.19	Normal	TEMPO 3:4 trial
Sex (% female)	48.4%	1.3%	Beta	TEMPO 3:4 trial
eGFR (ml/min/1.73 m^2)	81.61	0.57	Normal	TEMPO 3:4 trial
TKV (ml)	1692.30	23.82	Normal	TEMPO 3:4 trial

eGFR = estimated glomerular filtration rate; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

Moreover, renal replacement therapy (RRT) would start at eGFR < 8.5 ml/min/1.73 m^2. RRT consists of conservative care (management to prolong kidney function and control symptoms of ESRD), haemodialysis (HD; either hospital HD, satellite HD or home HD), peritoneal dialysis (PD; either ambulatory or continuous ambulatory PD) or kidney transplantation (either from a living or deceased donor). The model allows for different RRT in subsequent cycles (although switching between dialysis modalities was not possible) and dialysis complications (for both HD and PD) in terms of both costs and disutilities were incorporated.

Replaced by erratum

Table 5.6: Definition of CKD stage

	Definition	Description[62]
CKD stage 1	eGFR ≥ 90 ml/min/1.73 m^2	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
CKD stage 2	eGFR ≥ 60 ml/min/1.73 m^2 to < 90 ml/min/1.73 m^2	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease
CKD stage 3	eGFR ≥ 30 ml/min/1.73 m^2 to < 60 ml/min/1.73 m^2	Moderately reduced kidney function
CKD stage 4	eGFR ≥ 15 ml/min/1.73 m^2 to < 30 ml/min/1.73 m^2	Severely reduced kidney function
CKD stage 5	eGFR < 15 ml/min/1.73 m^2	Very severe, or end-stage kidney failure
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate		

ERG comments: The company provided an overly complicated description of the model. This severely hampers the accessibility of the results and hence the interpretation of the conclusions.

The description of the model and the flow diagrams presented by the company (Figures B13 and B14 of the CS) are an overly complicated representation of the actual model. The model consists of three health states (ADPKD, ESRD and death) wherein different attributes are assigned to individual patients (age, sex, eGFR, TKV and CKD stage) which are updated at the end of each cycle (i.e. each year). The age and CKD stage attributes are used to incorporate age-specific and CKD stage specific input parameters (see CS Table B35). For patients in the ESRD health state, different treatments are incorporated in the economic model. The company submission is lacking a succinct description and graphical presentation of the model, decreasing its accessibility. Moreover, the company provides confusing statements regarding the type of model that is used. Although it seems that a Markov (i.e. state-transition model) is used (Section 7.2.2 of the company submission states that a *"patient-level, fixed-time increment stochastic simulation model"* is used), Section 7.2.3 of the CS compares the *"coded simulation model"* with a Markov model which implicitly suggests that the model used is not a Markov model.[2] The ERG constructed a new figure of the model structure to improve the description and accessibility of the model (Figure 5.1). Based on the ERG's assessment of the model, it is considered to be an individual-patient state-transition model[63] (i.e. individual-patient Markov model). The ERG agrees that this type of model is appropriate given the decision problem.

Besides the overly complicated and confusing model description provided by the company, and the exclusion of all adverse events except kidney pain (see also Section 5.2.6), the ERG regards the model structure as appropriate given the decision problem.

5.2.3 Population

The final scope[1] stated people with ADPKD as the population of interest. According to the Company, the proposed licensed indication is: *"adults with ADPKD who have stage 1 to 3 CKD at initiation of treatment and evidence of rapidly progressing disease"*. The company stated that this population is broadly in line with the inclusion criteria of TEMPO 3:4

(Section 6.3.3) and hence is was considered reasonable to base the modelled population on the overall baseline characteristics of TEMPO 3:4.[2]

ERG comments: The population considered in the economic model (Table 5.3) seems to correspond with the population stated in the final scope and the proposed licensed indication. It should however be noted that the TEMPO 3:4 trial (primary source for the economic model) included only patients aged 18-50 years while no age restriction was included in the final scope and the proposed licensed indication. Moreover, only a small proportion of the TEMP 3:4 trial population was from the UK (5%; 73 out of 1,445).

5.2.4 Interventions and comparators

The final scope[1] defined *"standard care in combination with Tolvaptan"* as the intervention and *"standard care including routine surveillance without Tolvaptan"* as the comparator. According to the CS[2], the titration schedule expected to be included in the licensed indication is as follows:

"The initial dosage of Tolvaptan in ADPKD is 60 mg per day as a split-dose regimen of 45+15 mg (45 mg taken upon waking and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg per day (60+30 mg) then to a target split-dose regimen of 120 mg per day (90+30 mg) if tolerated, with at least weekly intervals between titrations. Patients may down-titrate to lower doses based on tolerability".

The company stated that this description differs slightly from the TEMPO 3:4 trial titration schedule. The trial titration schedule required that titration was performed at precise weekly intervals to the maximum tolerated dose while the expected licensed indication wording allows for flexibility of the time interval between titrations. Moreover, the company stated that *"it is not possible to know whether the TEMPO 3:4 mean exposure will reflect the actual dosing seen in clinical practice, however it is the best and most reasonable assumption in light of the similarities of the titration schedules"*.

ERG comments: The intervention and comparator correspond with the final scope and the titration schedule in the TEMPO 3:4 trial seems to correspond to a large degree with the titration schedule expected to be included in the licensed indication.

5.2.5 Perspective, time horizon and discounting

The perspective considers all health effects on individuals and costs for NHS and Personal Social Services (CS, page 62). The model is designed to simulate disease progression in a cohort of patients with ADPKD over a lifetime horizon of up to 80 years (the maximum possible age of a simulated patient is 101 years) and a discount rate of 3.5% for utilities and costs is applied.

ERG comments: The perspective and discount rates are in line with the NICE reference case. The time horizon of up to 80 years after initiation of treatment (up to a maximum age of 101 years), assumed in the base case, is in effect lifetime.

5.2.6 Treatment effectiveness and extrapolation

Individual disease progression was modelled using an equation for TKV (equation 1: dependent on age, gender and baseline TKV) and an equation for eGFR (equation 2:

dependent on TKV in previous cycle). This means that TKV was used as an intermediate outcome to model eGFR, the primary clinical outcome in the economic model. Each model cycle (year), the patient characteristics at the end of the previous year are used to predict TKV and eGFR in the current cycle (year). The two equations were derived from TEMPO 3:4 patient level data. Baseline characteristics (age, gender, TKV and eGFR) were taken from the placebo arm of the TEMPO 3:4 trial. The regression analyses are described in Appendix 10.14 of the CS.[27]

Equation 1: $$\mathbf{TKV_{t+1} = \lambda + \alpha.age + \beta.Ln(TKV_t) + \gamma.sex + \delta.age.Ln(TKV_t)}$$

Where TKV = total kidney volume, t = time, β=TKV coefficient, α=age coefficient, γ=sex coefficient, δ=age:LnTKV$_{t+1}$ and λ= intercept.

Table 5.7: Baseline patient characteristics and changes in TKV and eGFR as observed in the placebo arm of TEMPO 3:4
(based on Table B27 of the CS[2])

Characteristic		**Placebo population n=484**	
Gender		**n**	**%**
Male		251	51.9%
Female		233	48.1%
TKV (ml)		**Mean**	**SD**
Baseline		1,667.5	873.1
Mean annual change		114.4	113.2
eGFR		**Mean**	**SD**
Baseline	CKD-EPI (ml/min/1.73 m^2)	82.14	22.73
	1/serum creatinine ([mg/mL]$^{-1}$)	104.30	33.87
Mean annual change	CKD-EPI (ml/min/1.73 m^2)	-3.568	4.495
	1/serum creatinine ([mg/ml]$^{-1}$)	-3.682	6.361

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; SD = standard deviation; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

Table 5.8: TKV progression equation coefficients as derived from TEMPO 3:4
(based on Table B28 of the CS[2])

	Coefficient estimate	**SE**	**t value**	**Pr(>|t|)**
Intercept (λ)	0.8375	1.13227	0.739	0.4601
Age (years) (α)	0.1107	0.0287	3.858	0.0001
Ln(Baseline TKV) (β)	0.8027	0.1556	5.159	0.0000
Sex (female=1,male=0) (γ)	−0.0486	0.0266	−1.827	0.0684
Age: Ln(Baseline TKV) (δ)	−0.0160	0.0039	−4.058	0.0001

SE = standard error; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

The principle outcome of clinical interest is renal function, measured in TEMPO 3:4 as the rate of change in eGFR. eGFR was estimated and not measured for reasons of practicality (complex, expensive, difficult to perform in clinical practice, associated with error). Reciprocal of serum creatinine was used to estimate eGFR in the base case. In a scenario analysis eGFR calculated with CKD-EPI was used.

Equation 2: $$eGFR_{t+1} = \lambda + \beta.\ln(TKV_t)$$

Where eGFR = estimated glomerular filtration rate, TKV = total kidney volume, t = time, β *=* $Ln(TKV_t)$ *coefficient and* λ *= intercept.*

Table 5.9: eGFR progression equation coefficients as derived from TEMPO 3:4
(based on Table B30 of the CS[2])

	Coefficient estimate	SE	t value	Pr(>|t|)
1/serum creatinine				
Intercept (λ)	4.48474	0.08244	54.398	< 2e-16
ln(TKV) (β)	-0.06227	0.01124	-5.539	5.17e-08
CKD-EPI				
Intercept (λ)	4.46867	0.07616	58.672	< 2e-16
ln(TKV) (β)	−0.06002	0.01039	-5.779	1.4E-08

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; SE = standard error; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

The effectiveness of tolvaptan was modelled by directly adjusting annual eGFR decline, as observed in TEMPO 3:4 over the three year trial period, and not by introducing TKV as an intermediate outcome (TKV was the primary outcome of TEMPO 3:4). The company justifies this by arguing that the tolvaptan modifies disease progression, and as a consequence the relationship between eGFR and TKV may be different in patients receiving tolvaptan than in patients who do not receive active treatment. The treatment effect on eGFR was assumed to continue for as long as patients received tolvaptan.

Table 5.10: Annual eGFR decline, as observed during TEMPO 3:4
(based on Table B32 of the CS[2])

eGFR measurement	Treatment Arm		Control Arm		% reduction	
	Mean	SE	Mean	SE	Mean	SE
1/serum creatinine	-2.609	0.337	-3.812	0.295	31.6%	7.77%
CKD-Epi	-2.723	0.263	-3.700	0.209	26.4%	5.24%

Note: SE assumed equal to SE associated with reported unadjusted rate of change per year.

Data obtained from TEMPO 3:4 Clinical Study Report[29] Table CT – 6.1.4.1 (ITT population; estimated by CKD-EPI formula); Excluding observations deemed unreliable by investigators, within treatment period) and Table CT – 6.1.1.1 (ITT population; estimated by 100/Serum Creatinine (1/(mg/dl); Excluding observations deemed unreliable by investigators, within treatment period).

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; ITT = Intention to Treat; SE = standard error; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes

For the first three years, in the model treatment discontinuation was based on the observed annual discontinuation rate for any cause in TEMPO 3:4 (15.30%, 6.51%, 2.89%, respectively). After three years a discontinuation rate of 0.5% per annum was assumed. The company justifies this by stating it is *"broadly in line with the trend seen over the course of the trial"*.[2] In a scenario analysis this was varied between 0 and 2%.

With the exception of clinically significant pain, adverse events were not explicitly modelled depending on disease progression, but assumed to be incorporated in the costs and utilities assigned to the CKD and ESRD states. The probability of clinically significant pain was derived from the TEMPO 3:4 study, and applied to all pre-ESRD CKD stages. Patients who discontinued tolvaptan received the control arm probability of clinically significant pain.

Table 5.11: Annual probability of clinically significant kidney pain
(based on Table B35 of the CS[2])

Annual probability of significant kidney pain events	Value	SE
Placebo (no active treatment) arm		
CKD stage 1	0.07	0.004
CKD stage 2	0.07	0.004
CKD stage 3	0.07	0.004
CKD stage 4	0.07	0.004
Tolvaptan arm		
CKD stage 1	0.05	0.003
CKD stage 2	0.05	0.003
CKD stage 3	0.05	0.003
CKD stage 4	0.05	0.003
Placebo (no active treatment) arm / Tolvaptan arm		
CKD stage 5/ESRD	0.07	0.004
CKD = chronic kidney disease; ESRD = End-Stage Renal Disease; SE = standard error		

All-cause mortality was modelled using age and gender specific life tables from England and Wales.[64] Patients in ESRD are subject to a specific mortality risk, based on age-specific (18-64 and 65+) observed dialysis survival rates, using a Weibull model.[65] In the model, each cycle, the greater of the ESRD-specific and all-cause mortality rates was applied. Time-dependent mortality after transplant was based on the NHS transplant survival report.[66]

Table 5.12: Observed dialysis survival rates and the parameters of the Weibull curves
(based on Table B36 of the CS[2])

Observed survival (years)	Age 18-64	Age 65+
1	0.934	0.775
2	0.866	0.636
3	0.808	0.528
4	0.773	0.409
5	0.734	0.325
6	0.685	0.238

Observed survival (years)	Age 18-64	Age 65+
7	0.626	0.169
8	0.577	0.135
9	0.544	0.089
10	0.499	0.069
Parameters of fitted Weibull curves		
Scale	0.814	0.841
Shape	0.111	0.379

Table 5.13: Observed patient survival rates of transplant recipients and the parameters of resultant Weibull curves
(based on Table B37 of the CS[2])

Donor	Living	Deceased[a]
Observed Survival	Patient	Patient
Year 1	0.99	0.96
Year 2	0.98	0.94
Year 5	0.96	0.88
Year 10	0.90	0.72
Parameters of fitted Weibull curves		
Scale	0.012	0.036
Shape	0.976	1.000

[a] Patient survival rates associated with non-living donors were derived using a weighted average of brainstem dead and circulatory death donor rates, according to the proportion of kidney only transplants received from brainstem dead donors (61%) and circulatory death donors (39%) carried out between 1st April 2012 and 31st March 2013.

ERG comment: The regression analyses for disease progression based on TKV and eGFR were not described in detail (unclear which covariates were initially examined, why only age and gender are included in the final models, why gender was included to predict TKV progression despite it is not statistically significant, whether alternative models for the data were tested). These analyses assume that the rates of eGFR decline and TKV growth are constant. This was however not tested. As eGFR is predicted from TKV, and TKV is dependent on age, eGFR decline is probably not fully constant over time. Plots of predicted eGFR in the model show small signs of non-constant slope. The diagnostics plots for the regression models seemed satisfactory. The external validity of the regression models is described in Section 5.2.12.

eGFR was estimated, using reciprocal of serum creatinine and CKD-EPI, and not measured for reasons of practicality. The ERG thinks this introduced uncertainty, but the approach seems justifiable.

The treatment effect seen in TEMPO 3:4 was directly applied to 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.[2] There is however little evidence to sustain this hypothesis. In response to clarification question C3 the company performed a scenario analysis for the base case with the treatment effect directly applied to TKV (and not applied to eGFR). See Section 5.2.10 for the results of this scenario analysis.

The company assumes no decline of treatment effect based on the 3-year follow up in TEMPO 3:4, extended to five year data based on interim analyses of TEMPO 4:4. There is however little evidence to sustain this hypothesis; the opposite may also hold (see also Section 4.2.1). It is uncertain whether the treatment effect will sustain or decrease. In addition, in response to clarification question C15, the company provided the results of a scenario analysis with a treatment effect of 50% and 10% after three years.[9] See Section 5.2.10 for the results of this scenario analysis.

Evidence to underpin the estimated annual treatment discontinuation after year 3 (0.5%) was scarce. The company explored alternative estimates (0%, 2%) in a sensitivity analysis. The ERG considered this to be a small range, and conducted an exploratory analysis with a larger range (see Section 5.3).

Of all adverse events recorded in TEMPO 3:4, only clinically significant pain was modelled as a treatment dependent parameter. The ERG believes this may have introduced a downward bias to the ICER, as it is assumed that the difference in kidney pain as observed in TEMPO 3:4 is independent from the effect of tolvaptan on disease progression. This is questionable, as pain is a known symptom of chronic kidney disease, increasing with disease progression.[67] The separate modelling of pain may have led to a double counting. For more details see Section 5.2.7 on health-related quality of life.

Hepatotoxicity of tolvaptan was not included in the model, although the potential for hepatotoxicity of tolvaptan was noted on page 128 of the CS:

"The most notable safety issue associated with tolvaptan use, which was newly identified in the pivotal trial TEMPO 3:4, was the potential for hepatotoxicity."

In the TEMPO studies, three Hy's Law cases were found. 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 aetiologies other than the drug have been ruled out. Finding three 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.[16] In clarification question C8 the ERG requested a scenario analysis where the costs and quality of life impact of the occurrence of DILI is explored. The company responded: *"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".[9]

The ERG believes that the assumption that hepatotoxicity does not lead to any costs or health loss is unsustainable. At least two of the Hy's Law cases were admitted to hospital, two weeks and 36 days, respectively.[29] It is uncertain whether the proposed monitoring schedule will totally prevent (severe) cases of hepatoxicity as well as the costs and health consequences associated with this. Therefore, the ERG performed an exploratory analysis, incorporating consequences of hepatoxicity as a result of tolvaptan (see Section 5.3).

Mortality was not ADPKD specific for CKD stages 1-4, this could be an underestimation of the mortality risk. In response to clarification question C10[9], the company gave the following justification for this: *"…no [mortality] data was identified that was considered appropriate to model ADPKD specific mortality. The study by Florijn et al.*[68] *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.[68] 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".[9]

The ERG agrees that evidence regarding ADPKD specific mortality is scarce. However, the cost-effectiveness study by Erickson and colleagues[61] included ADPKD specific mortality and the assumption that mortality risk in ADPKD patients is equal to all-cause mortality may be in favour of tolvaptan, because patients receiving tolvaptan spend more time in CKD stage one to four than patients receiving standard care. The ERG explored a higher mortality in CKD stages 1-4 in an exploratory analysis (Section 5.3).

Replaced by erratum

5.2.7 Health related quality of life

In Section 7.4 of the CS the measurement and valuation of health (related quality of life) effects are described. It is stated that ADPKD results in an inevitable progressive increase in kidney volume. Prior to reaching ESRD, patients may suffer acute, debilitating pain due to cyst rupture or cyst infection, and/or chronic/nagging pain (i.e. daily pain lasting more than 4 to 6 weeks) due to increased renal volume. Furthermore, patients may develop other complications associated with ADPKD such as hypertension, hernia, microalbuminuria, gross haematuria, nephrolithiasis, proteinuria, anaemia and gout. Psychological impacts, such as depression and guilt at passing the disease on to children, also negatively impact.[69]

HRQoL is substantially impaired when developing ESRD. In addition to experiencing debilitating pain and other complications, most patients are required to attend hospital for haemodialysis three times a week or undergo peritoneal dialysis. Patients may also undergo surgery for kidney transplantation carrying a risk of transplant rejection and death, and may lead to complications including bleeding, infection, vascular thrombosis, and post-transplant lymphoproliferative disorder.

In addition, it is also mentioned that ADPKD patients experience potentially fatal complications, most notably cardiovascular disease, infection (e.g. renal cyst infection, urinary tract infection) and complications of dialysis (e.g. infected catheter or haemodialysis fistula) that occur during ESRD.

Review of quality of life studies

A systematic review of the literature was conducted to identify health state utility values (HSUVs) for patients with ADPKD or ESRD. The review identified 23 studies including 17 full papers, five conference abstracts and one congress poster. One further study also was identified from Lee et al 2012[70] bringing the total number of studies to 24. Details of the identified papers are given in Table B40 of the CS.[2]

No specific studies with HSUV estimates for patients with ADPKD were identified. However, the search strategy performed by the company identified several HSUV estimates for patients with CKD and ESRD associated with any cause. Two studies, from Miskulin et al 2014[69] and Suwabe et al 2013[71] were in particular identified and chosen which reported Short Form (36) Health Survey (SF-36) data for ADPKD patients. Miskulin found that ADPKD patients with CKD stage 1 to 3 had generally similar or higher SF-36 summary scores compared with age-matched population normative data while Suwabe reported that the mean physical component summary score (PCS) for ADPKD patients receiving dialysis was similar to that reported in two studies for Malaysian patients Ying 2014[72] and Yusop 2013[73] receiving HD for all-cause ESRD.

The systematic review identified also 11 studies that presented EQ-5D derived utility weights.[22, 74-83] Of these, two studies were performed in UK populations and used the UK EQ-5D value set (Lee et al 2005[22] and Neri et al 2012[81]). Lee et al 2005[22] presented estimates for CKD stage 5 (pre-dialysis, haemodialysis, peritoneal dialysis, and functional transplant.) while Neri et al 2012[81] presented estimates for ESRD patients with a kidney transplant with

various degrees of renal function (CKD stage 1-5). No EQ-5D UK valued estimates were identified by the systematic review for CKD stages 1 to 4.

ERG comment: The ERG considers the HRQoL review as appropriate. The quality of the search strategy is discussed in Section 4.1.1 of this report.

Modelling of health related quality of life

As mentioned above, the HRQoL review did not identify studies with HSUV estimates for patients with ADPKD. The company's base case analysis assumed based on the studies from Miskulin et al 2014[69] and Suwabe et al 2013[71] that HRQoL for ADPKD patients with early-stage CKD (i.e. CKD stages 1 and 2) is similar to the general population at the same age and that HSUVs for later-stage CKD and ESRD measured in the overall population are relevant for ADPKD patients at the same stage of renal disease.

Given the lack of estimates for CKD stages 1 to 4 that were measured using EQ-5D in a UK ADPKD population and valued using the UK general population value set, the CS explored EQ-5D for CKDs 1 to 4 measured in other populations and from estimates elicited using time trade-off methods. The explored studies included:

- Wu and Yang 2014[83] which reported estimates for CKD 3–4 measured using EQ-5D in a Chinese population and valued using the UK value set. This study was not selected for the base-case analysis as separate estimates for CKD stages 3 and 4 were not reported and other studies have demonstrated a reduction in HRQoL for CKD stage 4 compared with stage 3. Another argument for not selecting this study was that Asian populations may respond differently to EQ-5D compared to UK populations.
- Lee et al 2012[70] which reported estimates for CKD stage 1, 2 and 3 measured using EQ-5D in a Korean population and valued using the Korean value set. The study was not selected for the base-case analysis as CKD stage 4 estimates were not available and because of the Korean valuation.
- Rajan et al 2013[82] mapped SF-36 (SF-12) data from the 1999 US Large Veterans Health Survey, including 67,963 patients with CKD and diabetes, to EQ-5D. The study was not selected for the base-case analysis as utility estimates for CKD 0–1 were substantially lower than expected for ADPKD.
- Gorodetskaya et al 2005[84] reported estimates for CKD stage 1–2, 3, 4 and 5 (no dialysis, haemodialysis and all) using time trade-off methods in a sample of US patients. This study was selected for the base-case analysis

At the end, estimates from Gorodetskaya et al 2005[84] were chosen in the base case for CKD stage 1–2, 3, 4 while estimates from Wu and Yang 2014[83] were tested in sensitivity analysis. The estimates reported by Lee et al 2005[22] (EQ-5D data from UK sample on CKD stage 5 pre-dialysis, haemodialysis, peritoneal dialysis, and functional transplant) were selected in the base-case analysis for CKD stage 5 (after year 1). A complete overview of quality-of-life values for the base-case cost-effectiveness analysis is given in Table 5.14.

The base-case analysis assumes no disutilities for tolvaptan treatment. The CS argues this is based on the fact that *"…no evidence that HRQL is reduced by tolvaptan-related aquaresis"* and that "… *patients who cannot tolerate any negative impact of tolvaptan-related adverse*

events are within the group which discontinue treatment".[2] A separate sensitivity analysis explored a treatment disutility of 0.0123 as in Sullivan et al 2011[85] which was applied for the duration of tolvaptan treatment.

Table 5.14: Summary of quality-of-life values for the base-case cost-effectiveness analysis
(based on Table B41 of the CS[2])

Health State	Utility value[a]		Disutility vs. general population value		Reference in submission	Justification
	Mean	SE	Mean	SE		
CKD stage 1 & CKD stage 2	0.900	0.036	0.000[b]	-	Gorodetskaya 2005[84]	TTO, see text
CKD stage 3	0.870	0.034	0.030[c]	0.050[d]		
CKD stage 4	0.850	0.029	0.050[c]	0.046[d]		
CKD stage 5, pre-dialysis	0.688[e]	0.068[f]	0.222[g]	0.069[h]	Lee 2005[70]	EQ-5D, UK sample and value set
ESRD, Conservative Care	0.558[e]	0.041[f]	0.352[g]	0.041[h]		
ESRD, Hospital or Satellite HD	0.558[e]	0.041[f]	0.352[g]	0.041[h]		
ESRD, Home HD	0.558[e]	0.041[f]	0.352[g]	0.041[h]		
ESRD, PD	0.648[e]	0.048[f]	0.262[g]	0.049[h]		
Transplant Y1	0.762[i]	0.070[j]	0.148[i]	0.070[j]	Clinical opinion	No data were available
Transplant Y2+	0.828[e]	0.022[f]	0.082[g]	0.023[h]	Lee 2005[70]	EQ-5D, UK sample and value set
Disutility associated with treatment	-	-	0.000	-	Assumption (see Section 7.3.8 of the CS[2])	Impact counter-balanced by reduction in ADPKD complications
Disutility associated with HD Complications	-	-	0.060	0.009[k]	NICE CG125[86]	Consistency with CG125
Disutility associated with PD Complications	-	-	0.060	0.009[k]	NICE CG125[86]	Consistency with CG125
Disutility associated with significant pain			0.051	0.008	Dolan 1997[87]	EQ-5D calculated value
Age-specific general population values						
35-44	0.91	-	-	-	Centre for Health	HRQL declines

Health State	Utility value[a]		Disutility vs. general population value		Reference in submission	Justification
	Mean	SE	Mean	SE		
45-54	0.85	-	-	-	Economics 1999[88]	with increasing age
55-64	0.80	-	-	-		
65-74	0.78	-	-	-		
≥75	0.73	-	-	-		

CG = Clinical guideline; CKD = chronic kidney disease; EQ-5D = European Quality of Life-5 Dimensions; ESRD = End-Stage Renal Disease; HD = Haemodialysis; HRQoL = Health-related quality of life; HSUV = Health state utility values; PD = Peritoneal dialysis; SE = standard error; TTO = Time trade-off; UK = United Kingdom

[a] HSUV at start of model time (shown for reference only; the model applied the disutility vs general population value)

[b] Assumes CKD 1 & 2 are equivalent to the general population (Wu and Yang 2014[83]; Lee 2012[70]; Gorodetskaya 2005[84]; Centre for Health Economics 1999[88]; supported by clinical expert opinion)

[c] Calculated by subtracting the HSUV from the value for CKD 1

[d] Calculated as follows:

[e] Adjusted for age as the mean age at the start of model time is younger than that for the ESRD population in the study by Lee and colleagues. Adjustment of the value at the start of model time is necessary as the model assumes utility declines with age. With the adjustment, the value at the model time in which ESRD occurs is similar to that reported by Lee and colleagues. Mean age at start of model = 39 years (general population utility = 0.910). Mean age in Lee 2005[70]: men = 58.2 years; women = 55.5 years; 41.1% female. General population utility for this population = 0.792. HSUVs adjusted by 0.910 – 0.792 = 0.118.

[f] As mean was adjusted for age, the SE was assumed to be the same percentage of the mean for the original and adjusted values

[g] Calculated as general population value (0.91) minus health state value

[h] Calculated as follows: where is the standard error for the general population HSUV estimate.

[i] The decrement for yr1 was estimated be 1.8 times greater than for years 2 and beyond based on interviews with 4 clinical experts, November 2014. See Section 7.4.10 of the CS[2]

[j] Assumption (highest of other values, rounded)

[k] Assumed 15% of mean value

The disutility associated with dialysis complications was based on CG125. The disutility associated with a significant pain event was estimated from a study reported by Dolan et al 1997.[87]

The model utilised baseline age-adjusted utilities (general population values (Centre for Health Economics 1999[88])) with utility decrements applied for the various health states/events in the model.

All HSUVs have been expressed as disutility values. Utility inputs applied for each health state or event in the model were defined as the absolute disutility associated with that specific health state relative to the general population for the same age. The utilities for CKD stages 1 and 2 were assumed to be the same as for the general population. For each year, the utilities applied to simulated patients were equal to the age-adjusted baseline utility value (from the general population) minus the relevant health state disutility. The modelling approach adopted allowed for multiple utilities that could apply at a given time point for a simulated patient, and all utilities are applied additively. The utility decrement represents the average

for patients in that CKD stage. Table 5.15 shows that as patients' age increased with time in the model the utility value declined in line with general population estimates.

Table 5.15: HSUVs for CKD Stage 1 and 2 by age group
(based on Table B42 of the CS[2])

Age	HSUV
25 – 34 years	0.93
35 – 44 years	0.91
45 – 54 years	0.85
55 – 64 years	0.80
65 – 74 years	0.78
75 years and older	0.73

Source: Centre for Health Economics 1999[88]
CKD = chronic kidney disease; CS = company's submission; HSUV = Health state utility values

The validation of the HSUVs used in the model was done through asking four UK clinical experts (three nephrologists with experience of ADPKD management and a clinical nurse specialist) who were asked to rank the health states in ascending order of severity for a typical ADPKD patient with no complications. The results of this ranking exercise broadly support the rank order of the HSUVs selected for the base-case analysis (Table 5.16).

Table 5.16: Health state ranking by degree of severity (four UK clinical experts)
(based on Table B43 of the CS[2])

Health states	Mean Ranking (0 = best; 11.5 = worst)
CKD 1	0.0
CKD 2	0.8
CKD 3	2.0
Transplant - year 2 and beyond	2.8
CKD 4	4.8
Transplant - year 1	5.5
Home haemodialysis	6.8
Peritoneal dialysis	7.0
CKD 5, pre-dialysis	7.8
Hospital/Satellite haemodialysis	9.3
Conservative Care	9.3
Clinically significant pain	10.7
Peritoneal dialysis complications	10.8
Haemodialysis complications	11.5

CKD = Chronic kidney disease; CS = company's submission

ERG comment: The ERG considers the selection of the utility values in the base case scenario from Gorodetskaya et al 2005[84] (CKD stages 1-4) and Lee et al 2005[22] (CKD stage 5 pre-dialysis, haemodialysis, peritoneal dialysis, and functional transplant) as appropriate. Yet, no explanations were given in the submission on why HSUV estimates from Miskulin et al 2014[69] and Suwabe et al 2013[71] were not explored in sensitivity analyses. However, sensitivity analysis performed by the company showed that using the utility from Wu and Yang 2014[83] for CKD 3 and 4 did not impact the ICERs substantially (the ICER including the

PAS increased from £34,769 in the base case analysis to £35,211). However, the ERG notes that the way the (dis)utilities are included in the model are prone to possible errors and double counting. The company mentions that *"For each year, the utilities applied to simulated patients were equal to the age-adjusted baseline minus the relevant health state disutility.." and that "… multiple utilities that could apply at a given time point for a simulated patient, and all utilities are applied additively"* (pg. 200, CS).[2] Applying multiple disutility estimates additively to the age-adjusted baseline may result in lower utility absolute values for a certain health state. Moreover, treating the decrement associated with the adverse event as a constant value may be inappropriate and subtracting several utility decrements from the baseline separately may result in double counting errors.[89]

The ERG considers that including a disutility only for kidney pain (and therefore potentially favouring the tolvaptan arm) is not good practice (as it excludes other AEs, see also section below on HRQoL of AEs). Moreover, if this is done on top of the treatment effect (i.e. patients are already assumed to have on average a lower CKD stage because of the tolvaptan treatment), it may create risks of double counting. The ERG thinks this is not a conservative scenario and therefore has set this equal for both arms in the model in its base case analysis.

In addition, the ERG thinks that the (0.06) absolute value applied for disutility because of HD and PD complications is exaggerated and favours the tolvaptan arm. The CS states that this is consistent with CG125, i.e. 6% reduction from baseline based on Sennfalt et al 2002.[90] Yet, both in Sennfalt et al 2002[90] and in CG125[86] the absolute differences in utilities vary from 0.02 to 0.03 in absolute value. This is because the baseline value for calculating such differences are lower than the baseline HSUV at the beginning of the model. Giving this the ERG believes that the conservative approach is to set the absolute value of this disutility to 0.02 as this is more in line with Sennfalt et al 2002[90] and NICE CG125[86]. The ERG has explored this in its base-case analysis.

HRQoL of Adverse Events

In the base-case analysis of the economic model it was assumed that *"… adverse events associated with tolvaptan treatment do not affect HRQL"* (CS, page 205[2]) and therefore no adverse events (AEs) (besides kidney pain) were incorporated in the model. Events which were more common in the tolvaptan arm were the aquaretic effects of tolvaptan (polyuria, nocturia and pollakiuria). The CS argues that there is no evidence that tolvaptan-related aquaresis impacts HRQoL and the incidence of these events declined markedly after the first three months of treatment being similar to that of the placebo arm.

Other adverse events more common in patients receiving tolvaptan included diarrhoea, fatigue, dizziness and polydipsia. The CS argues that many of these are already common in ADPKD patients not receiving active treatment, and patients who cannot tolerate the adverse effects are expected to discontinue treatment.

ERG comment: In its request for clarification letter, the ERG has pointed out that Tables B18 and B19 in Section 6.9.2 of the submission show that numbers and percentages of patients with serious treatment-emergent AEs as well as the most common AEs and serious AEs 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. The ERG requested an appropriate justification of this and a scenario analysis for the base case incorporating treatment dependent AEs and related effects on HRQoL.

In its response to the clarification questions[9] the company has declined the request for a scenario analysis incorporating treatment dependent AEs and related effects on HRQoL based on the argument that *" … 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"* (page 29 of the response to the clarification questions[9]).

Given the different AE profiles and the exclusion of AE other than kidney pain in the economic model, the ERG would prefer a conservative base case assuming a disutility of 0.0123 for being on tolvaptan treatment.

5.2.8 Resources and costs

Categories considered for resource utilisation and costs were: costs of intervention and comparators, and health-state costs. Adverse events associated with tolvaptan treatment were not explicitly modelled as the costs associated with AEs were assumed to be captured within the CKD stage specific and ESRD costs. Estimations by clinical experts were used for the following resource uses: (i) additional visits and tests for patients receiving tolvaptan treatment (on top of those received currently by patients receiving no active treatment) and (ii) management of patients with CKD stage 1 and 2.

Two separate systematic literature reviews were conducted to identify cost and resource use in patients with ADPKD and ESRD. No further studies reporting estimates which were more appropriate for the economic model (other than those referenced in Section 7.5.1 of the CS [2]) were identified.

Costs of intervention and comparators

Intervention price - The base case analyses presented in the [redacted] The dose received in the TEMPO 3:4 trial (presented in Section 6.9 of the submission) are therefore not used in the model.

The cost of treatment was applied up to and including the year of discontinuation. A weighting factor (derived from the timings of discontinuation in the TEMPO 3:4 clinical study report[29]) was applied to the cost of treatment in the year of discontinuation to reflect the timing of discontinuation. For the first three cycles (years) this was based on the timing of discontinuation observed in TEMPO 3:4 (0.39, 0.59, and 0.68, respectively). For cycle 4 and beyond a weighting of 0.50 was assumed (effectively applying the half-cycle correction for cycle 4 and beyond).

ERG comment: The ERG thinks that the application of the half-cycle and weighting as such is appropriate and does not lead to a double correction to treatment costs.

Additional monitoring **-** Patients receiving tolvaptan require additional monitoring. The monitoring in the economic model include: (i) liver function test performed every month for the first 18 months and every three months thereafter, (ii) two additional consultant visits in their first year of treatment and one additional consultant visit in their second year of treatment for patients on tolvaptan, (iii) additional consultant time to review liver function test results and issue prescriptions. The model applies the cost of additional resources that are expected to be required for tolvaptan patients, in addition to those associated with current monitoring, as presented in Table 5.17. The cost for consultant visits and consultation with a specialist nurse were calculated from values reported in Unit Costs of Health and Social Care (Curtis 2014).[91] The remaining costs were based on NHS Reference Costs (Department of Health, 2012-13).[92]

ERG comment: in its request for clarification, the ERG has requested a proposed treatment pathway for tolvaptan including monthly monitoring of the liver function and possible transplantation required. The company in its response has provided a treatment pathway in line with the requirements of the anticipated final SmPC (response to question B2 on page 5-6).[9] However, as it is clear from this treatment pathway, increased frequencies of hepatologist consultations and monitoring of the patient can be necessary if signs of liver function are abnormal or if there are any other signs of liver injury are seen: *"…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 … 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"* (Response to question B2 on page 5-6).[9]. Therefore, the ERG has explored the effect of additional costs due to (i) assuming that 4.4% of the patients (patients with ALT>3 as in Table 8 of the response to the clarification questions[9]) will need more monitoring (doubling the monitoring for these patients) and (ii) assuming that patients after the second year need an extra consultation visit given the possible AEs. The ERG calculation was based on the unit costs associated with the technology as used in the economic model (Table B45 of the CS[2]) and the resulting costs for years 1, 2 and the subsequent years were £612.47, £379.47 and £262.29 respectively.

Table 5.17: Unit costs associated with the technology in the economic model
(based on Table B45 of the CS[2])

Items	Unit cost	Source	Annual frequency (in addition to standard care)			Ref. in submission
			Year 1	Year 2	Subsequent years	
Technology cost	*NHS list price* £43.15 per patient per day £1,208.20 per 28-day pack *PAS discount ([redacted])* £[redacted] per patient per day £[redacted] per 28-day pack	Otsuka, data on file	Same annual cost is applied in all model years			Section 1.1
Consultant visits	£139.00	PSSRU, 2013 - page 245	2	1	0	Text in this section
Consultant Review of LFT (10 minute review)	£23.17	PSSRU, 2013 - page 245	11	8	4	Text in this section -
Biochemistry test	£1.25	DAPS04 - NHS Reference Costs, 2012-13	11	8	4	Text in this section
Phlebotomy	£3.64	DAPS08 - NHS Reference Costs, 2012-13	11	8	4	Text in this section
Total cost in addition to the technology cost			**£586.57**	**£363.42**	**£112.21**	

DAPS = Direct Access: Pathology Services; LFT = liver function test; N/A = not available; NHS = National Health Service; PAS = patient access scheme; PSSRU = Personal Social Services Research Unit

CKD stage costs

The annual costs incurred by patients in CKD stages 1 to 4 are presented in Table 5.18. All patients incur the same health state costs while in a given health state, regardless of whether they are currently receiving tolvaptan, have discontinued tolvaptan or are in the no active treatment arm. Patients in these health states who are receiving treatment with tolvaptan also incur the treatment and monitoring costs presented in Table 5.17 (above).

Table 5.18: List of costs in the ADPKD health state
(based on Table B46 of the CS[2])

Health states	Annual cost	Reference in submission
CKD stage 1	£171.89	Text in Section 7.5.6 of CS
CKD stage 2	£171.89	Text in Section 7.5.6 of CS
CKD stage 3	£1,436.16	Text in Section 7.5.6 of CS
CKD stage 4	£3,357.65	Text in Section 7.5.6 of CS
Clinically significant pain	£648.21	Text in Section 7.5.6 of CS
CKD = chronic kidney disease; CS = company's submission		

The annual cost of £171.89 which is incurred for patients in CKD stages 1 and 2 was calculated as the sum of one consultant nephrologist visit (PSSRU, 2013)[91], one consultation with a specialist nurse (PSSRU, 2013)[91], one biochemistry test (DAPS04 – NHS Reference Costs, 2012-13)[92], one haematology test (DAPS05 – NHS Reference Costs, 2012-13)[92], and one phlebotomy (DAPS08 – NHS Reference Costs, 2012-13)[92]. The resource use was based on clinical opinion. The cost of ultrasound was excluded because it is common to all patients at referral (NICE CG 182).[17]

The annual cost of £3,357.65 which is incurred for patients in CKD stage 4, was calculated from a cost estimate for CKD stage 3 and 4 presented in NICE CG182[17] (which in turn were based on NICE CG73[93]), inflated to 2013 values as described in Section 7.5.2 of the CS.[2] Management costs for CKD stage 3 are expected to be lower than for stage 4. To estimate the model value for CKD stage 3, the calculated cost for stage 4 was adjusted using the ratio of costs for stage 3 and stage 4 from the medical record abstraction study Chamberlain et al 2014.[94]

The cost of a significant pain event used in the model was taken from the NHS Reference Costs (2012/13)[92]; Healthcare Resource Groups (HRG) AB04Z, major pain procedures, non-elective inpatient short stay, general medicine. The rationale for not modelling other ADPKD complication (such as hypertension, hernia, microalbuminuria, gross haematuria, nephrolithiasis, proteinuria, anaemia and gout) apart from the kidney pain was based on the lack of evidence supporting a (statistically significant) difference between arms observed in the TEMPO 3:4 trial.

Patients who reach CKD stage 5/ESRD and do not receive treatment immediately incur an annual cost associated with this pre-dialysis stage. A complete list of costs the ESRD module is given in Table 5.19.

Those patients who receive conservative care at the onset of ESRD or following graft failure, incur an annual cost associated with such management equivalent to that of the pre-dialysis stage noted above.

Costs associated with dialysis include costs for vascular access (NHS Reference costs 2012/13[92]), dialysis and complications (NICE CG125)[86], which differ according to whether a patient undergoes peritoneal dialysis (PD) or haemodialysis (HD). The annual cost of dialysis is defined by modality: hospital HD, satellite HD, home HD, automated PD (APD), or continuous ambulatory PD (CAPD). The annual cost estimate for each modality was inflated from a study reported by Baboolal et al 2008.[95]

If a patient receives a kidney transplant, they incur a one-off cost associated with the transplant operation (NHS Reference costs 2012/13[92]) and the transplant service (e.g. transport of the organ), differentiated by the type of donor (living or deceased). In each subsequent year, patients incur an annual cost associated with the maintenance of the transplant (Kerr et al 2012).[96] Maintenance costs include treatment with immunosuppressive drugs, which patients are required to receive for the rest of their lives, or at least long-term (NICE TA85[97]). Following graft failure, patients are assumed to no longer incur any transplant-related maintenance costs, although surviving patients may incur costs of care required as a result of graft failure, such as dialysis or conservative care. Costs associated with organ donation and transplantation activities conducted by NHS Blood and Transplant during 2011–2012.[98] These costs were then apportioned to each transplant event occurring during 2011–2012, to obtain a cost per transplant.

ERG Comment: the ERG considers the use of the references from NICE CG73 and NICE CG182 for CKD stage 4. However the ERG questions the adjustment of CKD stage 3 based on a single (multinational) reference found from the systematic review[94] for which *"…patients may not be fully representative sample of the population in the UK"* (pg. 210 of the CS[2]). The ERG thinks that this is not appropriate use of costs and does not represent a conservative alternative. Moreover this is not in line with previous NICE clinical guidelines (NICE CG182).[17] An alternative here would be to use the inflated costs for CKD stage 3 as in NICE CG182. The ERG has adapted this in its base case analysis (Section 5.3).

The ERG considers that including costs only for kidney pain (and therefore potentially favouring the tolvaptan arm) is not good practice (as it excludes other AEs, see also section above on HRQoL of AEs) and therefore has considered an alternative base case wherein the kidney pain probability was assumed equal for both arms

The ERG considers the use of the approach in estimating the costs of the dialysis as appropriate.

The background management costs and the maintenance costs for post kidney transplants may include similar resource use and hence a double counting risk can arise. Kerr et al 2012[96] describe maintenance costs mostly as post-transplant OP visits and immuno-suppression. Therefore, the ERG has run a separate sensitivity analysis where it subtracted the background management costs from the maintenance costs for all years (see Section 5.3).

Table 5.19: List of costs in the ESRD module
(based on Table B47 of the CS[2])

Health states	Cost item	Annual cost	% Patients	Source: Cost (% Patients)[a]
CKD stage 5/ ESRD, pre-dialysis	Background management	£5,238.59	100%	NICE CG182[17] appendix, inflated to 2012/13
Conservative care	Background management	£5,238.59	100%	Assumed equal to CKD stage 5
Haemodialysis	Background management Vascular access Hospital HD Satellite HD Home HD HD complications	£5,238.59 £1,246.10 £39,397.47 £36,749.45 £23,357.48 £5,288.85	100% 100% 39.1%[c] 42.9%[c] 4.0%[c] 6.0%	Assumed equal to CKD stage 5 NHS Reference costs 2012/13[92] Baboolal 2008[95], inflated to 2012/13 (Renal Association, 2013[65]) Baboolal 2008[95], inflated to 2012/13 (Renal Association, 2013[65]) Baboolal 2008[95], inflated to 2012/13 (Renal Association, 2013[65]) NICE CG125[86] / Kirby 2001[99], inflated to 2012/13 (NICE CG125[86] / Evans 2010[100]
Peritoneal dialysis	Background management Catheter placement ADP CAPD PD complications	£5,238.59 £1,049.46 £24,359.77 £17,514.74 £3,242.06	100% 100% 7.1%[c] 6.9%[c] 21.4%	Assumed equal to CKD stage 5 NHS Reference costs 2012/13[92] Baboolal 2008[95], inflated to 2012/13 (Renal Association, 2013[65]) Baboolal 2008[95], inflated to 2012/13 (Renal Association, 2013[65]) NICE CG125[86] / NHS Kidney Care 2009[101], inflated to 2012/13
Transplant[b]	Background management Living donor transplant Deceased donor transplant Organ transplantation service Maintenance year 1 Maintenance year 2+	£5,238.59 £18,639.68 £18,631.41 £15,791.32	100% 35.6% 64.4% 100%	Assumed equal to CKD stage 5 NHS Reference costs 2012/13[92], (NHSBT 2013/4 Activity Report[98]) NHS Reference costs 2012/13[92], (NHSBT 2013/4 Activity Report[98]) NHSBT FOI request[102] & NHSBT Activity report

Health states	Cost item	Annual cost	% Patients	Source: Cost (% Patients)[a]
		£19,044.44 £7,876.52	100% 100%	2011/12[103], inflated to 2012/13 Kerr 2012[96] Kerr 2012[96]

ADP = Automated peritoneal dialysis; CAPD = Continuous ambulatory peritoneal dialysis; CG = Clinical guideline; CKD = chronic kidney disease, FOI = freedom of information; HD = Haemodialysis; NHS = National Health Service; NHSBT = NHS Blood and Transplant; NICE = National Institute for Health and Care Excellence; PD = Peritoneal dialysis

[a] Additional information about the source unit costs is presented in Section 7.5.1.

[b] Patients may receive up to 2 transplants in the base-case analysis.

[c] Haemodialysis and Peritoneal dialysis.

5.2.9 Cost-effectiveness results

Patients in the tolvaptan cohort spend longer time in CKD stages 2, 3 and 4, and less time in ESRD (approximately two years). Tolvaptan patients are associated with approximately 0.5 years less on dialysis and 20% fewer transplants compared to no active treatment.

Table 5.20: Time spent in each CKD health state (years)
(based on Table B51 of the CS[2])

Health State	Control (no active treatment)	Tolvaptan	Incremental
CKD 1	0.00	0.00	0.00
CKD 2	5.61	7.13	1.52
CKD 3	5.29	6.74	1.45
CKD 4	2.40	3.03	0.64
ESRD	13.57	11.49	-2.07
CKD = chronic kidney disease; ESRD = End-Stage Renal Disease			

The discounted estimates for total expected lifetime costs were [redacted] for standard care. For tolvaptan, the costs were higher at [redacted] (excluding the PAS), and [redacted] (including the PAS). The health outcomes were higher for tolvaptan at 13.54 QALYs (discounted) and 17.58 life years (undiscounted) than for standard care at 12.63 QALYs and 16.76 life years. The ICER for tolvaptan was [redacted] per QALY gained excluding the PAS and £34,769 including the PAS.

Table 5.21: Mean discounted base-case results per patient
(based on Tables B52 and B53 of the CS[2])

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Excluding PAS							
No active treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.58	13.54	[redacted]	0.82	0.91	[redacted]
Including PAS							
No active treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.58	13.54	£31,583	0.82	0.91	£34,769
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

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 36%, 47% and 58%, respectively. Excluding the PAS, the probability of cost-effectiveness at a willingness-to-pay threshold up to £40,000 per QALY gained was [redacted].

Figure 5.2: Cost-effectiveness acceptability curve (including PAS)
(Figure B23 in the CS[2])

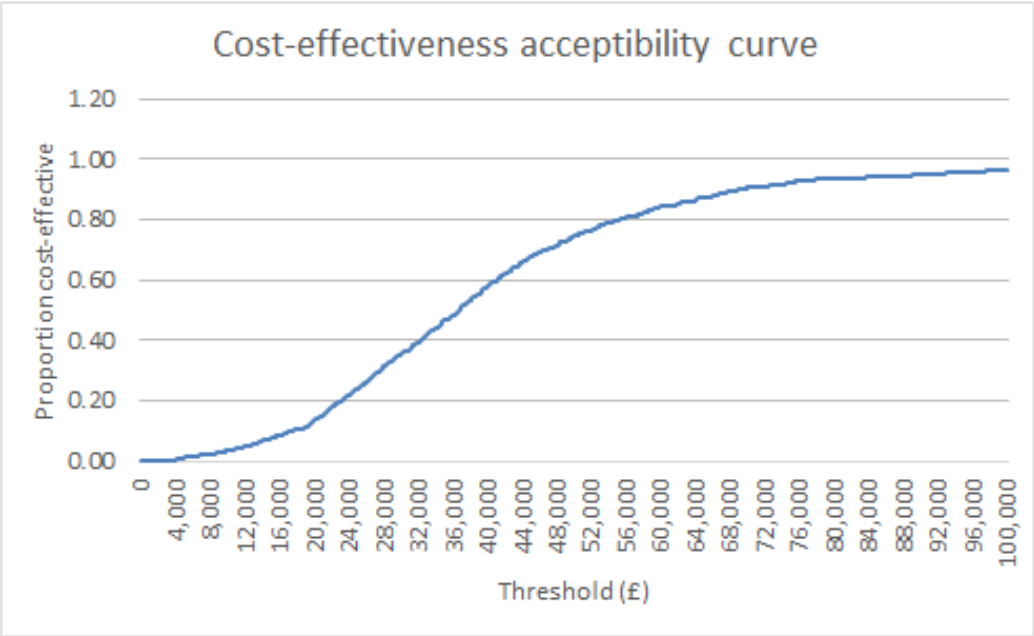


Figure 5.3: Cost-effectiveness acceptability curve (excluding PAS)
(Figure B22 in the CS[2])

[redacted]

ERG comment: The model code was not consistent with the CS and/or information from the Excel sheet. In response to clarification question C4, the company provided an updated excel file and, slightly different, revised base case results. The cost-effectiveness acceptability curve had only very minor changes.

Table 5.22: Mean discounted revised base-case results per patient
(based on Table C11 of the company response to clarification[9])

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Excluding PAS							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	[redacted]	0.83	0.92	[redacted]
Including PAS							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	£31,838	0.83	0.92	£34,733
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

5.2.10 Sensitivity and scenario analyses

The company did not perform one-way sensitivity analyses. This was justified by arguing that *"The stochastic individual patient simulation (with sampling of baseline characteristics) and probabilistic sensitivity analysis were programmed to run simultaneously (see section 7.7.6); therefore conventional deterministic sensitivity analyses (in which alternative fixed estimates of the mean values of model parameters are explored) were not performed"*.[2]

Scenario analyses were performed by the company to examine scenarios in which:

- ESRD treatment is started at an eGFR of 6 and 10 ml/min/1.73 m^2 (base case value 8.5 ml/min/1.73 m^2);
- Significant kidney pain is excluded;
- Alternative discount rates are applied;
- Treatment effect of 26.4% based on CKD-EPI is applied (instead of 31.6% based on serum creatinine level);
- Alternative treatment discontinuation probabilities are applied;
- Disease progression in the first three years is based on regression equations (instead of directly based on TEMPO 3:4 data);
- Alternative values are used for the proportion of patients that receive conservative care;
- Alternative health state utility values are applied;
- Treatment effect of 35.1% based on European patients only is applied (instead of 31.6% based on the intention to treat population);
- Alternative baseline characteristics are applied.

The three most influential scenario analyses were those that incorporated 1) treatment effect based on CKD-EPI (ICER with PAS: £47,722); 2) using 'minimum' utility decrements for ESRD (exact utility decrements not specified, ICER with PAS: £40,819) and; 3) using a disutility of 0.0123 for being on tolvaptan treatment (ICER with PAS: £39,959).

ERG Comments: The updated ICERs after correction of the model code error: 1) treatment effect based on CKD-EPI (ICER with PAS: £47,510); 2) using 'minimum' utility decrements for ESRD (exact utility decrements not specified, ICER with PAS: £40,615) and; 3) using a disutility of 0.0123 for being on tolvaptan treatment (ICER with PAS: £40,401).

The lack of one-way sensitivity analyses for stochastic input parameters is a serious shortcoming. Systematically examining uncertainty is a hallmark of good modelling practice.[104] Performing one-way sensitivity analyses provides an indication of the impact of input parameters on the outcomes. The justification for excluding one-way sensitivity analyses is not convincing, these could have been performed by setting the (stochastic) input parameter at a fixed minimum/maximum (e.g. using the 95% confidence interval) and subsequently running the analyses.

The ERG appreciated the scenario analyses performed by the company. However, the company did not explore scenarios considering the extrapolation of the treatment effect (see clarification question C15 and Section 5.2.6), which is probably one of the most influential uncertainties.[2, 9] Moreover, the ERG would have preferred additional scenario analyses including:

1. Liver complications based on Hy's Law cases (see Section 5.2.6 and clarification question C8)[2, 9]
2. ADPKD-specific mortality risks for CKD stage (see Section 5.2.6 and clarification question C10)[2, 9]
3. Different assumptions for the estimation of the treatment effect (see Section 5.2.6 and clarification question C3)[2, 9]
4. Different assumptions for the extrapolation of the treatment effect (see Section 5.2.6 and clarification question C15)
5. Treatment discontinuation of 6.5% (equal to discontinuation during year 2) after year 3 (see Section 5.2.6)[2]
6. Increased monitoring costs (see Section 5.2.8)[2]

In the response to the clarification letter, the company provided additional analyses for two (scenarios 3 and 4) of the above mentioned scenario analyses (see Tables 5.23-5.26).[9]

Table 5.23: Treatment effect in the model is incorporated using a constant reduction in TKV growth of 49.2% (with PAS)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
No active treatment	[redacted]	16.75	12.63				
Tolvaptan	[redacted]	17.10	12.99	£43,458	0.35	0.36	£119,684
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

Table 5.24: Treatment effect after three years is set at 50% of the observed treatment effect (with PAS)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
No active treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.17	13.08	£41,689	0.41	0.45	£92,051
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

Table 5.25: Treatment effect after three years is set at 10% of the observed treatment effect (with PAS)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
No active treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	16.93	12.82	£46,260	0.17	0.19	£238,750
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

Table 5.26: Treatment effect after three years is set at 0% of the observed treatment effect (with PAS)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
No active treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	16.88	12.77	£47,108	0.12	0.14	£328,941
ICER = incremental cost-effectiveness ratio; LY = life year(s); PAS = Patient access scheme; QALYs = quality-adjusted life years							

5.2.11 Subgroup analyses

Subgroup analyses were performed for patients in each CKD stage at treatment initiation (stage 1, stage 2, stage 3a and stage 3b). Analyses were performed by setting the initial patient characteristics in the model to the subgroup specific values using the baseline data from TEMPO 3:4 trial and data from the OVERTURE observational study.[105] The treatment effect was assumed to be equivalent to that for the overall population as a consistent benefit of tolvaptan was observed across CKD stage 1, 2 and 3.

Table 5.27: Summary of the characteristics of patients in the subgroup analyses
(Based on Table B59 of the CS[2])

CKD Stage	TKV (ml)	eGFR (ml/min/1.73 m^2)	Age (years)	Gender (% F)
All stages (base case)	[redacted]	[redacted]	[redacted]	[redacted]
Characteristics by CKD stage based on TEMPO 3:4 baseline characteristics				
Stage 1	[redacted]	[redacted]	[redacted]	[redacted]
Stage 2	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3a	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3b	[redacted]	[redacted]	[redacted]	[redacted]
Characteristics by CKD stage based on OVERTURE[105]				
Stage 1	[redacted]	[redacted]	[redacted]	[redacted]
Stage 2	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3a	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3b	[redacted]	[redacted]	[redacted]	[redacted]

CKD = chronic kidney disease; CS = company's submission; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

Table 5.28: Summary of the results of the subgroup analyses (probabilistic mean estimates, per-patient, including PAS[3])
(Based on Table B61 of the CS[2])

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental			Cost/QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC	costs (£)	LYs	QALYs	
Base-case analysis	[redacted]	[redacted]	17.58	16.76	13.54	12.63	£31,583	0.82	0.91	£34,769
Subgroup analyses based on TEMPO 3:4 baseline characteristics										
CKD stage 1	[redacted]	[redacted]	18.60	17.87	14.81	13.89	£33,824	0.73	0.92	£36,888
CKD stage 2	[redacted]	[redacted]	17.26	16.44	13.13	12.28	£32,150	0.82	0.86	£37,542
CKD stage 3a	[redacted]	[redacted]	15.36	14.67	11.01	10.34	£24,625	0.69	0.67	£36,916
CKD stage 3b	[redacted]	[redacted]	14.93	14.26	10.60	9.96	£22,473	0.68	0.64	£35,040
Subgroup analyses based on OVERTURE baseline characteristics										
CKD stage 1	[redacted]	[redacted]	20.09	19.34	16.45	15.53	£44,256	0.74	0.92	£48,239
CKD stage 2	[redacted]	[redacted]	16.03	15.39	11.98	11.17	£24,539	0.64	0.80	£30,496
CKD stage 3a	[redacted]	[redacted]	12.87	12.49	8.92	8.39	£11,670	0.38	0.53	£22,129
CKD stage 3b	[redacted]	[redacted]	11.58	11.25	7.57	7.14	£7,967	0.33	0.43	£18,579

CKD = chronic kidney disease; CS = company's submission; LY = Life year(s); QALY = quality-adjusted life year; SC = standard care; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume

The incremental QALYs and life-years as well as the incremental costs are higher when treating patients in an earlier stage of disease progression. The ICERS are higher in CKD stage 1 and 2 than in CKD stage 3 and 4. The analyses using the patient characteristics from OVERTURE show the same pattern, but more extreme.

[3] The results of the subgroup analyses excluding PAS are in Table B60 company submission, page 258

ERG comment: in the subgroup analyses based on CKD stages the treatment effect was assumed to be equivalent to that for the overall population (31.6%). However, the effect of tolvaptan on the annualised rate of change in renal function (eGFR) differs between the CKD stages. Based on Table B13 of the CS, it can be calculated that the treatment effect is lower than average in stage 1 and 2 and higher than average in stage 3. This implies that, if these CKD stage specific treatment effects would have been used, the ICERs in CKD stage 1 and 2 would increase further and the ICER in CKD stage 3 would decrease.

Table 5.29: Annual eGFR decline, as observed during TEMPO 3:4 for CKD subgroups (Based on Tables B13, B32 and B33 of the CS[2])

Population	Treatment Arm		Control Arm		% reduction	
	Mean	SE	Mean	SE	Mean	SE
Base case (all patients)	-2.609	0.337	-3.812	0.295	31.6%	7.77%
CKD 1	-1.831	-	-2.146	-	[redacted]	-
CKD 2	-2.683	-	-3.386	-	[redacted]	-
CKD 3	-3.873	-	-6.505	-	[redacted]	-

CKD = chronic kidney disease; CS = company's submission; SE = standard error; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes

The comparison of the subgroup analyses based on the TEMPO 3:4 and OVERTURE data shows that the ICERs are sensitive to differences in patient characteristics at initiation of therapy (eGFR, TKV, age, gender), even within a CKD stage. In this respect, it should also be noted that eGFR and TKV are highly variable among patients in the same CKD stage and within patients over time.

5.2.12 Model validation and face validity check

Transparency

In addition to the overly complicated and confusing model description (see Section 5.2.2), the company provided an overly complicated model file that is lacking transparency. This is mainly due to the use of a state-transition model that is coded in the Macro modules in Excel with parameters that are often redirected/renamed, sometimes multiple times (see also clarification question C5).[9] This severely hampered the model transparency and the ability (given the time available) of the ERG to perform additional analyses. Although the company made an effort to alleviate this issue in their response to clarification question C5, the model is still far from transparent and easily accessible.

Face validity

The company stated that a steering group of six European ADPKD expert clinicians were involved in the model development to ensure the face validity of the model structure, data sources, problem formulation and results. Specific attention was given to the predictions of disease progression as simulated by the model. The expert clinicians concluded that this model performed favourably as a simulation of ADPKD disease progression. Additionally, to

validate the model assumptions for clinical practice, the model was presented to UK clinical experts and HTA experts.

Internal validity

In response to clarification question C16, the company clarified that the internal validity was assessed by undertaking the following activities:

- 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, Visual Basic for Applications (VBA) code and data
- Review of model inputs against source material

Cross validation

Cross-validation includes examining different models that address the same problem and comparing their results. The company compared the base case results with the relevant economic evaluation[61] identified in the systematic review. The company stated that the estimated incremental QALYs are similar among both assessments, while the incremental life years presented by Erickson et al[61] were larger than those in reported in the CS (2.6 years versus 1.5 years).

External validity

To assess external validity, disease progression as estimated by the model was compared (CS Figure B29) with data from the The Health Improvement Network (THIN) database (n=64), which holds data from UK clinical practice.

The company concluded that *"there was some inconsistency in the observational data at the time of ESRD; this was potentially due to poor recording of eGFR once the decision to prepare the patient for RRT had been made"*.[2]

ERG comments: Transparency is a key aspect of modelling and in this specific case a more transparent model would be more convenient for an external reviewer to assess face validity and internal validity of the model and perform additional analyses. Moreover, a more commonly used individual-patient state-transition model with a Markov trace and formulas in the Microsoft Excel worksheets would be preferred (the arguments for a *"coded simulation model"* listed in Section 7.2.3 of the CS[2] are not convincing).

Face validity checks seem appropriate. However, the exclusion of all adverse events besides kidney pain (see also Sections 5.2.6 and 5.2.7) might be considered as a face validity issue.

The internal validity assessments seem robust based on the activities undertaken. However, the ERG found some obvious errors in the model code (see clarification question C4).[9] This questions the reliability of the internal validity assessment. Given this finding and the lack of transparency of the model not allowing the ERG to check all details of the model (see above), the ERG cannot guarantee that there are no additional model errors.

Based on the cross-validation, it was noted by the company that in all cases the estimation of incremental clinical benefit is lower in the economic evaluation presented in their submission compared to those in Erickson et al.[61] However, the company did not compare the estimated (incremental) costs. These were presumably not compared because of generalisability issues (i.e. differences in unit prices (including tolvaptan costs), resource use, perspective and discounting), but the order of magnitude of the difference in (incremental) costs is noticeable (incremental costs of $844,200 versus [redacted]) and would have been interesting to consider in more detail.

Finally, the comparison of predicted progression rates with real world data showed that the predicted time to ESRD, despite some inconsistencies, seems to correspond reasonably with the real world data (i.e. the THIN database).

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG performed additional scenario analyses (those mentioned in Section 5.2.10 and not performed by the company):

1. Liver complications based on Hy's Law cases (see Section 5.2.6 and clarification question C8)[9]
2. ADPKD-specific mortality risks for CKD stage (see Section 5.2.6 and clarification question C10)[9]
3. Treatment discontinuation of 6.5% (equal to discontinuation during year 2) after year 3 (see Section 5.2.6)
4. Increased monitoring costs (see Section 5.2.8)
5. Decreased post-transplant costs (see Section 5.2.8)

The base case ICERs calculated by the company (after correcting the model code error) were and £34,733 (with PAS). These ICERs increased to £35,751 when including liver complications based on Hy's Law cases (Table 6.1). For this exploratory analysis, a worst case scenario was adopted assuming that all Hy's Law cases would need a liver transplant at the end of year 1 and would die immediately thereafter (severe liver injury may expected in a frequency 1 out of 10 Hy's Law cases).[106] In total, 958 patients were exposed in the Tempo 3:4 and Tempo 4:4 studies and three patients have been identified as Hy's Law cases. Therefore, it was assumed that 0.3% (=3/958) of the patients would need a liver transplant at the end of year 1 and would die directly thereafter. Moreover, it was assumed that these patients would have a utility of 0.77 (= total QALYs / total LYs), an annual costs of £17,714 (= total costs / total LYs) and total transplantation costs of £34,425.67.

Moreover, the company's base case used general population mortality and is therefore most likely underestimating mortality for ADPKD (see Section 5.2.6 and clarification question C10)[9], which is probably not a conservative assumption. Therefore, mortality for ADPKD was multiplied with a hazard ratio of 2.0 to explore the impact of this assumption. This increased the ICER to £34,754.

Treatment discontinuation after three years was assumed to be 0.5%. This assumption was however not explored in scenario analyses. Scenario analyses conducted by the ERG showed that this was an assumption that has a noticeable impact on the ICER. When assuming a treatment discontinuation of 6.5% (equal as the second year), this ICER increased to £42,893.

Increasing monitoring costs did not have a substantial impact on the ICER: the ICER increased to £36,167.

Finally, the maintenance costs for post kidney transplants are likely to be overestimated as total costs for this state include both management costs and maintenance costs. The ERG showed that this was an assumption that has a noticeable impact on the ICER. Subtracting the background management costs from the maintenance costs for all years increased the ICER to £39,264.

Besides these additional exploratory scenario analyses, the ERG would prefer to apply the following changes to the base case analysis (as mentioned in previous sections):

1. Correct model code error (see Section 5.2.9)
2. Equal kidney pain probability for both arms (see Sections 5.2.6 and 5.2.7)
3. Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4 (see Section 5.2.8)
4. Disutility for tolvaptan treatment (see Section 5.2.7)
5. Disutility of 0.02 for HD and PD complications (see Section 5.2.7)

The company's base case results in an ICER of £34,769, correcting the model code error slightly decreased this ICER to £34,733.

5.4 Conclusions of the cost-effectiveness section

In a systematic review the company did not identify cost-effectiveness studies relevant to this submission. Therefore a *de novo* economic evaluation was performed. The model is a patient-level state-transition model, which the ERG believes is appropriate to model this decision problem. The population in the analysis is consistent with the scope, although it should be noted that the TEMPO 3:4 trial (primary source for the economic model) included only patients aged 18-50 years while no age restriction was included in the final scope and the proposed licensed indication. Moreover, only a small proportion of the TEMPO 3:4 trial population was from the UK (5%; 73 out of 1,445). The comparators are standard care with and without tolvaptan, which is in line with the scope. The base case amounted to £34,769 including PAS and to [redacted] excluding PAS. The costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS.

The model transparency was hampered by an overcomplicated description and model code, as well as errors in the code. The face validity checks seemed appropriate, apart from the

Replaced by erratum

exclusion of all (treatment related) adverse events besides clinically significant pain. The comparison of predicted progression rates with real world data showed that the predicted time to ESRD, despite some inconsistencies, seems to correspond reasonably with the real world data. The ERG questioned a number of assumptions that were made in the submission. Most importantly, the assumption that the treatment effect as observed in TEMPO 3:4 and TEMPO 4.4 (together maximum follow-up five years) will not decline over the lifetime of the population (approximately 17 years). The ERG argues there is little evidence to underpin this hypothesis; the opposite may also hold (see also Section 4.2.1). It is uncertain whether the treatment effect will sustain or decrease. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a [redacted] compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

In the base case, the company did not include a tolvaptan specific disutility, ignoring the impact of AEs due to tolvaptan on health related quality of life. In addition, the probability of kidney pain was modelled as a treatment dependent parameter. The ERG believes this may have introduced a downward bias to the ICER, as it is assumed that the difference in kidney pain as observed in TEMPO 3:4 is independent from the effect of tolvaptan on disease progression. This is questionable, as pain is a known symptom of chronic kidney disease, increasing with disease progression.[67] Additionally, the disutility applied to PD and HD seemed higher than found in the literature and the CKD stage 3 costs seemed underestimated, which both favoured tolvaptan. The ERG preferred to apply the following changes to the company's base case analysis: correct model code error, equal kidney pain probability, equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4, and a disutility for tolvaptan treatment. These adjustments led to an ERG base case ICER of £43,280, including PAS.

Besides this, the ERG undertook exploratory scenario analyses for the following issues:

- Hepatotoxicity of tolvaptan was observed in the TEMPO studies, but not incorporated in the model. According to the ERG, this assumption is unsustainable. It is uncertain whether the proposed monitoring schedule will totally prevent (severe) cases of hepatoxicity as well as the costs and health consequences associated with this. Assuming that three out of 10 Hy's Law cases would have a liver transplant and die immediately thereafter led to a slight increase in the ICER (£35,751, including PAS). The company assumed, in absence of reliable data, that mortality risk in ADPKD patients is equal to all-cause mortality. This overestimates survival, which may be in favour of tolvaptan, because patients receiving tolvaptan spend more time in CKD stage one to four than patients receiving standard care. Assuming increased mortality (HR 2.0) did however not substantially change the ICER.
- Evidence to underpin the estimated annual treatment discontinuation after year 3 (0.5%) was scarce. The company explored alternative estimates (0%, 2%) in a sensitivity analysis. The ERG considered this to be a small range, and conducted an exploratory analysis with a larger probability of discontinuation after year 3 (6.5%). This resulted in an ICER of £42.893, including PAS.

- The company included the costs of monitoring of patients receiving tolvaptan in the model. Costs of monitoring patients receiving tolvaptan did not take into account costs related to treatment of patients with elevated liver function test results. This may underestimate the monitoring costs in real practice. Increased monitoring costs increased the company's ICER to £36,167, including PAS.
- The maintenance costs for post kidney transplants are likely to be overestimated as total costs for this state include both management costs and maintenance costs. Subtracting the background management costs from the maintenance costs for all years had a noticeable impact on the ICER (£39,264, including PAS).

The ERG base case ICER is higher than the company's base case (£34,769 including PAS). Including the PAS the probability of cost-effectiveness, according to the ERG base case, at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 24%, 31% and 42%, respectively. However, it should be emphasized that not all uncertainty is incorporated in these probability estimates; most notably the uncertainty of the extrapolation of the treatment effect. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a strong increase compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 6.1: Exploratory scenario analyses performed by the ERG

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Assuming that 3 out of 10 Hy's Law cases would have a liver transplant at year 1 and would die immediately thereafter							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	£[redacted]	17.54	13.51	£31.341	0.78	0.88	£35,751
Assuming increased mortality (hazard ratio: 2.0)							
Standard treatment	[redacted]	16.36	12.37				
Tolvaptan	[redacted]	17.11	13.23	£29,902	0.75	0.86	£34,754
Assuming treatment discontinuation of 6.5% after year 3							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.32	13.26	£26,922	0.56	0.63	£42,893
Assuming increased monitoring costs							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.53	£32,744	0.82	0.91	£36,167
Assuming decreased post-transplant costs							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.53	£35,992	0.83	0.91	£39,264
ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; LY = life year(s); QALYs = quality-adjusted life years							

Table 6.2: Additional analyses performed by the ERG (with PAS)

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Company base case							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.58	13.54	£31,583	0.82	0.91	£34,769
Correct model code error							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	£31,838	0.83	0.92	£34,733

Technologies	Total			Incremental			
	costs (£)	LY	QALY	costs (£)	LY	QALY	Ratio (QALY)
Equal kidney pain probability for both arms[a]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.54	£31,964	0.83	0.91	£35,252
Equal CKD-stage costs for CKD-stage 3 as for CKD-stage 4[b]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.59	13.55	£33,216	0.83	0.92	£36,236
Disutility of 0.0123 for Tolvaptan treatment[c]							
Standard treatment	[redacted]	16.76	12.63				
Tolvaptan	[redacted]	17.57	13.41	£31,501	0.82	0.78	£40,401
Disutility of 0.02 for HD and PD complications[d]							
Standard treatment	[redacted]	16.76	12.66				
Tolvaptan	[redacted]	17.59	13.57	£31,838	0.83	0.91	£34,996
ERG base case (combination of the scenarios presented above)							
Standard treatment	[redacted]	16.76	12.66				
Tolvaptan	[redacted]	17.57	13.42	£33,015	0.82	0.76	£43,280

ICER, incremental cost-effectiveness ratio; LY, life year(s); QALYs, quality-adjusted life years

[a] Incorporated by adjusting H59:I62 in worksheet 'Control'

[b] Incorporated by adjusting E30:F30 in worksheet 'Cost & Utility Input'

[c] Incorporated by adjusting E92 in worksheet 'Cost & Utility Input'

[d] Incorporated by adjusting E102:E103 in worksheet 'Cost & Utility Input'

7 OVERALL CONCLUSIONS

This appraisal looks at the clinical and cost-effectiveness of standard care in combination with tolvaptan versus standard care including routine surveillance without tolvaptan for treating autosomal dominant polycystic kidney disease. The company submission is mainly based on one randomised controlled trial, the TEMPO 3:4 trial. In this phase 3, multicentre, double-blind, placebo-controlled, three year trial, 1,445 patients, 18 to 50 years of age, who had ADPKD with a total kidney volume of 750 ml or more and an estimated creatinine clearance of 60 ml per minute or more, were randomly assigned in a 2:1 ratio to receive tolvaptan or placebo. The trial found that tolvaptan, when given over a period of three years, slows the increase in total kidney volume and the decline in kidney function in patients with ADPKD. However, the potential benefit is not without risks. Thirst, polyuria, and related adverse events may affect the ability of some patients to take effective doses of tolvaptan. The potential effects on liver-enzyme levels and plasma levels of sodium and uric acid require monitoring.

In the remainder of this chapter we will discuss the main strengths and limitations of the TEMPO 3:4 trial. First of all, the TEMPO 3:4 trial is not a UK trial, most of the 1,445 included patients came from the USA (n=379), Japan (n=177) and Germany (n=157); only 73 patients came from the UK. During the scoping workshop, clinical experts commented that the UK has approximately 70,000 ADPKD patients, most of whom are managed in primary care. Therefore, the trial is not representative of UK practice.

In addition, the inclusion criteria were quite specific and also limit the representativeness of the trial for the total population of UK ADPKD patients:

- The trial included patients aged between 18 and 50 years. Therefore, the trial provides no evidence for patients over 50 years as well as for children and adolescents.
- Most patients in the trial were CKD stage 1 (35%) and 2 (48%). Therefore, there is limited evidence for CKD stage 3 patients (17%).
- Patients with a TKV of ≥ 750 ml ≥ 14 days before randomisation (as measured by MRI) were included. Normal kidney volume is around 250 ml, which means that included patients had TKV at least three times more than normal.

Before randomisation, 530 patients were excluded because they did not meet inclusion criteria for the trial (TKV of ≥ 750 ml (370 patients excluded), creatinine clearance of ≥ 60 ml per minute as estimated by means of the Cockcroft–Gault formula (119 patients excluded)). That also means results are not generalisable to all ADPKD patients.

The NICE final scope[1] mentions standard care without tolvaptan as the comparator. However, standard care is not defined. At the scoping workshop clinical experts agreed that standard care will vary depending on each patient and that it is not possible to define the standard of care treatment for this condition. The NICE final scope does state that *"therapies currently used aim to control symptoms and associated complications of kidney disease, such as pain, cyst infections, urinary tract infections and high blood pressure"*.[1] Therefore, standard treatment is not defined but includes monitoring of renal function, blood pressure control and treatment of complications (pain, urinary tract infections). It is not clear from the trial

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whether patients in the different countries included in the TEMPO 3:4 trial received this type of standard care, e.g. the CS describes "*a more intensive visit schedule in Japan*".[2]

Regarding the outcome measures used in the trial, there are two issues. First, the use of total kidney volume as a surrogate for treatment efficacy has been questioned.[107] At the scoping workshop clinical experts commented that TKV is not generally measured in the UK (or anywhere else). TKV is a good measure of extent of disease as it predicts future decline of renal function. However due to natural variation between patients and unreliability of measurement TKV is not a reliable measure of treatment effect. Measuring kidney volume in healthy persons is complex, but measuring kidney volume in patients with ADPKD is far more complex because in ADPKD the kidneys lose their predictable shape and become grossly distorted. Secondly, HRQoL has not been assessed in the TEMPO 3:4 trial. As a result, no ADPKD specific EQ-5D utilities were available which is inconsistent with the NICE reference case. This means utilities used in the economic model may not reflect the same patient population as other effectiveness outcomes used in the model are based on. This diminishes the reliability of the model outcomes.

Spital commented in a letter[108] in response to the main trial publication in the New England Journal of Medicine[24], that *"given that the beneficial effect of tolvaptan is thought to operate through the inhibition of V2-receptor activation and the suppression of cyclic AMP (cAMP), it seems likely that a similarly beneficial effect on the course of ADPKD could be achieved with a high fluid intake alone, because this suppresses vasopressin release and cAMP formation. Therefore, it is hard to understand why the investigators did not instruct both groups to ingest large amounts of water, as two of the authors had previously recommended.*[109] *Had they done so, we would have known whether tolvaptan is superior to a high fluid intake alone. In view of the worrisome adverse effects of tolvaptan seen in the trial, including elevated liver enzyme levels, as well as the high cost of tolvaptan (cost of daily 90 mg dose >$25,000 per month*[110]*, a monitored high water intake may be safer, far cheaper, and equally effective"*. Torres et al. replied[111] that *"adherence to a regimen of high water intake that would be sufficient to suppress vasopressin during prolonged periods of time may be difficult*[112] *and, as some authors have suggested, possibly deleterious.*[113] *(...) A specifically designed clinical trial would be necessary to determine whether high water intake and tolvaptan are equally effective treatments"*.

It should be noted that other treatment options, such as aggressive blood pressure management, could modify the cause of disease in early ADPKD. Results of a recently published RCT of 558 hypertensive participants with ADPKD concluded that "*compared with standard blood-pressure control, rigorous blood-pressure control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion*".[23] Target blood pressure was < 110/75 mm Hg.

In the TEMPO 3:4 trial, adverse events consistent with the natural history of ADPKD were more frequent among patients who received placebo than among those who received tolvaptan. Adverse events more common in the tolvaptan group were consistent with its aquaretic effect. Aquaresis-related adverse events led to the discontinuation of tolvaptan in

approximately 8% of participants, mostly within the first month. Adverse events related to aquaresis in previous clinical trials of tolvaptan for hyponatremia or heart failure were similar to those observed in the current trial, but the higher frequency of liver enzyme elevations was not observed in the previous trials.[114-117]

In response to adverse events related to the liver, the U.S. Food and Drug Administration (FDA) has determined that tolvaptan *"should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death. Samsca is used to treat low sodium levels in the blood. An increased risk of liver injury was observed in recent large clinical trials evaluating Samsca for a new use in patients with autosomal dominant polycystic kidney disease (ADPKD)"*.[118]

The ERG questioned a number of assumptions underlying the economic evaluation of tolvaptan, and addressed several of these issues in the ERG base case. The ERG base case ICER amounts to £43,280, including PAS. This ICER is higher than the company's base case (£34,769 including PAS). Hence, the costs of tolvaptan are at a level at which it is [redacted] that the ICER will be below a threshold of £30,000 to £40,000 per QALY [redacted] a PAS. Including the PAS the probability of cost-effectiveness, according to the ERG base case, at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 24%, 31% and 42%, respectively. However, not all uncertainty is incorporated in these probability estimates; most notably the uncertainty of the extrapolation of the treatment effect. In response to clarification question C13, the company provided a scenario analysis with diminished treatment effect after three years. The ICERs with a 50% reduction of treatment effect after three years show a strong increase compared to the base case: [redacted] excluding PAS and £92,051 including PAS.

7.1 Implications for research

Long term follow-up of the effects of tolvaptan is warranted, including clinical benefit and liver complications. Evidence regarding health-state utilities and mortality in ADPKD patients is scarce.

On page 8 of the CS it was emphasised that *"tolvaptan is the first treatment to delay renal progression in AKPKD"*.[2] According to page 13 of the CS, *"tolvaptan is a selective vasopressin antagonist that specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron. Inhibition of vasopressin binding to V2 receptors leads to reduction of cell proliferation, cyst formation and fluid excretion"*.

The ERG is not aware of factors which might suggest differences in effectiveness between blocking the V2 receptor with tolvaptan and stimulating it by inhibiting arginine vasopressin release by increasing the fluid intake, e.g. by drinking more water. Post-hoc analyses of TEMPO 3:4 data suggested that participants with lower urine osmolality had lower increases in TKV and within the tolvaptan group the patients whose urine osmolality decreased the most (i.e. who increased their water intake most) were most likely to maintain stable renal function.[37] As detailed above, Spital commented to that effect in a letter[108] in response to the main trial publication in the New England Journal of Medicine[24]. He also highlighted a

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previous study (published in 2009)[109] conducted by the main author of the TEMPO 3:4 trial. One might argue that drinking four litres of water evenly spaced over the day (with an extra glass if one wakes at night to go to the toilet) over years may be difficult for a patient but that it hardly differs from the aquaresis-related side effect of taking tolvaptan. A small observational study of drinking more water has been launched in 2011 but no results are available yet (NCT01348035)[119].

As noted before, other treatment options, such as aggressive blood pressure management, could modify the cause of disease in early ADPKD. Results of a recently published RCT of 558 hypertensive participants with ADPKD concluded that *"compared with standard blood-pressure control, rigorous blood-pressure control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion"*.[23]

Given that, it would be very useful to conduct a trial in which all of these treatment options are assessed, allowing a direct comparison of tolvaptan, increased fluid intake and aggressive blood pressure control which is line with a statement by the main author of TEMPO 3:4 trial that *"a specifically designed clinical trial would be necessary to determine whether high water intake and tolvaptan are equally effective treatments"*.[111]

Furthermore, Torres et al in a recent review discussed somatostatin analogs (i.e. octreotide) as about as promising as V2 receptor blockers (i.e. tolvaptan) and stressed that greater understanding of the cellular pathophysiologic mechanism has laid the foundation for potential therapies. The authors mentioned 25 therapies in six groups and stressed that *"Because effective treatments for PKD are likely to be long term (possibly lifelong), low toxicity and safe profile are of the utmost importance"*.[120]

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APPENDIX 1: ERG SEARCH STRATEGIES

(Further critique of company searches)

Clinical effectiveness

An additional synonym for polycystic kidney disease 'polycystic renal disease' could have been included in the strategy. This could have been further extended to 'polycystic kidney*' or 'polycystic renal'. These terms do not however appear to have high recall, so it is unlikely that relevant records have been missed.

Indirect and mixed treatment comparisons

The same searches for Section 6.1 were used for this section; therefore the same comments apply as for clinical effectiveness searches (6.1).

Non-RCT Evidence

The same searches for Section 6.1 were used for this section; therefore the same comments apply as for clinical effectiveness searches (6.1).

Adverse events

The same searches for Section 6.1 were used for this section; therefore the same comments apply as for clinical effectiveness searches (6.1).

Cost-effectiveness

The same searches for Section 6.1 were used for this section; therefore the same comments apply as for clinical effectiveness searches (6.1).

Measurement and valuation of health effects

Additional synonyms for end stage renal disease could have been included, such as ESKD, stage 5 kidney/renal disease or chronic renal/kidney failure. These terms do not however appear to greatly increase recall, so it is unlikely that relevant records have been missed.

The quality of life facet was limited, but sufficient. Specific renal quality of life measures such as the Kidney Disease Quality of Life Short Form may have been useful additions to the strategy.

Resource identification, measurement and valuation

An additional synonym for polycystic kidney disease 'polycystic renal disease' could have been included in the strategy. This could have been further extended to 'polycystic kidney*' or 'polycystic renal'. These terms do not however appear to have high recall, so it is unlikely that relevant records have been missed.

Additional synonyms for end stage renal disease could have been included, such as 'ESKD', stage 5 kidney/renal disease or chronic renal/kidney failure. These terms do not however appear to greatly increase recall, so it is unlikely that relevant records have been missed.

The search terms used in the cost facet for end-stage renal disease were very narrow and focussed. This was justified in the company's response to the POC letter as 'economic evaluations of ESRD were not required specifically, and as a result a more focused set of research terms could be employed'.

APPENDIX 2: PHILLIPS ET AL CHECKLIST

Question(s)	Response (Y, N or N/A)	Comments
Is there a clear statement of the decision problem?	Y	
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	The comparator defined in the NICE scope was, *"Standard care, including routine surveillance without tolvaptan"*. Standard care was not fully defined in the final scope.[1] According to the CS, the standard care does not involve any active treatment for ADPKD (there are no pharmacological treatments indicated for ADPKD).
Is the primary decision-maker specified?	Y	
Is the perspective of the model stated clearly?	Y	
Are the model inputs consistent with the stated perspective?	Y	
Has the scope of the model been stated and justified?	Y	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	
Are the sources of data used to develop the structure of the model specified?	Y	
Are the causal relationships described by the model structure justified appropriately?	Y	
Are the structural assumptions transparent and justified?	N	The ERG believes that the assumption that hepatotoxicity does not lead to any costs or health loss is unsustainable (see 5.2.6 in this report)
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	N	See comment above
Is there a clear definition of the options under evaluation?	Y	
Have all feasible and practical options been evaluated?	Y	
Is there justification for the exclusion of feasible options?	N/A	
Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	

Question(s)	Response (Y, N or N/A)	Comments
Is the time horizon of the model sufficient to reflect all important differences between options?	Y	
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	
Is the cycle length defined and justified in terms of the natural history of disease?	Y	
Are the data identification methods transparent and appropriate given the objectives of the model?	Y	
Where choices have been made between data sources, are these justified appropriately?	Y	
Has particular attention been paid to identifying data for the important parameters in the model?	Y	
Has the quality of the data been assessed appropriately?	Y	
Where expert opinion has been used, are the methods described and justified?	Y	
Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	
Is the choice of baseline data described and justified?	Y	
Are transition probabilities calculated appropriately?	Y	
Has a half-cycle correction been applied to both cost and outcome?	Y	
If not, has this omission been justified?	NA	
If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	Relative treatment effect is derived from one study, TEMPO 3:4
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and	N	The company assumes no decline of treatment effect based on the 3-year follow up in TEMPO 3:4, extended to 5 year data based on interim analyses of TEMPO 4:4. There is

Question(s)	Response (Y, N or N/A)	Comments
justified?		however little evidence to sustain this hypothesis; the opposite may also hold.
Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	In response to clarification question C15[9], the company provided the results of a scenario analysis with a treatment effect of 50% and 10% after 3 years. See Section 5.2.10 for the results of this scenario analysis.
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	The ERG has questioned the assumptions made (see above)
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Y	In response to clarification question C15, the Company provided the results of a scenario analysis with a treatment effect of 50% and 10% after 3 years. See Section 5.2.10 for the results of this scenario analysis.
Are the costs incorporated into the model justified?	Y	
Has the source for all costs been described?	Y	
Have discount rates been described and justified given the target decision-maker?	Y	
Are the utilities incorporated into the model appropriate?	N	The ERG thinks that the (0.06) absolute value applied for disutility because of HD and PD complications is exaggerated and favours tolvaptan. The ERG considers not including a disutility for tolvaptan treatment as inappropriate.
Is the source for the utility weights referenced?	Y	
Are the methods of derivation for the utility weights justified?	Y	
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Y	
Is the process of data incorporation transparent?	Y	
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Y	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Y	

Question(s)	Response (Y, N or N/A)	Comments
Have the four principal types of uncertainty been addressed?	Y	Partially, no one-way sensitivity analyses have been performed.
If not, has the omission of particular forms of uncertainty been justified?	Y	Partially. The lack of one-way sensitivity analyses for stochastic input parameters is a serious shortcoming. Systematically examining uncertainty is a hallmark of good modelling practice.[104]
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Y	
Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	
Are the methods of assessment of parameter uncertainty appropriate?	Y	Partially, no one-way sensitivity analyses have been performed.
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	
Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Y	In response to clarification question C16, the company clarified that the internal validity was assessed by undertaking various methods. However, the ERG found some obvious errors in the model code (see clarification question C4). This questions the reliability of the internal validity assessment
Are any counterintuitive results from the model explained and justified?	NA	
If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
Have the results of the model been compared with those of previous models and any differences in results explained?	Y	The life years and QALYs have been compared to a previous model.

ADPKD = Autosomal Dominant Polycystic Kidney Disease; CS = company's submission; ERG = Evidence Review Group; HD = Haemodialysis; N/A = not applicable; NICE = National Institute for Health and Care Excellence; PD = Peritoneal dialysis; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes