NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Submission synopsis

- Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a serious, inherited, progressive disease characterised by the development and expansion of fluid-filled cysts in the kidneys that ultimately leads to renal failure and reduced life expectancy
- No licensed treatment for ADPKD is currently available that delays renal progression
- Tolvaptan (Jinarc®), a selective vasopressin antagonist, is a new treatment for ADPKD that represents a step-change in the management of ADPKD, being the first treatment proven to delay renal progression in ADPKD
- The proposed indication considered in this submission is in adult (18+ years) ADPKD patients with chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment, and evidence of rapidly progressing disease
- 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. Treatment is continued long-term and withdrawn at the onset of end-stage renal disease (ESRD)
- In the pivotal TEMPO 3:4 study, tolvaptan was associated with significant reductions in the rates of total kidney volume (TKV) growth and renal function decline over 3 years, as compared with placebo ($P < 0.001$)
- Tolvaptan has a manageable tolerability profile with only 15.4% of patients discontinuing due to adverse events in TEMPO 3:4, compared to 5% in the placebo arm
- Hepatotoxicity was observed in some ADPKD patients receiving tolvaptan; in all cases abnormalities resolved and there were no reports of persistent sequelae. To mitigate this risk, regular monitoring of liver enzymes will be implemented as part of a Risk Management Plan
- Long-term outcomes modelling estimates that tolvaptan is likely to lead to increased life expectancy, improvements in quality of life and cost offsets due to delay of the onset of ESRD
- Tolvaptan is the first treatment to delay renal progression in ADPKD, leading to maintenance of quality of life and increased life expectancy for ADPKD patients, whilst reducing the burden on transplant and dialysis services to the NHS
- It fulfills the criteria to be considered an innovation: need , originality/creativity and value
- Under the terms of a patient access scheme (PAS), in the base case tolvaptan is associated with an ICER of approximately £34,800 per QALY gained
- As such, tolvaptan can be confidently regarded as a cost-effective use of NHS resources

Basic product information

- UK approved name: Tolvaptan
- Brand name: Jinarc
- Marketing status: UK launch anticipated Q2 2015
- Principal mechanism of action: Vasopressin antagonist
- Formulation: Tablet
- Strength(s) and pack size(s): 15 mg, 30 mg, 60 mg, and 90 mg tablets (provided in 28-day packs of split-dose tablets).
- Acquisition cost (NHS list price): £1,208.20 per 28-day pack (flat price) or £43.15 per day
- Acquisition cost (patient access scheme): [redacted]
- Proposed indication: To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease in patients with CKD [chronic kidney disease] stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease. Tolvaptan is indicated in adults.
- Recommended course of treatment: Continued long-term, withdrawn at the onset of end-stage renal failure (ESRD)

ADPKD background

ADPKD is a serious, inherited and progressive disease that is primarily characterised by the development and expansion of fluid-filled cysts in the kidneys, leading to renal enlargement and damage of the renal nephrons. The disease is manifested by pain, infections, kidney stones, bleeding and ultimately renal failure (Takiar and Caplan, 2011; Patel *et al*., 2009). Despite being an orphan disease with an estimated UK prevalence of 4.3 per 10,000 (Otsuka Data on File: OPUK-DOF-JIN-2014-001) and diagnosed prevalence of 3.9 per 10,000 (Patch *et al*., 2011), ADPKD is the fourth-leading cause of chronic renal failure (Grantham *et al*., 2006).

Whilst the disease is predictably progressive, ADPKD is heterogeneous in its natural course with respect to the frequency and severity of complications and the rate of renal function decline towards end-stage renal disease (ESRD) (Torres *et al*., 2007; Harris and Rossetti, 2010). This heterogeneity contributes to the difficulty in

establishing a prognosis in ADPKD. Data from a large UK retrospective cohort study (52,608 renal replacement therapy patients including 3,598 with ADPKD) reveals that ADPKD patients begin renal replacement therapy (RRT) at a median age of 55 years, and this has not changed substantially in the past 10 years. The study estimates this to be seven and 11 years sooner than patients with diabetes or other primary renal diagnoses begin RRT, respectively. A substantial proportion of ADPKD patients reach ESRD at a younger age (interquartile range 47-63 years) (Shaw *et al*., 2014).

Patient burden of ADPKD

Further data from the UK cohort study reports that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years) (Shaw *et al*., 2014), as compared to the current UK life expectancy of 81.5 years (World Bank, 2014). However, the life expectancy in a faster progressing patient population (i.e. the proposed licensed indication for tolvaptan considered in this submission) is likely to be even lower. Outputs from the long-term outcomes modelling used to inform the economic evaluation estimate the mean natural life expectancy for ADPKD patients eligible for tolvaptan to be approximately 64-65 years (Section 7.7).

Multiple studies in cohorts from the EU (including the UK, Denmark, and Spain) and the US have shown that the most common cause of death in patients with ADPKD is as a result of cardiovascular complications, which accounts for approximately 1 in 5 patient deaths (Martinez *et al.,* 2013; Shaw *et al.,* 2014; Rahman *et al.,* 2009; Fick *et al.,* 1995; Ørskov *et al.,* 2012). Other common causes of death include infections, and death from central nervous system disorders (Rahman *et al*., 2009). Many infection-related deaths in ADPKD are due to renal causes (e.g. renal cyst infection, urinary tract infection), or dialysis-related causes (e.g. infected catheter or haemodialysis fistula) (Fick *et al*., 1995).

As cysts develop, they become filled with fluid and fibrotic, enlarge and compress adjacent normal tissue, displacing and obstructing the flow in normal tubules, blood vessels, and lymphatics (Grantham *et al*., 2011). A cyst-filled kidney in an advanced ADPKD patient can weigh up to 30 pounds (~13.6 kg), approximately 80-120 times the weight of a normal adult kidney (Torres and Harris, 2009; National Institute of Health, 2010). Extra-renal manifestations of ADPKD include hepatic, pancreatic, thyroid, subarachnoid, and seminal vesicle cysts; intracranial aneurysms; cardiac

valvular disease; and male infertility (Torres and Harris, 2009; Halvorson *et al*., 2010).

As such, ADPKD-related complications significantly reduce health-related quality of life (HRQoL) (Rizk *et al*., 2009). As renal function declines in patients with ADPKD, HRQoL is reduced further (Miskulin *et al*., 2014). As a genetic disease with no available disease modifying treatment, many ADPKD patients experience debilitating psychological conditions, with >60% of patients having depression (de Barros *et al*., 2011; Marsick *et al*., 1998). Being an autosomal dominant disease, affected individuals have a 50% risk of passing on the disease to their children, meaning patients may choose not to have a family. It is not uncommon for ADPKD patients to be diagnosed after having children of their own, leaving difficult decisions regarding screening of children and potential resultant guilt, anxiety and depression.

RRT itself, particularly dialysis, has a negative impact on patient HRQoL. The inconvenience and discomfort associated with the process of establishing vascular access, the frequency of dialysis procedures and the restrictions to diet and fluid intake all combine to significantly impact HRQoL. Dialysis also superimposes significant new clinical risks, particularly the risk of vascular access-related serious infection, onto the existing risk of ADPKD complications.

As noted above, ADPKD patients reach ESRD at a relatively younger age compared to other causes of ESRD. As such, the earlier requirement for dialysis will impact ability to work and to enjoy leisure time. Although there are limited data evaluating the burden of RRT on HRQoL in patients with ADPKD, it has been reported that on average, patients in ESRD would be willing to give up ten years of life on dialysis in exchange for four years with normal renal function (Couser *et al*., 2011).

Economic burden of ADPKD

While medical resource utilisation is high across all stages of ADPKD, resource use increases as the disease progresses, due to frequent hospital visits and management of complications (Knight *et al*., 2014). Management of ESRD by dialysis and kidney transplantation poses a particularly significant burden to the healthcare system (Quinn *et al*., 2009). A UK retrospective review of hospital admissions showed that all-cause ESRD was the fourth most important primary admission diagnosis in terms of bed occupancy after stroke, heart failure and chronic obstructive pulmonary disease over the five-year study period (Quinn *et al*., 2009).

According to the latest figures from the UK Renal Registry, ADPKD accounts for approximately 7% of incident cases accepted for RRT in the UK, and approximately 13% of prevalent RRT cases (Renal Association 2013)

The overall cost of chronic kidney disease (CKD), of which ADPKD is one cause, in England in 2009–10 was estimated at £1.45 billion, which was approximately 1.3% of all NHS spending in that year (NICE CG 182). More than half of this amount was spent on RRT for the 2% of people with CKD that progresses to kidney failure. Even allowing for an optimistic increase in donor organ supply, numbers on dialysis have been predicted to continue to rise substantially, especially in the elderly. One 2004 study predicted a substantial future growth in the RRT population, particularly in the elderly and those on haemodialysis, with a steady state not being reached for at least 25 years (Roderick *et al.*,2004). The average waiting time for an adult donor kidney – which accounts for 85% of all transplant operations – rose from 1088 in the five year period between 2003 and 2007, to 1114 in 2006 to 2011 (organdonation.nhs.uk current activity report 2013/2014 & organdonation.nhs.uk current activity report 2009/2010). This is clearly an area of NHS priority, as noted in NICE Clinical Guideline 182: "*Strategies aimed at earlier identification and prevention of progression to [ESRD], are clearly needed*".

Current management of ADPKD

Current standard of ADPKD care is related solely to the management of ADPKD complications such as hypertension, pain and infections as well as preparation for and continued care in renal failure (Danish Society of Nephrology, 2012; Ars *et al*., 2014). No licensed treatment for ADPKD is currently available that delays ADPKD progression.

Accordingly, there are currently no ADPKD-specific NICE or UK guidelines. NICE Clinical Guideline 182 covers management of chronic kidney disease. The majority of patients progressing to ESRD are treated with RRT (dialysis or kidney transplant), which, as noted above, has substantial healthcare resource use and economic implications, as well as having a negative impact on patient HRQoL (Rizk *et al*., 2009; Baboolal *et al*., 2008; Szende *et al*., 2014). Conservative care is also a shorter-term option in ESRD, often towards the end of life, where the patient is made as comfortable as possible in the absence of dialysis or transplant (van de Luijtgaarden *et al*., 2013).

Tolvaptan: A step-change in the management of ADPKD

Tolvaptan is a selective vasopressin antagonist that specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron (Otsuka 2014). Inhibition of vasopressin binding to V2 receptors leads to reduction of cell proliferation, cyst formation and fluid excretion (Wang *et al*., 2005).

Tolvaptan will be the first and only licensed disease-modifying treatment indicated for ADPKD, slowing total kidney volume (TKV) growth and the rate of renal function decline. The British Society of Genomic Medicine, the PKD Charity, Renal Association and Royal College of Pathologists acknowledged in their comments on the draft scope for this appraisal that the introduction of tolvaptan would be a 'step-change' in the management of ADPKD.

The proposed licensed indication is as follows:

"*To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease in patients with CKD [chronic kidney disease] stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease. Tolvaptan is indicated in adults*."

Tolvaptan clinical efficacy and safety

Evidence on the clinical efficacy and safety of tolvaptan presented in this submission is derived principally from the pivotal TEMPO 3:4 trial; a large global phase 3 double-blind, randomised clinical trial that included UK sites. The study randomised 1,445 ADPKD patients (18 to 50 years of age, TKV of 750 mL or more and an estimated creatinine clearance of 60 ml per minute or more) in a 2:1 ratio to receive tolvaptan at the highest of three twice-daily dose regimens that the patient found tolerable, or placebo (Torres *et al*., 2012). Treatment duration and follow-up was planned for a minimum of three years.

The primary endpoint of the TEMPO 3:4 trial was the annual rate of change in TKV. The key composite secondary endpoint was time to multiple investigator-assessed ADPKD progression events (defined as worsening kidney function, clinically significant kidney pain, hypertension, and albuminuria). Other secondary endpoints included the rate of change in renal function and risk of clinically significant renal pain.

In TEMPO 3:4, tolvaptan demonstrated a significant relative reduction of 49.2% on TKV growth over three years when compared with placebo (absolute reduction of -2.71% per year; $p<0.0001$) (Torres *et al*., 2012). Within the proposed licensed indication, tolvaptan has a consistent effect on TKV growth across different pre-defined patient subgroups. In parallel with the effects on TKV growth, tolvaptan was associated with a continuous and significant relative reduction of 31.6% in the annual slope of renal function decline, compared with placebo (absolute reduction of 1.20mg/mL^{-1} serum creatinine, $p<0.001$) (Torres *et al*., 2012).

Despite each treatment arm in the trial receiving analgesics as part of supportive care, treatment with tolvaptan was associated with a statistically significant 29% relative reduction in the risk of clinically significant renal pain compared with placebo (5 events vs 7 events per 100 person-years; $p=0.007$) (Torres *et al*., 2012). Overall, treatment with tolvaptan was associated with a reduction in the rate of the key ADPKD progression event composite endpoint of 13.5%. The number of recurrent events per 100 follow-up years was 44 for tolvaptan and 50 for placebo; absolute reduction: 6 events per 100 person-years; HR 0.87; 95% CI: 0.78, 0.97; $p<0.01$) (Torres *et al*., 2012).

In TEMPO 3:4, tolvaptan showed an acceptable tolerability profile, with 15.4% of patients assigned to the tolvaptan arm (versus 4.9% in the placebo arm) discontinuing due to adverse events (AEs) over the 3-year pivotal trial. Adherence to treatment among patients was 88% in the tolvaptan arm (with an average daily dose of 95 mg) and 93% in the placebo arm (with an average sham dose of 110 mg placebo per day). The rate of AEs was similar between the tolvaptan (97.9%) and placebo (97.1%) treatment arms. The rate of serious adverse events (SAEs) was similar across treatment arms 18.4% in the tolvaptan arm and 19.7% in the placebo arm.

Aquaresis is an expected effect of tolvaptan treatment which, though commonly reported as an AE in the clinical trial, led to discontinuation of tolvaptan in only 8.3% of patients. These discontinuations mostly occurred early in the treatment period. Liver enzyme elevations have been reported in fewer than 5% of patients and were reversible following treatment discontinuation. As part of a Risk Management Plan (RMP) to ensure the safety of all patients receiving tolvaptan, patients will receive monthly liver function tests for the first 18 months and three-monthly thereafter to monitor enzyme levels.

Longer-term efficacy and safety of tolvaptan is currently being studied in a phase 3b single active arm extension study with total follow-up of up to six years (TEMPO 4:4) (Torres *et al*., 2014). A total of 871 patients (535 from the tolvaptan group, 296 from the placebo group) were enrolled in TEMPO 4:4 having completed other tolvaptan ADPKD studies, including TEMPO 3:4.

Long-term clinical benefits of tolvaptan

In order to estimate the longer-term outcomes of ADPKD patients, a patient simulation model was constructed to predict the lifetime underlying disease progression of ADPKD patients according to variable baseline characteristics, and the associated longer-term potential benefits of tolvaptan based on the results seen in TEMPO 3:4. Underlying disease progression in the model was informed by regression equations specified on the patient-level data from the placebo group of TEMPO 3:4. Simulated patients experienced progressing ADPKD (via TKV growth and renal function decline) and were modelled through a UK-specific ESRD pathway from the point of renal failure.

The average ADPKD patient randomised in TEMPO 3:4 (in terms of baseline age, gender, TKV and renal function), which is representative of the proposed licensed indication for tolvaptan, was predicted to enter ESRD at approximately age 52 years and have a life expectancy of approximately 65.6 years. These results are in line with the hypothesis that patients randomised to TEMPO 3:4 are more likely to experience rapidly progressing disease. The results from the model have been externally validated against two UK data sources (Otsuka Data on File [THIN], Thong *et al*., 2013) and another from a large observational study in the US (CRISP).

When the clinical efficacy of tolvaptan seen in TEMPO 3:4 on the slowing of renal function decline is applied to the underlying disease progression, the model estimates significant long-term clinical benefits in terms of delay to ESRD, RRT outcomes and life expectancy. The model predicts that patients representative of the licensed indication initiated on tolvaptan, incorporating the effect of discontinuation rates seen in TEMPO 3:4, would be expected to enter ESRD 3.7 years later, spend two years less in ESRD and live approximately 1.5 years longer than those receiving no active treatment.

This model formed the basis for the economic evaluation presented in the submission.

Tolvaptan Economic Value

The model described above was used to assess the cost-effectiveness of tolvaptan to the NHS in England and Wales compared to no active treatment (both in addition to best supportive care). Costs associated with tolvaptan acquisition (under the terms of a patient access scheme offered by the manufacturer), routine monitoring and disease management were applied, along with utility decrements associated with progressing disease and RRT modalities.

The long-term clinical benefits outlined above translate into significant HRQoL gains (0.9 additional discounted quality-adjusted life years (QALYs)) for patients initiated with tolvaptan compared to no active treatment. In addition, initiation of tolvaptan is associated with an approximate 0.5 year reduction in time on dialysis and 20% reduction in the number of kidney transplants in this patient population.

Under the terms of the patient access scheme, in the base case tolvaptan is estimated to be associated with an incremental cost-effectiveness ratio (ICER) of approximately £34,800 per QALY gained. A range of structural and scenario sensitivity analyses were conducted to ensure that this result was robust. Given that tolvaptan can be regarded as a step-change in the management of ADPKD, this ICER can be regarded as good value-for-money to the NHS.

With flat pricing across all doses, and the low prevalence of ADPKD, tolvaptan will have a predictable budget impact to the NHS.

Conclusions

- ADPKD is a serious, inherited and progressive disease characterised by the development and expansion of fluid-filled cysts in the kidneys that ultimately leads to renal failure and reduced life expectancy
- No licensed treatment for ADPKD is currently available that delays time to ESRD; there is a need for a disease-modifying therapy that delays progression
- NICE Clinical Guideline 182 (CKD) states: "…*Strategies aimed at earlier identification and prevention of progression to [ESRD] are clearly needed*…", highlighting this as an area of NHS priority.
- Tolvaptan will be the first and only licensed disease-modifying treatment indicated for ADPKD, slowing total kidney volume growth and the rate of renal function decline.
- In the TEMPO 3:4 phase 3 clinical trial, tolvaptan demonstrated a significant relative reduction of 49.2% on TKV growth over three years and a significant relative reduction of 31.6% in the annual slope of renal function decline, as compared with placebo ($p<0.001$).
- Tolvaptan has a manageable tolerability profile with only 15.4% of patients assigned to the tolvaptan arm discontinuing due to adverse events over the 3 year pivotal trial, compared to 5% in the placebo arm
- Long-term outcomes modelling in the proposed license population suggests that in the base case the benefits of tolvaptan would yield to a mean delay to ESRD of approximately 3.7 years, leading to increased life expectancy (mean additional 1.5 years), maintenance of patient HRQoL (mean 0.9 additional discounted QALYs) and reduced demand of RRT services in the NHS (mean two years less in ESRD, and mean 20% reduction in transplantation)
- Tolvaptan is a step-change in the management of ADPKD, being the first licensed intervention to delay ADPKD progression that will permit the time to ESRD to be delayed, reducing pressure on transplant and dialysis services
- Under the proposed patient access scheme, in the base case tolvaptan is associated with an ICER of approximately £34,800 per QALY gained, and accordingly represents a cost-effective use of NHS resources

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

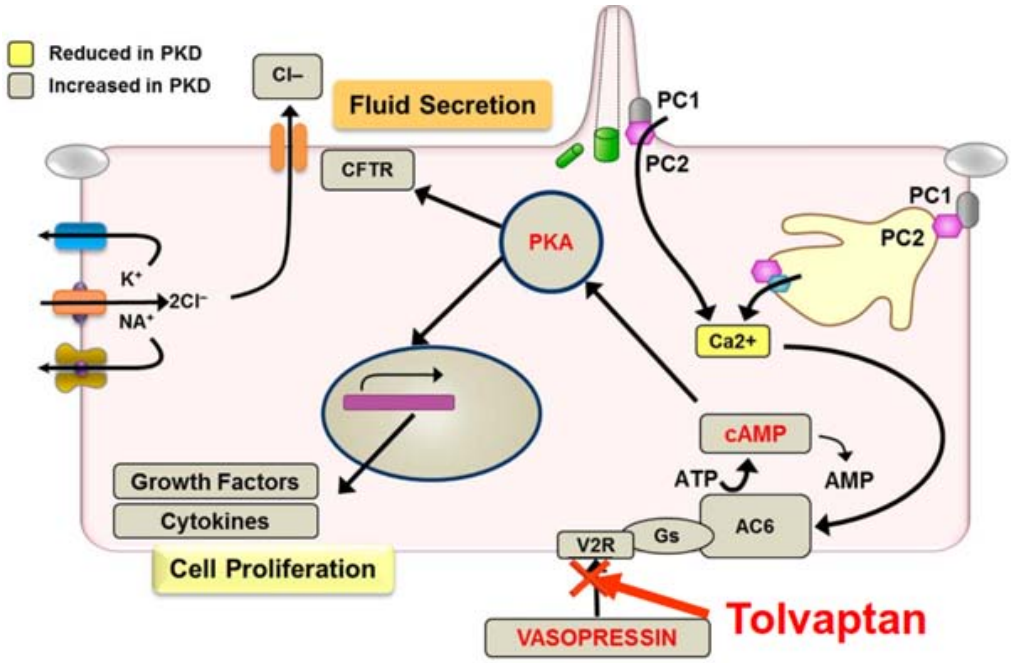
- Brand name: Jinarc
- Approved name: Tolvaptan
- Therapeutic class: Vasopressin antagonist

1.2 What is the principal mechanism of action of the technology?

Tolvaptan is a selective vasopressin antagonist that specifically blocks the binding of vasopressin to the V2 receptors of the distal portion of the nephron (Figure A1) (Otsuka, 2014). Inhibition of V2 receptors leads to reduced intracellular cyclic adenosine monophosphate (cAMP) concentration; reduced protein kinase A (PKA) signalling; and reduction of cell proliferation, cyst formation, and fluid excretion (Wang *et al*., 2005), thereby reducing kidney growth and protecting kidney function.

The affinity of tolvaptan for the human V2 receptor is 1.8 times that of native vasopressin (Yamumara *et al*., 1998). Therefore, tolvaptan binds to the V2 receptor more strongly than vasopressin and is able to displace vasopressin from the receptor (Yamumara *et al*., 1998).

Figure A1. Mechanism of action of tolvaptan



AC6 = adenylate cyclase; AMP = 3'-5'-cyclic adenosine monophosphate; ATP = adenosine triphosphate; Ca2+ = calcium ions; cAMP = cyclic 3'-5'-cyclic adenosine monophosphate; CFTR = cystic fibrosis transmembrane conductance regulator; CI- = chloride ions; Gs = G protein alpha subunit; K+ = potassium ions; NA+ = sodium ions; PC1 = proprotein convertase 1; PC2 = proprotein convertase 2; PKA = protein kinase A; PKD = polycystic kidney disease; V2R = vasopressin 2 receptor.

Source: Otsuka (2013).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

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.

On 5 August 2013, the European Commission granted orphan designation (EU/3/13/1175) to Otsuka Pharmaceutical Europe Ltd for tolvaptan for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD) of which the indication detailed in the submission is a significant subset.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Since the date of submission to NICE pre-dates the anticipated date of CHMP positive opinion, the EPAR is not yet available.

Hepatotoxicity has been observed in some ADPKD patients receiving tolvaptan. To mitigate this risk, measures are described in the EU Risk Management Plan (RMP) to ensure that patients receive monthly liver function tests for the first 18 months of treatment with tolvaptan, and at three-monthly periods thereafter. These measures will also include the mandatory provision of training material and 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. Post-authorisation studies will be conducted to ensure the effectiveness of these measures.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Tolvaptan is anticipated to be indicated as follows:

"*To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease in patients with CKD [chronic kidney disease] stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease. Tolvaptan is indicated in adults*." (Otsuka, 2014).

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Table A1 presents a summary of ongoing studies from which additional evidence is expected to be available in the next 12 months.

Table A1. List of ongoing studies (sponsored by the manufacturer) in adults with ADPKD from which additional evidence is expected to be available in the next 12 months

Study acronym; phase (other study ID number)	Study design and objectives	Study status	NCT number
Ongoing trial of tolvaptan in adults with ADPKD			
TEMPO 4:4 Phase 3 (156-08-271)	Non-randomised, parallel-group, open-label, multicentre extension study to demonstrate benefit of cumulative treatment of tolvaptan on ADPKD progression	Ongoing Interim analysis available (Torres *et al*., 2014) Anticipated trial completion in late 2014 with patients having the option to roll over into study 156-13-211 in countries where the product is not commercially available	NCT01214421
Ongoing Otsuka-sponsored non-interventional study			
OVERTURE NCT01430494 Observational study (156-10-291)	Multicentre, prospective, observational cohort study to identify and characterise factors that predict rapid progression toward, or higher frequency of, clinically relevant morbidities in ADPKD The study also will assess PROs for pain, HRQL, and ADPKD-associated health burden and will summarise the impact of disease on MRU and productivity	Ongoing Database locked on 30th October 2014. Study CSR not yet available.	NCT01430494

ADPKD = autosomal dominant polycystic kidney disease; HRQL = health-related quality of life; ID = identification; MRU = medical resource use; NCT = National Clinical Trial; PRO = patient-reported outcomes; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of availability of tolvaptan in the UK for the indication detailed in this submission is during Q2/Q3 2015.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

On 24 March 2014, tolvaptan was approved in Japan for the treatment of ADPKD. Tolvaptan for the treatment of ADPKD has also been submitted for regulatory approval in Canada and Switzerland.

On 05 August 2013, the US FDA Advisory Committee voted not to recommend tolvaptan for treatment of ADPKD. [redacted](study 156-13-210, identifier NCT02160145) [redacted]

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Tolvaptan for the treatment of ADPKD is expected to undergo a health technology assessment by the Scottish Medicines Consortium in Q2 2015.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A2. Unit costs of technology being appraised

Pharmaceutical formulation	Tablet
Acquisition cost (excluding VAT)	NHS list price: £1,208.20 for each 28-day pack (£43.15 per day) [redacted]
Method of administration	Oral
Doses	Tolvaptan 15 mg, 30 mg, 60 mg, and 90 mg tablets (provided in 28-day packs of split-dose tablets).
Dosing frequency	Twice daily (upon waking and 8 hours later) [a]
Average length of a course of treatment	To be continued long-term; withdrawn at onset of ESRD or renal replacement therapy if ESRD has not been reached
Average cost of a course of treatment	N/A (dependent on length of treatment, which will be variable)
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	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.

ESRD = end-stage renal disease; N/A = not applicable; VAT = value-added tax.

[a] The manufacturer does not yet have CHMP positive opinion or a finalised SPC.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

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. 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 for all PKD patients over 20 years of age (NICE, 2014).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

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.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other therapies are required over and above those used as best supportive care to manage the signs and symptoms associated with ADPKD complications as they arise.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

Context summary

- Autosomal dominant polycystic kidney disease (ADPKD) is a serious, inherited and progressive cystic renal disease which, despite being rare, is the fourth-leading cause of chronic renal failure.
- ADPKD is associated with a significant reduction in patient HRQoL and life expectancy
- The requirement for renal replacement therapy (RRT) in the form of dialysis or kidney transplantation in ADPKD patients represents a large burden to the NHS
- The estimated diagnosed prevalence of ADPKD in the UK is 3.9 per 10,000, of which, the population eligible for tolvaptan under the proposed licensed indication is a significant subset.
- Although ADPKD eventually leads to ESRD for most patients, substantial heterogeneity exists, both in terms of the rate of disease progression and the frequency/severity of ADPKD complications.
- ADPKD complications can lead to substantial morbidity, even early in the disease, and include pain, hypertension, recurrent urinary tract infections, haematuria and nephrolithiasis.
- Total kidney volume (TKV) has been validated in long-term follow-up studies as a prognostic indicator of disease progression and can be used to help identify patients at risk of rapid progression prior to the onset of significant renal function decline
- No licensed treatment is currently available that delays renal progression in ADPKD; a disease-modifying therapy that delays renal progression in ADPKD is needed.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

ADPKD overview

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 (Takiar and Caplan, 2011; Patel *et al*., 2009). It is estimated to affect 3.56 per 10,000 of the EU population (diagnosed prevalence) (EU/3/13/1175; Otsuka, data on file, 2013b; Willey, 2013; Patch *et al*., 2011). 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 (Patch *et al*., 2011).

ADPKD has a highly heterogeneous disease course (Torres *et al*., 2007; Harris and Rossetti, 2010). Although the majority of patients with ADPKD eventually develop ESRD, substantial heterogeneity exists in terms of presentation, severity, and the rate of disease progression (Harris and Rossetti, 2010). This heterogeneity contributes to the difficulty in establishing a prognosis in ADPKD.

ADPKD is a genetic disease. Two types of polycystic kidney disease (PKD) exist, both of which are inherited disorders characterised by cystic expansion of the kidneys leading to progressive kidney enlargement, tissue damage, renal failure, as well as extra-renal manifestations (Halvorson *et al*., 2010; Dell, 2011). The two types are ADPKD and autosomal recessive PKD (ARPKD) (Halvorson *et al*., 2010).

ARPKD is caused by mutation in the *PKHD1* gene that codes for a protein called fibrocystin (Halvorson *et al*., 2010). ARPKD generally presents in a younger population than ADPKD and has a faster and more severe disease course (Halvorson *et al*., 2010; Capisonda *et al*., 2003). As ARPKD is autosomal recessive it is extremely rare, with an estimate incidence of 1 in 20,000 live births (Halvorson *et al*., 2010). ARPKD is a distinct disease from ADPKD and is not discussed further in this submission.

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 (Torres *et al*., 2007).

The proteins encoded by PKD1 and PKD2 are known as polycystin-1 and polycystin-2 respectively. The two gene products associate with one another (as well as other proteins) to form a complex that is localised to membranes in multiple cell types, including renal epithelial cells. In tubular epithelial cells, the polycystin complex localises predominantly to the primary cilium, a single hair-like organelle projecting from the surface of many cells. On renal epithelial cells, the primary cilium extends into the lumen of the renal tubule, where it acts as a mechano- and chemo-sensory probe to assess a variety of features of the renal filtrate. Whether a third gene is involved in a small number of unlinked families is considered uncertain (Torres *et al*., 2007).

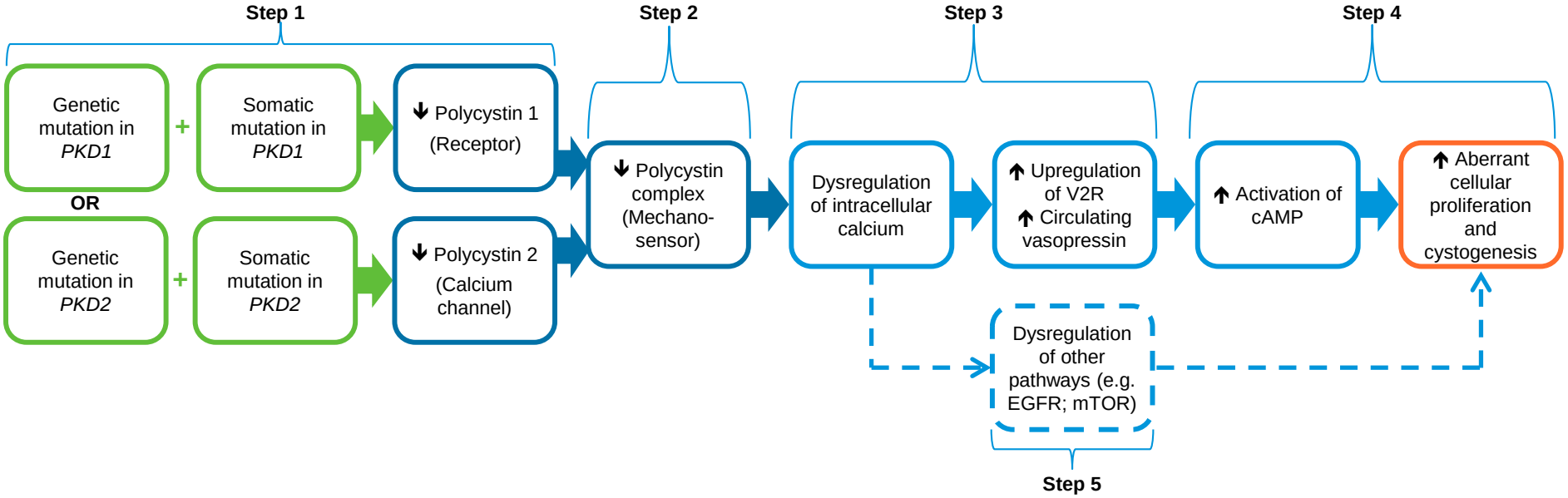
In ADPKD, the patient only needs to receive the abnormal gene from one parent to inherit the disease (autosomal dominant). Due to its autosomal dominance, each patient has a 50% risk of passing the disease on to their offspring. It is a highly penetrant disease (i.e., almost everyone that inherits an ADPKD mutation develops multiple renal cysts during their lifetime) (Harris and Rossetti, 2010). However, the observed phenotype varies considerably among individuals, even those from within the same family (Torres *et al*., 2007; Harris and Rossetti, 2010). The variation between patients as to the exact mutation that exists within a single gene means that genetic factors have limited sensitivity for renal disease prognosis on an individual patient level (Torres *et al*., 2007; Harris and Rossetti, 2010). For *PKD1*, 436 different mutations have been identified accounting for the disease in 544 families (Harris and Rossetti, 2010). For *PKD2*, 115 different mutations have been identified accounting for the disease in 198 families (Harris and Rossetti, 2010).

Genetic factors are also thought to impact cyst formation. Cyst formation in ADPKD occurs focally, sporadically, and in an age-dependent manner, with relatively few renal cysts typically being observed during the first few decades of life (although ADPKD may be diagnosed in prebirth scans [Dell, 2011]), increasing to many hundreds or thousands of cysts by the fifth decade (Pei, 2011).

Pathophysiology of ADPKD progression

An overview of the pathophysiology of ADPKD is presented in Figure A2 and explained in more detail in the following paragraphs.

Figure A2. Overview of pathophysiology of cyst formation in ADPKD



ADPKD = autosomal dominant polycystic kidney disease; cAMP = cyclic adenosine monophosphate; EGFR = epidermal growth factor receptor; mTOR = mammalian target of rapamycin; V2R = vasopressin V2 receptor.

Sources: Torres *et al*. (2007); Grantham *et al*. (2011); Dell (2011); Pei (2011); Torres and Harris (2006).

PKD1 encodes the protein polycystin 1, which is expressed throughout the body, including the kidney, liver, pancreas, heart, and blood vessels (Dell, 2011). *PKD2* encodes the protein polycystin 2 (Dell, 2011).

Polycystin 1 and polycystin 2 interact to form a polycystin complex that regulates intracellular levels of calcium (Dell, 2011; Pei, 2011). Disruption of the polycystin complex in renal tubular epithelial cells leads to increased cellular proliferation and cyst formation (Pei, 2011). Because the action of both Polycystin 1 and polycystin 2 is mediated via the polycystin complex, mutations in either *PKD1* or *PKD2* can result in an identical clinical phenotype in terms of renal and extra-renal manifestations (Pei, 2011).

Low calcium levels in animal models of ADPKD and in patients with ADPKD are associated with an increase in intracellular cyclic AMP (cAMP) (likely due to the inappropriate activation of adenylyl cyclase and inhibition of phosphodiesterase). Cyclic AMP, an intracellular signalling molecule, stimulates cell division in many different cell types and likely plays a central role in the induction and growth of cysts.

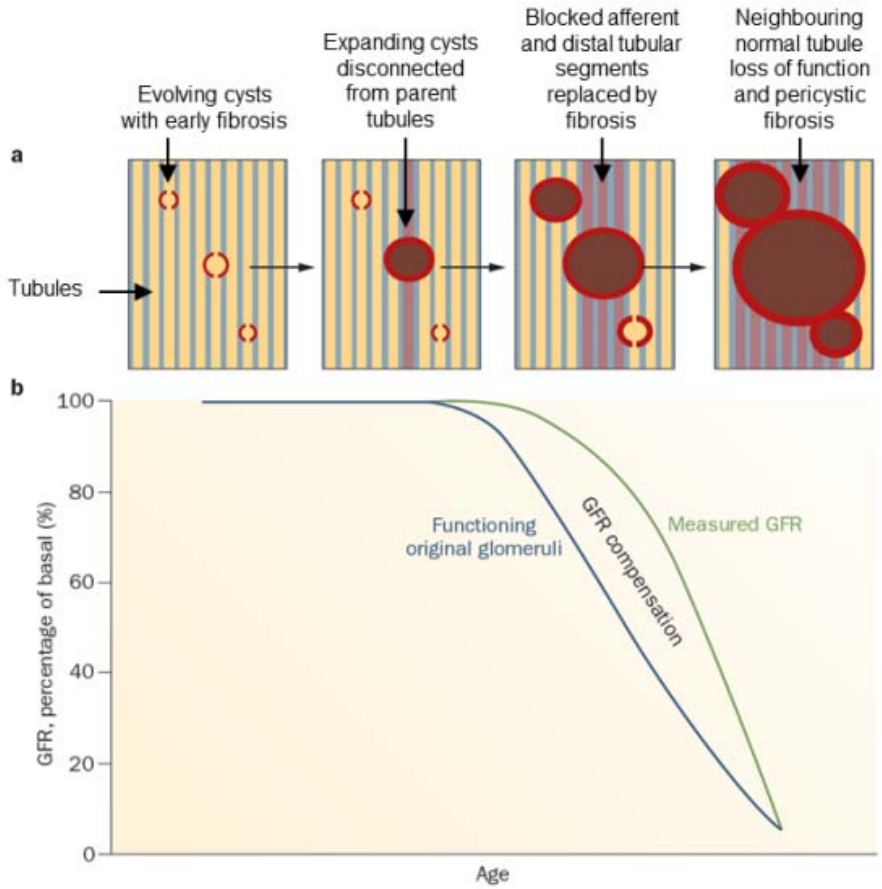
In ADPKD, high concentrations of circulating vasopressin lead to an increased intracellular cAMP concentration, which promotes cyst formation and fluid accumulation (Torres *et al*., 2007; Dell, 2011; Takiar and Caplan, 2011) and is a dominant factor controlling the rate of cyst and kidney enlargement in ADPKD (Grantham *et al*., 2011; Meijer *et al*., 2011).

An overview of how cyst formation leads to renal functional decline in ADPKD is presented in Figure A3a. As cysts develop and grow, they damage the kidney by structural compression, obstruction of urine flow, and through intracellular inflammation and fibrosis, leading to progressive nephron loss (Grantham *et al*., 2011). As cysts enlarge over time, the kidney expands.

Despite the continuous loss of functioning nephrons throughout this process, kidney function does not decline until later in the course of ADPKD (Figure A3b) (Grantham *et al*., 2011). This is due in part to a compensatory mechanism known as hyperfiltration that occurs in the polycystic kidney. As the number of functioning nephrons decrease, the remaining nephrons compensate by increasing the volume of filtrate through the glomerulus which is sufficient to maintain creatinine clearance rates at relatively normal levels for decades (Grantham *et al*., 2011).

The expanding cysts and surrounding fibrotic material eventually replace enough functional parenchyma to begin to have observable effects on the clearance capacity of the kidney and kidney function begins to drop until ESRD is reached. Late in the disease, hypoxia, inflammation, and fibrosis contribute to declining GFR (Grantham *et al*., 2011).

Figure A3. How cyst growth leads to renal functional decline in ADPKD



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

Notes:

a. Schematic of renal tissue showing tubules (yellow lines); evolving cysts with thickened basement membrane and early fibrosis (red broken circles); expanding cysts disconnected from parent tubules (brown-filled red circles); blocked afferent and distal tubular segments that are destroyed by atrophy or apoptosis (cell death) and replaced by fibrosis (pink lines); physically displaced and compressed neighbouring normal tubules leading to loss of function and pericystic fibrosis (red lines).

b. GFR in relation to physical changes within the kidneys. Note that age is not defined in Figure A4b to allow for the variable ages when the GFR decline might be detected in individual patients.

Source: Grantham *et al*. (2011).

Potential therapies that target the mechanism of cyst growth and can be initiated early in the disease course before the renal tissue has been irreversibly damaged would be expected to be more effective than treatments initiated after renal function has started to decline (Grantham *et al*., 2011). Recent advances in ADPKD research have identified several pathways implicated in cyst formation (proliferation, secretion, and fibrosis) that may prove to be key therapeutic targets (Meijer *et al*., 2011; Norman, 2011).

Diagnosis

As a genetic disorder, ADPKD is present from birth; however the presentation of disease-related complications is highly heterogeneous and may present at different ages and stages of the disease (Thong and Ong, 2013). In a patient with a family history of ADPKD, renal ultrasound is the most common modality used to diagnose the disease and is recommended in NICE Clinical Guideline 182 for patients with a family history of polycystic kidney disease (Torres *et al*., 2007; Danish Society of Nephrology, 2012; NICE 2014). Diagnostic imaging criteria are available to interpret the results of ultrasound scanning and are detailed in Table A3. Until recently, the Ravine criteria were used to interpret ultrasound findings in ADPKD; however, these criteria generally have been replaced by the Pei criteria (Danish Society of Nephrology, 2012; Pei *et al*., 2009; Ravine *et al*., 1994). Table A3 provides a summary of the Ravine and Pei criteria. The Pei criteria cover patients with *PKD1* or *PKD2* mutations, whereas the Ravine criteria only cover patients with *PKD1* mutations (Danish Society of Nephrology, 2012; Pei *et al*., 2009; Ravine *et al*., 1994). The Pei criteria are more stringent and require three or more unilateral or bilateral renal cysts to minimise false-positive diagnoses in younger patients (i.e. those aged 15 to 39 years) (Pei *et al*., 2009).

Table A3. Diagnostic imaging criteria for patients with a family history of ADPKD

Ravine criteria (Ravine *et al*., 1994)		Pei criteria (Pei *et al*., 2009)	
Age	**Diagnostic criteria (for patients with a 50% risk of *PKD1* mutation)**	**Age**	**Diagnostic criteria (for patients with a family history of *PKD1* or *PKD2* mutations)**
< 30 years	≥ 2 unilateral or bilateral cysts	15-39 years	≥ 3 unilateral or bilateral cysts
30-59 years	≥ 2 cysts in each kidney	40-59 years	≥ 2 cysts in each kidney
≥ 60 years	≥ 4 cysts in each kidney	≥ 60 years	≥ 4 cysts in each kidney
ADPKD = autosomal dominant polycystic kidney disease. Note: Under the Pei criteria, the finding of < 2 cysts in patients aged > 40 years excludes an ADPKD diagnosis.			

Use of either of these ultrasound diagnostic imaging criteria is associated with good diagnostic accuracy, with sensitivity and specificity generally >85%, and therefore tests other than ultrasound are not generally required for the diagnosis of ADPKD (Ravine *et al*., 1994; Pei *et al*., 2009).

Genetic testing for ADPKD is not routinely carried out in the UK, but is used in certain situations, for example, when a clear diagnosis cannot be ascertained from imaging (Torres *et al*., 2007; Danish Society of Nephrology, 2012; Pei *et al*., 2009; Ars *et al*., 2014). It is complicated by the large size and complexity of the PKD gene and the substantial heterogeneity of possible mutations (Torres *et al*., 2007; Harris and Rosseti, 2010; Rossetti *et al*., 2007).

Clinical features/complications

Renal cysts are the first verifiable manifestation of ADPKD. Cyst formation always precedes flank pain, hypertension, gross haematuria, nephrolithiasis, kidney infections, and reduced renal function in patients with ADPKD. Kidney volume expansion and cyst development are the major determinants of renal outcomes in ADPKD. The inverse correlation between kidney volume and function is well established (see later sub-section).

Clinical features in ADPKD consist of renal manifestations (those related to the kidneys) and extra-renal manifestations (those unrelated to the kidneys) (Table A4). Renal manifestations comprise renal cysts and complications caused by their development and enlargement: a cyst-filled kidney can weigh up to 30 pounds (~13.6 kg), which is 80-120 times the weight of a normal adult kidney (125-170 grams in

males, and 115-155 grams in females) (Torres and Harris, 2009; National Institute of Health, 2010). Extra-renal manifestations of ADPKD include hepatic, pancreatic, thyroid, subarachnoid, and seminal vesicle cysts; intracranial aneurysms; cardiac valvular disease; and male infertility (Torres and Harris, 2009; Halvorson *et al*., 2010).

Table A4. Renal and extrarenal manifestations of ADPKD

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. Sources: Takiar and Caplan (2011); Patel *et al*. (2009); Parfrey *et al*. (1990); Halvorson *et al*. (2010).	

In addition to the risk of progression to ESRD, patients with ADPKD often experience substantial complications, often prior to significant decline in renal function, including pain, hypertension, and recurrent urinary tract infections (Halvorson *et al*., 2010; Torres and Harris, 2009). There is large variability between individuals with ADPKD, even amongst those in the same family, in terms of presentation, severity and progression of ADPKD (Harris and Rossetti, 2010). Symptoms may appear early or late in the disease course and may not necessarily prompt diagnosis (Halvorson *et al*., 2010). In patients who experience early disease manifestations, symptoms may include hypertension, acute abdominal or flank pain, haematuria, palpable kidneys, kidney stones, diverticulosis, and recurrent urinary tract infections (Halvorson *et al*., 2010). Progressive development of renal cysts leads to impaired renal function, and ultimately ESRD in many affected patients (Halvorson *et al*., 2010; Torres and Harris, 2009).

ESRD and mortality

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 (Martinez *et al*., 2013; Ørskov *et al*., 2010; Shaw *et al*., 2014; Spithoven *et al*., 2014). By age 70 years, 75% of patients with ADPKD will reach ESRD (Parfrey *et al*., 1990). However, there is a wide variation in the rate of progression, and many patients progress at a faster rate and reach ESRD at a much younger age.

In particular, the patient population considered in this submission is those "with evidence of rapidly progressing disease" and therefore likely to progress to ESRD more rapidly than average. Outputs from long-term outcomes modelling used to inform the economic evaluation (Section 7.7) estimate that the average ADPKD patient randomised in TEMPO 3:4 (in terms of baseline age, gender, TKV and renal function), which is representative of the proposed licensed indication for tolvaptan, is predicted to enter ESRD at approximately age 52 years.

The age-standardised mortality rate in patients with ADPKD is 60% higher than in the general population (Florijn *et al*., 1995). Data from a UK cohort study reports that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years) (Shaw *et al*., 2014), as compared to the current UK life expectancy of 81.5 years (World Bank, 2014). However, the life expectancy in a faster progressing patient population considered in this submission is likely to be even lower. Outputs from the long-term outcomes modelling noted above estimate the mean natural life expectancy for ADPKD patients eligible for tolvaptan to be approximately 64-65 years (Section 7.7).

Data suggest that whilst time to renal failure has not changed substantially, the mean age at death in ADPKD has increased over time, most likely due to reductions in cardiovascular and cerebrovascular mortality. This implies that more patients with ADPKD reach ESRD and require renal replacement therapy (Shaw *et al*., 2014; Ørskov *et al*., 2012).

Data indicating the disease stage at which death occurs in patients with ADPKD are limited and inconclusive. A retrospective study of patients with ADPKD in the UK found that the majority (68%) of deaths over the period of 1991–2008 occurred in patients prior to the requirement for RRT (Patch *et al*., 2011). A US follow-up study

(1956–1993) found that 23% of patients died prior to ESRD (Fick and Johnson, 1995). The beneficial effects of transplant are supported by a study of the Danish national registries, in which data from 823 patients with ADPKD in ESRD were collected from 1993–2008 (Ørskov *et al*., 2012). The death rate per 1,000 patient years was 164.6 in patients on dialysis compared with 44.7 in patients who had received a transplant.

The most frequent cause of death in patients with ADPKD across all disease stages including patients with ESRD or in RRT is cardiovascular disease (Rahman *et al*., 2009; Fick *et al*., 1995; Ørskov *et al*., 2012; Martinez *et al*., 2013; Shaw *et al*., 2014; Spithoven et a., 2014). However, death due to infections occur in approximately 1 in 5 patients, with many patients' deaths linked to complications of ADPKD (e.g. renal cyst infection, urinary tract infection) or renal replacement therapy (e.g. infected catheter or haemodialysis fistula) (Rahman *et al*., 2009; Fick *et al*., 1995).Since ADPKD has a highly heterogeneous disease course, those patients at risk of rapid progression to ESRD are the patients with the greatest burden and unmet need (i.e. those considered in this submission).

Disease burden

Despite being rare, ADPKD is the fourth leading cause of end-stage renal disease (ESRD) in adults and is associated with substantial burden to healthcare services due to increasingly frequent hospital visits, management of complications, and, particularly, renal replacement therapy (dialysis and kidney transplantation) (Covance, 2014; Szende *et al*., 2014; Knight *et al*., 2013; Grantham *et al*., 2006). 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 (Couser *et al*., 2011). Alongside the direct loss of renal function, ESRD can be associated with acute, life-threatening complications such as hyperkalaemia, pulmonary oedema and metabolic disturbances, which may have a negative impact on patient HRQL (Devine and Aisling, 2014).

ESRD is also associated with a substantial economic burden due to frequent hospital visits, management of complications, and, particularly, dialysis or kidney transplantation (Covance, 2014; Szende *et al*., 2014; Knight *et al*., 2013). In addition to the risk of progression to ESRD, patients with ADPKD often experience substantial complications, often beginning prior to the loss of renal function, including acute or

chronic pain, hypertension, and recurrent urinary tract infections (Halvorson *et al*., 2010; Torres and Harris, 2009).

There are currently no validated ADPKD-specific health-related quality of life (HRQL) instruments available; as a result, generic HRQL instruments such as the SF-36 Health Survey (SF-36) and the EuroQol 5 Dimensions (EQ-5D) are used to measure HRQL burden in patients with ADPKD. However, these generic measures are likely to be insensitive to the full burden experienced in patients with ADPKD, as these instruments may be unable to detect clinically relevant dissatisfaction with quality of life (Rizk *et al*., 2009; Perrone *et al*., 2013).

Renal size is a strong predictor of decline in renal function (Chapman *et al*., 2010; Chapman, 2013), which in turn is associated with decline in HRQL. In a study of 1,043 patients with ADPKD, patients with higher eGFR (> 60 mL/min/1.73m^2) had higher (i.e., better) scores on the physical functioning, role-physical, general health, vitality, and physical component summary domains of the SF-36 than patients with lower eGFR (20 to 44 mL/min/1.73m^2; $P < 0.05$ across eGFR groups for males and females). Patients with lower eGFR also were more likely to experience pain that interfered with daily life than patients with higher eGFR (Miskulin *et al*., 2014).

ADPKD-related complications inevitably will significantly reduce health-related quality of life (HRQoL) (Rizk *et al*., 2009). Patients with ADPKD may experience acute/debilitating pain due to cyst rupture or cyst infection, or chronic/nagging pain (i.e., daily pain lasting more than 4 to 6 weeks) due to increased renal volume. Patients with ADPKD who are taking pain medications have been shown to have significantly reduced physical component summary scores and physical function index bodily pain index scores (as measured by the SF-36), compared with patients who do not require pain medications (Rizk *et al*., 2009). Patients with ADPKD have reported experiencing pain (measured using SF-36) that interfered with activities of daily life, including sleep, mood, enjoyment of life, work, walking ability, social activities or hobbies, relations with others, and strenuous physical activity (Miskulin *et al*., 2014).

As a genetic disease with no available disease modifying treatment, many ADPKD patients experience debilitating psychological conditions, with >60% of patients having depression (de Barros *et al*., 2011; Marsick *et al*., 1998). Being an autosomal dominant disease, affected individuals have a 50% risk of passing on the disease to their offspring, meaning many patients choose not to have a family. It is not

uncommon for ADPKD patients to be diagnosed after having children of their own, leaving difficult decisions regarding screening of children and potential resultant guilt. Patients with ADPKD report experiencing anxiety and guilt at passing the disease on to their children (Palsgrove *et al*., 2014). Feelings of guilt may be brought to the surface by diagnostic testing to identify family members and children who may carry the genetic mutation and who may be at risk (McAllister *et al*., 2007). Reproductive choices of patients with genetic diseases such as ADPKD may be affected if patients are concerned about passing on the condition to their children (McAllister *et al*., 2007). Caregivers of patients with ADPKD also experience a negative societal, physical, and emotional burden due to ADPKD (Palsgrove *et al*., 2014).

RRT itself, particularly dialysis, has a negative impact on patient HRQoL. The inconvenience and discomfort associated with the process of establishing vascular access, the frequency of dialysis procedures and the restrictions to diet and fluid intake all combine to significantly impact HRQoL. Dialysis also superimposes significant new clinical risks, particularly the risk of vascular access-related serious infection, to the already burdensome ADPKD complications.

As noted above, unlike other causes of ESRD, ADPKD patients reach ESRD at a relatively young age. As such, the relatively early requirement for dialysis will impact the ability to work and enjoy leisure time.

Current management and unmet need

No licensed treatment for ADPKD is currently available that has been demonstrated to delays 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 (NICE Clinical Guideline 182, 2014; Danish Society of Nephrology, 2012). 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 (Rizk *et al*., 2009; Covance, 2014; Szende *et al*., 2014; Lee *et al*., 2005).

Evaluating renal disease progression in ADPKD

As noted above, the principle clinical manifestations of ADPKD progression are growth in renal size and decline in renal function. Both of these measures can be evaluated in several ways.

Measurement of renal size

Increase in renal size is an important manifestation of ADPKD progression which occurs even before kidney function declines (Chapman *et al*., 2012). Historically, renal size was measured in terms of renal length (Sanusi *et al*., 2001). However, total kidney volume (TKV) is now considered to be a superior indicator of kidney mass in healthy and diseased kidneys (Sanusi *et al*., 2001). Whilst TKV is used relatively less frequently in routine practice it has been used as an inclusion criterion and primary efficacy endpoint in the most significant studies of ADPKD in recent years as well as being identified as the most important predictor of clinical outcome in the CRISP cohort. ADPKD clinical studies which have used TKV as an inclusion criterion and primary efficacy endpoint including the following:

- TEMPO 3:4 (Torres *et al*., 2012)
- HALT PKD A (Torres *et al*., 2012)
- Sirolimus trial (NCT00346918; Serra *et al*., 2010)
- Sirolimus SIRENA trial (NCT00491517; Perico *et al*., 2010)
- Everolimus trial (NCT00414440; Walz *et al*., 2010)
- Somatostatin ALADIN trial (NCT00309283; Caroli *et al*., 2013)

Imaging techniques used in assessment of TKV include ultrasound, CT, and MRI.

- Renal ultrasound has several advantages, including low cost and resource use (Bae *et al*., 2010), and has been shown to perform as well as MRI in monitoring renal volume changes over time (Chapman *et al*., 2014).
- Computed tomography using an iodinated contrast agent is an accurate imaging method to assess renal structures (e.g., cysts) and to determine renal size (Bae *et al*., 2010). However, because CT requires the use of ionizing radiation and an iodinated contrast medium, it is contraindicated in some patients (Bae *et al*., 2010).
- Magnetic resonance imaging provides high-resolution images without the patients being exposed to ionizing radiation or an iodinated contrast medium (Bae *et al*., 2010).

TKV can be measured by use of either the stereology method or the ellipsoid method.

- Stereology method
  - TKV is estimated using measurements from imaging slices taken through the kidneys (Nyengaard, 1999).
  - First, the number of intersections of a randomly oriented and positioned grid over the kidney are counted. Then, TKV is calculated from a set of slice images by summing the products of the area measurements by the slice thickness (Chapman *et al*., 2003).
  - A disadvantage of using stereology to measure TKV is that it is time-consuming and relies on specialised software that is not readily available (Nyengaard, 1999; Irazabal *et al*., 2014).

- Ellipsoid method
  - TKV is calculated by measuring three orthogonal axes (i.e. renal length, lateral renal diameter and anterior-posterior renal diameter) of the kidney and using a formula known as the ellipsoid formula[1] to determine TKV (Bakker *et al*., 1999; Breau *et al*., 2013).
  - Measurements can be performed by ultrasound or by CT/MRI (Breau *et al*., 2013).
  - The ellipsoid method for measuring TKV is gaining use as evidenced by the Mayo Clinic online TKV and progression risk calculator[2] (Breau *et al*., 2013).
  - 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 (Breau *et al*., 2013).
  - This method allows the calculation of TKV in 7 minutes (Breau *et al*., 2013).

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[1] Ellipsoid formula: renal length × lateral renal diameter × anterior-posterior renal diameter × (π/6).

[2] Available at: http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754.

In some studies, TKV has been adjusted for height (hTKV) as a proxy to control for a differential effect by gender.

Measurement of renal function

Once a patient is diagnosed with ADPKD, calculation of and monitoring of changes to renal function is standard clinical practice (Stevens *et al*., 2006; Wolyniec *et al*., 2008). Glomerular filtration rate (GFR) is widely accepted to be the best overall marker of renal function (Stevens *et al*., 2006). GFR can be either measured or estimated (Stevens *et al*., 2006; Lamb and Stevens, 2014). Table B5 provides an overview of renal function measurement and estimation. GFR can be measured (mGFR) as the urinary or plasma clearance of exogenous markers such as inulin, radiolabelled iothalamate, EDTA or DTPA, or iohexol. (Stevens *et al*., 2006; Lamb and Stevens, 2014).

Estimated GFR (eGFR) is derived based on its reciprocal relationship with serum creatinine concentration (i.e. higher serum creatinine is associated with lower glomerular filtration) (Stevens *et al*., 2006; Lamb and Stevens, 2014). GFR can also be estimated using cystatin C, a small protein that has a plasma concentration inversely related to GFR (Lamb and Stevens, 2014).Various estimating equations for creatinine clearance or eGFR have also been developed to account for potential influencing factors (e.g., age, sex, and race), namely Cockcroft-Gault, MDRD (Modification of Diet in Renal Disease), CKD-EPI (CKD Epidemiology) (Stevens *et al*., 2006; Lamb and Stevens, 2014). The accuracy of the different equations is also affected by the level of existing renal function. For example, the CKD-EPI equation is generally more accurate than the MDRD equation for patients with GFR >60mL/min/1.73m^2 whereas the MDRD equation is more accurate than the CKD-EPI equation for patients with GFR below this level (Lamb and Stevens, 2014). A 2013 systematic review conducted by the Swedish Council on Health Technology Assessment concluded that the accuracy of the Cockcroft-Gault equation is insufficient (P30 <75%), particularly at low GFR levels (<60mL/min/1.73m^2) (Swedish Council on Health Technology Assessment, 2013).

Table A5. Overview of renal function evaluations

Type of renal function evaluation	Details
Measured GFR (mGFR)	• Measured as the urinary or plasma clearance of exogenous markers, for example inulin, radiolabelled 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:
	  o Cockcroft-Gault equation
	  o Modification of Diet in Renal Disease (MDRD) study equation
	  o 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: Stevens *et al*. (2006); Lamb and Stevens, 2014.	

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 (Stevens *et al*., 2006). 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).

Correlation between renal size (TKV) growth and functional decline (GFR)

Changes in TKV can be reliably measured in early ADPKD, and kidney volume growth is directly correlated with a subsequent loss of renal function (as measured by GFR) (Grantham and Torres, 2006; Chapman *et al*., 2012; Wuthrich *et al*., 2009; Kistler *et al*., 2009; Chapman *et al*., 2003).

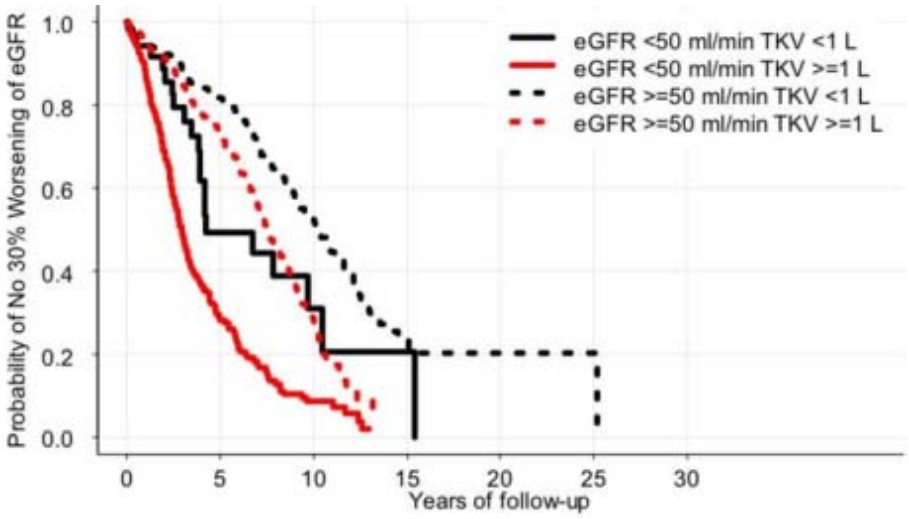
Baseline TKV is considered a reliable indicator of renal disease progression, as outlined in several longitudinal studies, including CRISP I and CRISP II and those from the PKD Outcomes Consortium (PKDOC) (Grantham *et al*., 2006; Chapman *et al*., 2008; Chapman *et al*., 2012; Perrone *et al*., 2014a; Perrone *et al*., 2014b; Perrone *et al*., 2014c). Data from CRISP indicated that TKV is more predictive of future renal function decline than age, gender or genotype.

Although eGFR does not always reflect early kidney damage in ADPKD, later in the disease process a decrease in eGFR is reciprocally associated with an increase in TKV. Data from CRISP I after 3 years of follow up showed that the slope in eGFR was not significantly different from zero in patients with a baseline TKV under 750 ml (1.39 ± 6.61 ml per minute per year, P = 0.063) or 750 to 1500 ml (−0.69 ±9.47 ml per minute per year, P = 0.57). However, in patients with TKV of greater than 1,500 mL at study baseline, the GFR declined by 4.33 ± 8.07 mL/min per year ($P < 0.001$) (Grantham *et al*., 2006; Chapman *et al*., 2008). These findings were confirmed by eight-year follow-up data from CRISP II, which re-enrolled 201 patients from CRISP 1 (Chapman *et al*., 2012). In CRISP II, TKV was referenced to height (hTKV). There was a strong negative correlation between baseline hTKV and iothalamate GFR measurement at each of six visits over 7.9 years (from r = 0.22, $P = 0.02$ at baseline to r = 0.65, $P < 0.001$ at year 8; n = 114 with complete data) (Chapman *et al*., 2012).

An analysis of combined data from CRISP and from other longitudinal renal registries (University of Colorado, Emory University and Mayo Clinic) suggested that both baseline TKV and baseline eGFR can be used as prognostic outcomes measures to estimate the risk of eGFR decline in patients with ADPKD (Perrone *et al*., 2014b). The endpoint of this study was worsening of eGFR by 30% from baseline value.

As shown in Figure A4, the predicted median time to 30% worsening of eGFR was longer in patients with smaller kidneys at baseline (black lines) than in patients with larger kidneys at baseline (red lines) for a given baseline eGFR status. Furthermore, the predicted median time to 30% worsening of eGFR was longer in patients with better baseline renal function (dashed lines) than in patients with poorer baseline renal function (solid lines) for a given baseline TKV (Perrone *et al*., 2014b). Overall, the combination of TKV less than 1 L and eGFR of 50 mL/min or greater at baseline was associated with the best prognosis in terms of renal decline, whereas the combination of TKV of 1 L or greater and eGFR of 50 mL/min or less at baseline was associated with more rapid renal decline (Perrone *et al*., 2014b).

Figure A4. Kaplan-Meier curve for worsening eGFR by baseline TKV and eGFR



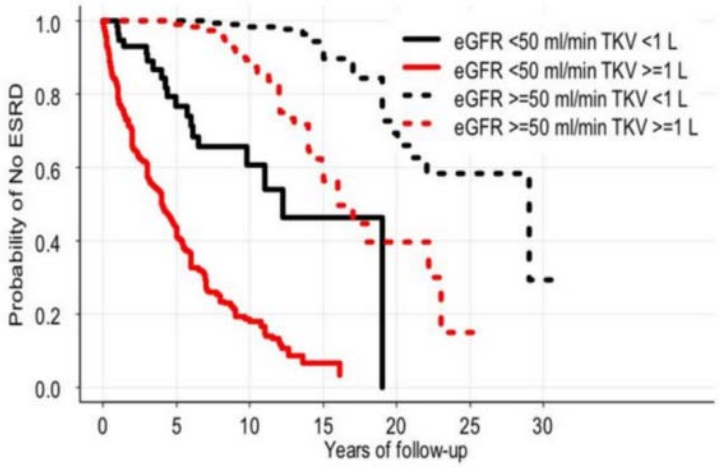
eGFR = estimated glomerular filtration rate; TKV = total kidney volume

Source: (Perrone *et al*., 2014b).

Further analysis of the PKDOC data set suggested that baseline TKV and baseline eGFR also can be used to predict time to ESRD (Perrone *et al*., 2014a). As shown in Figure A5, the predicted median time to ESRD was longer in patients with smaller kidneys at baseline (black lines) than in patients with larger kidneys at baseline (red lines) for a given baseline eGFR status. Furthermore, the predicted median time to ESRD was longer in patients with better baseline renal function (dashed lines) than in patients with poorer baseline renal function (solid lines) for a given baseline TKV (Perrone *et al*., 2014a). Overall, the combination of TKV of less than 1 L and eGFR of 50 mL/min or greater at baseline was associated with the best prognosis in terms of time to ESRD, whereas the combination of TKV of 1 L or greater and eGFR of less

than 50 mL/min at baseline was associated with a shorter time to ESRD (Perrone *et al*., 2014a).

Figure A5. Kaplan-Meier curve for ESRD by baseline TKV and eGFR



eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; TKV = total kidney volume

Source: (Perrone *et al*., 2014a).

The PKDOC analysed data for patients with ADPKD who had multiple measurements of TKV collected up to 30 years of follow-up (N = not stated) (Perrone *et al*., 2014c). This study evaluated the predictive value of TKV, baseline eGFR, baseline age, and other prognostic factors (e.g., sex, PKD mutation, and race) in estimating the risk of worsening of eGFR and ESRD. Baseline TKV was found to be the single strongest prognostic outcome measure for time to ESRD, and the association was found to be highly significant. This study demonstrated that TKV is a strong surrogate measurement for predicting ADPKD progression (Perrone *et al*., 2014c).

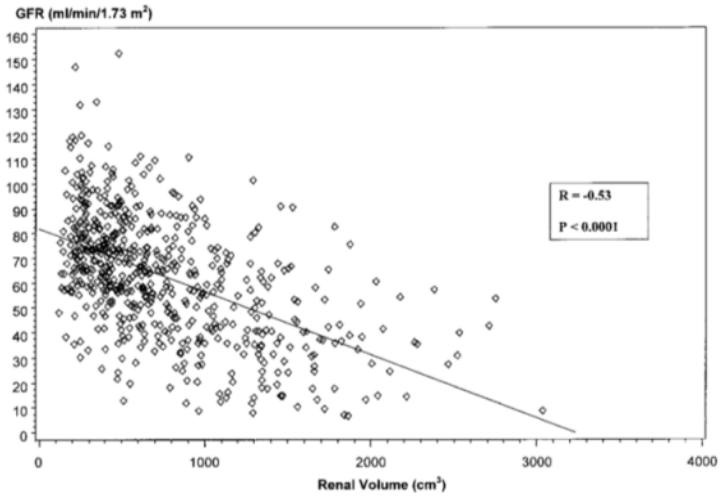
In addition to TKV at baseline, the rate of increase in renal volume has also been shown to correlate with renal disease progression (Fick-Brosnahan *et al*., 2002). A United States (US) longitudinal study in 229 patients with ADPKD used sequential ultrasound scans to determine the relationship between renal volume, rate of renal volume growth, and disease progression (Fick-Brosnahan *et al*., 2002):

- Patients who had stable GFR over time had significantly smaller initial renal volumes and slower renal growth rates over time than those patients in whom GFR declined over time.
- Correlational analyses showed the following:

- GFR (all data points) correlated significantly with renal volume over time (all data points; Figure A6) and initial age.
- Both follow-up GFR and rate of decline in GFR correlated significantly with initial renal volume, follow-up renal volume, renal volume growth rate, and age at study entry (Figure A7 shows the correlation between rate of decline in GFR and renal volume growth rate).

- Multiple linear regression analyses showed a significant relationship between rate of change of GFR and renal volume growth rate ($P < 0.01$), initial renal volume ($P = 0.001$), initial age ($P < 0.0001$), baseline GFR ($P < 0.0001$), and proteinuria ($P = 0.0004$).

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

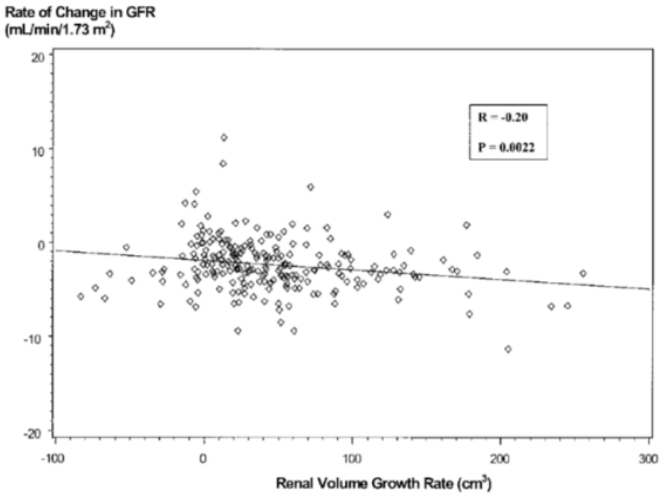


ADPKD = autosomal dominant polycystic kidney disease; GFR = glomerular filtration rate.

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

Source: (Fick-Brosnahan *et al*., 2002).

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



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

Note: N = 229.

Source: (Fick-Brosnahan *et al*., 2002).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

An estimated 2,972 people will have ADPKD with CKD stage 1 to 3 and evidence of rapidly progressing disease in England and Wales in 2015. This estimate is based on the following:

- The diagnosed prevalence of ADPKD was estimated as 3.9 per 10,000 (Patch *et al*., 2011). The diagnosis rate has been estimated as 90%; therefore the total prevalence (diagnosed and undiagnosed) is estimated as 4.3 per 10,000 (Willey, 2013).
- The proportion of patients age 18 years and over was estimated as 79% (Office for National Statistics, 2014)
- The proportion of patients with CKD stage 1, 2 and 3 was estimated as 17.0%, 17.0% and 23.0%, respectively (Otsuka, 2014), and

- The proportion of patients with rapidly progressing disease in CKD stage 1, 2, and 3 was estimated as 16.0%, 23.0%, and 44.0%, respectively (Otsuka, 2014).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

In the UK, data from a UK cohort study report that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years) (Shaw *et al*., 2014), as compared to the current UK life expectancy of 81.5 years (World Bank, 2014). However, the life expectancy in a faster progressing patient population (i.e. the proposed licensed indication for tolvaptan considered in this submission) is likely to be even lower. Outputs from the long-term outcomes modelling used to inform the economic evaluation estimate the mean natural life expectancy for ADPKD patients eligible for tolvaptan to be approximately 64-65 years (Section 7.7).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There is no NICE clinical guideline or protocol directly relevant to ADPKD. Table A6 summarises guidance issued by NICE on CKD and the subgroups considered; these recommendations have only limited and indirect relevance to ADPKD.

Table A6. Guidance on chronic kidney disease issued by NICE

Guideline	Issue date	Subgroups considered
CG 182[a] Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care	July 2014	N/A
CG 125 Peritoneal dialysis in the treatment of stage 5 chronic kidney disease	July 2011	Patients with stage 5 chronic kidney disease
Quality Standard No. 5 Chronic kidney disease	March 2011	N/A
NICE Pathway Chronic kidney disease	May 2011	N/A
CG = Clinical Guideline; N/A = not applicable; NICE = National Institute for Health and Care Excellence. [a] This guideline updates and replaces CG No. 73, published in September 2008.		

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There are no NICE guidelines with direct relevance to ADPKD. NICE Clinical Guideline 182 addresses treatment of symptoms and complications of CKD and provides recommendations for blood pressure control, lipid modification, and prevention of cardiovascular disease. However, these guidelines do not include recommendations on the management of ADPKD (NICE, 2014). NICE Clinical Guideline 182 states that CKD patients suspected of having a genetic source should be referred to a specialist and that ultrasound is recommended for PKD patients over 20 years of age (NICE, 2014).

Current treatments generally target symptoms and complications of kidney disease, such as hypertension. None of the current treatments address the mechanisms of disease progression or the underlying pathology of cyst formation and growth. Tolvaptan is the first licensed disease-modifying therapy for ADPKD that delays disease progression and, as such, will introduce a new treatment paradigm.

The proposed use of tolvaptan is for the treatment of adults with CKD stage 1 to 3 at initiation of treatment and with evidence of rapidly progressing disease. See Sections 2.6 and 2.9 for estimations regarding frequency of contact with health care professionals with and without tolvaptan.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

No clear strategy exists for routine screening of patients at-risk for ADPKD in the early stages of the disease. Despite the majority of patients having a family history of ADPKD, the condition is often diagnosed relatively late and as an incidental finding during investigation of disease symptoms. Without a clear classification system and with no disease-modifying therapies available, clinicians have used different information to predict future progression rates, including renal size, renal function, family history, genetics, history of complications etc. Individual clinical judgement is currently exercised to determine the risk of fast progression. Accordingly, in the anticipated licensed indication for tolvaptan, clinician judgement of what constitutes "*evidence of rapidly progressing disease*" will be relevant as opposed to pre-set objective criteria.

As described in the previous section, no therapies are available to target the underlying pathophysiology of the disease. Once kidney function is compromised beyond an eGFR of 30 mL/min/1.73m^2, health care utilisation costs in patients with ADPKD tend to rise sharply (Lentine *et al*., 2010) (see Section 0 for details on patient burden in ADPKD). For patients with CKD stage 1 to 4, one or two monitoring visits per year are recommended and an ultrasound scan is recommended for certain patients (NICE clinical guideline 182).

Patients with ESRD require substantial health care resources for monitoring (four visits per year, NICE clinical guideline 182), haemodialysis (e.g. establishment of vascular access and 3 hospital attendances per week for dialysis; NICE clinical guideline 125), peritoneal dialysis (NICE clinical guideline 125) and/or kidney transplantation and graft maintenance (Kerr *et al*., 2012). This underscores the importance to patients, their families, the NHS and society at large of an intervention that delays ADPKD disease progression.

2.7 Please identify the main comparator(s) and justify their selection.

As described above, there are currently no pharmacological treatments licensed for ADPKD. Tolvaptan will be the first indicated treatment to delay the progression of ADPKD. Patients with ADPKD currently receive “best supportive care” to control symptoms and complications associated with the disease, and this will not change irrespective of the choice to initiate tolvaptan in the future. The provision of best supportive care is unaffected by the decision to initiate tolvaptan (i.e., the choice for the prescriber at the point of treatment decision is “initiate tolvaptan” or “do nothing different”). Therefore, the most appropriate comparator is placebo or no active treatment (with best supportive care in the background for both treatment strategies).

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Adverse drug reactions are managed by dose reductions, treatment interruption, or treatment discontinuation. In the TEMPO 3:4 trial, the dose of tolvaptan was up-titrated at weekly intervals according to patient-reported tolerability. Of the patients who completed 36 months of treatment with tolvaptan, 404 (55%) took the high dose (a total daily dose of 120 mg), whereas 157 (21%) and 179 (24%) took the middle dose (90 mg) and low dose (60 mg), respectively. Adverse events led to treatment discontinuation in 15.4% of patients in the tolvaptan group (compared with 5.0% of patients in the placebo group).

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Tolvaptan treatment will be initiated and managed in secondary care by specialist nephrologists. Based on NICE clinical guideline 182 (CG182) and information provided by clinical experts, patients with ADPKD currently receive regular monitoring in the form of an annual consultant and specialist nurse visit with or without an ultrasound scan, and blood tests (biochemistry and haematology). Patients receiving tolvaptan may be expected to receive more consultant visits in the first years of treatment compared with no active treatment; this is explored in the economic evaluation. In addition, liver function tests will be performed monthly for the first 18 months and 3-monthly thereafter. It is envisaged that additional consultant

time will be involved with review of the test results and issue of the tolvaptan prescription.

2.10 Does the technology require additional infrastructure to be put in place?

No, the technology will not require additional infrastructure.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g., by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues have been identified.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

Innovation summary

- Otsuka firmly believes that tolvaptan is innovative in its potential to make a significant and substantial impact on health-related benefits, and that it represents a 'step-change' in the management of ADPKD.
- In order to assess whether tolvaptan can be considered as innovative, we propose three key criteria: need, originality/creativity and value
- The burden of ADPKD can be extremely high to patients, leading to an extremely poor long-term prognosis particularly for patients experiencing more rapidly progressing disease (as per this submission)
- ADPKD patients begin renal replacement therapy (RRT) at a relatively young age; we estimate that underlying disease progression in ADPKD patients within the anticipated licensed indication for tolvaptan would be expected to lead to ESRD at a mean age of approximately 52 years
- The early onset of ESRD in ADPKD patients has serious consequences for overall life expectancy; we estimate that mean life expectancy for ADPKD patients eligible for tolvaptan to be approximately 65.6 years
- Compared with the general population, these patients are estimated to live an average of 17.5 years less and lose approximately 16.6 QALYs. By any objective measure, these estimates mark ADPKD as an extremely serious disease with poor long-term prognosis.
- Delaying time to ESRD and reducing the strain on RRT services is an area of NHS priority
- Tolvaptan's development captures the risk and creativity required to produce the evidence to turned the concept of delaying ADPKD progression into reality, in a therapeutic area with no previous success and several failures
- The benefits of tolvaptan treatment are based on high quality evidence and are clinically meaningful which, importantly, will translate into substantial improvements in long-term outcomes that will be valuable to patients and the NHS alike.

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Otsuka firmly believes that tolvaptan is innovative in its potential to make a significant and substantial impact on health-related benefits, and that it represents a 'step-change' in the management of ADPKD.

In order to provide rationale for this assertion it is helpful suggest a set of criteria under which it may be possible to judge a technology as potentially innovative. We propose that these criteria can be described by three key themes:

1. The technology addresses a clear and specific (clinical unmet) **need**
2. The technology has **original/creative** properties
3. The technology provides **value** to end users

Need

Need in this context is directly related to the level of demand for an innovative solution to a well-defined problem. More specifically with regards to this submission:

- Is the burden of ADPKD high for patients?
- Does ADPKD cause significant resource and service impact on the NHS?
- Could a new treatment option for ADPKD potentially bring significant value to relieve the burden of ADPKD, both to patients and the NHS?

Clearly, the answer to all of these questions is yes.

ADPKD burden to patients

The burden of ADPKD can be extremely high to patients. Despite the perception that ADPKD can be "asymptomatic" for long periods of the patient's life, the disease ultimately leads to an extremely poor long-term prognosis. This is particularly the case for the patients eligible for treatment with tolvaptan under the proposed licensed indication who are likely to experience more rapidly progressing disease.

Data from a large UK retrospective cohort study (52,608 renal replacement therapy patients including 3,598 with ADPKD) reveals that ADPKD patients begin renal

replacement therapy (RRT) at a median age of 55 years, and this has not changed substantially in the past 10 years. The study estimates this to be seven and 11 years sooner than patients with diabetes or other primary renal diagnoses begin RRT, respectively (Shaw *et al*., 2014).

However, a substantial proportion of ADPKD patients reach ESRD at an even younger age. Results from the long-term disease model (presented in Section 7.7) estimate that the ADPKD patients within the anticipated licensed indication for tolvaptan would be expected to enter ESRD at a mean age of approximately 52 years. As such, the very early requirement for dialysis will impact the patient's ability to work and to enjoy leisure time at a time when they could reasonably expect to be otherwise relatively healthy. Although there are limited data evaluating the burden of RRT on HRQoL in patients with ADPKD, it has been reported that on average, patients in ESRD would be willing to give up ten years of life on dialysis in exchange for four years with normal renal function (Couser *et al*., 2011).

The early onset of ESRD in ADPKD patients has serious consequences for overall life expectancy. Further data from the UK cohort study reports that the median age at death for ADPKD patients was 70 years (interquartile range 62-78 years) (Shaw *et al*., 2014), as compared to the current UK life expectancy of 81.5 years (World Bank, 2014). However, the life expectancy in a faster progressing patient population such as that considered in this submission is likely to be even lower. Outputs from the long-term outcomes model estimate the mean natural life expectancy for ADPKD patients eligible for tolvaptan to be approximately 65.6 years (Section 7.7).

Compared with the general population, the ADPKD patient population considered in this submission are estimated to live an average of 17.5 years less and lose approximately 16.6 QALYs (undiscounted; 6.1 QALYs discounted). This represents a 40% and 47% proportional loss in life years and QALYs respectively for the base case patient considered in this submission. By any objective measure, these estimates mark ADPKD as an extremely serious disease with very poor long-term prognosis.

ADPKD impact on the NHS

The total cost of treating CKD (irrespective of underlying cause) in England has been estimated at £1.44 to £1.45 billion, accounting for approximately 1.3% of the total NHS spend (NICE CG 182). Over half of this amount was spent on the 2% of

patients in CKD that progression to renal failure and require RRT (dialysis and transplantation).

This burden is likely to increase over time. Even allowing for an optimistic increase in donor organ supply, numbers on dialysis have been predicted to continue to rise substantially, especially in the elderly. One 2004 study predicted a substantial future growth in the RRT population, particularly in the elderly and those on haemodialysis, with a steady state not being reached for at least 25 years (Roderick *et al*., 2004). The average waiting time for an adult donor kidney – which accounts for 85% of all transplant operations – rose from 1088 in the five year period between 2003 and 2007, to 1114 in 2006 to 2011 (organdonation.nhs.uk current activity report 2013/2014 & organdonation.nhs.uk current activity report 2009/2010).

ADPKD is the fourth-leading cause of ESRD (Grantham *et al*., 2006). According to the latest figures from the UK Renal Registry, ADPKD accounts for approximately 7% of incident cases accepted for RRT in the UK, and approximately 13% of prevalent RRT cases (Renal Registry 2013). Accordingly it follows that ADPKD contributes significantly to the RRT burden on the NHS, to say nothing of the impact of non-ESRD related ADPKD complications that arise during the course of disease.

Potential value of a new ADPKD treatment option

There are currently no licensed treatments available to delay renal progression in ADPKD. In light of the severe disease burden outlined above, it is clear that a new treatment option has the potential to provide great value for patients.

Delaying time to ESRD and reducing the strain on RRT services is clearly an area of NHS priority, as noted in NICE Clinical Guideline 182: "*Strategies aimed at earlier identification and prevention of progression to [ESRD], are clearly needed*".

To summarise, ADPKD, and the patient population considered in this submission in particular, is associated with a well-defined problem and high level of need for an innovative solution.

Originality/creativity

Originality and creativity in this context speak to the process of developing an innovation, i.e. turning a new idea of how to potentially address the need outlined above into a real-life product or offering. For this purpose of assessing the originality

of tolvaptan for ADPKD, we can assert that it can be considered novel with respect to certain properties.

Tolvaptan will achieve a number of significant “firsts”:

- First product to be studied in such a comprehensive ADPKD clinical programme and successful pivotal trial (TEMPO 3:4), which captures the necessary risk and creativity required to produce the evidence that has turned the concept into reality, in a therapeutic area with no previous success and several failures
- First treatment licensed specifically to treat ADPKD
- First treatment demonstrated to delay renal progression in ADPKD in terms of both TKV growth and rate of renal function decline
- First treatment with the potential to delay time to ESRD in any therapeutic area

As such, tolvaptan demonstrates original and creative properties.

Value

However, even if the technology addresses a clear need and demonstrates original and/or creative properties, it cannot truly be regarded as an innovation unless it actually follows through on the promise (delivers value). Value in this context relates to the tangible benefit that will be gained from investment, i.e. will the product work in the real world and are the benefits of significant value to patients and the NHS?

The benefits of tolvaptan treatment are based on high quality evidence and are clinically meaningful (section 6.5). The results from TEMPO 3:4 show that tolvaptan significantly reduces the rate of TKV growth and rate of renal function decline. Importantly, these benefits translate into substantial improvements in long-term outcomes that will be valuable to patients and the NHS alike.

Results of the long term outcomes model indicate that the impact of slowing the rate of renal function decline, as shown with tolvaptan in TEMPO 3:4, can ultimately lead to a substantial mean delay of approximately 3.7 years to the onset of ESRD for the patient population considered in this submission (section 7). This delay to ESRD has knock-on consequences for RRT outcomes for tolvaptan patients (mean approximately 0.5 years less on dialysis, and mean 20% reduction in kidney

transplantation), HRQoL (mean 0.9 additional discounted QALYs) and life expectancy (mean approximately 1.5 years additional life).

In conclusion, the introduction of tolvaptan meets the three criteria of innovation described above: need, originality/creativity and value. Therefore it can be confidently regarded as a step-change in the management of ADPKD that will, for the first time, make available an effective treatment option to delay ADPKD progression, leading to significant long-term benefits for patients and the NHS.

In addition, several external organisations representing ADPKD patients and clinicians, including the PKD Charity, the Renal Association, the Royal College of Pathologists, and the British Society of Genomic Medicine, have already independently asserted that tolvaptan represents a step-change in the management of ADPKD (comments to draft scope for this appraisal available on NICE website).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

There are several potential health-related benefits of tolvaptan treatment that are not captured by the QALY calculation, which include the following:

- Long-term disease modelling estimates that the delay to ESRD associated with tolvaptan treatment will lead to an approximate 20% reduction in kidney transplants for the patient population considered in this submission. This reduction in demand on transplantation services will confer important indirect health benefits for other ESRD patients awaiting donor kidneys
- An improvement in the psychological impact suffered by ADPKD given the availability of an active therapy may be expected; the evidence is not yet available to quantify this benefit as part of the economic evaluation
- A reduction in loss of productivity and greater ability to enjoy leisure time for patients resulting from delay or prevention of the onset of ESRD
- A reduction in the impact on the lives of carers' of ADPKD patients

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Data on the clinical effectiveness of tolvaptan is drawn primarily from the TEMPO 3:4 trial (section 6.5).

Evidence on the long-term naturalistic outcomes of the ADPKD population considered in this submission, in addition to the long-term benefits of tolvaptan are presented in Section 7.7.

Several useful sources in the published literature help to build the picture of ADPKD burden to patients and the NHS:

- Shaw et al., 2014
- Renal Registry 2013
- NICE Clinical Guideline 182
- Roderick et al., 2004
- Couser et al., 2011

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with ADPKD	People with ADPKD	N/A
Intervention	Standard care in combination with tolvaptan	Standard care in combination with tolvaptan	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 HRQL	Rate of decline of renal function (including percentage change in TKV)[a] Symptoms of chronic disease[b] (including pain) Mortality Adverse effects of treatment HRQL	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 between the technologies being compared	NICE reference case	N/A

	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; HRQL = 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).

Section B – Clinical and cost-effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year.

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Clinical summary

- The principal clinical evidence for tolvaptan in ADPKD is derived from the pivotal TEMPO 3:4 study: 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
- The primary endpoint in TEMPO 3:4 was the annual rate of change in TKV. Sequential secondary endpoints included a composite of time clinical progression (defined as worsening kidney function, kidney pain, hypertension and albuminuria) and rate of kidney function decline
- The results of TEMPO 3:4 demonstrate that tolvaptan is associated with significant improvements in the following outcomes compared to placebo:
    - Rate of TKV growth (49% relative reduction, p<0.001)
    - Time to clinical progression (HR = 0.87, p=0.01)
    - Rate of renal function decline (31.6% relative reduction, p<0.001)
    - Risk of clinically significant kidney pain (HR = 0.64, p-0.007)
- Tolvaptan has a manageable tolerability profile, with 15.4% of patients (vs. 5% in the placebo arm) discontinuing due to AEs over the course of TEMPO 3:4. The incidence of serious AEs in the tolvaptan (18.4%) and placebo treatment arms (19.7%) was similar
- Hepatotoxicity has been observed in some ADPKD patients receiving tolvaptan, which was reversible on treatment discontinuation
- The longer-term efficacy and safety of tolvaptan is currently being studied in a phase 3b single active arm extension study with total follow-up of up to 6 years (TEMPO 4:4). A total of 871 patients have enrolled from other tolvaptan ADPKD trials, including TEMPO 3:4 (535 from the tolvaptan group, 296 from the placebo group)
- In summary, tolvaptan has demonstrated consistent and clinically meaningful improvements in ADPKD renal outcomes that may translate into significant long-term benefits, with a manageable tolerability profile

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic review was undertaken to identify clinical and cost-effectiveness evidence relating to tolvaptan for the treatment of ADPKD. Within this systematic review, different search strategies (with respect to databases, conference proceeding, inclusion/exclusion criteria etc.) were combined for clinical and cost-effectiveness evidence, however these (along with disaggregated results) are detailed separately in Section 6.1 and 6.2 (clinical) and Section 7.1 (cost-effectiveness) as appropriate. Combined search results are presented in both sections.

Prior to initiating the systematic literature review, a protocol was developed to outline the methodology to be used for the searches, the screening process (inclusion and exclusion criteria), and the data extraction. From methods defined *a priori*, 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.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

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.

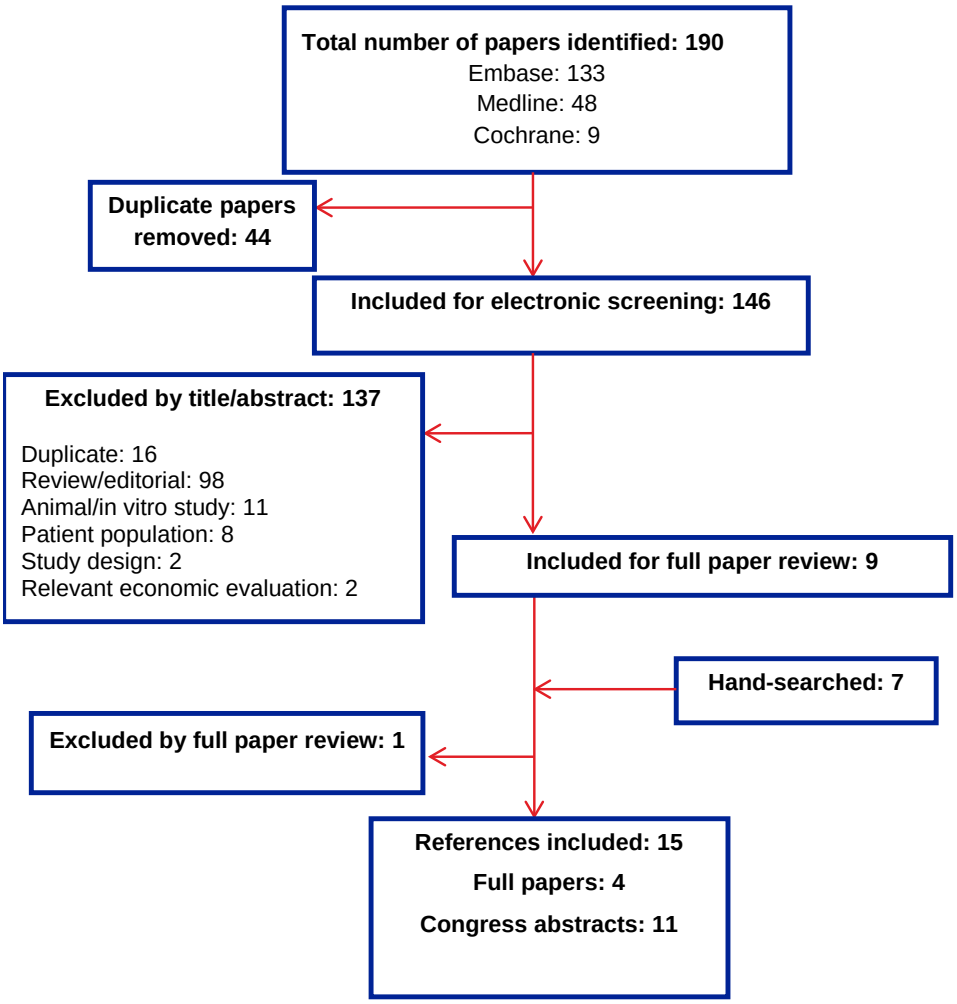
Table B1. Eligibility criteria used in search strategy

	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
RCT, randomized controlled trial; N/A, not applicable		

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The study selection process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (0).

Table 1 Flow diagram of identification process for systematic review of tolvaptan clinical studies



The searches identified the following eight publications:

- One full publication (with supplementary index) (Torres *et al*., 2012a; Torres *et al*., 2012b) and six abstracts (Czerwiec *et al*., 2013; Horie *et al*., 2013; Devuyst *et al*., 2014; Gansevoort *et al*., 2013; Perrone *et al*., 2013; Chapman *et al*., 2005) present RCT data
- Three full publications (Irazabal *et al*., 2011, Boertien *et al*., 2013, Higashihara *et al*., 2011), four abstracts (Boertien *et al*., 2012a; Boertien *et al*., 2012b, Torres *et al*., 2007b, Torres *et al*., 2014a) present non-RCT data (non-RCTs are summarised in Section 6.8)

The identified publications above were then cross-matched against the full list of clinical studies identified in the Otsuka internal database (Table B2).

Table B2 Identified tolvaptan clinical studies

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 *et al*., 2011	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 *et al*., 2005	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 *et al*., 2011 Torres *et al*., 2007b	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 *et al*., 2012a; 2012b Czerwiec *et al*., 2013 Horie *et al*., 2013 Devuyst *et al*., 2014 Gansevoort *et al*., 2013 Perrone *et al*., 2013	Yes. Full presentation.	Pivotal phase 3 study (n > 1400)
156-06-260	Yes	No	Yes	Irazabal *et al*., 2011	No	20 patients, 1 week study, phase 1b
156-08-271 (TEMPO 4:4)	Yes	No	Ongoing	Torres *et al*., 2014a	Yes. Limited presentation.	Open-label extension study of several completed trials. Interim analysis only as it is an ongoing study.
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 *et al*., 2012a; 2012b; 2013	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

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Of the publications identified above, one full publication and five abstracts refer to a single RCT (TEMPO 3:4).

- The primary report was Torres *et al*., 2012a (journal article), with Torres *et al*., 2012b (supplementary index)
- Three publications report post-hoc analyses (Devuyst *et al*., 2014 [abstract]; Gansevoort *et al*., 2013 [abstract]; Perrone *et al*., 2013 [abstract])
- A further two secondary publications are available (Czerwiec *et al*., 2013 [abstract]; Horie *et al*., 2013 [abstract]).
    - Czerwiec *et al*., 2013, reported an analysis of clinical outcomes from the global TEMPO 3:4 trial. Patients treated with tolvaptan (n = 961) had fewer ADPKD-related systemic and fewer kidney events ($P < 0.05$) than the placebo group (n = 484). Renal pain, haematuria, and urinary tract infection occurred less frequently with tolvaptan than with placebo ($P < 0.05$).
    - Horie *et al*., 2013, described a subgroup analysis of the global TEMPO 3:4 trial to determine the efficacy and safety of tolvaptan in Japanese patients (n = 177). Tolvaptan significantly ($P < 0.05$) inhibited renal function decline compared with placebo. The safety profile of tolvaptan in Japanese patients with ADPKD was similar to that in the overall TEMPO 3:4 population.
- Devuyst *et al*., 2014, reported a post-hoc subgroup analysis of urine osmolality (Uosm) of participants in the global TEMPO 3:4 trial. Baseline Uosm in ADPKD patients reflected age, renal function, and TKV. Tolvaptan treatment (n = 668) reduced Uosm by 200 to 250 mOsm/kg, with no loss of effect over 36 months when compared with placebo (n = 333).
- Gansevoort *et al*, 2013, reported a post-hoc subgroup analysis on the effect of tolvaptan on albuminuria in the global TEMPO 3:4 trial. Tolvaptan decreased the albumin:creatinine ratio (–0.40 mg/mmol) compared with

placebo (+0.23 mg/mmol), independent of blood pressure (BP). The effect of tolvaptan remained after study drug withdrawal.

- Perrone *et al*., 2013, correlated TKV and eGFR results from patients in the TEMPO 3:4 trial. Correlations between height-adjusted TKV and eGFR improved from baseline to year 3, with no difference in correlation between the tolvaptan (n = 961) and placebo (n = 483) groups. Results support baseline height-adjusted TKV as a predictor of eGFR decline.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The single relevant RCT (pivotal phase 3 study) identified by the systematic review is presented in Table B2.

Table B2. List of relevant RCTs

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 *et al*., 2012a
RCT = randomised, controlled trial.				

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The TEMPO 3:4 trial compares tolvaptan directly with no active treatment (represented by the placebo arm), which is the only relevant comparator (see Section 2.7).

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Please refer to Table B2 for a full list of identified studies and rationale for exclusion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Relevant non-RCTs are summarised in Table B3. The rest of the non-RCTs identified by the review were excluded (see Table B2).

Table B3. List of relevant non-RCTs

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	Otsuka, data on file (2011a); Higashihara *et al*. (2011); Torres *et al*., 2012a	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 $eGFR_{MDRD}$ ≥ 30 mL/min/1.73 m^2	Non-randomised, parallel group, open-label extension study to investigate whether tolvaptan modifies ADPKD progression	Otsuka, data on file (2011b); Torres *et al*. (2014a)	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.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The TEMPO 3:4 clinical trial was a phase 3, multicentre, double-blind, placebo-controlled, parallel-arm trial to determine the safety and efficacy of split-dose oral regimens of tolvaptan tablets in a range of 60 to 120 mg per day in adults with ADPKD.

The TEMPO 3:4 trial enrolled patients from 129 sites in 15 countries worldwide. Of the 2,122 patients screened, 1,445 patients were randomised in a 2:1 ratio to either the tolvaptan or the placebo arm (Figure B1). The randomisation was stratified according to the following:

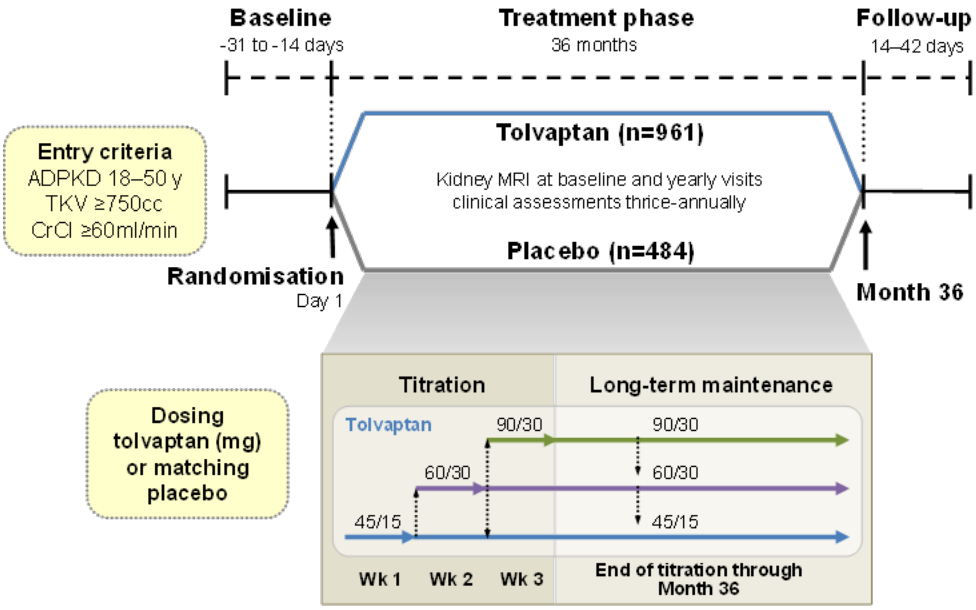
- Hypertension status (present vs. absent): defined as systolic blood pressure (sBP) > 139 mmHg and diastolic blood pressure (dBP) > 89 mmHg or treatment for elevated BP
- Creatinine clearance (< 80 mL/min vs. ≥ 80 mL/min)
- TKV (< 1,000 mL vs. ≥ 1,000 mL)

These strata were selected as important disease severity indicators such that equal numbers of subjects enrolled in the placebo and tolvaptan treatment groups within each stratum would provide an unbiased treatment effect of tolvaptan in this

indication. Thus, there were eight strata in this trial. Subjects were randomised to tolvaptan or placebo in a 2:1 ratio within each of the eight strata. Because the subjects enrolled in Japan were formally analysed for registration in that country and because differences in clinical care existed in different regions (including a more intensive visit schedule in Japan), centralised randomisation was performed in each region independently (the Americas [Argentina, Canada, and US], Japan, Europe plus the rest of the world [notably Australia]).

This trial involved stratified parallel randomisation to placebo or tolvaptan with forced titration. Randomisation used an interactive voice response system to ensure appropriate stratification in the main regions (the Americas, Japan, and Europe plus rest of the world). The investigational medicinal product (IMP) was supplied in kits containing blister cards of 15 mg or 30 mg tolvaptan tablets or matching placebo. Neither subjects nor the principal investigators were aware of whether the IMP was active or placebo.

Figure B1. Design schematic of Study TEMPO 3:4



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.

Source: adapted from Figure 1, Torres *et al*. (2012a).

Tolvaptan and placebo were administered orally, twice daily (in the morning and afternoon). The planned treatment period was 36 months. The dose was titrated in weekly intervals over a 3-week period (Figure B1). Tolvaptan was initially

administered at a dose of 45 mg and 15 mg, in the morning and afternoon, respectively, and titrated to 60 mg and 30 mg, respectively, and then to 90 mg and 30 mg, respectively, according to patient-reported tolerability. Following the titration period, the patient received the maximum tolerated dose (MTD) for the remainder of the treatment period.

Patients who could not tolerate the lowest dose were asked to continue follow-up by telephone. Throughout the 36-month treatment period, investigators could choose to up-titrate a patient's dosage if approved by the medical monitor. Patients also had the option to down-titrate at the investigators' discretion.

Patients were monitored every 4 months during the 36-month treatment period. Two additional follow-up visits also were conducted 7 to 21 days after month 36 and 7 to 21 days after the first follow-up visit.

Table B4 summarises the methodology of the TEMPO 3:4 RCT.

Table B4. Summary of methodology of Study TEMPO 3:4

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 o Onset or progression of HTN (BP measurement, need for treatment) o Clinically significant renal pain (requiring medical intervention)[b] o Worsening albuminuria (by category) o 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; $eGFR_{MDRD}$ = estimated GFR by Modification of Diet in Renal Disease; $eGFR_{CKD\text{-}EPI}$ = estimated GFR by Chronic Kidney Disease Epidemiology Collaboration; 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 (Boertien *et al*., 2013). 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 *et al*., 2012a).

[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.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B5 presents the inclusion and exclusion criteria for TEMPO 3:4.

Table B5. Eligibility criteria in TEMPO 3:4

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 $eCrCl_{CG}$ ≥ 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 generalizability of the results such as disorders in thirst recognition or inability to access fluids.

Source: CSR TEMPO 3:4 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 (Torres *et al*., 2012b).

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B6 presents the baseline characteristics of patients in TEMPO 3:4. The baseline demographics of the patient population in the study were well balanced in terms of age, sex, race, and factors influencing ADPKD progression. Of the total study population, 51.5% were male, and the majority of patients were Caucasian (84.3%). The mean age of the randomised patients was 38.7 years. The mean TKV was 1,705 mL and 1,668 mL in the tolvaptan and the placebo groups, respectively. Approximately 80% of patients were hypertensive at baseline. Using estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$), tolvaptan and placebo patients were evenly distributed at baseline across Kidney Disease Outcomes Quality Initiative CKD stages 1 (34.5% and 35.9%), 2 (48.5% and 46.5%), and 3 (17.0% and 17.4%), respectively (Otsuka, data on file, 2013c).

Table B6. Characteristics of participants in TEMPO 3:4

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
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

Trial no. (acronym) Baseline characteristic	Tolvaptan	Placebo
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 *et al*. (2012a); Table 8.2-1, CSR TEMPO 3:4 (Otsuka data on file, 2013c).

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B7 presents primary and secondary outcomes measured in TEMPO 3:4.

Table B7. Primary and secondary outcomes of TEMPO 3:4

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/ validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
156-04-251 NCT00428948 (TEMPO 3:4)	Rate of TKV change (normalised as percentage) from baseline for tolvaptan (combining all doses) relative to placebo MRI was performed to evaluate TKV at baseline (31 to approximately 14 days prior to randomisation) and at month 12, 24, and 36 or ET visits	TKV was the prospectively defined primary endpoint. Total kidney volume is believed to be an acceptable surrogate endpoint for cystogenesis since it can sensitively track cyst development in human disease responsive to prospective clinical therapies that have been effective in treating animal models. Measurement of TKV as a surrogate marker of disease progression in clinical trials for ADPKD fulfils these criteria for the following reasons: • The CRISP and the Swiss ADPKD studies have shown that TKV as measured by MRI is a strong and early predictor of renal functional decline in ADPKD and that changes in renal volume can be accurately detected over relatively short periods of time, before renal function declines (Grantham *et al*., 2006; Chapman *et al*., 2012; Torres, 2010; Chang *et al*., 2012). • Increasing kidney volume is clinically important in itself, as it is associated with development of hypertension, pain, and	Key composite secondary endpoints • Time to multiple[a] investigator-reported ADPKD clinical progression events, including o Onset or progression of HTN (BP measurement, need for treatment) o Clinically significant renal pain (requiring medical intervention) [b] o Worsening albuminuria (by category) o 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]	These endpoints are used within UK clinical practice

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/ validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
		haematuria, even early in the disease (Torres, 2010). • TKV can be measured by imaging techniques over a short period of time, such as a clinical trial, relative to the length of disease.		

ADPKD = autosomal dominant polycystic kidney disease; BP = blood pressure; CRISP = Consortium for Radiologic Imaging Study of Polycystic Kidney Disease; dBP = diastolic blood pressure; $eCrCl_{CG}$ = estimated creatinine clearance by means of the Cockcroft-Gault formula (with correction for sex and race where possible); eGFR = estimated glomerular filtration rate; $eGFR_{MDRD}$ = estimated GFR by Modification of Diet in Renal Disease; $eGFR_{CKD\text{-}EPI}$ = estimated GFR by Chronic Kidney Disease Epidemiology Collaboration; ET = early termination; GFR = glomerular filtration rate; HTN = hypertension; MAP = mean arterial pressure; MRI = magnetic resonance imaging; PKD = polycystic kidney disease; PKDOC = PKD Outcomes Consortium; sBP = systolic blood pressure; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV = total kidney volume; UK = United Kingdom

[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 (Boertien *et al*., 2013). 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 *et al*., 2012a).

[d] The primary measure was 1/serum creatinine. The estimate of renal function using 1/serum creatinine is independent of spurious changes in body weight and, therefore, is more likely to represent a more accurate assessment of change in renal function based on a simple blood test. Thus, 1/serum creatinine was used for all endpoint assessments, as it provided a measure of change in GFR. The slope of renal function decline using 1/serum creatinine assesses an overall effect on renal function and not only a progression of subjects who are declining most rapidly. Additional exploratory measures were based on

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/ validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
estimates using demographic and/or anthropomorphic variables— $eCrCl_{CG}$, or $eGFR_{MDRD}$' or $eGFR_{CKD\text{-}EPI}$ (with the latter two potentially having a higher degree of accuracy for segments of the overall population, but their limitation is that they do not accurately reflect eGFR across the full spectrum of patients in the study). 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.				

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B8 presents a summary of the statistical analyses conducted in TEMPO 3:4.

Table B8. Summary of statistical analyses in TEMPO 3:4

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.	

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Pre-specified subgroup analyses were carried out for the primary and secondary endpoints in TEMPO 3:4. Subgroups were selected based on important demographic, disease-specific, and prognostic criteria, and include the following:

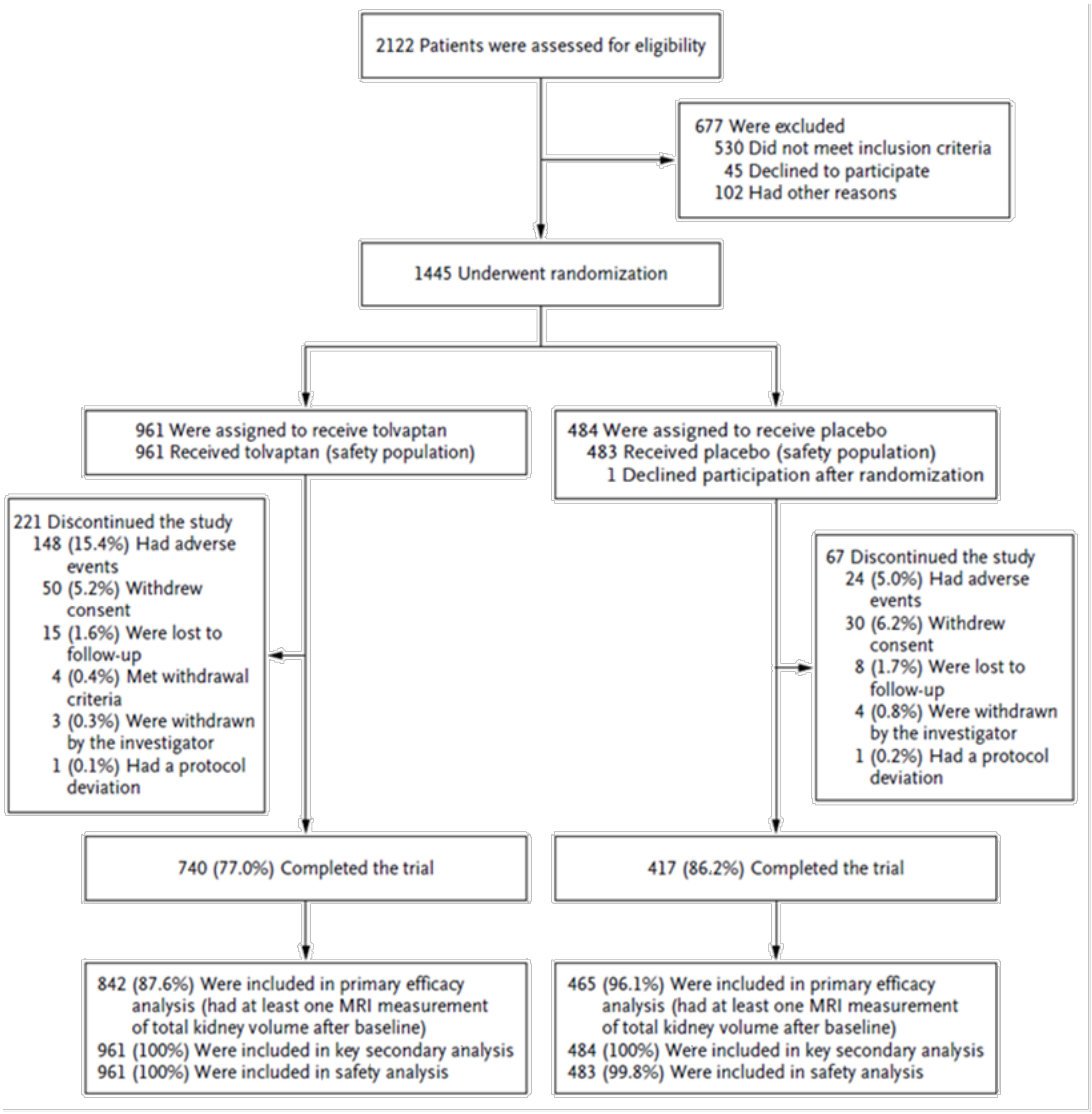
- Sex (male vs. female)
- Age (< 35 years vs. ≥ 35 years)
- Hypertension (yes vs. no)
- Estimated creatinine clearance (< 80 mL/min vs. ≥ 80 mL/min)
- Total kidney volume (< 1,000 mL vs. ≥ 1,000 mL)
- Height-adjusted total kidney volume (< 600 mL/m vs. ≥ 600 mL/m)
- Microalbuminuria (yes vs. no)
- Geographic 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)

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A total of 961 patients received tolvaptan and 483 patients received placebo. Figure B2 presents CONsolidated Standards of Reporting Trials (CONSORT) flow chart that provides details of the numbers of patients who were eligible to enter TEMPO 3:4, who underwent randomisation, and who were allocated to each treatment.

Figure B2. Patient enrolment in TEMPO 3:4



MRI = magnetic resonance imaging; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

Source: adapted from Figure 1, Torres *et al*. (2012a).

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The

following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Since there is only one relevant RCT, this information is presented in Section 6.4.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Quality assessment results for TEMPO 3:4 are presented in Table B9.

Table B9. Quality assessment results for TEMPO 3:4

Trial no. (acronym)	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; NA = not applicable; 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).

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.

- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Primary Efficacy Analysis

Results of TEMPO 3:4 demonstrate that tolvaptan provides a clinically and statistically significant reduction in kidney growth, renal function decline, and clinically significant kidney pain.

- A significant relative reduction of 49.2% on TKV growth over 3 years when compared with placebo (absolute reduction of –2.71% per year; 95% CI, –3.27% to –2.15%; $P < 0.0001$) (Torres *et al*., 2012a).
- A continuous and significant relative reduction of 31.6% in renal function decline (eGFR) over 3 years compared with placebo (absolute reduction of 1.20 mg/mL^{-1} serum creatinine; 95% CI, 0.62-1.78 g/mL^{-1}; $P < 0.001$) (Torres *et al*., 2012a).
- 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 no active treatment (2 events per 100 person-years vs. 5 events per 100 person-years; HR, 0.39; 95% CI, 0.26-0.57; $P < 0.001$) (Torres *et al*., 2012a).
- A significant 29% relative reduction (absolute reduction, 2 events per 100 person-years) in the risk of clinically significant renal pain compared with placebo (5 events per 100 person-years vs. 7 events per 100 person-years; HR, 0.64; 95% CI, 0.47-0.89; $P = 0.007$) (Torres *et al*., 2012a).

Annual rate of percentage change in TKV

The primary endpoint 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) (Otsuka data on file, 2013c) (Table B10).

Table B10. Rate of change in total kidney volume within the treatment period

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; 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.

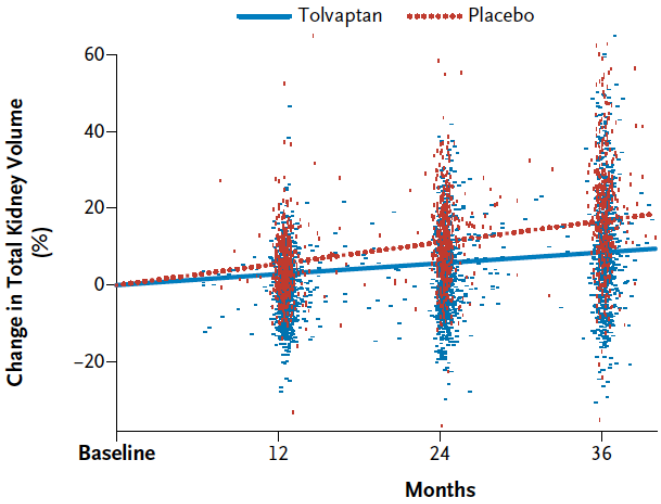
[b] Derived from delta method assuming independence between the estimates of the slope between the two treatments. Differences in slope were produced post hoc to facilitate clinical interpretation.

[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 (Otsuka data on file, 2013c).

Tolvaptan changed the rate of growth by −2.7 percentage points per year (95% CI, −3.27 to −2.15); the ratio of the geometric means of growth rate was 0.97 (95% CI, 0.97 to 0.98; *P* < 0.001) (Torres *et al*., 2012a) (Figure B3).

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



Source: Figure 2A, Torres *et al*. (2012a).

The significantly reduced rate of TKV growth in the tolvaptan arm compared with the placebo arm over the 3-year treatment period also was confirmed for each individual year of the trial in the mixed-model repeated-measures (MMRM) analysis, which tests year-to-year change (Table B11).

Table B11. MMRM sensitivity analysis of the percentage change from baseline in TKV within the treatment period

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		

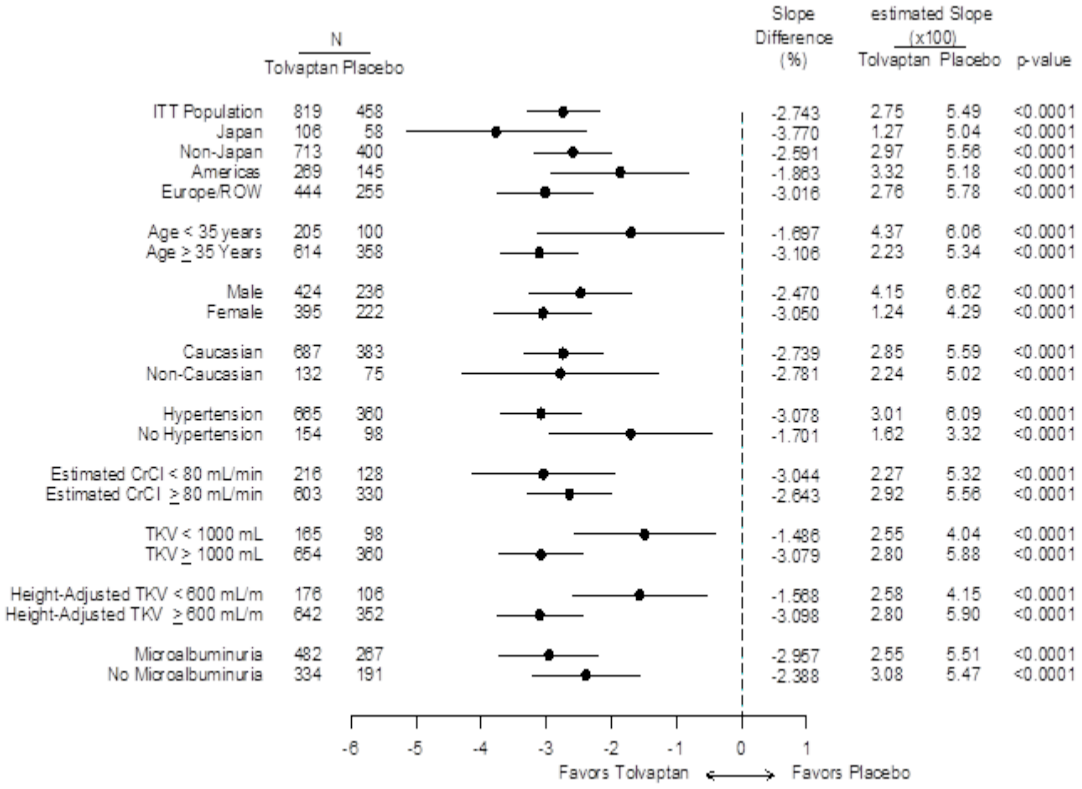
CI = confidence interval; LS = least square; MMRM = mixed-model repeated-measures; SD = standard deviation; TKV = total kidney volume.

Source: CSR TEMPO 3:4 Table 9.3.2.1-1 (Otsuka, data on file, 2013c); Figure S1 (Torres *et al*., 2012a).

A larger treatment effect for tolvaptan was observed on the primary endpoint in the first year than in the second and third years and included negative cyst growth for the tolvaptan arm (–1.65%) compared with positive cyst growth in the placebo arm (4.62%), resulting in a statistically significant treatment effect of –6.27% ($P < 0.0001$) (Otsuka, data on file, 2013c).

Across all pre-specified patient subgroups studied (sex, age, TKV at baseline, estimated creatinine clearance level at baseline, and hypertension status), similar relative reductions in the rate of TKV growth were observed. In all subgroups, tolvaptan had a significant beneficial effect on TKV, compared with placebo ($P \leq 0.02$ for all subgroups) (Figure B4) (Otsuka data on file, 2013c).

Figure B4. Subgroup analyses of TKV slope difference



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

Source: CSR TEMPO 3:4 Figure 9.3.3-1 (Otsuka, data on file, 2013c); Figure 2B (Torres *et al*., 2012a).

Post-hoc analysis of TKV in subgroups of patients at each CKD stage (1, 2, or 3 at baseline) showed a consistent and significant effect favouring tolvaptan across all stages (Table B12) (Otsuka Pharmaceutical Europe Ltd. data on file, 2014; Torres *et al*., 2014a).

Table B12. Effect of tolvaptan on TKV growth in CKD stages 1 to 3

Baseline CKD stage by $eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	N	Slope % (annualised)	Ratio of geometric mean (annualised growth rate)*	95% CI	P
Stage 1 (≥ 90)					
Tolvaptan	267	3.02%	[redacted]	[redacted]	< 0.0001
Placebo	158	5.07%			
Stage 2 (89-60)					
Tolvaptan	402	2.08%	[redacted]	[redacted]	< 0.0001
Placebo	214	5.27%			
Stage 3 (< 60)					
Tolvaptan	147	4.11%	[redacted]	[redacted]	0.0004
Placebo	84	6.83%			

CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration

* By the formula, % change = 100 x (1-ratio of geometric mean), the annual ratio of geometric mean effect size of 0.981 is approximately -1.9% per year change in TKV.

Source: Otsuka responses to EMA Day 120 list of questions 2014: Table 3.2.3.7-1, Table 3.2.3.7-5, Table 3.2.3.6-7 (Otsuka Pharmaceutical Europe Ltd. data on file, 2014); Torres *et al*., 2014a.

Secondary Efficacy Analysis

Time to multiple ADPKD progression endpoints

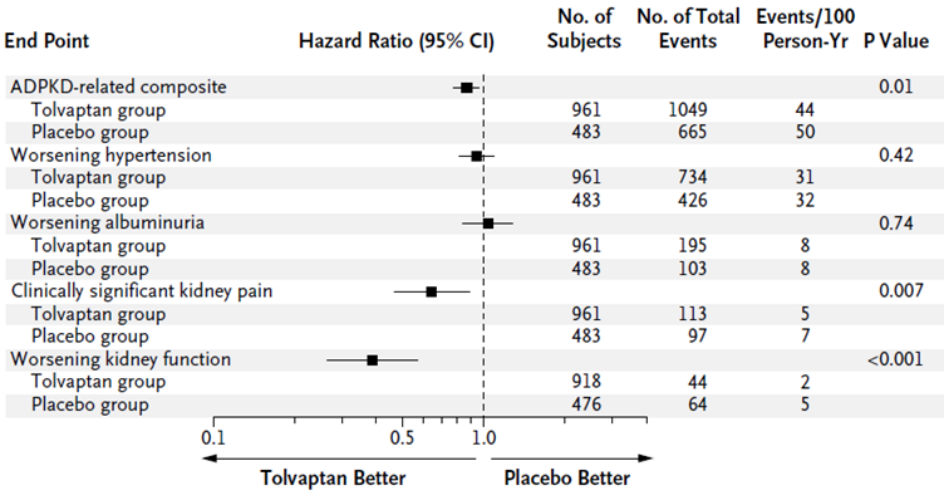
The key composite secondary endpoint was time to multiple investigator-assessed ADPKD progression events, defined as follows:

- Worsening renal function (25% decrease in 1/serum creatinine as a measure of GFR from steady-state post-titration baseline value)
- Clinically significant renal pain (requiring medical intervention, including a prescribed surgical or invasive radiological procedure; the introduction of, or increased dose of, narcotic or antinociceptive medicine; a prescribed medical leave or activity restriction due to the pain or the prescription of relatively contraindicated, that is, “last resort” non-narcotic analgesics)
- Worsening hypertension (BP measurement, need for treatment)
- Worsening albuminuria (by category, including “normal” [urine albumin/creatinine of < 2.8 mg/mmol female or < 2.0 mg/mmol male], “microalbuminuria” [urine albumin/creatinine of 2.8-28 mg/mmol female or

2.0-20 mg/mmol male], and “overt proteinuria” [urine albumin/creatinine of > 28 mg/mmol female or > 20 mg/mmol male])

Overall, treatment with tolvaptan was associated with a statistically significant 12% relative reduction in the risk of ADPKD-related events, compared with placebo (44 events per 100 person-years vs. 50 events per 100 person-years; absolute reduction: 6 events per 100 person-years; hazard ratio [HR], 0.87; 95% CI, 0.78-0.97; *P* < 0.01) (Figure B5) (Torres *et al*., 2012a).

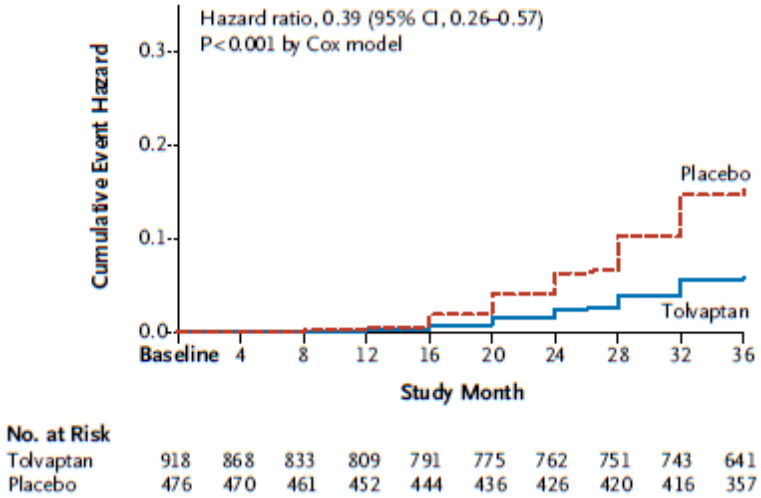
Figure B5. Forest plot of the treatment effect in the time to investigator-assessed multiple ADPKD progression



ADPKD = autosomal dominant polycystic kidney disease; CI = confidence interval; Yr = year.
Source: Figure 3A, Torres *et al*. (2012a).

The significant reduction in renal function decline in the tolvaptan arm contributed the most to the overall reduction in the risk of ADPKD-related events, compared with the placebo arm. 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) (Figure B6) (Torres *et al*., 2012a).

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

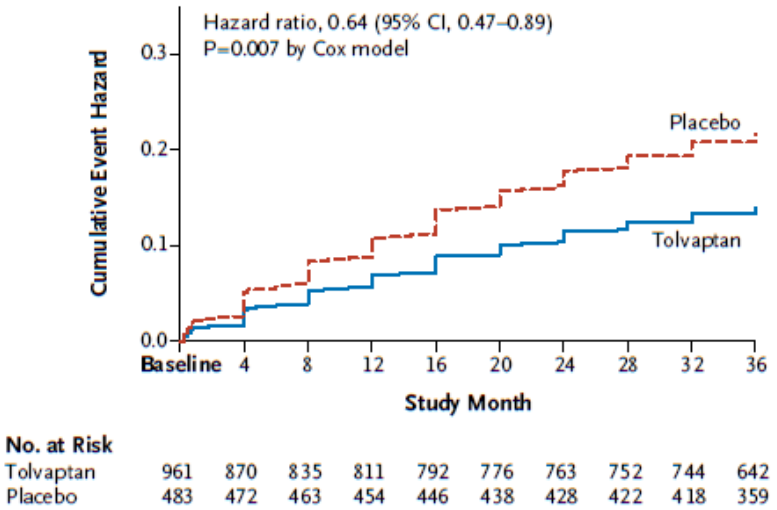


CI = confidence interval.

Source: Figure 3C, Torres *et al*. (2012a).

Treatment with tolvaptan was associated with a significant 29% relative reduction (absolute reduction: 2 events per 100 person-years) in the risk of clinically significant renal pain, compared with placebo (5 events per 100 person-years vs. 7 events per 100 person-years; HR, 0.64; 95% CI, 0.47-0.89; *P* = 0.007 and the separation of event rates between the arms occurred early in the study (Figure B7) (Torres *et al*., 2012a).

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



CI = confidence interval.

Source: Figure 3D, Torres *et al*. (2012a).

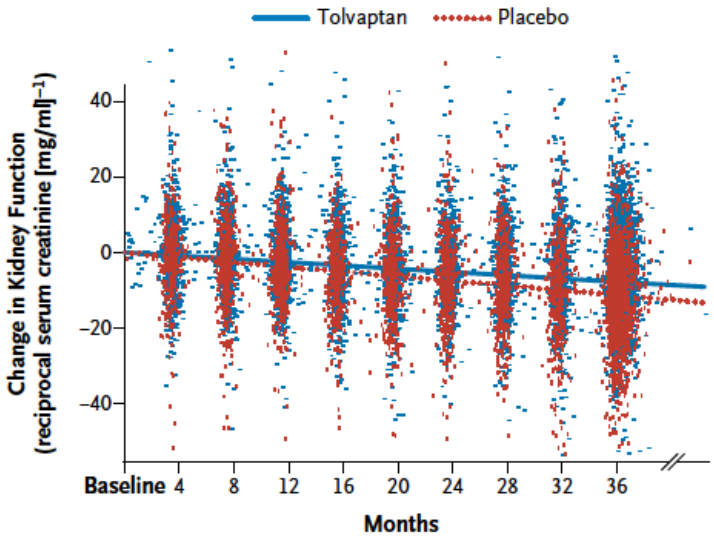
No treatment difference was detected between the tolvaptan and the placebo treatment arms in events of worsening hypertension or worsening albuminuria events (Figure B8) (Otsuka data on file, 2013c). However, this may be expected, due to the high proportion of patients (approximately 80%) entering the trial with diagnosed hypertension and with approximately 70% of those patients receiving antihypertensive treatment. Moreover, approximately 50% of patients had microalbuminuria, and 25% had proteinuria upon study entry (Otsuka data on file, 2013c).

Rate of change in renal function

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; $P < 0.001$) (Figure B8) (Otsuka data on file, 2013c). 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; $P < 0.001$) (Torres *et al*., 2012a).

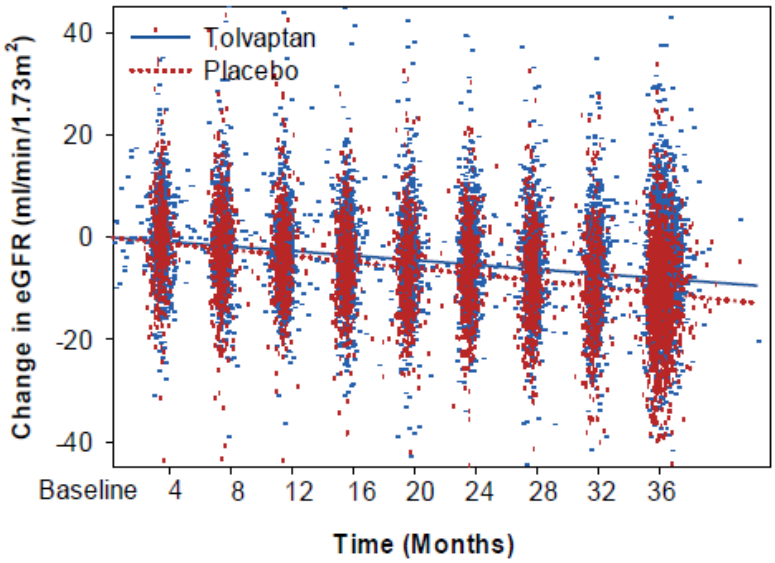
Figure B8. Rate of change in renal function (measured using reciprocal serum creatinine [mg/mL^{-1}])



Source: Adapted from Figure 2C, Torres *et al*. (2012a).

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; $P < 0.001$) (Torres *et al*., 2012a) (Figure B9).

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

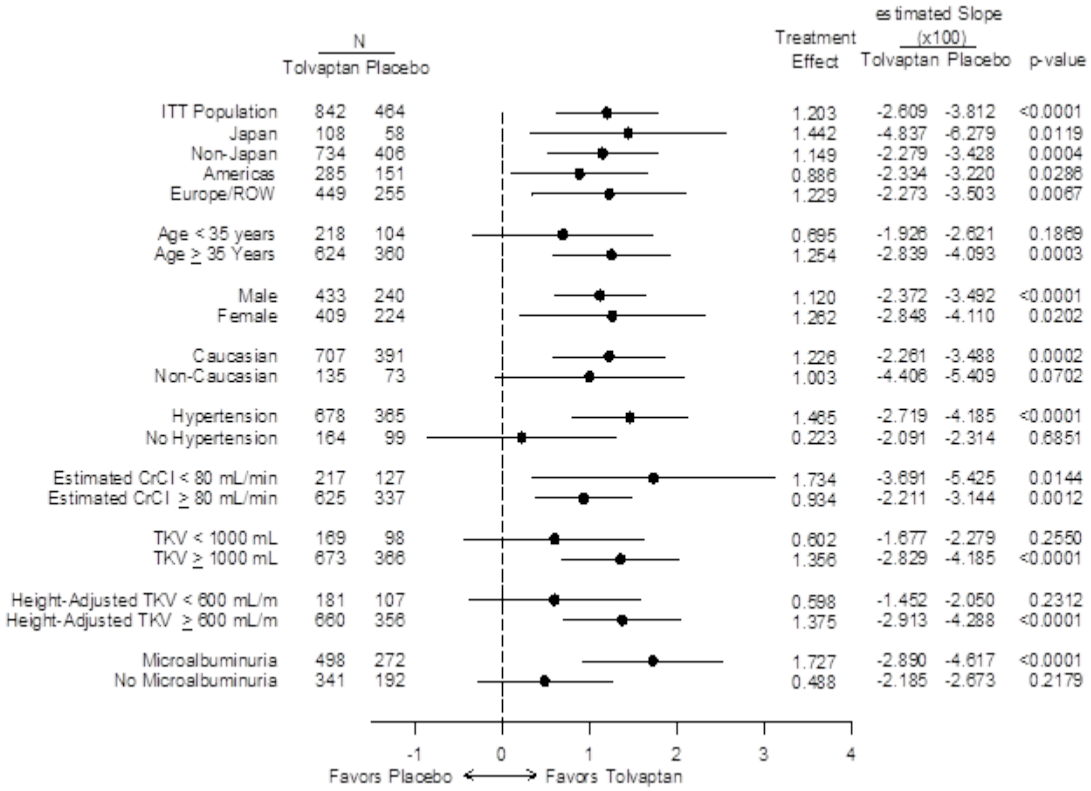


eGFR = estimated glomerular filtration rate; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration.

Source: Adapted from Figure S3, Torres *et al*. (2012a).

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 (Figure B10).

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



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

Source: CSR TEMPO 3:4 Figure 9.5.1.3-1 (Otsuka data on file, 2013c).

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 (Table B13) (Otsuka Pharmaceutical Europe Ltd. data on file, 2014; Torres *et al*., 2014a). 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.

Table B13. Effect of tolvaptan on annualised rate of change in renal function (measured using reciprocal serum creatinine [mg/mL-1]) from baseline by CKD stage

Baseline CKD stage by $eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	N	Estimated slope (annualised)	Treatment effect	95% CI	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

Source: OPEL responses to EMA Day 120 list of questions 2014: Table 3.2.3.7-3 Table 3.2.3.7-7 and Table 3.2.3.6-11 (Otsuka Pharmaceutical Europe Ltd. data on file, 2014); Torres *et al*., 2014a.

Change from baseline in resting mean arterial pressure

In non-hypertensive patients with at least 4 months of follow-up before taking antihypertensive medication, there was a mean increase in arterial pressure of 2.6 mmHg per year in both treatment groups (Table B14). No significant difference was detected between the groups; however, since the majority of trial patients were already hypertensive, the number of patients included in this analysis was small (129 patients in the tolvaptan group and 74 patients in the placebo group) (Otsuka data on file, 2013c).

Table B14. Rate of change per year in mean arterial pressure (mmHg)

Treatment group	N	Mean	Estimated slope[a]	Estimated treatment effect[b]	95% CI	*P* Value[a]
Tolvaptan	129	2.561	0.837	−0.246	−1.059, 0.566	0.5520
Placebo	74	2.592	1.084			

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

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

[b] The difference between the slopes for tolvaptan and placebo.

Source: CSR TEMPO 3:4 Table 9.5.2-1 (Otsuka data on file, 2013c); Table S1, Torres *et al*., 2012a.

Change from baseline in renal pain

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 (Table B15) (Otsuka data on file, 2013c). 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 B15. Time average AUC of change from baseline in renal pain scale (0-10)

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 (Otsuka data on file, 2013c); Table S1, Torres *et al*., 2012a.

[redacted]

Time to Hypertensive Events

No difference between treatment groups was observed in the time to hypertensive events in non-hypertensive patients (Table B16).

Table B16. Time to multiple event analysis of hypertensive events

Treatment group	N	Events per 100 follow-up years	HR[a]	95% CI[a]	*P* Value[a]
Tolvaptan	174	31.80	0.996	0.805, 1.233	0.9704
Placebo	79	29.60			

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

[a] Derived from rate and mean model of time to recurrent event analysis with factor treatment.

Source: CSR TEMPO 3:4 Table 9.5.4-1 (Otsuka data on file, 2013c); Table S1, Torres *et al*., 2012a.

Percentage of hypertensive patients with sustained reduction in antihypertensive therapy

No difference between treatment groups was observed in the percentage of hypertensive patients with a sustained reduction in antihypertensive therapy (Table B17).

Table B17. Number of patients with clinically sustained decreases of blood pressure leading to a sustained reduction in antihypertensive therapy

Treatment group	N	Number of decreases in BP (%)	RR[a]	95% CI[a]	*P* Value[a]
Tolvaptan	481	30 (6.24)	1.100	0.602, 2.017	0.7532
Placebo	267	15 (5.62)			

BP = blood pressure; CI = confidence interval; CSR = clinical study report; RR = relative risk; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

[a] Derived using Cochran-Mantel-Haenszel test stratified by trial centre.

Source: CSR TEMPO 3:4 Table 9.5.5-1 (Otsuka data on file, 2013c); Table S1, Torres *et al*., 2012a.

TEMPO 3:4 efficacy conclusion

The results of TEMPO 3:4 have demonstrated that, as compared with placebo, tolvaptan provides a consistent, durable and significant reduction in the rate of total kidney volume growth, the rate of renal function decline, and the occurrence of clinically significant kidney pain in patients with ADPKD.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No meta-analysis was undertaken because the relevant clinical evidence for tolvaptan comes from a single study.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable.

6.7 Indirect and mixed treatment comparisons

Data from head−to−head RCTs should be presented in the reference-case analysis, if available. If data from head−to−head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

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.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable.

6.7.6 Please present the results of the analysis.

Not applicable.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

The following relevant non-RCTs are briefly described in this section:

- TEMPO 2:4
- Study 156-09-283
- TEMPO 4:4

TEMPO 2:4

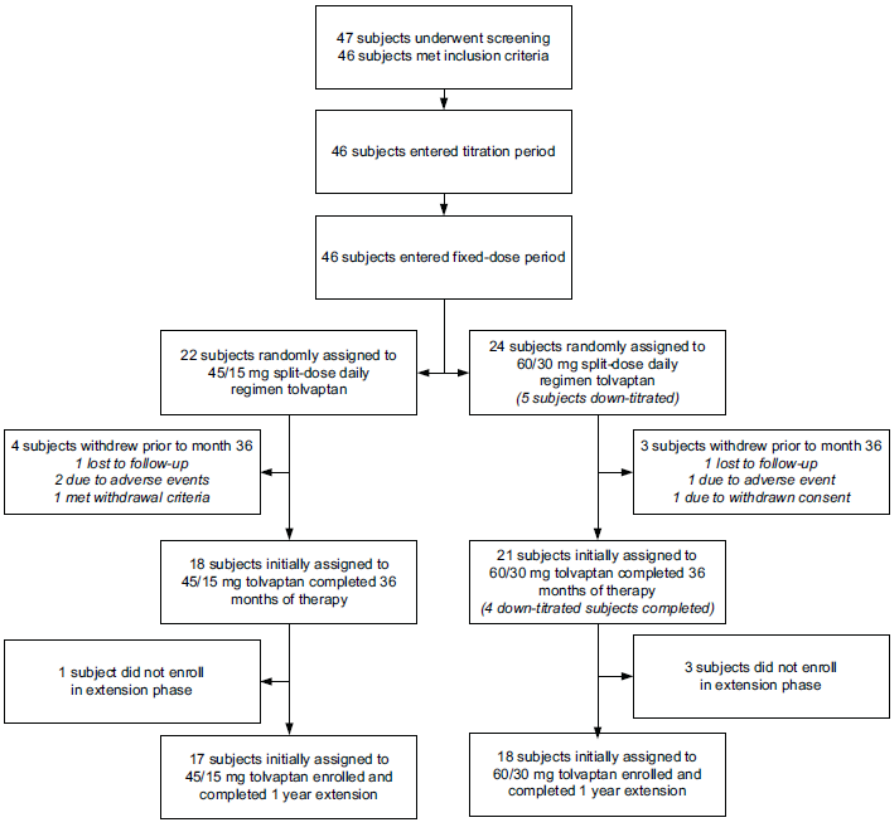
This was a phase 2, multicentre, open-label, parallel-group, dose-finding study evaluating the long-term safety and pilot efficacy of split-dose regimens. This was a 36-month trial with a 12-month extension period (Otsuka data on file, 2014). The split-dose, twice-daily regimen was selected for use in the pivotal trial (TEMPO 3:4) based on the titration scheme developed in TEMPO 2:4. This regimen, with a higher morning dose and a lower dose 8 hours later, produces maximal V2R inhibition during daytime hours, with a gradual fall-off to prevent excess urine production during sleep and reduce nocturia while maintaining efficacy.

All 46 of the patients who entered the titration period were treated in the fixed-dose period and were included in the analysis of safety, including 22 patients in the

tolvaptan 45+15 mg group and 24 patients in the tolvaptan 60+30 mg group. Of the 46 enrolled patients, 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%) (Figure B11) (Otsuka data on file, 2011a).

Demographic and baseline characteristics were generally similar between the two treatment groups. In both groups, most patients were females (16/22, 72.7%, in the tolvaptan 45+15 mg group; 18/24, 75.0%, in the tolvaptan 60+30 mg group), and most were Caucasian (21/22, 95.5%; 24/24, 100.0%; respectively). The mean age was 39.3 years for the tolvaptan 45+15 mg group and 43.9 years for the tolvaptan 60+30 mg group (Otsuka data on file, 2011a).

Figure B11. Patient disposition in TEMPO 2:4



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

Source: Otsuka data on file (2011a).

Safety was assessed by regular monitoring of AEs, directed physical examinations, vital signs, clinical laboratory, and electrocardiogram (ECG) measurements (Otsuka data on file, 2011a). 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

Trough urine osmolality prior to the first daily dose decreased from baseline (472.28 mOsm/kg) throughout the course of the trial and was sustained through 36 months in both treatment groups. Mean urine osmolality (at 3 time points, prior to each daily dose and prior to bedtime) for the total population was maintained at < 300 mOsm/kg throughout the 36 months of the trial (Otsuka data on file, 2011a).

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) (Otsuka data on file, 2011a). 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 (Otsuka data on file, 2011a).

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 (Otsuka data on file, 2011a)

Study 159-09-283

The objective of this study was 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.

Due to data availability, for matched-control pairing the pool of matches was restricted to CRISP subjects for TKV, but included both CRISP and MDRD subjects for eGFR. Once identified, each control subject was used only once. 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/1.73m2 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/1.73m2/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 ($r = -0.21$, $p < 0.01$). Similar small mean decreases in blood pressure were observed in tolvaptan-treated subjects and their case-matched controls. The analysis of time to onset of hypertension therapy was not performed due to a small number of subjects in the non-hypertensive category at baseline ($n = 8$).

The progression of ADPKD, as evidenced by increasing total kidney volume and declining eGFR rate, was statistically significantly slowed after 3 years of tolvaptan treatment compared with historic controls. Previous data have demonstrated a correlation between increase in kidney volume and decline in renal function. These data were (at the time of presentation) the first to demonstrate than an intervention which significantly decreases the growth rate of kidney volume can also be shown to positively impact renal function.

TEMPO 4:4

This 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 (Torres *et al*., 2014a). This is an ongoing study; with limited interim results.

Eligible patients were 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. A total of 871 patients were enrolled in the TEMPO 4.4 trial.

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) (Torres *et al*., 2014a).

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%; $P = 0.048$) (Torres *et al*., 2014a).

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) (Torres *et al*., 2014a).

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%; $P < 0.0001$) (Torres *et al*., 2014a).

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

None of the identified studies were designed to assess safety as a primary outcome.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The majority of subjects receiving tolvaptan (80.9%) and placebo (93.8%) were up-titrated to the maximum daily dose of 120 mg/day by the end of the 3-week titration

period. Thereafter, the average daily dose of tolvaptan received was greater than 90 mg/day for the duration of the trial. For those who continued on maintenance treatment, more than 50% of tolvaptan subjects and over 80% of placebo subjects received the highest dose of 120 mg/day. The average daily dose of tolvaptan received at month 36 was 96.45 mg/day. A total of 404/742 subjects (54.4%) in the tolvaptan group received a modal dose of 120 mg/day at this visit. Overall, 742/961 tolvaptan subjects and 418/483 placebo subjects were still receiving treatment with any dose at month 36 (Figure B12).

Figure B12. Exposure by modal dose (0, 60, 90, and 120mg) over time in TEMPO 3:4

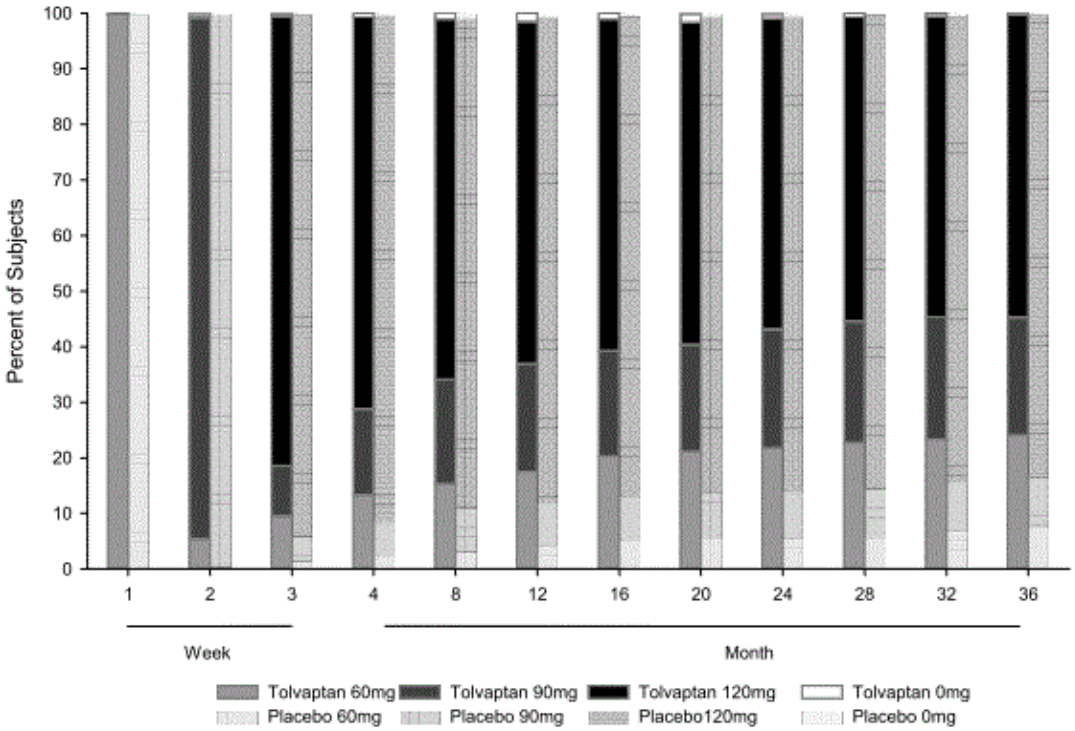


Table B18 presents the numbers and the percentages of patients with serious treatment-emergent AEs, by system organ class.

Table B18. Serious treatment-emergent adverse events by system organ class

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
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 (Otsuka data on file, 2013c).

The most common AEs and serious adverse events (SAEs) are presented in Table B19.

Table B19. Most common adverse events and serious adverse events

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
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

Adverse event	Tolvaptan (n = 961) n (%)	Placebo (n = 483) n (%)	Relative risk: tolvaptan vs. placebo (95% CI)	Risk differences
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 *et al*. (2012a).

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Data from the clinical trials support the use of tolvaptan to achieve its therapeutic benefit in ADPKD with appropriate patient guidance and monitoring to mitigate common and uncommon observed and potential risks. 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 (Otsuka data on file, 2014). Aquaresis-related symptoms led to the discontinuation of tolvaptan in 8.3% of participants, mostly within the first month (Torres *et al*., 2012a). 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 (Otsuka data on file, 2013c).

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 (Otsuka data on file, 2014).

The incidence of serious treatment-emergent adverse events in the pivotal trial was numerically lower for patients treated with tolvaptan (177/961; 18.4%) than for patients treated with placebo (95/483; 19.7%), and no patient died during trial participation (Otsuka data on file, 2014).

Overall, the safety results of individual supportive long-term and short-term tolvaptan trials within the ADPKD programme were consistent with those observed in the pivotal trial (TEMPO 3:4) (Otsuka data on file, 2014).

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 (Otsuka data on file, 2013c).

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 (Otsuka data on file, 2014). 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.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Tolvaptan is currently the only disease-modifying therapy for ADPKD that significantly delays renal progression in ADPKD, by reducing kidney growth and slowing renal function decline. Despite ADPKD being a rare disease, the benefits of tolvaptan have been demonstrated in a large, global, phase 3 clinical trial (TEMPO 3:4; N > 1,400). Longer-term efficacy and safety of tolvaptan are currently being studied in a phase 3b extension study with follow-up of more than 5 years (TEMPO 4:4). Interim results indicate a continuation of benefit for patients exposed to tolvaptan over the longer-term.

In TEMPO 3:4, tolvaptan demonstrated a significant relative reduction of 49.2% in TKV growth over 3 years when compared with placebo (absolute reduction of -2.71% per year; 95% 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 3 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: 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).

Tolvaptan reduced the risk of clinically significant kidney pain by 29% (absolute reduction: 2 events per 100 person-years) compared with placebo (5 events per 100 person-years vs 7 events per 100 person-years; HR 0.64; 95% CI: 0.47, 0.89; p=0.007). Within the licensed indication, tolvaptan has a predictable, consistent, and clinically meaningful effect on the renal progression of ADPKD.

Consistent results of subgroup analyses across the first three trial endpoints (rate of change in total kidney volume, time to multiple investigator-reported ADPKD clinical progression events [including onset or progression of hypertension, clinically significant renal pain, worsening albuminuria, and worsening renal function], and renal function rate of change) support broad applicability of these efficacy results to patients with ADPKD. Evidence of efficacy was observed in all subgroups analysed.

For the primary endpoint, all examined subgroups (sex, age, TKV at baseline, estimated creatinine clearance level at baseline, hypertension status, and microalbuminuria) yielded statistically significant favourable results for tolvaptan treatment.

For the primary endpoint, tolvaptan showed a consistent and significant effect favouring tolvaptan across all studied CKD stages. Within CKD stage 1 patients only, the difference between treatment groups showed no significant difference for renal function decline, although this 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. In patients whose renal function decline was already detectable (CKD 2 and 3) tolvaptan improved both the rate of TKV growth and GFR decline (Torres *et al*., 2014b). Tolvaptan also demonstrated continued efficacy over longer periods of exposure, as observed from the interim results from TEMPO 4:4.

Tolvaptan has an acceptable tolerability profile, with 15.4% of patients assigned to the tolvaptan arm (vs. 5% in the placebo arm) discontinuing due to AEs over the course of the 3-year pivotal trial. The rate of AEs was similar between the tolvaptan (97.9%) and placebo (97.1%) treatment arms. The incidence of SAEs in the tolvaptan (18.4%) and placebo treatment arms (19.7%) was similar. Aquaresis is an expected effect of tolvaptan treatment that, although commonly reported as an AE in the clinical trial, led to discontinuation of tolvaptan in only 8.3% of patients and occurred mostly over the first month.

Hepatotoxicity has been observed in some ADPKD receiving tolvaptan, including three cases meeting Hy’s Law criteria. However 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. To mitigate this risk, measures are described in the EU 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. Post-authorisation studies will be conducted to ensure the effectiveness of these risk mitigation measures.

The principal findings from the clinical evidence suggest that tolvaptan provides a clinically and statistically significant reduction in the rate of TKV growth, renal function decline and clinically significant kidney pain. Most patients with ADPKD ultimately develop ESRD and require interventions such as dialysis and transplant, which have a substantial clinical and economic impact. Reduction in the rate of kidney function decline is likely to prevent or delay ESRD, which would be of high clinical and economic value. The subsequent reduction in the need for dialysis is likely to reduce the associated NHS costs and service use as well as have a positive impact on patient and family HRQoL and productivity. Reduction in the need for transplants is likely to reduce the accompanying costs, and consumption of donor organs, which could be made available to other patients.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

- Although ADPKD is a rare disease, the primary efficacy and safety evidence for tolvaptan is based on a large, global, phase 3 clinical trial with 3-year follow-up (N > 1,400).
- A large trial population enabled the evaluation of disease progression and rate of progression in patient subgroups.
- The duration of studies allowed for the longer-term evaluation of treatment effect.
- The tolvaptan dosing regimen was established by an open-label, dose-finding study (TEMPO 2:4).
- The patient population included CKD stages 1-3 and the results for the primary efficacy analysis were consistent across all CKD stages
- The primary outcome, TKV growth rate, was measured in adherence to a strict MRI protocol, ensuring robustness of the primary efficacy evaluation
- There was clear demonstration of efficacy (statistically significant) across multiple outcome measures and subgroups, confirming the robustness of the results
- The TEMPO 3:4 trial included multiple measures of renal function, including 1/serum creatinine, Cockroft-Gault, MDRD, and CKD-EPI. The results for tolvaptan were consistent across all four measures providing confidence in the findings.

- Tolvaptan has a manageable tolerability profile, with 15.4% of patients assigned to the tolvaptan arm (versus 5% in the placebo arm) discontinuing due to AEs over the 3-year pivotal trial.
- There was a low rate of patients lost due to follow up (less than 2% in each arm).

Limitations

- TEMPO 3:4 assessed an intermediate disease endpoint (TKV) as the primary outcome, and it was not feasible to capture the final outcome of interest (ESRD) as a primary endpoint, as ADPKD is a chronic disease and ESRD develops over the long term. However, the selection of TKV as the primary endpoint was ratified by the EMA, and the findings of the key secondary composite endpoint (the time to multiple ADPKD clinical progression events for tolvaptan relative to placebo during the treatment period) were significant and consistent with the results of the primary endpoint. The results for renal function decline (eGFR), which is directly related to ESRD, were also consistent and were statistically significant.
- Most patients randomised in TEMPO 3:4 were in CKD stages 1 and 2 at baseline (34.5% and 48.5%, respectively, for tolvaptan). There were relatively few patients in CKD stage 3 (17%) randomised in the trial.
- In TEMPO 3:4, 80% of patients had hypertension at baseline, limiting the possibility of detecting a potential beneficial effect of tolvaptan on the development or progression of hypertension (Torres *et al*., 2012a).
- The consideration of missing data presents many challenges. Patient discontinuation rates were 23% for tolvaptan and 14% for placebo. The 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 (Medpage Today, 2013). 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 (Otsuka data on file, 2014).

- To assess the primary endpoint, patients 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.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

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 (Grantham *et al*., 2006; Chapman, 2008; Chapman *et al*., 2003). 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.

TKV was defined as the primary endpoint of TEMPO 3:4 and was accepted by the EMA as an appropriate prognostic indicator of disease progression. This has been demonstrated in long-term follow-up studies in large patient cohorts, including CRISP I and CRISP II and those from the PKDOC (Grantham *et al*., 2006; Chapman *et al*., 2008; Chapman *et al*., 2012; Perrone *et al*., 2014a; Perrone *et al*., 2014b; Perrone *et al*., 2014c). Increasing kidney volume is clinically important in itself, as it is associated with development of hypertension, pain, and haematuria, even early in the disease. TKV can be used to identify those patients with the greatest clinical need for treatment (Grantham *et al*., 2006; Chapman, 2008; Chapman *et al*., 2012; Perrone *et al*., 2014a; Perrone *et al*., 2014b; Perrone *et al*., 2014c; Perrone *et al*., 2014d). TKV is believed to be an acceptable surrogate endpoint for cystogenesis

because it can sensitively track cyst development in human disease that is responsive to prospective clinical therapies effective in treating animal models (Grantham *et al*., 2006). As ADPKD is characterised by cyst growth, it is important in a clinical study to understand the impact of treatment on cystogenesis, as well as the more clinically relevant endpoints. Moreover, changes in TKV can be reliably measured by MRI in early stages of disease (Grantham *et al*., 2006; Chapman *et al*., 2012; Wuthrich *et al*., 2009; Kistler *et al*., 2009; Chapman *et al*., 2003). In TEMPO 3:4, MRI assessments took place at baseline and at months 12, 24, and 36/early termination.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

As described in Section 6.3.2, pivotal study TEMPO 3:4 was conducted in different countries across the world and therefore accounted for differences across countries in disease management.

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.

The patient population for whom tolvaptan is indicated includes patients with CKD stage 1 to 3 at initiation of treatment and evidence of rapidly progressing disease. This patient population corresponds with patients included in TEMPO 3:4; the inclusion criteria of the trial were defined with prognostic enrichment in mind. The

patient baseline characteristics are also comparable to those reported in a number of natural history studies conducted in the UK (Thong and Ong, 2013; Shaw *et al*., 2014; McGovern *et al*., 2014).

In TEMPO 3:4, standard of care recommendations were defined in the protocol and additional measures with the Steering Committee throughout the trial. These recommendations included prescription of sodium and/or protein restriction appropriate to each subject's condition per local guidelines, and maintenance of adequate hydration (in advance of thirst). It is likely that these measures were more rigorously adhered to in the trial than is usual in routine clinical practice. In addition, the primary efficacy analysis of TEMPO 3:4 was powered for 7% TKV growth in the placebo arm; however, TKV growth of only 5.5% was actually observed. Despite this, the efficacy of tolvaptan was clearly demonstrated.

7 Cost-effectiveness

Cost-effectiveness summary

- A *de novo* patient-level, fixed-time increment stochastic simulation model was developed to assess the cost-effectiveness of tolvaptan for the treatment of ADPKD in England and Wales
- Efficacy and safety data was sourced from the large TEMPO 3:4 RCT, with supporting parameter values such as health state utilities and unit costs sourced from the literature
- Initiation with tolvaptan is estimated to lead to significant long-term clinical benefits, including maintenance of HRQoL, reduction of time in dialysis, fewer transplants and increased life expectancy
- The mean base-case ICER excluding the PAS was [redacted], and including PAS was £34,769. Including the PAS, the probability of cost-effectiveness at a willingness-to-pay threshold of, £35,000 and £40,000 per QALY gained was 47% and 58%, respectively
- In the structural sensitivity analysis (including the PAS), the ICER ranged from £22,993 to £47,722 indicating the results were robust to the majority of sensitivity analysis and providing ICERs below £35,000
- Subgroup analyses were performed by CKD stage (1 to 3) at initiation which revealed that the overall clinical benefit in terms of QALYs and life-years increases when treating patients in an earlier stage of disease progression, whilst cost-effectiveness was stronger amongst patients
- The submitted analyses have not accounted for the potential impact of the recent ruling regarding the applicability of PPRS 2014 when assessing the cost effectiveness of tolvaptan. Accordingly, the cost effectiveness case presented here may be considered as conservative in this respect
- Tolvaptan represents a step-change in the management of ADPKD, being the first treatment proven to delay ADPKD renal progression, leading to clinically meaningful long-term benefits for patients, whilst reducing the burden on transplant and dialysis services for the NHS
- Under the terms of the PAS tolvaptan represents a cost-effective use of NHS resources

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Searches for relevant cost-effectiveness studies were performed as part of the combined systematic literature review to identify relevant clinical and cost-effectiveness data described in section 6.1 and Appendix 10.2. Prior to initiating the systematic literature review, a protocol was developed to outline the methodology to be used for the searches, the screening process (inclusion and exclusion criteria), and the data extraction. From methods defined *a priori*, 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 included review of congress abstracts for the following meetings from January 2012 to August 2014:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

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

In addition to congresses, the Cost Effectiveness Analysis (CEA) Registry was interrogated.

Table B20 provides the inclusion exclusion criteria used in selecting relevant cost-effectiveness studies.

Table B20. Eligibility criteria for cost-effectiveness studies

	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 per outcome	• Cost minimization • Resource use
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
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PRO, patient-reported outcome; HRQoL, health-related quality of life		

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more

than one study is identified, please present in a table as suggested below.

One relevant cost-effectiveness study was identified in the searches (Erickson *et al*., 2013). The study aimed to determine how the benefits of tolvaptan observed in the TEMPO 3:4 trial may translate to longer-term health outcomes, such as progression to 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. A Markov model was used, populated with aggregated, published clinical data from the TEMPO 3:4 trial.

The base case results estimated 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. The incremental cost-effectiveness ratio (ICER) was estimated as $744,100 per quality-adjusted life year (QALY). A summary of the study is presented in Table B21.

The cost-effectiveness results from this study are not relevant to decision-making in England and Wales. The cost of tolvaptan applied to the Erickson analysis is an order of magnitude higher than the actual cost of tolvaptan to the NHS in England and Wales. In addition, resource use and unit costs in the United States are unlikely to be generalisable to the NHS in England and Wales. Furthermore, the analysis took the societal perspective (although model inputs were consistent with a third party payer perspective) and costs and outcomes were discounted at a rate of 3% per annum.

With respect to the modelling approach to outcomes, there were several limitations with the Erickson model. Only aggregated results from TEMPO 3:4 on renal function decline were utilised to define fixed relative rates of disease progression, and a single set of patient baseline characteristics. Health states were defined by CKD stages and ESRD was simplified to a single cost and utility value. Tolvaptan adverse events and ADPKD complications not directly related to renal function decline were assumed to exactly offset in terms of cost and HRQoL impact.

Given these limitations, it was deemed necessary to construct a *de novo* model that would be capable of accounting for the underlying inter-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.

Table B21. Summary list of other cost-effectiveness evaluations

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 *et al*., 2013	2013	US	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

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); US, United States.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[3] or Philips *et al*. (2004).[4] For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, Appendix 11.

One cost-effectiveness study was identified (Erickson *et al*., 2013). A complete quality assessment is provided in section 10.11, Appendix 11.

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[3] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[4] Philips Z, Ginnelly L, Sculpher M, *et al*. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The final scope states that tolvaptan will be appraised within its licensed indication. Therefore the base-case modelled population was selected to best reflect the proposed licensed indication.

The proposed licensed indication is in adults with ADPKD who have stage 1 to 3 CKD at initiation of treatment and evidence of rapidly progressing disease (as presented in section 1). This proposed indication is broadly in line with the inclusion criteria of TEMPO 3:4 (outlined in section 6.3.3). The trial population was enriched for those who were likely to progress during the trial, therefore basing the modelled population on the overall baseline characteristics of TEMPO 3:4 is a reasonable approach, in the base case, in order to approximate patients eligible under the proposed label (Table B22).

Table B22. Baseline patient profile based on mean overall TEMPO 3:4 patient characteristics

Patient characteristic	Mean (standard error)
Mean age (years)	38.7 (0.190)
Sex (% female)	48.40 (1.3)
Mean TKV (mL)	1,692.30 (23.820)
Mean eGFR (mL/min/1.73 m^2)	81.61 (0.570)
ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; TKV = total kidney volume.	

It is important to note that the base-case patient profile for the economic evaluation described above may not reflect the typical patient case-mix seen in current UK practice. There are important dynamics to consider with respect to the time point at which ADPKD patients typically present in routine practice, and also as to which patients would be considered eligible for treatment under the proposed licensed

indication. These issues are explored in greater detail in scenario analysis and in section 7.10.

Model structure

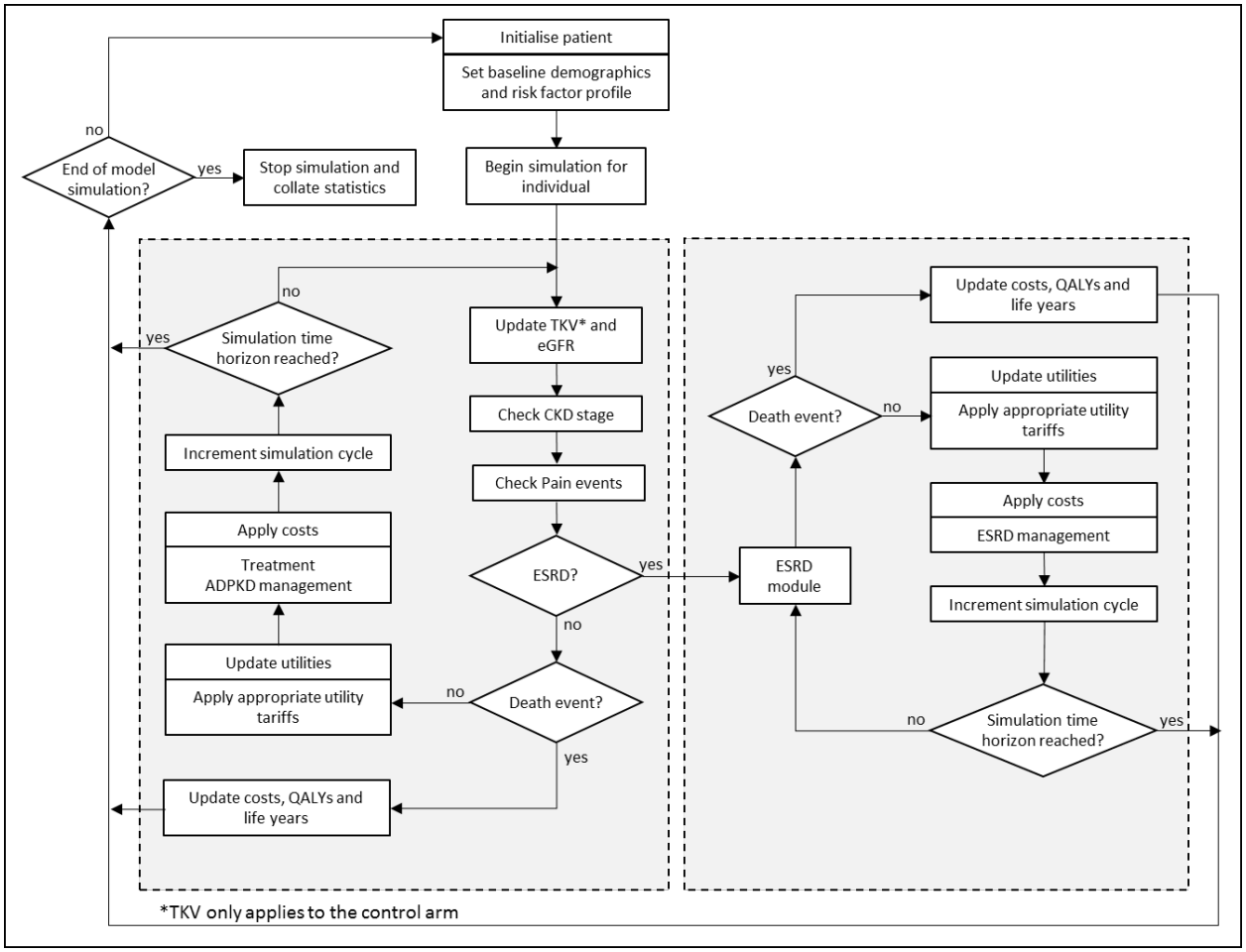
7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The *de novo* cost-effectiveness model is a “patient-level, fixed-time increment stochastic simulation model”. The model encompasses the entire disease pathway and consists of two distinct elements:

1. The period of ADPKD progression (up to the development of ESRD); the treatment effect for tolvaptan may apply during this period
2. An ESRD module in which the patient pathway is independent of the allocated treatment (tolvaptan or no active treatment), i.e. tolvaptan is withdrawn at onset of ESRD

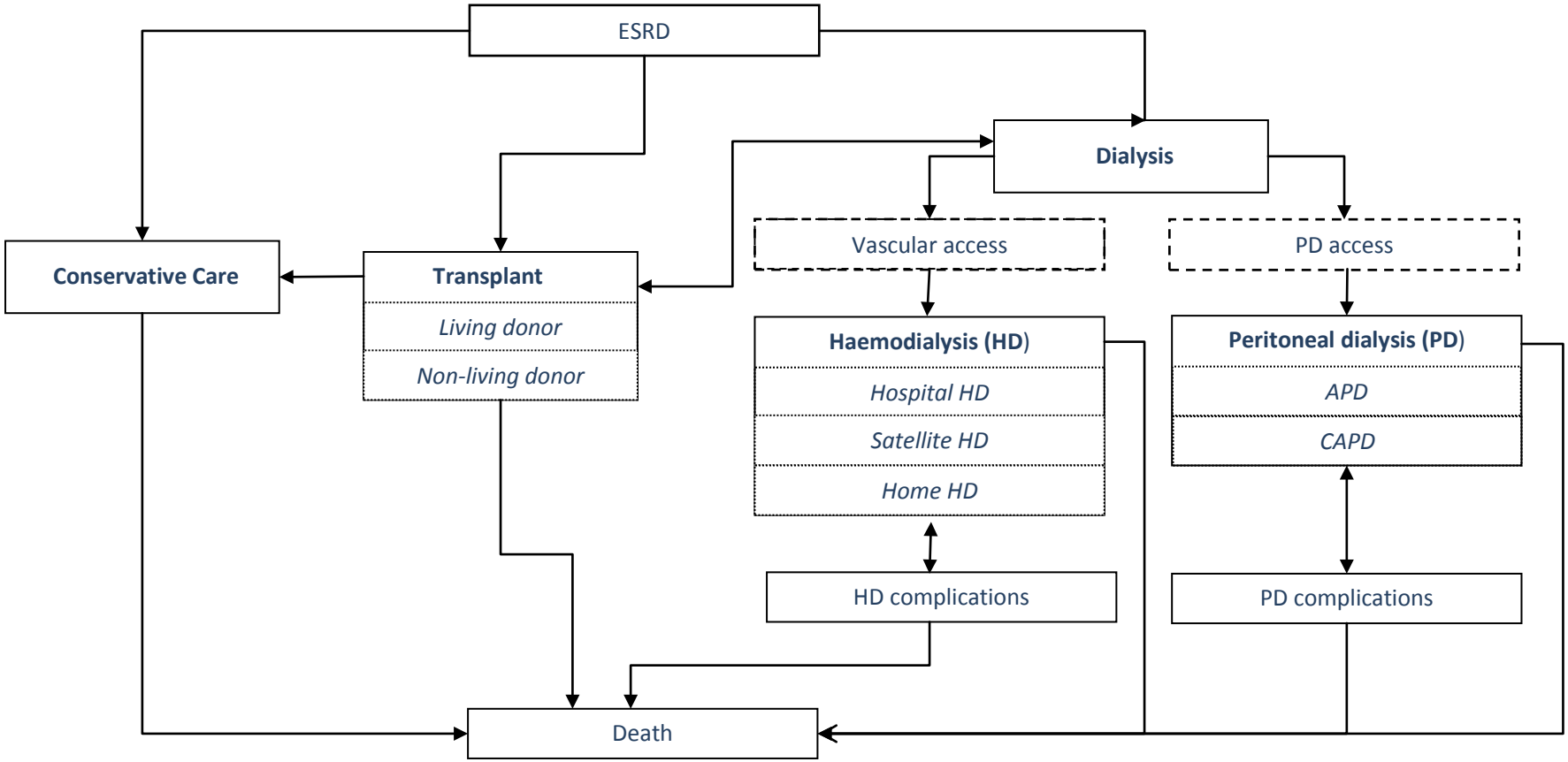
Figure B13 shows the logical flow of the overall model combining these two elements. Figure B14 shows the detailed flow of the ESRD-specific module.

Figure B13. Flow diagram of patient simulation process in the cost-effectiveness model



ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; QALY, quality-adjusted life-year; TKV, total kidney volume.

Figure B14. Flow diagram of the end-stage renal disease module



APD, ambulatory peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; ESRD, end-stage renal disease; HD, haemodialysis, PD, peritoneal dialysis.

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). The model predicts the underlying progression of ADPKD over time for patients receiving no active treatment, tracked via TKV and eGFR as continuous variables (see section 7.3.2). The treatment effect of tolvaptan on eGFR is used to adjust the natural history trajectory for patients receiving tolvaptan (see sections 7.3.1 and 7.3.2). ESRD states are modelled as the transition between key RRT modalities and events in line with UK pathways. Clinically significant kidney pain (clinically significant renal pain) was also modelled and could occur in the model in CKD stages 1 to 5. Pain was independent of treatment after CKD 4 (no pain occurred after transplant). See sections 7.2.3 and 7.2.4 for more detailed description of health states and possible transitions.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model captures the patient pathway from the point at which the decision to initiate tolvaptan is made until death, including the key clinical aspects of the disease (i.e., declining renal function and ESRD). The design encompasses the expected differences in costs and outcomes for patients receiving tolvaptan compared with those receiving no active treatment, resulting from a reduction in the rate of kidney function decline, and from delay or prevention of the onset of ESRD. The two distinct elements of the model (the first capturing worsening CKD up to the onset of ESRD, and the second capturing the complex management of ESRD) allow separation of the period during which patients receive tolvaptan treatment (and the treatment effect is applied) and the period during which the consequences of ESRD are modelled and treatment is no longer given.

Underlying disease progression is tracked via TKV and eGFR. TKV and eGFR trajectories were estimated on a continuous scale, as expected under the natural history of ADPKD for the control group. This approach leverages the benefits of both endpoints, with TKV being a reliable indicator of disease progression, and eGFR being a direct measure of renal function and the principal clinical outcome of interest (see section 2.1). TKV has been validated in long-term follow-up studies as a strong prognostic indicator of ADPKD progression (see section 7.3.8).

Clinically significant kidney pain was the only ADPKD complication explicitly modelled given that it was the only non-TKV or renal function outcome associated

with a significant difference between arms in TEMPO 3:4. Explicit modelling of other complications (such as hypertension, hernia, microalbuminuria, gross haematuria, nephrolithiasis, proteinuria, anaemia and gout) was deemed to be trivial for the purposes of assessing the cost-effectiveness of tolvaptan given the lack of evidence supporting a difference in effect on these outcomes.

The choice of modelling approach for ADPKD (pre-ESRD) meets the stated *a priori* objectives, namely: capable of accounting for the underlying inter-patient heterogeneity in ADPKD progression; permits the exploration of clinically-relevant subgroups, assesses the relative impact of tolvaptan tolerability and ADPKD complications.

ESRD is a complex and severe disease state with significant implications for patients and health services alike that can vary widely. It was deemed inappropriate to assume ESRD to be a single state (as per Erickson *et al*., 2013), therefore an ESRD-specific module was developed within which patients could enter multiple states, including conservative care, haemodialysis (HD), peritoneal dialysis (PD), and transplantation, along with associated costs, utilities, and mortality rates.

The ESRD module was based on a model developed as part of NICE CG125 (peritoneal dialysis). This was further adapted as follows:

- Addition of a conservative care health state
- Replacement of fixed annual patient or graft survival rates with survival specified by age group
- Removal of patients switching between dialysis modalities (simplifying assumption)

Though ESRD onset is deemed to occur at eGFR < 15 mL/min/1.73m^2, the initiation of RRT may not occur in clinical practice until eGFR declines further. For example, mean eGFR was found to be 8.7 mL/min/1.73m^2 among ADPKD patients initiating RRT in England and Wales (Shaw *et al*., 2014). Therefore a pre-RRT/CKD stage 5 health state was also included in the ESRD module.

The choice of a patient-level simulation was driven by the following factors:

- Coded simulation models are far more flexible and more easily adapted; this was important during the development of this model as there were no models

published in this disease area (at initiation of the project) and the model structure evolved in many iterations, in collaboration with a panel of experts.

- Modelling the logic associated with complex patient flows, such as those involved in the modelling of ESRD, is more easily achieved in code than in alternative approaches such as a Markov model
- Age dependent transition rates cannot easily be accommodated in Markov models
- Modelling disease progression rates that differ between patients dependent on whether or not they continue treatment and the individual timing of discontinuation cannot easily be accommodated within a Markov model
- Patient-level simulations enable the interrogation of simulated patients as they progress through the simulation and the output of patient-specific data to support ad-hoc analyses

The choice of a fixed-time increment stochastic simulation was made over a discrete event simulation due to the ease with which they can be described, coded and validated. The existence of annual disease progression rates in the published literature also lends itself to the use of a fixed annual cycle, rather than the continuous simulation clock that is utilised in a discrete event simulation, updating only when an event occurs.

Studies comparing simulation modelling with Markov models have demonstrated that, under consistent assumptions regarding model settings, the two approaches will provide very similar results.

7.2.4 Please define what the health states in the model are meant to capture.

Whilst TKV and eGFR were tracked as continuous variables, CKD stage “health states” were retro-fitted according to the progression of each patient. Health states included in the ADPKD progression module and ESRD module are presented in Table B23 and Table B24, respectively.

Table B23. Modelled health states in ADPKD progression module

Health state	Definition	Captures
CKD stage 1	eGFR ≥ 90 mL/min/1.73 m^2	• The costs and HRQL of typical background ADPKD complications associated with this CKD stage (excluding significant pain). These are assumed to increase with each advancing CKD stage, with the exception of CKD 1 and 2 HRQL where this is assumed not to differ from the general population.
CKD stage 2	eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2	• The costs and HRQL of typical background ADPKD complications associated with this CKD stage (excluding significant pain). These are assumed to increase with each advancing CKD stage, with the exception of CKD 1 and 2 HRQL where this is assumed not to differ from the general population, increasing annual cost[a] (These were all assumed to be equivalent to CKD stage 1 in the base-case analysis)
CKD stage 3	eGFR ≥ 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2	• The costs and HRQL of typical background ADPKD complications associated with this CKD stage (excluding significant pain). These are assumed to increase with each advancing CKD stage, with the exception of CKD 1 and 2 HRQL where this is assumed not to differ from the general population. Increasing annual cost[a] • Increasing utility decrement[a]
CKD stage 4	eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2	• The costs and HRQL of typical background ADPKD complications associated with this CKD stage (excluding significant pain). These are assumed to increase with each advancing CKD stage, with the exception of CKD 1 and 2 HRQL where this is assumed not to differ from the general population. Increasing annual cost[a] • Increasing utility decrement[a]
Significant pain (event occurring within any health state)	Clinically significant kidney pain necessitating medical leave, pharmacologic treatment (narcotic or last-resort analgesic agents), or invasive intervention	• Specific cost and utility decrement associated with this event.
Dead	—	—

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease.
[a] Excludes clinically significant kidney pain which is a treatment-dependent event not included within the CKD stage cost or utility estimates.

Table B24. Modelled health states in ESRD module

Health state	eGFR range	Captures
CKD stage 5 prior to ESRD treatment	< 15 mL/min/1.73m^2 to 8.5 mL/min/1.73m^2	• Period between ESRD onset and initiation of renal replacement therapy (RRT) • The costs and HRQL of typical background ADPKD complications associated with this CKD stage (excluding significant pain). These are assumed to increase with each advancing CKD stage, with the exception of CKD 1 and 2 HRQL where this is assumed not to differ from the general population. Annual cost for management of ADPKD and related complications, excluding ESRD treatment • Increasing utility decrement for CKD stage 5/ESRD
Conservative care	< 8.5 mL/min/1.73m^2	• Management to prolong kidney function and control symptoms of ESRD • Annual cost for management of ADPKD and related complications • Increased utility decrement • Increased risk of death for ESRD
Haemodialysis	< 8.5 mL/min/1.73m^2	• Placement of vascular access for catheter • Cost of haemodialysis (hospital, home or satellite) • Annual cost for management of ADPKD and related complications, and dialysis related complications including vascular access failure • Increased utility decrement and disutility associated with complications • Increased risk of death for ESRD and from dialysis
Peritoneal dialysis	< 8.5 mL/min/1.73m^2	• Placement of vascular access for catheter • Cost of peritoneal dialysis (CAPD or APD) • Annual cost for management of ADPKD and related complications, and dialysis related complications • Utility impairment compared with pre-dialysis health states but improvement compared with haemodialysis, disutility associated with complications • Increased risk of death for ESRD and from dialysis

Health state	eGFR range	Captures
Transplant	< 8.5 mL/min/1.73m^2	• Cost of transplant surgery, transplant service and maintenance cost (higher in the first year after transplant) • Possible graft failure and subsequent ESRD treatment or further transplant (maximum of 2 transplants per patient) • Annual cost for management of ADPKD and related complications, and transplant complications • Utility improved compared with ESRD (less so in the first year after transplant) • Increased risk of death for ESRD and from transplant
Dead	—	—
CKD, chronic kidney disease; ESRD, end-stage renal disease.		

Conservative care aims to maintain a good quality of life by prolonging kidney function and controlling symptoms in the absence of dialysis or transplant. Conservative care is usually given to patients at their request, or if they are contraindicated for RRT (i.e., dialysis or transplant). Once patients reach the threshold for ESRD treatment, the model allows for a proportion to receive conservative care while others receive dialysis (haemodialysis or peritoneal dialysis) or transplant. Patients may also receive conservative care following the renal graft failure, rather than receiving dialysis.

The haemodialysis (HD) process replaces the cleaning function normally carried out by the kidneys; blood is removed from the body, flows around a dialysis machine, through a dialyser, which cleans the blood of waste products, and is returned to the body. Haemodialysis usually needs to be undertaken three times a week and may be undertaken at home, in hospital or using a satellite dialysis unit in the community.

Peritoneal dialysis (PD) is another technique that can be used to clean the blood of waste products. During PD, waste products are removed from the body using the peritoneal membrane in the abdomen as a natural filter. A catheter is inserted into the abdomen that allows fluid to be drained in and out of the peritoneal cavity. There are two types of PD: continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). CAPD requires dialysis four times a day for 20-30 minutes. APD takes about 30minutes and fluid is exchanged during the night. The model allows for patients to receive either HD (home, hospital or satellite) or PD (APD or CAPD).

Simulated patients may receive a transplant immediately on reaching ESRD, or in subsequent years when undergoing HD or PD. The annual probability of transplant is age-dependant, defined by the following age categories; 18–34, 35–44, 45–54, 55–64 and 65+. The probability of transplant reflects both the probability of a patient being eligible for transplant and the availability of donor organs. Simulated patients may receive a transplant from a living donor or a deceased donor, including brainstem death (DBD) or circulatory death (DCD).

Following transplant, graft survival and mortality are modelled. Patients receiving organs from living or deceased donors are subject to source-specific survival probabilities. If a patient experiences graft failure, and survives, they may receive conservative care, otherwise they will receive dialysis. Patients with ADPKD develop ESRD at a younger age on average than ESRD associated with other underlying causes (e.g., diabetes); therefore, they are more likely to require a second kidney transplant than other patients with ESRD. The model allows the possibility of a subsequent kidney transplant for patients with transplant failure.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure encompasses the key clinical aspects of ADPKD, which is characterised primarily by the development and expansion of fluid-filled cysts in the kidney, leading to an increase in kidney volume, and progressive loss of renal function (section 2.1; Takiar and Caplan, 2011; Patel *et al*., 2009). The model captures the primary consequence of ADPKD and the resulting costs and HRQL impact. All major aspects of ESRD are modelled, including conservative management, haemodialysis, peritoneal dialysis and kidney transplantation.

Underlying disease progression (the no active treatment arm) is characterised in the model by the tracking of TKV on a continuous scale, with renal function (eGFR) predicted from TKV (also on a continuous scale). The progression trajectories were driven by regression equations estimated from data from the TEMPO 3:4 trial; the regression equations are described in section 7.3.2 (initial simulation).

At the start of a simulation, a patient cohort is generated based upon mean demographic and risk factor profiles (in the base case, the average baseline characteristics of the TEMPO 3:4 trial, see section 7.1.3). TKV and eGFR trajectories are estimated on a continuous scale as expected under the natural history of ADPKD for the control group. Each simulated subject of the generated cohort is progressed through the model in annual time increments (1 year = 1 cycle). At each time cycle, checks are made to track movements between chronic kidney disease (CKD) stages, for the incidence of renal failure (ESRD/CKD stage 5 proxy) and for the incidence of all-cause mortality. If a patient's simulated eGFR falls below a pre-specified threshold (in the base case, this is set at 15 mL/min/1.73m^2), the patient is deemed to suffer from ESRD. Their continued progression and management is modelled in the ESRD module; once this stage is reached, patients may receive conservative care management, dialysis or undergo kidney transplant.

At the end of each cycle, a subject's disease state is assessed and any appropriate decrement in health utility is applied, together with any relevant costs. Assuming a subject does not die in a given cycle, the simulation clock is advanced until the model time horizon is reached. If a fatal event occurs, all costs, life years and quality-adjusted life years (QALYs) are accumulated and the simulation ends for that subject. Once the simulation ends, the model selects the next subject to simulate and the process begins again. Table B25 describes the baseline cohort characteristics required to run the model and their influence within the analysis.

Table B25. Description of patient characteristics

Patient characteristic	Description of influences in the model
TKV	TKV is updated as the simulation clock is progressed through the use of the natural history equation (i.e. TEMPO PLD) which then effects the progression of eGFR
Age (years)	Age was updated as the simulation clock progressed. Age impacted disease progression, the probability of all-cause mortality, which was updated annually based on the life tables, ESRD mortality/survival and may have influenced the probability of transplantation
Sex (% female)	Sex impacted the probability of all-cause mortality, which was updated annually based on the provided life tables. Sex also influences rate of TKV progression
eGFR (mL/min/1.73 m^2)	eGFR was updated as the simulation clock progressed through the use of natural history equations and affected the progression of CKD up until onset of ESRD
ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; TEMPO = Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes	

The treatment arm of the model (tolvaptan) utilises the same patient cohort data (i.e., baseline demographics and risk factors) as the initial simulation (no treatment), but applies a treatment effect to the predicted eGFR trajectory (see section 7.3.1), which will ultimately impact the incidence and timing of renal failure (ESRD/CKD stage 5). The model then simulates each of the patients in the treatment arm in the same manner as the initial simulation, with the exception of treatment-related discontinuation, clinically significant pain events and any additional treatment-specific costs and health utility impact.

The incidence of clinically significant kidney pain is modelled separately from disease progression. The model simulates the prevalence of clinically significant kidney pain events associated with ADPKD, based on the annual probability of occurrence. Once all individuals have been simulated the process ends and all summary statistics are collected for that particular run of the model.

Table B26. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (up to 80 years after initiation of treatment)	A lifetime horizon was judged to be most appropriate to capture differences in costs and outcomes associated with a delay in ADPKD progression and occurrence of ESRD as it is a long term condition. An 80-year time horizon was chosen to capture the lifetime of patients who start the model with a mean age of 39 years. Deterioration of GFR, and thus CKD stage progression, occurs relatively later in the disease course and is highly variable between patients	CRISP I (Grantham, 2006)
Cycle length	1 year	Based on clinical input a 1-year cycle length was considered to be an appropriate interval for assessing in pathology or symptoms.	
Half-cycle correction	Yes	A half-cycle correction is good practice in decision analytic modelling	Philips *et al*., 2004
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference Case	NICE, 2013
Discount of 3.5% for utilities and costs	3.5%	Costs and outcomes are discounted at a default annual rate that is set to 3.5% for costs and outcomes, in line with the NICE Reference Case.	NICE, 2013
Perspective (NHS/PSS)	NHS + PSS	The model takes the perspective of the NHS and PSS in England and Wales to analyse health care costs This is in line with the final scope and the NICE Reference Case	NICE, 2013

CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Study of Polycystic Kidney Disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

Technology

7.2.6 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Tolvaptan clinical effectiveness was implemented in the model according to the results of TEMPO 3:4. The study utilised a forced-titration protocol; therefore the model assumes that tolvaptan will be administered according to the mean observed exposure in the TEMPO 3:4 trial. The comparator in the model was no active treatment, represented by the placebo arm of the TEMPO 3:4 trial; no drug cost was included for the comparator.

The titration schedule expected to be included in the licensed indication differs only very slightly from that in the TEMPO 3:4 trial and 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."*

This titration schedule is therefore the same as that in the TEMPO 3:4 trial with one slight exception: in the trial, the protocol required that titration be performed at precise weekly intervals to the maximum tolerated dose. The expected label wording allows for flexibility of the time interval between titrations to accommodate appointment scheduling in routine clinical practice.

The exposure data from TEMPO 3:4 are presented in section 6.9.2.

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.

7.2.7 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional

treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Under the proposed label, treatment with tolvaptan is to be initiated in CKD stages 1 to 3 and continued long-term through CKD stage 4. Treatment in CKD stage 5/ESRD will be contraindicated and it is therefore withdrawn at this point. The model reflects this posology: treatment was continued until a patient reached CKD stage 5/ESRD, or upon death, and also took treatment discontinuation for other reasons into account (based on observed discontinuation in the TEMPO 3:4 trial). The definition of CKD stage 5, (eGFR of 15 mL/min/1.73 m^2 or less, Table B24), is the same as that which is outlined in NICE CG 182.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Underlying risk of disease progression

Disease progression in the control (no active treatment) arm was modelled using equations derived from TEMPO 3:4 patient level data (PLD), as described in section 7.3.2. At the start of the simulation, the baseline population characteristics (age, gender, TKV, and eGFR) are sampled from pre-defined distributions. Changes in TKV and eGFR in each annual cycle are predicted from the disease progression equations, with one equation for TKV and one equation for eGFR (dependent on TKV). This process is repeated in each model year (cycle), utilising the patient characteristics at the end of the previous year to predict the values for the current year (cycle); thus building up a lifetime trajectory of TKV and eGFR describing the natural history of ADPKD. This trajectory is used in the model to represent the natural history (i.e., control (no active treatment) arm).

Treatment effect

The principle outcome of clinical interest is renal function, which was robustly measured in the TEMPO 3:4 trial as the rate of change in eGFR. In the tolvaptan arm, the modelled natural history trajectory (renal function) was directly adjusted according to the relative treatment effect on rate of renal function observed in the TEMPO 3:4 trial.

The correlation between TKV and eGFR during the natural history of disease progression has been well studied in ADPKD patients in naturalistic settings/receiving no active treatment (see section 2.1). However, the same relationship may not hold for patients who have received tolvaptan, an intervention which modifies natural disease progression. To assume the same relationship in tolvaptan patients may misrepresent the ultimate treatment effect on the principal outcome of interest, renal function. Therefore, it was deemed most appropriate to directly apply the treatment effect seen in TEMPO 3:4 to renal eGFR, rather

than introduce TKV as an intermediate outcome for assessing treatment effect which may confound the results (see section 7.3.8).

The effect applied was the annual eGFR slope observed over the 3-year trial period (the absolute change in eGFR mL/min/1.73m^2/year). After the first 3 years, this treatment effect was assumed to continue for as long as treatment was continued.

GFR can be “measured” (mGFR) or “estimated” (eGFR). Calculation of mGFR with exogenous markers is complex, expensive, difficult to perform in routine clinical practice, and associated with a margin of error. Estimation of GFR from endogenous markers such as creatinine is the most pragmatic and common approach for the assessment of renal function due to its relative simplicity. There are several different methods to calculate eGFR which each have strengths and weaknesses (National Kidney Disease Education Program, 2014; Stevens *et al*., 2006).

In the steady state, the serum level of creatinine is related to the reciprocal of the level of GFR and can be used to estimate GFR without a timed urine collection. TEMPO 3:4 defined this (reciprocal of serum creatinine) as the primary measure of renal function in the trial, and also included three other creatinine-based measures of renal function, namely: eGFR (calculated by CKD-EPI and MDRD equations) and creatinine clearance (Cockroft-Gault formula).

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

Accordingly, as a measure independent of spurious changes in body weight and therefore more likely to represent an accurate assessment of change in renal function based on a simple blood test, the primary measure of renal function from TEMPO 3:4 (reciprocal of serum creatinine) was applied to the base case of the economic model. The results for eGFR (CKD-EPI) were also presented as a secondary analysis of renal function in the principle publication of TEMPO 3:4 (Torres *et al*., 2012). Accordingly, this measure will also be explored in the economic model as a scenario analysis.

Treatment discontinuation

The model utilises annual rates of treatment discontinuation based on those observed during the three-year data from TEMPO 3:4 (see section 7.3.2). No treatment benefit is applied during the year of discontinuation. Thus, if a patient discontinues during year 1, they follow natural history trajectory of disease progression as modelled for patients in the control (no active treatment) arm. If a patient discontinues during year 3, they receive 2 years of treatment benefit, and the natural history progression applies from the beginning of year 3 onwards.

The incidence of clinically significant kidney pain events in each treatment arm is derived from the TEMPO 3:4 study; applied as an annual probability (see section 7.3.6, Table B35). Whilst it is expected that kidney pain will worsen as kidney disease progresses, in order to accurately reflect the incidence of significant kidney pain observed in patients receiving tolvaptan and placebo (no active treatment) in TEMPO 3:4, the observed probability in each treatment arm was applied for all (pre-ESRD) CKD stages in the model. Following disease progression to ESRD/CKD stage 5, therapy is discontinued, and so patients in the treatment arm receive the same annual probability of significant kidney pain events as those in the control arm. Similarly, patients who discontinue treatment receive the same annual probability of significant kidney pain events as those in the control arm. Clinically significant kidney pain events are not modelled for patients following transplantation.

The probability of all-cause mortality among ADPKD patients in all CKD stages is modelled according to age and gender-specific probabilities up to age 100 from life tables for England and Wales obtained from the Office for National Statistics (ONS, 2014) (see section 7.3.7). The probability of mortality at age 101 is assumed to be equal to 1. Patients who are receiving RRT are subject to increased mortality risk, described in section 7.3.7.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Equations describing underlying risk of disease progression

Disease progression in the control (no active treatment) cohort was modelled using equations derived from TEMPO 3:4 patient-level data (PLD). Summary information from the placebo arm of TEMPO 3:4 is presented in Table B27.

Table B27. Baseline patient characteristics and changes in TKV and eGFR as observed in the placebo arm of TEMPO 3:4 study

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/1.73m^2)	82.14	22.73
	1/serum creatinine ([mg/mL]$^{-1}$)	104.30	33.87
Mean annual change	CKD-EPI (ml/min/1.73m^2)	-3.568	4.495
	1/serum creatinine ([mg/mL]$^{-1}$)	-3.682	6.361

The patient-level data were analysed under the assumption that it sufficiently represents the natural history of ADPKD disease progression. Evaluation of eGFR change was estimated according to both reciprocal serum creatinine and CKD-EPI equation.

Statistical analyses were first undertaken to:

- Identify significant relationships between TKV, eGFR and other patient risk factors;
- Explore the relationship observed between TKV, eGFR and age;
- Explore the relationship observed between TKV, eGFR and time.

Regression analyses were then undertaken to:

- Identify predictive risk factors for change in TKV;
- Develop a statistical model to enable the prediction of annual change in TKV in terms of significant patient characteristics;
- Identify predictive risk factors for change in eGFR;
- Develop a statistical model to enable the prediction of annual change in eGFR in terms of significant patient characteristics.

The structure of the resultant equations to predict annual change in TKV and eGFR (Equation 1 and Equation 2 are detailed below). The coefficient estimates are provided for the TKV equation in Table B28 and for the eGFR equations in Table B30; variance covariance matrices for these coefficients are detailed in Table B29 and Table B31, respectively.

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

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 B28. Estimated TKV progression equation coefficients as derived from TEMPO using patient-level data

	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

Table B29. Variance covariance matrix for the TEMPO PLD TKV equation coefficients

Covariance	Intercept	Age (years)	Ln(TKV)	Female	Age: Ln(TKV)
Intercept	1.283078	-0.031774	-0.175809	-0.002014	0.004361
Age (years)	-0.031774	0.000823	0.004361	-0.000016	-0.000113
Ln(TKV)	-0.175809	0.004361	0.024207	0.000155	-0.000601
Female	-0.002014	-0.000016	0.000155	0.000708	0.000002
Age: Ln(TKV)	0.004361	-0.000113	-0.000601	0.000002	0.000016

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 B30. Estimated eGFR progression equation coefficients as derived from TEMPO using patient-level reciprocal of serum creatinine measurements or CKD-EPI

	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

Table B31. Variance covariance matrix for the TEMPO PLD eGFR equation coefficients

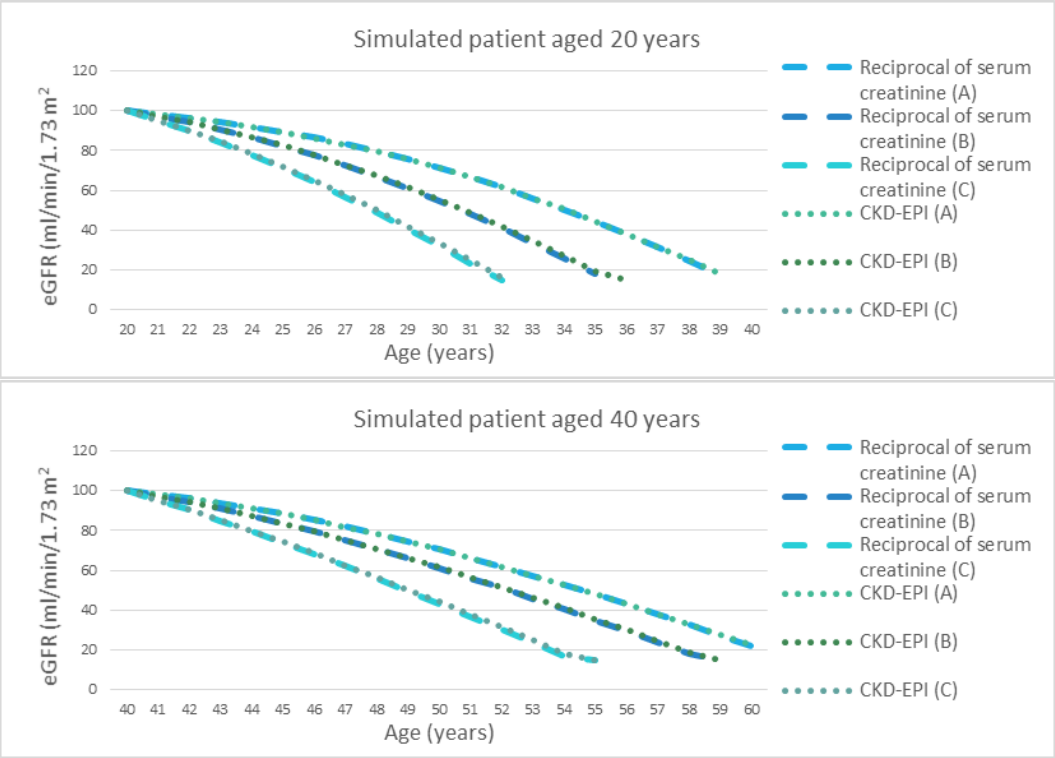
Covariance	1/serum creatinine		CKD-EPI	
	Intercept	ln(TKV)	Intercept	ln(TKV)
Intercept	0.006797	-0.000925	0.005801	-0.000790
ln(TKV)	-0.000925	0.000126	-0.000790	0.000108

Since the TEMPO 3:4 study included only patients with TKV ≥ 750 mL and aged 50 years or less at baseline, some pragmatic implementation restrictions were required in the model:

- For patients with TKV < 850 mL, the equation utilised a value of 850ml.
- Change in TKV in patients aged over 50 years was assumed equal to the change at 50 years.

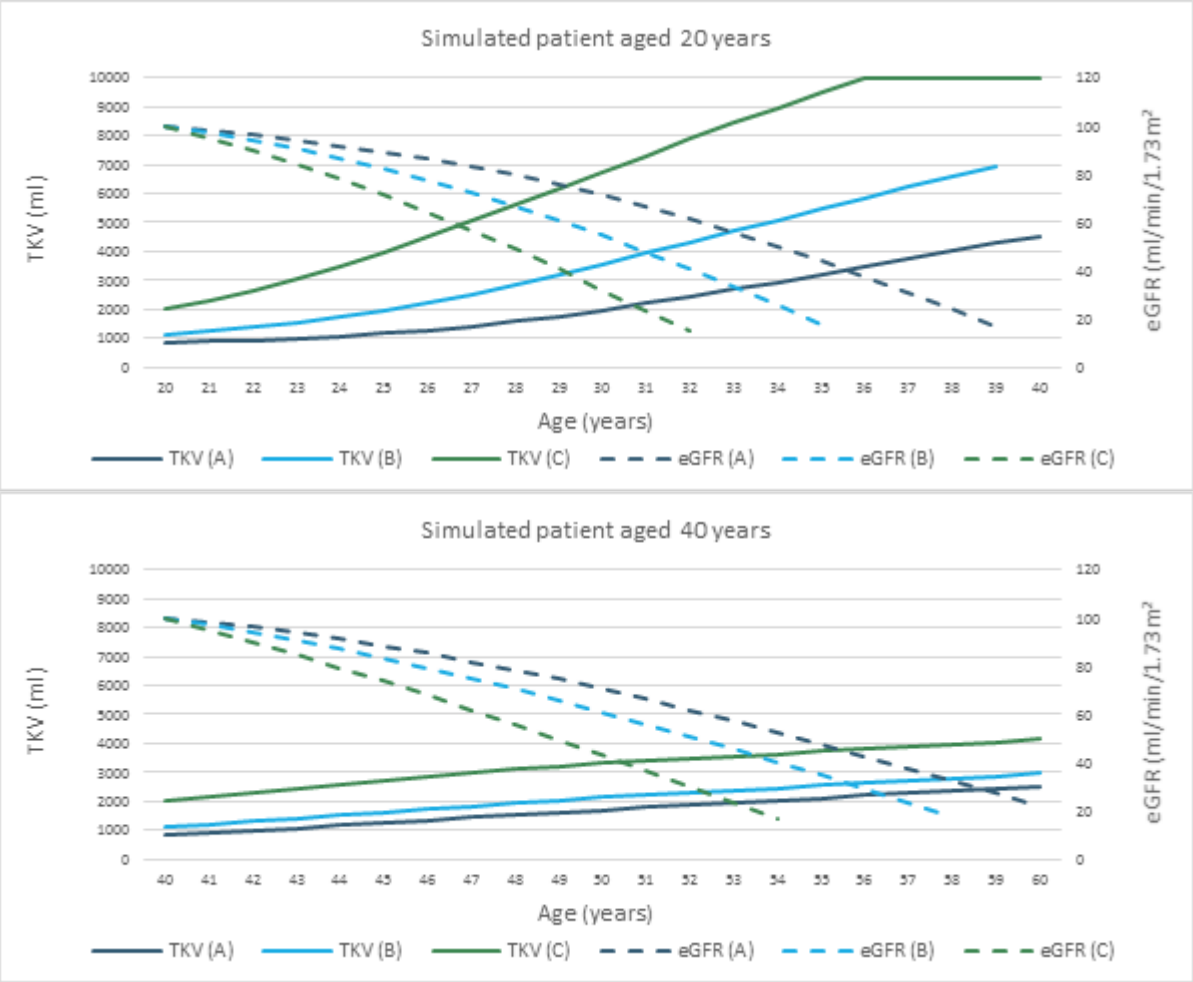
Figure B15 demonstrates the similarity in eGFR trajectories predicted using coefficient estimates derived from reciprocal of serum creatinine or CKD-EPI data. The predicted trajectories for the two measures are almost identical. Figure B16 presents example TKV and eGFR trajectories, estimated using the reciprocal serum creatinine measures.

Figure B15. Prediction of eGFR trajectories using the coefficient estimates derived from reciprocal of serum creatinine and CKD-EPI measurements



Example eGFR trajectories using the coefficient estimates derived from CKD-EPI (dotted line) and reciprocal of serum creatinine (dashed line) data, weighted by a 50:50 gender split, for simulated patients aged 20 and 40 years, with eGFR 100 mL/min/1.73m^2 and TKV (A) 850 mL, (B) 1,125 mL and (C) 2,000 mL, at baseline.

Figure B16. Example eGFR (reciprocal serum creatinine) and TKV trajectories estimated using TEMPO 3:4 patient-level data equations



Example TKV (solid line) and eGFR (CKD-EPI; dashed line) trajectories estimated using equations derived from TEMPO 3:4 patient-level data, weighted by a 50:50 gender split, for simulated patients aged 20 and 40 years, with eGFR 100 mL/min/1.73m^2 and TKV (A) 850 mL, (B) 1,125 mL and (C) 2,000 mL, at baseline. Maximum TKV of 10,000 mL applied.

Treatment effect

The treatment effect was applied using the relative difference in annual eGFR slopes estimated over the 3-year trial period (the absolute change in eGFR mL/min/1.73m^2/year) using data observed during the TEMPO 3:4 trial (Table B32).The slope was measured from post-titration baseline to the end of the study (3 years). An ITT analysis was used within the treatment period and unreliable estimates were excluded (Torres *et al*., 2012).

Changes in treatment effect during the first 3 years in the model were directly replicated from the trial data using data for each individual year.

Table B32. Annual eGFR slope, as observed during the TEMPO 3:4 trial period

eGFR measurement	Treatment Arm		Control Arm	
	Mean	**SE**	**Mean**	**SE**
1/serum creatinine	-2.609	0.337	-3.812	0.295
CKD-Epi	-2.723	0.263	-3.700	0.209
Note: SE assumed equal to SE associated with reported unadjusted rate of change per year. Data obtained from TEMPO 3:4 Clinical Study Report 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).				

These values yield the percentage reduction in annual eGFR decline, presented in Table B33; the 1/serum creatinine values were applied in the base-case analysis.

Table B33. Treatment effect on eGFR applied beyond the trial follow-up period for patients continuing on tolvaptan treatment

Measure of eGFR	Percentage reduction in annual eGFR decline	
	Mean	**SE**
1/serum creatinine	31.6%	7.77%
CKD-EPI	26.4%	5.24%

The treatment effect on eGFR was assumed to continue for as long as treatment is continued (see section 7.3.7).

Treatment discontinuation

The annual discontinuation rate in each of the first three years of treatment was based on observed discontinuation for any cause in the TEMPO 3:4 trial (Table B34). Beyond the trial follow-up period, an ongoing discontinuation rate of 0.5% was assumed which is broadly in line with the trend seen over the course of the trial. This value was varied in sensitivity analysis. The cost of treatment was applied up to and including the year of discontinuation. However, a weighting factor was applied to the cost of treatment in the year of discontinuation to reflect the timing of discontinuation, where a weighting of 0 would relate to the patient discontinuing treatment at the start of the year and a weighting of 1 to the patient discontinuing at the end of the year. These weightings were derived from the timings of discontinuation in the TEMPO clinical study report, as demonstrated in, with a weighting of 0.5 assumed for ongoing discontinuation from cycle 4 and beyond.

Table B34. Derivation of the annual discontinuation rates and weightings.

Time point*	Patients completing treatment (N)	Patients ending treatment (N)	Total annual discontinuations (N)	Annual discontinuation rate	Among patients discontinuing			Weighting
					Treatment duration (months)	Treatment months	Total months of treatment	
Start	961	-	-	-	-	-	-	-
Year 1								
Week 1	940	21	147	147/961 = 15.3%	0.23	4.85	689.23	689.23/147/12 = 0.39
Week 2	933	7			0.46	3.23		
Week 3	914	19			0.69	13.15		
Month 4	862	52			4	208		
Month 8	833	29			8	232		
Month 12	814	19			12	228		
Year 2								
Month 16	790	24	53	53/814 = 6.5%	4	96	376	376/53/12 = 0.59
Month 20	773	17			8	136		
Month 24	761	12			12	144		
Year 3								
Month 28	756	5	22	22/761 = 2.9%	4	20	180	180/22/12 = 0.68
Month 32	745	11			8	88		
Month 36	739	6			12	72		
Year 4+	N/A	N/A	N/A	0.50%a	N/A	N/A	N/A	N/A

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded. .

Disease progression (TKV and GFR change for the natural history), treatment discontinuation, and all-cause mortality rates were varied over time as appropriate, as described in sections 7.3.1, 7.3.2, and 7.3.7.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

TKV was used as an intermediate outcome measure in order to most accurately model the underlying disease progression in the control (no active treatment) cohort, using the association between TKV and eGFR. The outcome used as a measure of treatment effect, renal function (eGFR), is the primary clinical outcome of interest in this population. The final outcomes, CKD stage and the development of ESRD, were defined in terms of eGFR categories (see section 7.2.4).

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical parameter values used in the model have been estimated by clinical experts. The model structure and parameters were reviewed by clinical experts as part of the validation process (see section 7.8).

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below. .

The variables included in the cost-effectiveness analysis are summarised in Table B35.

Table B35. Summary of variables applied in the economic model

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
Model settings					
Time horizon	80	N/A	N/A	Grantham *et al*., (2006)	Section 7.2.6
ESRD therapy starts at eGFR level (ml/min/1.73m^2)	8.5	N/A	N/A	Shaw (2014)	Section 7.2.4
Annual discount rates					
Benefits	3.5%	N/A	N/A	NICE (2013)	Section 7.2.6
Costs	3.5%	N/A	N/A	NICE (2013)	Section 7.2.6
Baseline patient profile					
Current age (years)	38.7	0.19	Normal	TEMPO 3:4, mean for both arms	Section 6.3.4; section 7.2.1
Sex (% female)	48.4%	1.3%	Beta	TEMPO 3:4, mean for both arms	Section 6.3.4; section 7.2.1
eGFR (ml/min/1.73m^2)	81.61	0.57	Normal	TEMPO 3:4, mean for both arms	Section 6.3.4; section 7.2.1
Total kidney volume (ml)	1692.3	23.82	Normal	TEMPO 3:4, mean for both arms	Section 6.3.4; section 7.2.1
Disease progression (percentage TKV change from baseline observed over trial period in placebo (no active treatment) arm)					
Year 1	5.05	0.44	Normal	TEMPO 3:4	Section 6.5.2
Year 2	11.49	0.55	Normal	TEMPO 3:4	Section 6.5.2
Year 3	18.85	0.84	Normal	TEMPO 3:4	Section 6.5.2
TKV and eGFR regression equation parameters	See Table B28 and Table B30, section 7.3.2	Variance covariance matrix, Table B29 and Table B31, section 7.3.2	Normal	Regression analysis of TEMPO 3:4	Section 7.3.2
Treatment effect					
Annual eGFR slope, year 1-3					
Placebo (no active treatment) arm	-3.81	0.30	Normal	TEMPO 3:4	Section 7.3.2
Tolvaptan arm	-2.61	0.34	Normal	TEMPO 3:4	Section 7.3.2
Treatment effect on eGFR applied after trial follow-up (3 years)					

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
Reduction in annual eGFR decline (%)	31.6%	7.77%	Normal	TEMPO 3:4	Section 7.3.2
Treatment discontinuation					
Percentage discontinuation					
Year 1	15.30%	1.16%	Beta	TEMPO 3:4	Section 7.3.2
Year 2	6.51%	0.86%	Beta	TEMPO 3:4	Section 7.3.2
Year 3	2.89%	0.61%	Beta	TEMPO 3:4	Section 7.3.2
Year 4+	0.50%	0.20%	Beta	Assumed	Section 7.3.2
Treatment cost weighting					
Year 1	0.39	0.01	Beta	Calculated from TEMPO 3:4	Section 7.3.2
Year 2	0.59	0.01	Beta	Calculated from TEMPO 3:4	Section 7.3.2
Year 3	0.68	0.01	Beta	Calculated from TEMPO 3:4	Section 7.3.2
Year 4+	0.50	0.01	Beta	Assumed	Section 7.3.2
Incidence of significant kidney pain events (annual probability)					
Placebo (no active treatment) arm					
CKD stage 1	0.07	0.004	Beta	TEMPO 3:4	Section 6.5
CKD stage 2	0.07	0.004	Beta	TEMPO 3:4	Section 6.5
CKD stage 3	0.07	0.004	Beta	TEMPO 3:4	Section 6.5
CKD stage 4	0.07	0.004	Beta	TEMPO 3:4	Section 6.5
Tolvaptan arm					Section 6.5
CKD stage 1	0.05	0.003	Beta	TEMPO 3:4	Section 6.5
CKD stage 2	0.05	0.003	Beta	TEMPO 3:4	Section 6.5
CKD stage 3	0.05	0.003	Beta	TEMPO 3:4	Section 6.5
CKD stage 4	0.05	0.003	Beta	TEMPO 3:4	Section 6.5
CKD stage 5/ESRD	0.07	0.004	Beta	TEMPO 3:4	Section 6.5
Conservative care					
Proportion that receive conservative care upon ESRD onset	0.100	0.105	Beta	NHS (2010) Chronic kidney disease FAQ suggests 15-20% patients approaching ESRD choose conservative care. Assumed likely to be lower in ADPKD.	None
Proportion that receive	0.100	0.105	Beta	Assumed equal to the above	None

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
conservative care after graft failure					
Dialysis modality distribution					
Proportion hospital haemodialysis	0.391	0.02	Beta	Renal registry 2013 - Chapter 2	Section 7.5.6
Proportion satellite haemodialysis	0.429	0.02	Beta	Renal registry 2013 - Chapter 2	Section 7.5.6
Proportion home haemodialysis	0.040	0.01	Beta	Renal registry 2013 - Chapter 2	Section 7.5.6
Proportion automated peritoneal dialysis (APD)	0.071	0.01	Beta	Renal registry 2013 - Chapter 2	Section 7.5.6
Proportion continuous ambulatory peritoneal dialysis (CAPD)	0.069	0.01	Beta	Renal registry 2013 - Chapter 2	Section 7.5.6
Vascular access					
Proportion of HD vascular access: AVF	0.412	0.062	Beta	NHS vascular access audit report 2012	None
Proportion of HD vascular access: AVG	0.016	0.002	Beta	NHS vascular access audit report 2012	None
Proportion of HD vascular access: TL	0.358	0.008	Beta	NHS vascular access audit report 2012	None
Proportion of HD vascular access: NTL	0.213	0.007	Beta	NHS vascular access audit report 2012	None
Complications					
Annual probability of HD related complications	0.060	0.009	Beta	NICE CG125 / Kirby *et al* 2001	None
Annual probability of PD related complications	0.214	0.005	Beta	NICE CG125 / Evans *et al* 2010	None
Probability death following HD complications	0.001	0.000	Beta	NICE CG125 / Johnson *et al*. 2009	None
Probability death following PD complications	0.002	0.000	Beta	NICE CG125 / Johnson *et al*. 2009	None
Transplant					

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
Proportion of organs that are from a living donor	0.356	0.053	Beta	NHSBT 2013/4 Activity Report - Chapter 11	Section 7.5.6
Maximum number of transplants per patient	2	N/A	N/A	Assumption	Section 7.5.6
Annual probability of transplant (initial transplant)					
Age group					
18-34	0.152	0.023	Beta	Calculated from probability of transplant and annual probability of transplant	Section 7.5.6
35-44	0.135	0.020	Beta	Calculated from probability of transplant and annual probability of transplant	Section 7.5.6
45-54	0.114	0.017	Beta	Calculated from probability of transplant and annual probability of transplant	Section 7.5.6
55-64	0.075	0.011	Beta	Calculated from probability of transplant and annual probability of transplant	Section 7.5.6
65+	0.039	0.006	Beta	Calculated from probability of transplant and annual probability of transplant	Section 7.5.6
Probability of transplant eligibility					
Age group					
18-34	0.747	N/A	N/A	Renal Registry/NHSBT 2000-12	None
35-44	0.663	N/A	N/A	Renal Registry/NHSBT 2000-12	None
45-54	0.562	N/A	N/A	Renal Registry/NHSBT 2000-12	None
55-64	0.368	N/A	N/A	Renal Registry/NHSBT 2000-12	None
65+	0.191	N/A	N/A	Renal Registry/NHSBT 2000-12	None
Annual probability of transplant					
Age group					
18-34	0.204	N/A	N/A	NICE CG125/NHSBT 2009	None
35-44	0.204	N/A	N/A	NICE CG125/NHSBT 2009	None
45-54	0.204	N/A	N/A	NICE CG125/NHSBT 2009	None
55-64	0.204	N/A	N/A	NICE CG125/NHSBT 2009	None
65+	0.204	N/A	N/A	NICE CG125/NHSBT 2009	None
Probability of transplant (subsequent transplants) [*Probability of transplant eligibility * Annual probability of transplant]*					
Age group					

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
18-34	0.152	0.023	Beta	Assumed equal to first transplant	None
35-44	0.135	0.020	Beta	Assumed equal to first transplant	None
45-54	0.114	0.017	Beta	Assumed equal to first transplant	None
55-64	0.075	0.011	Beta	Assumed equal to first transplant	None
65+	0.039	0.006	Beta	Assumed equal to first transplant	None
Annual costs of tolvaptan treatment					
Drug list price (excluding discount)	£15,760.54	N/A	N/A	Otsuka, data on file	Section 1.10
PAS discount (%)	[redacted]	N/A	N/A	PAS	Section 1.10
Additional non-drug costs					
Administration & monitoring					
Year 1	£308.57	£46.29	Gamma	Curtis, 2014; NHS Reference Costs, 2012-13.	Section 7.5.5
Year 2	£224.42	£33.66	Gamma	Curtis, 2014; NHS Reference Costs, 2012-13.	Section 7.5.5
Subsequent years	£112.21	£16.83	Gamma	Curtis, 2014; NHS Reference Costs, 2012-13.	Section 7.5.5
Increased nephrologist visits					
Year 1	£278.00	£41.70	Gamma	Curtis, 2014	Section 7.5.5
Year 2	£139.00	£20.85	Gamma	Curtis, 2014	Section 7.5.5
Subsequent years	£0.00	£0.00	Gamma	Curtis, 2014	Section 7.5.5
Annual health state costs (CKD 1 to CKD 5 pre-dialysis, including complications)					

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
CKD stage 1	£171.89	£25.78	Gamma	Curtis, 2014; NHS Reference Costs, 2012-13.	Section 7.5.6
CKD stage 2	£171.89	£25.78	Gamma	Curtis, 2014; NHS Reference Costs, 2012-13.	Section 7.5.6
CKD stage 3	£1,436.16	£215.42	Gamma	NICE CG73 draft update CKD 3/4, inflated to 2012/13, and adjusted according to chart review	Section 7.5.6
CKD stage 4	£3,357.65	£503.65	Gamma	NICE CG73 draft update CKD 3/4, inflated to 2012/13	Section 7.5.6
CKD stage 5 (prior to ESRD treatment)	£5,238.59	£785.79	Gamma	NICE CG73 draft update CKD 5, inflated to 2012/13	Section 7.5.6
Serious kidney pain event	£648.00	£97.20	Gamma	NHS Reference costs 2012/13	Section 7.5.7
Annual costs of background management of ADPKD and related complications, in addition to ESRD treatment					
ADPKD (Conservative Care)	£5,238.59	£785.79	Gamma	Assumed equal to CKD 5	Section 7.5.5
ADPKD (HD)	£5,238.59	£785.79	Gamma	Assumed equal to CKD 5	Section 7.5.5
ADPKD (PD)	£5,238.59	£785.79	Gamma	Assumed equal to CKD 5	Section 7.5.5
ADPKD (Transplant)	£5,238.59	£785.79	Gamma	Assumed equal to CKD 5	Section 7.5.5
Vascular access costs					
Cost of HD access	£1,246.10	£801.50	Gamma	NHS Reference costs 2012/13	Section 7.5.5
Cost of PD access	£1,049.46	£176.83	Gamma	NHS Reference costs 2012/13	Section 7.5.5
Annual costs of conservative care, dialysis and dialysis related complications					
Conservative Care	£5,238.59	£785.79	Gamma	TBC: placeholder is equal to CKD 5	Section 7.5.6
Hospital HD	£39,397.47	£1,627.90	Gamma	Baboolal *et al*. 2008, inflated to 2012/13	Section 7.5.6
Satellite HD	£36,749.45	£1,943.93	Gamma	Baboolal *et al*. 2008, inflated to 2012/13	Section 7.5.6
Home HD	£23,357.48	£943.92	Gamma	Baboolal *et al*. 2008, inflated to 2012/13	Section 7.5.6
APD	£24,359.77	£685.73	Gamma	Baboolal *et al*. 2008, inflated to 2012/13	Section 7.5.6
CAPD	£17,514.74	£672.59	Gamma	Baboolal *et al*. 2008, inflated to 2012/13	Section 7.5.6
Cost of HD Complications	£5,288.85	£2,531.22	Gamma	NICE CG125 / Kirby *et al*. 2001, inflated to 2012/13	Section 7.5.6
Cost of PD Complications	£3,242.06	£1,491.55	Gamma	NICE CG125 / Kidney Care 2009, inflated to 2012/13	Section 7.5.6
Transplant costs					

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
Living donor tx cost	£18,639.68	£5,763.27	Gamma	NHS Reference costs 2012/13	Section 7.5.6
Deceased donor tx cost	£18,631.41	£3,271.54	Gamma	NHS Reference costs 2012/13	Section 7.5.6
Organ Transplantation Service	£15,791.32	£2,368.70	Gamma	NHSBT FOI request & NHSBT Activity report 2011/12, inflated to 2012/13	Section 7.5.6
Maintenance Year 1	£19,044.44	£2,856.67	Gamma	Kerr *et al*. 2012	Section 7.5.6
Maintenance Year 2+	£7,876.52	£1,181.48	Gamma	Kerr *et al*. 2012	Section 7.5.6
Health-related utility					
Disutility of CKD relative to general population (for general population values see section 7.4.13)					
CKD stage 1	0.000	0.000	Beta	Gorodetskaya *et al*., 2005	Section 7.4.9
CKD stage 2	0.000	0.000	Beta	Gorodetskaya *et al*., 2005	Section 7.4.9
CKD stage 3	0.030	0.05	Beta	Gorodetskaya *et al*., 2005	Section 7.4.9
CKD stage 4	0.050	0.046	Beta	Gorodetskaya *et al*., 2005	Section 7.4.9
CKD stage 5	0.222	0.069	Beta	Lee *et al*., 2005; ESRD pre-dialysis (EQ-5D; age standardised)	Section 7.4.9
Disutility associated with treatment	0.000	0.000	N/A	Assumption	Section 7.4.9
Disutility associated with serious kidney pain (3 month duration)	0.051	0.008	Beta	Estimated via Dolan, P. (1997). Med Care. 35(11):1095-108	Section 7.4.9
Disutility of ESRD relative to general population					
Conservative Care	0.352	0.041	Beta	Lee *et al*., 2005; ESRD pre-dialysis (EQ-5D; age standardised)	Section 7.4.9
Hospital/Satellite HD	0.352	0.041	Beta	Lee *et al*., 2005; ESRD HD (EQ-5D; age standardised)	Section 7.4.9

Variable	Value	Standard Error	Distribution in PSA	Source	Section in submission
Home HD	0.352	0.041	Beta	Lee *et al*., 2005; ESRD HD (EQ-5D; age standardised)	Section 7.4.9
PD	0.262	0.049	Beta	Lee *et al*., 2005; ESRD CAPD (EQ-5D; age standardised)	Section 7.4.9
Transplant Year 1	0.148	0.070	Beta	Lee *et al*., 2005; ESRD transplant: (EQ-5D; age standardised) and clinical opinion	Section 7.4.9
Transplant Year 2+	0.082	0.023	Beta	Lee *et al*., 2005; ESRD transplant: (EQ-5D; age standardised)	Section 7.4.9
Disutility associated with HD Complications	0.060	0.009	Beta	NICE CG125 -Appendix B2 (6% decrement)	Section 7.4.9
Disutility associated with PD Complications	0.060	0.009	Beta	NICE CG125 -Appendix B2 (6% decrement)	Section 7.4.9
Mortality rates					
General population		N/A	Fixed	Office for National Statistics, 2013	Section 7.3.7

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan−Meier plots. .

The treatment effects on eGFR and serious kidney pain presented in section 7.3.2 were assumed to continue for as long as treatment is continued (treatment terminated upon reaching ESRD). No treatment effect was applied during the year of discontinuation (see section 7.3.1).

The probability of death among patients on dialysis was modelled via Weibull curves (Table B36) fitted to up to 10 years of survival rate data for the age groups 18–64 and 65+ (7.3.7); the source data were reported by the UK Renal Registry (The Renal Association, 2013). It was assumed that patients receiving HD and PD experience the same rate of ESRD-specific mortality.

Similarly, four Weibull curves were fitted to rates of patient and graft survival following transplant (Table B37), among recipients of organs from living and non-living donors (Table B38). Survival rates for recipients of organs from non-living donors were calculated as the weighted average of survival associated with DBD and DCD donors, weighted for the proportion of kidney only transplants received from DBD (61%) and DCD (39%) (data for organs donated between 1st April 2012 and 31st March 2013; NHS transplant survival report, 2013).

Survival among patients receiving conservative care was modelled via a Weibull function, with a median survival of approximately 1.5 years (based on a systematic review of conservative management of ESRD without dialysis by O'Connor and Kumar, 2012). The resultant shape and scale coefficients were 0.173 and 3.426, respectively.

The greater of the estimated ESRD-specific and all-cause mortality rates was applied each year, rather than treating them additively which has the potential for double counting.

Table B36. Observed dialysis survival rates and the parameters of resultant Weibull curves

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
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 B37. Observed graft failure and patient survival rates of transplant recipients and the parameters of resultant Weibull curves

Donor	Living		DBD		DCD		Deceased[a]	
Observed Survival	Graft	Patient	Graft	Patient	Graft	Patient	Graft	Patient
Year 1	0.97	0.99	0.94	0.96	0.92	0.95	0.93	0.96
Year 2	0.95	0.98	0.91	0.95	0.92	0.93	0.91	0.94
Year 5	0.91	0.96	0.85	0.89	0.86	0.87	0.85	0.88
Year 10	0.78	0.90	0.71	0.74	0.68	0.68	0.70	0.72
Parameters of fitted Weibull curves								
Scale	0.030	0.012	-	-	-	-	0.065	0.036
Shape	0.947	0.976	-	-	-	-	0.756	1.000

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

Table B38. Number of transplants received from living and deceased donors in the UK in 2012/13

Donor	Living	Deceased	
		DBD	DCD
Total kidney only transplants (1st April 2012 -31st March 2013)	1068 (36%)	1181 (39%)	749 (25%)
Percentage of deceased donors: DBD versus DCD (%)	-	61%	39%

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption. .

Table B39. Model assumptions

Assumption	Justification
Changes in TKV are predictive of changes in renal function (as measured by eGFR) in the control group, and therefore CKD stage and the development of ESRD	TKV has been validated in long-term follow-up studies as a prognostic indicator of disease progression, including the CRISP I and CRISP II, and those from the PKDOC, (Grantham and Torres, 2006; Chapman, 2008; Chapman *et al*., 2012; Perrone *et al*., 2014a; Perrone *et al*., 2014b; Perrone *et al*., 2014c; Perrone *et al*., 2014d; Wuthrich *et al*., 2009; Kistler *et al*., 2009).
Disease progression in the long-term may be predicted from observations for patients at different stages of progression in the TEMPO 3:4 trial	The model predictions for disease progression have been validated by comparison with predictions based on equations from other datasets (CRISP, PKDOC, Sheffield data) see section 7.8. The patient population included in TEMPO 3:4 best reflects the patient population eligible for tolvaptan under the proposed licensed indication.
The treatment effect observed during the TEMPO 3:4 trial (difference in the rate of change in eGFR) is continued for as long as patients remain on treatment	There is no evidence to suggest that tolvaptan treatment effect on rate of renal function decline wanes over the long-term. Limited evidence of continuing treatment effect over longer periods of exposure has been presented in interim analyses of TEMPO 4:4.
Treatment discontinuation after 3 years is 0.5%	Discontinuation declined year on year in TEMPO 3:4. Additionally patients will receive counselling, online support and access to nurses. Also this patient group is highly motivated to persist and comply with treatment as this is the only active treatment which is able to delay the progression of their disease. The discontinuation rate is explored in sensitivity analysis
Adverse events associated with tolvaptan have a negligible effect on HRQL over the period of treatment	Adverse events more common in patients receiving tolvaptan treatment include thirst / dry mouth, polyuria, pollakiuria, nocturia, diarrhea, fatigue, dizziness and polydipsia. Many of these are already common in ADPKD patients not receiving treatment, and patients who cannot tolerate the adverse effects discontinue treatment in the model. Including a utility decrement associated with treatment was explored in sensitivity analysis
Complications associated with progressive ADPKD (such as hypertension, hernia, microalbuminuria, gross haematuria, nephrolithiasis, proteinuria, anaemia and gout) are not explicitly modelled (with the exception of clinically significant pain, for which a statistically significant difference between arms was observed in the TEMPO 3:4 trial)	Explicit modelling of other complications (such as hypertension, hernia, microalbuminuria, gross haematuria, nephrolithiasis, proteinuria, anaemia and gout) was deemed to be trivial for the purposes of assessing the cost-effectiveness of tolvaptan given the lack of evidence supporting a difference in effect on these outcomes. This assumption is likely to be conservative.

Assumption	Justification
The model took into account ESRD as a downstream consequence of ADPKD; however, not all downstream consequences of ADPKD symptoms have been modelled. For example, an increased risk of heart attack or stroke due to hypertension has not been incorporated.	There is no evidence that tolvaptan has an effect on extra-renal complications associated with ADPKD.
It was assumed that there would be no switching between dialysis modalities	This was a simplifying assumption to reduce the complexity of the ESRD module that has a negligible impact on overall results
The utilisation of life tables derived from the general population implies the assumption that mortality in ADPKD patients prior to CKD stage 5 is the equal to mortality in the general population.	In the absence of ADPKD-specific mortality risk multipliers (pre-ESRD), the general population life tables were applied as a conservative assumption. The majority of excess mortality in ADPKD compared to the general population is assumed to occur in ESRD
Utility declines as a function of age for all CKD stages	UK general population norms for EQ-5D data, Kind *et al*., 1999 show a decline in utility with age.
Differences in utility between health states may be represented by adjusting age-specific values for the general population using a decrement	NICE Decision Support Unit Technical Support Document (Ara and Wailoo, 2011)

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

ADPKD results in an inevitable progressive increase in kidney volume, accompanied by a decline in renal function which may eventually lead to ESRD. 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 a host of 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 HRQL (Miskulin *et al*., 2014).

On development of ESRD, HRQL is substantially impaired. 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, which substantially limit normal activities of daily living and lead to additional complications including abdominal infection. Patients may also undergo surgery for kidney transplantation which carries a risk of transplant rejection and death, and may lead to complications including bleeding, infection, vascular thrombosis, and post-transplant lymphoproliferative disorder.

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.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

The impact of ADPKD on HRQL is expected to increase as the disease progresses, due to increasing kidney volume and declining kidney function (Rajan *et al*., 2013), and is particularly marked in patients receiving dialysis (Torres *et al*., 2012).

There is large variability between individuals with ADPKD in terms of disease phenotype (i.e., symptoms, complications, rate of progression, development of renal failure), even amongst those in the same family (Torres, 2007; Harris, 2010; Schrier, 2014). Symptoms may appear early or later in the disease course but generally appear between the ages of 30 and 50 years (Halvorson, 2010). In patients who experience early disease manifestations, these may include hypertension, acute abdominal or flank pain, haematuria, palpable kidneys, kidney stones, diverticulosis and recurrent urinary tract infections (Halvorson, 2010). Progressive development of renal cysts leads to urinary concentration defects, hypertension, pain, kidney stones, haematuria, cyst and urinary tract infections, impaired renal function and ultimately ESRD in many of those affected (Halvorson, 2010; Torres, 2009).

Due to the mass effect of cysts reducing blood flow through the kidneys, hypertension (i.e., blood pressure >140/90 mmHg) frequently occurs early in the course of ADPKD and is present in approximately half of patients aged 20 to 34 years with normal renal function (Torres, 2007; Grantham, 2011). Hypertension is present in almost all patients by the time they reach ESRD.[5]

- In the CRISP I observational study, 61% of patients with ADPKD had hypertension at baseline, with 44% receiving treatment with angiotensin converting enzyme (ACE) inhibitors and 21% with angiotensin receptor blockers (note that the mean age of the cohort at baseline was 32.4±8.9 years) (Grantham *et al.*, 2006).[2]
- In a retrospective UK study, 70% of patients with ADPKD had hypertension, with 41% receiving treatment with a single antihypertensive agent, predominantly ACE inhibitors or calcium channel blockers (note that the mean age of the cohort at clinical assessment was 45.6±16.2 years) (Thong *et al.,* 2013).

Pain is a common complication in ADPKD and often occurs early in the course of the disease (Thong, 2013; Hogan, 2010; Bajwa, 2004). In the majority of cases pain in ADPKD is due to either a mass effect from enlarged kidneys or from acute events such as cyst rupture (Halvorson, 2010).

- In a retrospective UK study, 26% of patients with ADPKD experienced lumbar or abdominal pain (Figure 2) (Thong *et al.,* 2013).

- Questionnaire data from 171 US patients with PKD (mean age 47.4 years, range 10 to 79) showed that, back (62% of those reporting pain) and abdominal pain (50% of those reporting pain) are particularly common in patients with PKD (Bajwa, 2004). Other common sources of pain are leg pain, headache and chest pain (Bajwa, 2004). The majority (70%) of patients with pain had more than one source of pain (Bajwa *et al.*, 2004).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No clinical trials identified in section 6 collected utility data.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.

- Details of the methodology used.
- Details of validation of the mapping technique.

No such mapping was performed.

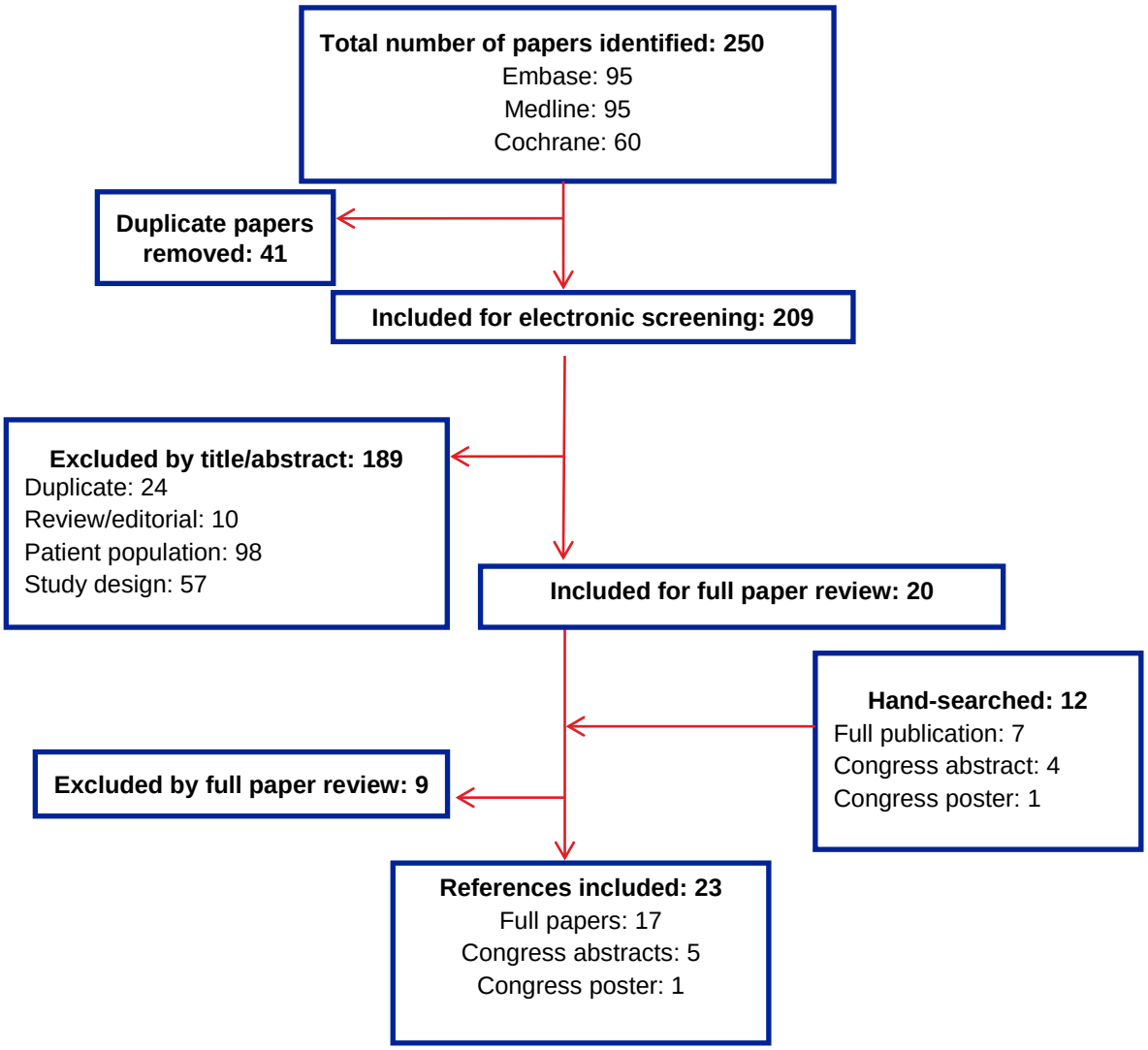
HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic review of the literature was conducted to identify health state utility values (HSUVs) for patients with ADPKD or ESRD. Studies reporting mapping algorithms between disease-specific instruments and preference-based utility measures were also of interest. Details of the search are outlined in section 10.12, appendix 12.

The study selection process is presented in 0. One further study also was identified (Lee *et al*., 2012) bringing the total number of studies to 24.

Figure B17. Flow diagram of identification process for systematic review of HSUV studies



7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.

- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Details of the studies are provided in Table B40.

Table B40. Details of the studies in which HRQL is measured

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
Ahn (2014) [abstract & poster], South Korea	Single-centre, cross-sectional study assessed EQ-5D and its relationship to the Hospital Anxiety and Depression Scale, Multidimensional Scale of Perceived Social Support, Montreal Cognitive Assessment, Pittsburgh Sleep Quality Index and laboratory/clinical data including hemoglobin, vitamin D (25(OH)D, 1,25(OH)2D3), albumin, Kt/V (a marker of dialysis adequacy), normalised protein catabolic rate (nPCR), ferritin, bone mass index (BMI), duration of HD Assessments carried out from September to October 2013.	Patients on haemodialysis at the Daegu Catholic University Medical Center. Patients with acute kidney injury, and those on haemodialysis < 3 months were excluded.	September to October 2013	107; 103/NR	Moderate, EQ-5D data from S Korea	ESRD only
Bass (2004), USA	Cross-sectional study using an instrument developed specifically for the assessment of patient preference values regarding dialysis treatment.	Adult patients with ESRD diagnosis who had begun dialysis at least 3 months before interview, spoke English, and lived	Study took place in 1996 and 1997	188; 188/204	Moderate, directly elicited utilities	ESRD only

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
		within 1-hour drive to city limits were included.				
Davison (2008), Canada	Prospective trial assessing HUI2 and HUI3, KDQOL-SF, BDI-II and Charlson Comorbidity Index. The construct validity of HUI2 and HUI3 was tested by relating these scores to other HRQL scales.	Incident adult chronic dialysis patients and stage 4 and 5 CKD patients anticipated to undergo dialysis within next 12 months.	January 2005 to June 2006 (recruitment period)	185; 185/230	Poor, HUI2 and HUI3 only	Dialysis and pre-dialysis only
Davison (2009), Canada	Prospective study comparing HUI-3 and SF-6D, assessing their ability to discriminate between patients groups based on dialysis treatment, BDI-II, and Charlson Comorbidity Index	Incident adult chronic dialysis patients and patients with stage 4 and 5 CKD clinically anticipated to require dialysis within 12 months.	January 2005 to June 2006 (recruitment period)	185; 185/230	Poor, HUI3 and SF-6D only	Dialysis and pre-dialysis only
Gorodetskaya (2005), USA	Subjects pooled from two studies: 1) Cross sectional (surveyed once); 2) Longitudinal study of self-reported outcomes (surveyed 2 to 8 times over subsequent 2 years). Longitudinal group was subset of	Patients with CKD pooled from a cross-sectional and longitudinal study (longitudinal study patients had CKD stages 4 and 5).	May 2002 to June 2004	Cross-sectional: 205 Longitudinal subset: 115; 115/205	Good-to-Moderate, directly elicited utilities (US patients) using time trade-off methods	Good by CKD stage

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	cross-sectional group. Patients were administered various questionnaires and TTO interviews at each point of follow-up.					
Herczeg (2010), Hungary	Cross-sectional study in which clinical and socio-demographic status of Hungarian patients with renal transplantation were recorded together with the KDQoL-SF. KDQoL-SF results were converted to SF-6D utility values by employing the Brazier algorithm.	Patients who have undergone renal transplantation	NR	833; 833/NR	Poor, mapping to SF-6D	Post-transplant only
Kontodimopoulos (2005), Greece	Cross-sectional study in which patients were randomly selected to undergo HRQL assessment. Patients were administered SF-36 and KDQoL-SF; utilities were calculated by transforming raw scale scores. A Cost analysis was also performed for each type of dialysis. Controls from the general population were also assessed with	Inpatients with ESRD who were undergoing dialysis treatment at a single centre	NR	Dialysis: 78 Controls: 39; 78/NR	Poor, SF-6D	Dialysis and pre-dialysis only

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	SF-36.					
Kontodimopoulos (2006), Greece	A survey containing TTO, SG, and two willingness-to-pay were self-administered to ESRD patients. The methods were considered non-standard as surveys were modified based on concerns raised from review boards and clinical staff (see note column for details).	Cross-sectional study of patients on dialysis from a randomly selected group of dialysis facilities in Greece. Patients were excluded if they were deemed unable to self-complete the surveys.	Surveys completed between April and December 2004	504; 476/504	Poor, direct elicitation but not given as utilities	Dialysis only
Kontodimopoulos (2008), Greece	Cross-sectional and modelling study in which a nationally representative sample of different treatment modalities for ESRD was self-administered the SF-36 Health Survey. Utilities were measured using SF-6D (derived from SF-36), life expectancy was taken from ERA-EDTA 2003, and cost data was obtained from public and private clinics.	Patients who were on their current treatment for ≥ 1 year were identified from Hellenic Renal Registry.	Estimated QALYs were "lifelong" [no additional information]	874; 874/NR	Poor, SF-6D	Dialysis only
Lee (2005), UK (Wales)	Cross-sectional study of patients who were administered surveys at	Patients identified from renal unit departmental	Data retrieved in August 2002	416; 416/1251	Good, EQ-5D data from UK	Good, ESRD (pre-dialysis, HD, CAPD, functional transplant

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	home or while receiving dialysis treatment. Surveys used included EQ-5D, SF-36, and KDQOL short form.	database were grouped into four cohorts: 1) patients who had received a functioning graft following transplant, 2) those on peritoneal dialysis (CAPD), 3) those on haemodialysis, 4) those awaiting initiation of dialysis				
Lee *et al*., 2012	EQ-5D data for adults from the 3rd Korean National Health and Nutritional Examination Survey 2005.	Subjects aged 18 years or older who had an eGFR ≥ 30 mL/min/1.73 m^2	NR	5,555 subjects with CKD of 34,145 participants; 9,720 did not complete EQ-5D	Moderate, EQ-5D measured in Korean respondents, Korean value set	Good, CKD 1, 2 and 3
Neri (2009), USA	Cross-sectional study with patients completing a self-administered questionnaire; associations between effort-reward imbalance (ERI), SF-12, SF-6D, KDWOL-36, and work ability (WAI) were assessed.	Haemodialysis patients who were of working age (18–67 years) and still professionally active.	NR	40; 40/46	Poor, SF-6D	Dialysis only
Neri (2011), USA	Cross-sectional study. Patients completed a self-administered questionnaire during post-transplant visit,	Kidney transplant recipients who visited one of two outpatient clinics over a 27-month	Enrolled from May 2007 to August 2009	386; 386/577	Moderate, EQ-5D for USA	Transplant only

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	including EQ-5D, HUI-3, KDQOL-36, and RAND SF-12	period				
Neri (2012) [abstract + poster], UK and USA	Cross-sectional study with patients' HRQL, demographic, and employment data collected through a self-administered questionnaire (EQ-5D, HUI-3, SF-6D). Relevant clinical data were abstracted from electronic and paper medical charts.	Kidney transplant recipients from a hospital outpatient surgery clinic.	NR	233; 233/294	Good, EQ-5D for UK patients using UK value set	Moderate, post-transplant by CKD stage
Ortega (2007), Spain	Prospective study included patient data collected before transplant, after 3 months, 6 months, and 1 year. Surveys administered included SF-36 Health Survey, EQ-5D, and ESRD-SCL.	Patients with ESRD who were on renal transplant waiting list, and who had received their first cadaveric renal transplant between July 2003 and December 2005	Data collected from July 2003 to December 2006	307; 307/380	Moderate, EQ-5D for Spanish population	Pre and post-transplant only
Plantinga (2007), USA	The cohort was assembled from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study enrolled between October 1995 and June 1998. Patients were	National cohort of incident haemodialysis patients treated at dialysis clinics throughout the country.	October 1995 to June 1998	567; 567/767	Moderate, TTO for US population	Dialysis only

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	given a series of TTO questions during study enrollment.					
Punal Rioboo (2009), Spain	Cross-sectional study in patients on haemodialysis in multiple hospitals. Patients on short daily vs conventional haemodialysis completed EQ-5D and a separate questionnaire with additional questions. Differences in QoL were analyzed using six models that differed with respect to the existence or not of an informative prior and the dependent variable (VAS score, EQ-5D).	Patients with ESRD who were on the same haemodialysis schedule for ≥ 3 months and who had been receiving dialysis for less than 5 years	Patients recruited between Dec 2006 and Mar 2007	85; 85/93	Poor, utilities not reported	Dialysis only
Rajan (2013), USA	Cross-sectional survey of a sample selected from a longitudinal cohort of veterans with diabetes from the Veterans Health Survey, assessing SF-36/SF-12. Six previously published SF-36/SF-12-to-utility transformations were used to estimate utilities for each subject.	Veterans with diabetes who participated in the survey in 1999 and who had records from a cohort in 2000 or 2001.	1999 to 2001	67,963; 67,963/141,747	Moderate, EQ-5D but for US population with diabetes	Good, by CKD stage

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	Generalised linear regression models estimated the disutility associated with each CKD stage.					
Roderick (2005), UK	Health Technology Assessment containing cross-sectional prevalence study of patients in 12 RSUs and a comparable group of patients in their parent MRUs. The main unit patients were group matched on suitability for RSU care and, where possible, age and gender. Patients completed the questionnaire whilst on dialysis or later at home. The questionnaire included KDQOL, SF-36, patient satisfaction, and EQ-5D. A corresponding clinical questionnaire was completed by the hospital for each patient.	Patients were selected by senior nurses from a stratified random sample of RSUs over a broad geographical range. Inpatients from MRUs were excluded.	Patients assessed between June 2000 and July 2001	Total: 736 MRU: 342 RSU: 394; Phase 1 - 74/80 Phase 2 - 736/898	Good, EQ-5D data from UK	Poor, results by renal dialysis unit
Saban (2008), USA	Multi-site, Prospective observational study comparing outcomes and costs of care in US	Patients who received care at a Veterans Affairs facility within the	NR	322 [364 consented but not all completed	Poor, SF-6D from US population	Dialysis only

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	veterans undergoing dialysis. Patients were administered 3 HRQL measures (QWB-SA, SF-6D and KDQOL), with baseline QWB-SA and SF-6D converted into utility scores based on established algorithms.	prior 3 years and who were receiving haemodialysis for CKD.		baseline assessment]; 364/NR		
Sakthong (2012), Thailand	Cross-sectional study of randomly selected patient using EQ-5D and VAS to assess QoL, including a range of health state utility values. Interviews conducted from October 2008 to February 2009.	Patients undergoing peritoneal dialysis, randomly selected from hospitals across Thailand.	Data collected from October 2008 to February 2009	102; 102/120	Moderate, EQ-5D from Thailand population	Dialysis only
Vorobyev (2011), Russia	Cross-sectional health survey of patients in dialysis departments of multiple regions. Patients assessed for medical information and HRQL measured by EQ-5D.	Patients in terminal stage of chronic renal failure on dialysis for ≥ 4 months	Surveys administered May to Jun 2010; study reports patients completing as of Sep 2010	1395; 1395/~1400	Poor, EQ-5D from VAS for Russian population	Dialysis only
Wu and Yang (2014) [abstract only], China	Patients or their carers were interviewed regarding QoL using EQ-5D and absenteeism from work in the past year, using UK weight to	Patients with CKD in urban China	Recruitment occurred between November and December	401; 401/NR	Moderate., EQ-5D measured in Chinese population (UK value set)	CKD 3–4, HD, PD

Author (year), country	Study design/methods	Patient population	Time horizon	No. patients; response rate	Appropriateness for CE analysis	Appropriateness of health states
	estimate utility (EQ-5D index score).		2012			
NR, not reported; US, United States.						

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No values were reported in or mapped from the clinical trials.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

The most common adverse events and serious adverse events observed in the TEMPO 3:4 trial are presented in section 6.9.2 (Table B24). Events which were more common in the tolvaptan arm with a difference between groups of 10% or more included events associated with the aquaretic effects of tolvaptan (polyuria, nocturia and pollakiuria). There is no evidence that tolvaptan-related aquaresis impacts HRQoL and high water intake was also used as part of standard care (no active treatment). The incidence of these events declined markedly after the first 3 months of treatment. After month 3, the overall incidence of renal and urinary disorders over the 3-year treatment period was similar to that of the placebo arm.

Other adverse events more common in patients receiving tolvaptan included diarrhoea, fatigue, dizziness and polydipsia. 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.

There is currently no evidence that tolvaptan treatment is associated with a decrease in other ADPKD complications.

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

HSUVs applied in the cost-effectiveness analysis were selected from the published estimates presented in section 7.4.6 and adapted for use in the model (which applied a disutility compared with the general population of the same age). The selection criteria included compliance with the NICE Reference Case and relevance to the health states in the economic model.

No HSUV estimates were identified for patients with ADPKD specifically; however, several estimates for patients with CKD and ESRD associated with any cause were identified. The relevance of HSUV values for all-cause CKD and ESRD to ADPKD patients with CKD and ESRD was explored using published SF-36 data for these populations. In a recent systematic literature review of SF-36 data for ADPKD and CKD/ESRD patients (Otsuka [Utility SR], data on file) two studies were identified which reported SF-36 data for ADPKD patients (Miskulin *et al*. 2014 and Suwabe *et al*. 2013).

- Miskulin *et al*. 2014 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.

- Suwabe reported SF-36 data for ADPKD patients with ESRD in Japan. The mean PCS score for ADPKD patients receiving dialysis (45.5) was similar to that reported in two studies for Malaysian patients receiving haemodialysis for all-cause ESRD (49.61 and 39.6 reported by Ying 2014 and Yusop 2013, respectively).

Therefore, the base-case analysis assumed that HRQoL for ADPKD patients with early-stage CKD 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.

The systematic review identified eleven studies that presented EQ-5D derived utility weights (Ahn *et al*. 2014a, 2014b; Ortega *et al*., 2007; Sakthong *et al*. 2012; Roderick *et al*. 2005; Lee *et al*. 2005; Vorobyev *et al*. 2011; Puñal Rioboo *et al*. 2009; Neri *et al*. 2011; Neri *et al*. 2012; Rajan *et al*., 2013; Wu and Yang, 2014). Of these, two studies were performed in UK populations and used the UK EQ-5D value set:

- Lee *et al*., 2005 presented estimates for CKD stage 5 pre-dialysis, haemodialysis, peritoneal dialysis, and functional transplant.
- Neri *et al*., 2012 presented estimates for ESRD patients with a kidney transplant with various degrees of renal function (CKD stage 1-5).

The estimates reported by Lee *et al*., 2005 were selected for the base-case analysis for CKD stage 5 pre-dialysis, haemodialysis, peritoneal dialysis, and transplant (after year 1) as this study provided values for multiple relevant health states. The model value for the first year after a transplant was based on the value for functional

transplant reported by Lee and colleagues (2005), adjusted for the lower HRQL expected in the post-operative period (based on clinical opinion, see footnote to table B30). Alternative values estimated using EQ-5D or time trade-off methods were explored in sensitivity analysis.

No estimates were identified 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. Therefore, EQ-5D measured in other populations and estimates elicited using time trade-off methods also were explored. Four studies were identified:

- Wu and Yang, 2014 reported estimates for CKD 3–4 (as well as haemodialysis and peritoneal dialysis) 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 HRQL for CKD stage 4 compared with stage 3 (e.g., Gorodetskaya *et al*., 2005; Rajan *et al*., 2013). Furthermore, other studies have suggested that Asian populations may respond differently to EQ-5D than Western European populations and the estimates for haemodialysis and peritoneal dialysis reported in this study were substantially higher than those reported for a UK population (Lee *et al*., 2005).

- Lee *et al*., (2012) reported estimates for CKD stage 1, 2 and 3 measured using EQ-5D in a Korean population and valued using the Korean value set. This study was not selected for the base-case analysis because no estimate was available for CKD stage 4 and EQ-5D measured in a Korean population and valued using the Korean health state value set are unlikely to be generalisable to the UK.

- Rajan *et al*. (2013) mapped SF-36 (or SF-12) data from the 1999 US Large Veterans Health Survey, including 67,963 patients with CKD and diabetes, to EQ-5D (as well as HUI2 and VR-6D). Utility estimates for CKD 0–1 were substantially lower than expected for ADPKD patients with CKD 0-1 (expected to be similar to that for the general population of the same age) which may be a result of all patients having diabetes. Estimates ranged from approximately 0.69 to 0.72 for patients with CKD 0-1 and recent onset or prevalent diabetes.

- Gorodetskaya *et al*., 2005 reported estimates for CKD stage 1–2, 3, 4, and 5 (no dialysis, haemodialysis and all) using time trade-off methods in a US patient sample.

The values reported by Gorodetskaya *et al*., 2005 were selected for the base-case analysis; estimates from Wu and Yang, 2014 and Lee *et al*., 2012 were explored in sensitivity analysis.

We have no evidence that HRQL is reduced by tolvaptan-related aquaresis. The base-case analysis assumes that patients who cannot tolerate any negative impact of tolvaptan-related adverse events are within the group which discontinue treatment. Therefore no disutility associated with treatment is applied in the base-case analysis. A disutility of 0.0123 was explored in sensitivity analysis (Sullivan *et al*., 2011) and was applied for the duration of tolvaptan treatment. We expect this to be a highly conservative analysis as additive disutility is possibly not appropriate over patients' lifetime, and those unable to tolerate tolvaptan are likely to discontinue treatment.

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).

The values applied in the base-case cost-effectiveness analysis are presented in Table B41. The model utilised baseline age-adjusted utilities [general population values (Centre for Health Economics, 1999)], with utility decrements applied for the various health states/events in the model. Utility inputs applied for each health state or event within the model were defined as the absolute disutility associated with the specified health state relative to the general population mean for the same age. In each year, the utilities applied to simulated patients were equal to the age-adjusted baseline minus the relevant health state disutility. Multiple utilities could apply at a given time point for a simulated patient, and all utilities are applied additively, however this does not happen frequently as the probability of clinically significant pain events is small.

Table B41. Summary of quality-of-life values for the base-case cost-effectiveness analysis

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 *et al*., 2005	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 *et al*., 2005	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 *et al*., 2005	EQ-5D, UK sample and value set
Disutility associated with treatment	-	-	0.000	-	Assumption (see section 7.3.8)	Impact counter-balanced by reduction in ADPKD complications
Disutility associated with HD Complications	-	-	0.060	0.009[k]	NICE CG125	Consistency with CG125
Disutility associated with PD Complications	-	-	0.060	0.009[k]	NICE CG125	Consistency with CG125
Disutility associated with significant pain			0.051	0.008	Dolan *et al*., 1997	EQ-5D calculated value
Age-specific general population values						
35-44	0.91	-	-	-	Centre for Health Economics, 1999	HRQL declines with increasing age
45-54	0.85	-	-	-		
55-64	0.80	-	-	-		
65-74	0.78	-	-	-		
≥75	0.73	-	-	-		

SE, standard error.
[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; Lee *et al*., 2012; Gorodetskaya *et al*., 2005; Centre for Health Economics, 1999; supported by clinical expert opinion)

Health State	Utility value[a]		Disutility vs general population value		Reference in submission	Justifi-cation
	Mean	SE	Mean	SE		
[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 *et al*., 2005: 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. [j] Assumption (highest of other values, rounded) [k] Assumed 15% of mean value						

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

In order to help select the HSUVs for the base-case analysis, a ranking exercise was performed by four UK clinical experts (all experts who were approached participated) with substantial experience of nephrology and ADPKD:

- Three nephrologists with experience of ADPKD management
- A clinical nurse specialist

The experts were asked to rank the health states in ascending order of severity for a typical ADPKD patient with no complications. The transplant health state reflected a functional transplant (with no declining renal function). The results are presented in Table B42.

Table B42. Health State Ranking by Degree of Severity (4 UK Clinical Experts)

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

The results broadly support the rank order of the HSUVs selected for the base-case analysis (Table B41). There was a discrepancy for transplant year 2+, which fell between CKD stage 3 and 4 in the ranking exercise, while it fell between CKD stage 4 and 5 in the base-case value set. However, this may be reasonable and expected as, in the ranking exercise transplant year 2+ represented a fully functioning transplant, while in the model the value is applied as the average for all transplant

patients including those with declining renal function (as the transplant begins to fail). HRQL has been demonstrated to fall substantially in transplant patients with worsening CKD stage (Neri *et al*., 2012; UK EQ-5D data). In this study, the mean value fell from 0.86 to 0.49 for transplant and CKD stage 4. Therefore, the utility value for Transplant Year 2+ in the model is expected to be lower than that for a fully functioning transplant.

As no estimates were identified for Transplant Year 1, the difference in HRQL for patients with a functional transplant between the first year after surgery and the second and subsequent years was estimated by the clinical experts. The experts were asked the following question: For a typical patient with ADPKD and no/minimal comorbidities:

1. Please estimate the utility for your best (best quality of life) health state
2. Please estimate the utility for your worst (worst quality of life) health state
3. Please estimate the utility for the remaining states

The decrement from the health state for Transplant Year 1 was estimated to be approximately 1.8 times greater than that for Transplant Year 2+. This was applied to the decrement for Transplant Year 2+ in Table B41 in order to estimate the decrement for Transplant Year 1.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL may be expected to decline as patients progress through a CKD stage, with HRQL being higher when they first enter the health state than when they are close to moving to the next stage. The utility decrement represents the average for patients in that CKD stage. In the base-case analysis, patients are expected to remain in each CKD stage for several years. Therefore, since ADPKD is a progressive disease, the CKD stage health state is intended to capture the full progression experienced by the patient during their time in that stage. Whilst the value is constant, there is clearly a high-level of intra- and inter-patient variability of contemporaneous health statuses experienced during the accumulation of time in each health state, and the average values are assumed to account for this variability.

As discussed in section 7.4.10, HRQL has been demonstrated to fall substantially in transplant patients with worsening CKD stage (Neri *et al*., 2012; UK EQ-5D data).

The utility decrement in the model represents the average for all transplant patients including those with declining renal function (as the transplant begins to fail).

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Other than ADPKD complications for which there is no evidence of an effect with tolvaptan, no other health effects identified in the literature or clinical data were excluded.

7.4.13 No health effects were excluded. Adverse events associated with tolvaptan treatment and complications associated with ADPKD are independently modelled. The base-case analysis assumes that adverse events associated with tolvaptan treatment do not affect HRQL. We have no evidence that tolvaptan treatment is associated with a decrease in adverse events other than significant pain. Therefore significant pain is modelled explicitly, whereas other adverse events are modelled implicitly within CKD stage health states. If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

In the base-case analysis, the baseline HSUV at the beginning of the model was 0.91; based on the mean value for the general population of the same age as the TEMPO 3:4 population at baseline (mean age at start of model = 39 years; Centre for Health Economics, 1999). A subgroup of patients in CKD stage 1 with a mean age of 33.90 years based on the OVERTURE study population was explored as a subgroup analysis (see section 7.9.1).

As patients age with increasing time in the model, the utility value declined in line with general population estimates (Table B43).

Table B43. HSUVs for CKD Stage 1 by Age Group

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)	

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

In line with ADPKD being a chronic, progressive, irreversible disease, HRQL is assumed to decline as the disease advances through the CKD stages and, ultimately, into ESRD. Average HRQL for patients declined over time as their disease progressed and they moved through the series of health states.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The HSUVs assumed at the start of model time for CKD stage 5, ESRD and transplant were adjusted for age. This was necessary because the mean age of the population entering the model is lower than that for the ESRD population in the source study (Lee and colleagues, 2005) and the model assumes that utility declines with age (see section 7.4.13 and 7.4.14). If the source value were applied without adjustment, the value for ESRD applied at the model time at which ESRD occurs would be lower than that reported in the source study. The adjustment was performed to avoid this. Details of the adjustment are provided in the footnote to Table B42.

No adjustment for age was performed for the HSUVs for CKD stage 1-4 reported by Gorodetskaya *et al*. (2005) because these values are used in the model earlier in the model time horizon. The reported value for CKD stage 1-2 (0.90) was similar to that for the general population at the start of the model (0.91). This is in line with the observation that ADPKD patients with CKD stage 1 to 3 have generally similar HRQL compared with age-matched population normative data (Miskulin *et al*., 2014; see section 7.4.9).

All HSUVs have been expressed as disutility values (compared with CKD stage 1) in order to be applied in the model (see section 7.4.13 and 7.4.14). Details of these calculations are provided in the footnote to Table B42.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

There are no NHS reference costs or PbR tariffs specific to ADPKD management *per se*. Costs related to management of CKD and ESRD are available in the NHS reference costs and relevant estimates also have been reported in NICE clinical guidelines; these are summarised below. These estimates were selected for the model as they may be expected to represent high quality estimates which reflect clinical practice in the UK.

- Costs for CKD stages 3 to 5 used in the model were sourced from NICE CG182.
- Vascular access costs for haemodialysis and peritoneal dialysis were sourced from NHS reference costs using HRG codes QZ13Z (Vascular Access for Renal Replacement Therapy) and LA05Z (Renal Replacement Peritoneal Dialysis Associated Procedures), respectively.
- Annual costs for dialysis were sourced from a study reported by Baboolal *et al*. (2008) which was used to inform PbR tariffs.
- The costs of complications related to dialysis were sourced from NICE CG125.
- Transplant costs from living and deceased donors were sourced from the NHS reference costs using HRG codes LA03A (Kidney Transplant, 19 years

and over, from Live Donor) and LA01A (Kidney Transplant, 19 years and over, from Cadaver Non Heart-Beating Donor), respectively.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Costs related to management of CKD and ESRD available in the NHS reference costs and NICE clinical guidelines are assumed to be appropriate for ADPKD patients with CKD and ESRD. We have no evidence to suggest that there are more appropriate sources for this analysis. Costs were inflated to 2013 values where necessary using the Hospital and Community Health Services (HCHS) inflation indices (PSSRU, 2012/2013).

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Two separate systematic literature reviews were conducted to identify cost and resource use in patients with ADPKD and ESRD. The search strategies and results are described in section 10.13, appendix 13. No studies reporting estimates which were more appropriate for the economic model than those described in section 7.5.1 were identified.

A medical record abstraction study was performed by the manufacturer of tolvaptan which estimated resource use and costs associated with managing ADPKD patients

across all disease stages in the UK, France, Germany, Sweden, Spain, and Italy. This study was not used as a primary source of costs for the model as it was based on a convenience sample, the number of patients contributing data to each disease stage in the UK was relatively small (between 15 and 46), patients therefore may not be fully representative sample of the population in the UK. However, this study was used to adjust cost estimates for CKD stage 3 and 4 reported in NICE CG182 as a single cost for CKD 3 and 4 (see section 7.5.6).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The cost estimates used in the model were reviewed by clinical experts. For the following parameters, the resource use was estimated by clinical experts:

- Additional visits and tests for patients receiving tolvaptan treatment (over and above those received currently by patients receiving no active treatment
- Resource use for management of patients with CKD stage 1 and 2.

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The cost of treatment with tolvaptan is applied annually and consists of drug costs and additional monitoring costs.

The NHS list price for tolvaptan is £1,208.20 per each 28-day pack (irrespective of tablet strengths), equating to £43.15 per day. The analyses presented in section 0 incorporate a Patient Access Scheme which applies a [redacted] discount in all model years to the acquisition cost of tolvaptan (equating to [redacted] per day). Details of the dose received in the TEMPO 3:4 trial are presented in section 6.9, but are not used in the model. A fixed annual drug cost is applied in the model. The cost of treatment was applied up to and including the year of discontinuation. However, a weighting factor was applied to the cost of treatment in the year of discontinuation to reflect the timing of discontinuation (see section 7.3.2). These weightings were derived from the timings of discontinuation in the TEMPO clinical study report.

Patients receiving tolvaptan will require additional monitoring. A liver function test will be performed every month for the first 18 months and every 3 months thereafter. In addition to the standard monitoring currently performed for patients with ADPKD, it is expected that tolvaptan patients will receive two additional consultant visits in their first year of treatment and one additional consultant visit in their second year of treatment. Additional consultant time is expected to be needed to review liver function test results and issue prescriptions.

The resource use and cost associated with current monitoring of ADPKD patients is presented in Table B44, and was based on NICE clinical guideline 182 (CG182) and clinical expert input. The additional resource use and cost required for patients receiving tolvaptan is presented in Table B45. The model applies the cost of additional resources that are expected to be required for tolvaptan patients, over and above those associated with current monitoring, presented in in Table B45 (estimates presented in Table B44 are shown for information only and were not used in the economic model).

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). The remaining costs were based on NHS Reference Costs (Department of Health, 2012-13).

Table B44. Resource Use for Current Monitoring of ADPKD Patients Following Referral[a]

Diagnosis, Monitoring and Management	Unit Cost	Year 1		Year 2		Year 3+	
		Frequency	Cost	Frequency	Cost	Frequency	Cost
Consultant visits (Nephrologist)	£139.00	1	£139.00	1	£139.00	1	£139.00
Consultation with a specialist nurse	£25.00	1	£25.00	1	£25.00	1	£25.00
Biochemistry test	£1.25	1	£1.25	1	£1.25	1	£1.25
Haematology test	£3.01	1	£3.01	1	£3.01	1	£3.01
Phlebotomy	£3.64	1	£3.64	1	£3.64	1	£3.64
Ultrasound (one time only)	£51.00	1	£51.00	0	£0	0	£0
TOTAL			£222.90		£171.90		£171.90

[a] Data in this table are shown for illustrative purposes only and are not used in the economic model. The model applies the additional cost associated with tolvaptan treatment presented in Table B45.

Source: Resource use estimates were based on NICE CG182 and clinical expert input. 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). The remaining costs were based on NHS Reference Costs (2012-13)

Table B45. Unit costs associated with the technology in the economic model

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 *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**	

LFT, liver function test; N/A, not available; PAS, patient access scheme

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

The annual costs incurred by patients in CKD stages 1 to 4 are presented in Table B46. 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 cohort. Patients in these health states who are receiving treatment with tolvaptan also incur the treatment and monitoring costs presented in Table B46.

Table B46. List of health states and associated costs in the ADPKD module

Health states	Annual cost	Reference in submission
CKD stage 1	£171.89	Text in this section
CKD stage 2	£171.89	Text in this section
CKD stage 3	£1,436.16	Text in this section
CKD stage 4	£3,357.65	Text in this section
Clinically significant pain	£648.21	Text in this section
CKD, chronic kidney disease		

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), one consultation with a specialist nurse (PSSRU, 2013), one biochemistry test (DAPS04 – NHS Reference Costs, 2012-13), one haematology test (DAPS05 – NHS Reference Costs, 2012-13), and one phlebotomy (DAPS08 – NHS Reference Costs, 2012-13). 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).

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 (which in turn were based on NICE CG73), inflated to 2013 values as described in section 7.5.2. 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 described in section 7.5.3.

The cost of a significant pain event used in the model was taken from the NHS Reference Costs (2012/13); HRG AB04Z, major pain procedures, non-elective inpatient short stay, general medicine. The rationale for explicitly modelling only one ADPKD complication (other than CKD/ESRD) is provided in section 7.3.8.

The costs incurred by patients in the ESRD health states are presented in Table B47.

Patients who reach CKD stage 5/ESRD and do not receive treatment immediately incur an annual cost associated with this pre-dialysis stage. It should be noted that some of the patients in CKD stage 5 will have numerous elective admissions resulting in substantial costs.

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), dialysis and complications (NICE CG125), 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).

If a patient receives a kidney transplant, they incur a one-off cost associated with the transplant operation (NHS Reference costs 2012/13) 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). 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). 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. These costs were then apportioned to each transplant event occurring during 2011–2012, to obtain a cost per transplant.

Table B47. List of health states and associated costs in the ESRD module

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 appendix, inflated to 2012/13
Conservative care	Background management	£5,238.59	100%	Assumed equal to CKD stage 5
Haemodialysis	Background management	£5,238.59	100%	Assumed equal to CKD stage 5
	Vascular access	£1,246.10	100%	NHS Reference costs 2012/13
	Hospital HD	£39,397.47	39.1%[c]	Baboolal *et al*., 2008, inflated to 2012/13 (Renal Association, 2013)
	Satellite HD	£36,749.45	42.9%[c]	Baboolal *et al*., 2008, inflated to 2012/13 (Renal Association, 2013)
	Home HD	£23,357.48	4.0%[c]	Baboolal *et al*., 2008, inflated to 2012/13 (Renal Association, 2013)
	HD complications	£5,288.85	6.0%	NICE CG125 / Kirby *et al*., 2001, inflated to 2012/13 (NICE CG125 / Evans *et al* 2010)
Peritoneal dialysis	Background management	£5,238.59	100%	Assumed equal to CKD stage 5
	Catheter placement	£1,049.46	100%	NHS Reference costs 2012/13
	ADP	£24,359.77	7.1%[c]	Baboolal *et al*., 2008, inflated to 2012/13 (Renal Association, 2013)
	CAPD	£17,514.74	6.9%[c]	Baboolal *et al*., 2008, inflated to 2012/13 (Renal Association, 2013)
	PD complications	£3,242.06	21.4%	NICE CG125 / Kidney Care 2009, inflated to 2012/13
Transplant[b]	Background management	£5,238.59	100%	Assumed equal to CKD stage 5
	Living donor transplant	£18,639.68	35.6%	NHS Reference costs 2012/13, (NHSBT 2013/4 Activity Report)
	Deceased donor transplant	£18,631.41	64.4%	NHS Reference costs 2012/13, (NHSBT 2013/4 Activity Report)
	Organ transplantation service	£15,791.32	100%	NHSBT FOI request & NHSBT Activity report 2011/12, inflated to 2012/13
	Maintenance year 1	£19,044.44	100%	Kerr *et al*., 2012
	Maintenance year 2+	£7,876.52	100%	Kerr *et al*., 2012

ADP, Automated peritoneal dialysis; CAPD, Continuous ambulatory 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.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

As noted above, adverse events associated with tolvaptan treatment were not explicitly modelled; the cost associated with adverse events is assumed to be captured within the CKD health state costs.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

In the model, stochastic (individual patient simulation) and probabilistic simulations were performed in a single analysis. Therefore all base case and sensitivity analysis results reported in section 7 are probabilistic mean values. Within each probabilistic iteration, 500 patients with identical baseline characteristics are simulated. Between each successive probabilistic iteration, the baseline characteristics of the 500 identical patients are sampled from their distributions (based on the baseline characteristics of the TEMPO 3:4 trial population) and the mean values of all model parameters (see section 7.3.6) are sampled from their individual distributions.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Investigations of structural uncertainty in the model are summarised in Table B48.

Table B48. Structural uncertainty analyses

Scenario	Description and rationale	Base-case approach	Alternative approach
ESRD therapy eGFR start level (mL/min/1.73m2)	Patients in the model receive treatment for ESRD (i.e., dialysis or transplant) once their eGFR levels have decreased to below 8.5 mL/min/1.73 m2. Alternative values are tested.	8.5 (mL/min/1.73m2)	6 & 10 (mL/min/1.73m2)
Significant pain	Modelling of the impact of significant pain events on HRQL and costs.	Significant pain events included; probability by treatment based on 3-year TEMPO 3:4 data	Significant pain events excluded

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The stochastic individual patient simulation (with sampling of baseline characteristics) and probabilistic sensitivity analysis were programmed to run simultaneously accounting for first and second order uncertainty. As a result conventional deterministic sensitivity analysis of the majority of parameters was not performed. However, scenario analyses of key parameters were performed to identify which parameters were most influential upon cost-effectiveness. These are summarised in Table B49.

Table B49. Scenario analysis

Scenario	Description and rationale	Base-case value	Alternative parameters tested
Discount rates	Tolvaptan treatment has the potential to improve HRQL and prevent or delay death due to the complications of ADPKD and ESRD. The benefits of treatment are realised over a very long period of time (the mean age at which ESRD develops in the model is 56 years and the mean age of death is 66 years, for patients entering the model with a mean age of 39 years; a difference of 17 and 27 years, respectively).	3.5% for costs and outcomes	0% for costs and outcomes 1.5% for costs and outcomes
Treatment effect on eGFR	Treatment effect is based on the difference between groups in the slope of kidney function as measured by the reciprocal of the serum creatinine level. The slope was also measured based on CKD-EPI in TEMPO.	31.6% (slope based on 1/serum creatinine)	26.4% (slope based on CKD-EPI)
Treatment discontinuation	The model uses annual discontinuation rates from the TEMPO study for the first 3 years. In years 4+ the treatment discontinuation is assumed to be 0.5%. Alternative rates are tested in year 4+.	0.5%	0% & 2%
Disease progression	Outcomes during the first 3 years in the model use the disease progression equations	Use disease progression equation from year 0 in simulation	Disease progression for the first 3 years based on TEMPO 3:4
Proportion that receive conservative care	Assumption based on NHS (2010) Chronic kidney disease FAQ. Alternative values are tested.	10%	5% &15%
Health state utility values	CKD stage 3-4 utility decrements based on TTO study by Gorodetskaya *et al*., 2005. Alternative utility decrements tested.	Gorodetskaya *et al*., 2005	Wu and Yang, 2014
Health state utility values	ESRD (and CKD 5) utility decrements based on study by Lee *et al*. 2005. Alternative utility decrements tested.	Lee *et al*. 2005	Minimum and maximum of the reported range of EQ-5D index and time trade-off values
Disutility with treatment	Any HRQL impairment due to tolvaptan treatment is assumed to be counterbalanced by reduction in ADPKD complications (e.g., hypertension, gout etc). A decrement of 0.05 in each year of treatment was explored in sensitivity analysis	0.00	0.05

Scenario	Description and rationale	Base-case value	Alternative parameters tested
Geographic location of trial population	The treatment effect on eGFR is based on the Full Analysis Set from the TEMPO study. A sensitivity analysis using data (slope in 1/serum creatinine) for patients located in Europe is presented	31.6% (ITT analysis for 1/serum creatinine)	35.1% (Europe subgroup analysis for 1/serum creatinine; TEMPO 3:4 CSR p 223)
Characteristics of patients entering the model	In the base case, the average age, % female, eGFR and TKV were taken from the baseline characteristics of the TEMPO 3:4 study. Patient profiles from the OVERTURE real world study (CKD stages 1-3) were explored in sensitivity analysis	38.7 y/48.40%F/eGFR 81.61/TKV 1692.30 Subgroup analyses also were performed for CKD stage 1, 2, 3a and 3b using TEMPO 3:4 data for each subgroup	Subgroup analyses also were performed for CKD stage 1, 2, 3a and 3b using OVERTURE data for each subgroup

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

In the model, stochastic (individual patient simulation) and probabilistic simulations are performed in a single analysis. Therefore all base case and sensitivity analysis results reported in section 7 are probabilistic mean values. All parameters and variables were included in the PSA. The distributions and their sources are described in Table B35 in section 7.3.6.

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

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000 −£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Since the first three years of the model is pegged to the TKV growth and eGFR observed in TEMPO 3:4 in the base case, it is trivial to present comparisons of these modelled outcomes with the trial data. A summary of other model outcomes compared with population norms is provided in Table B50. Further validation with respect to external data is presented in the validation section (see section 7.8.1)

Table B50. Summary of model results compared with clinical data

Outcome	Clinical trial/study result	Model result
Survival at 3 years	100% in both arms	99.7% control; 99.6% treatment
Mean age at ESRD (years)	55[a] (45 – 67)[b]	52[c]
Mean age at death (years)	70[d]	65.6

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

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

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

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

The model estimate for the mean age at ESRD was similar to that observed in the UK renal registry and other published studies, and within the plausible range that may be expected for a patient population with evidence of rapidly progressing disease. A detailed comparison is provided in section 7.8.1.

Underlying life expectancy is estimated to be a mean of 65.6 years of age for patients receiving no active treatment and eligible for tolvaptan (section 0). In the UK, registry data indicate that the mean age of death of patients with ADPKD and ESRD is approximately 70 years (Shaw *et al*., 2014). Since this analysis focusses on patients with evidence of rapidly progressing disease, the modelled value for underlying life expectancy appears plausible.

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

The proportion of patients in each ESRD health state over time in the no active treatment and the tolvaptan cohorts is presented in Figure B18 and Figure B19, respectively. The distribution of patients among the CKD health states is presented in Table B51.

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

Table B51. Time spent in each CKD health state (years)

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

Figure B18. Distribution of patients among ESRD treatment modalities: no active treatment cohort

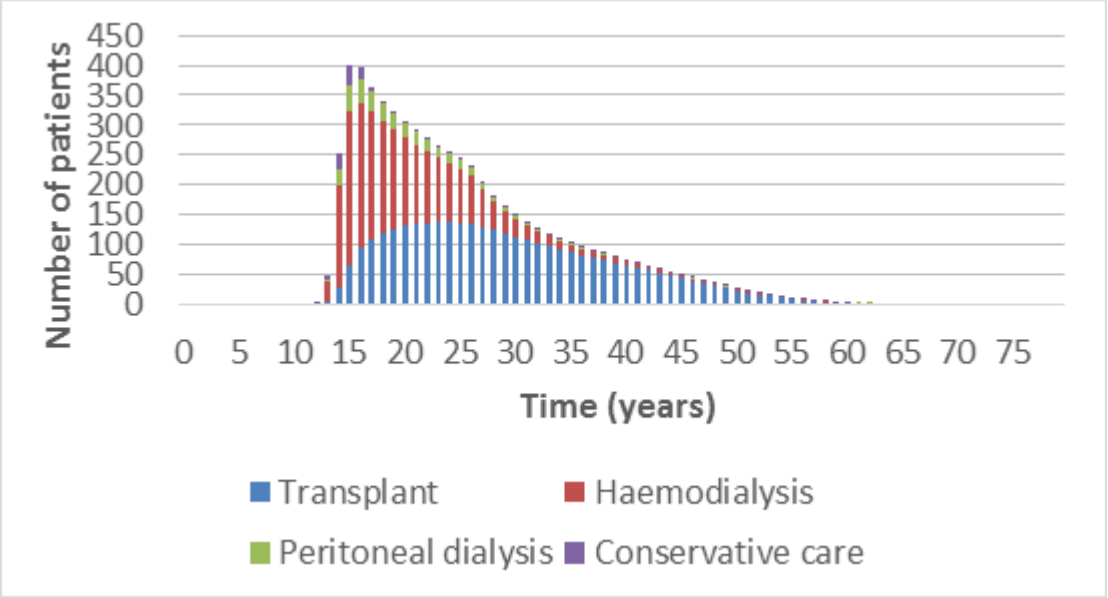
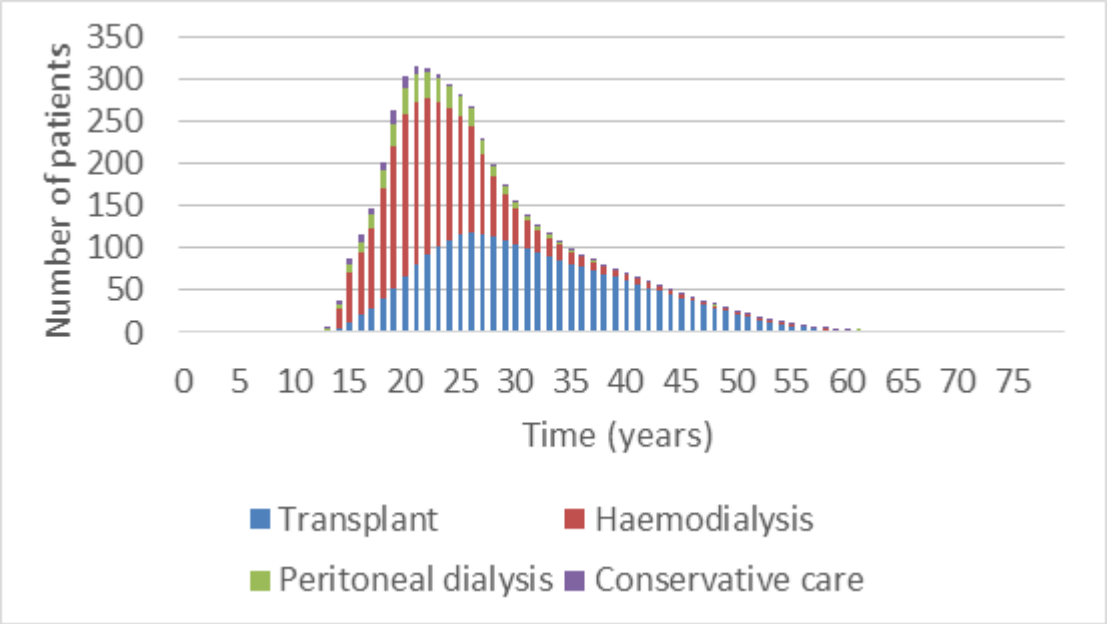


Figure B19. Distribution of patients among ESRD treatment modalities: tolvaptan cohort



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

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

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

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

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The probabilistic mean base-case results are presented in Table B52 (excluding the PAS) and 0 (including the PAS), based on 500 patients simulated with sampling of baseline characteristics; 1,000 PSA iterations. The number of simulations was selected based on ICER convergence, see Figure B24 in section 7.7.8).

The discounted estimates for total expected lifetime costs were £[redacted] for the control (no active treatment) cohort. For the tolvaptan cohort, the cost estimates were higher at £[redacted] (excluding the PAS), and £[redacted] (including the PAS). The health outcomes in the form of QALYs and life years gained were higher for the tolvaptan patient cohort at 13.54 QALYs (discounted) and 17.58 life year (undiscounted) than for the control (no active treatment) cohorts 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 B52. Mean discounted base-case results per patient (probabilistic mean estimates, excluding PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£[redacted]	16.76	12.63				
Tolvaptan	£[redacted]	17.58	13.54	[redacted]	0.82	0.91	£[redacted]

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

Total expected lifetime results, mean per patient, based on 500 patients simulated with sampling of baseline characteristics; 1,000 PSA iterations. The number of simulations was selected based on ICER convergence (see Figure B24 in section 7.7.8)

Table B53. Mean discounted base-case results per patient (probabilistic mean estimates, including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
No active treatment	£[redacted]	16.76	12.63				
Tolvaptan	£[redacted]	17.58	13.54	[redacted]	0.82	0.91	£34,769

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

Total expected lifetime results, mean per patient, based on 500 patients simulated with sampling of baseline characteristics; 1,000 PSA iterations. The number of simulations was selected based on ICER convergence (see Figure B24 in section 7.7.8)

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

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. However, structural sensitivity analyses were performed (described in section 7.6.1) and scenario analyses were performed in which alternative sources for individual parameters and assumptions were explored (described in section 7.6.2). The results of these analyses are presented in section 7.7.9.

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

The results of 1,000 probabilistic simulations (each including 500 patients with identical characteristics) are presented on the cost-effectiveness plane in Figure B20 (excluding the PAS) and Figure B21 (including the PAS). The vast majority of simulations fell in the north east quadrant in both cases.

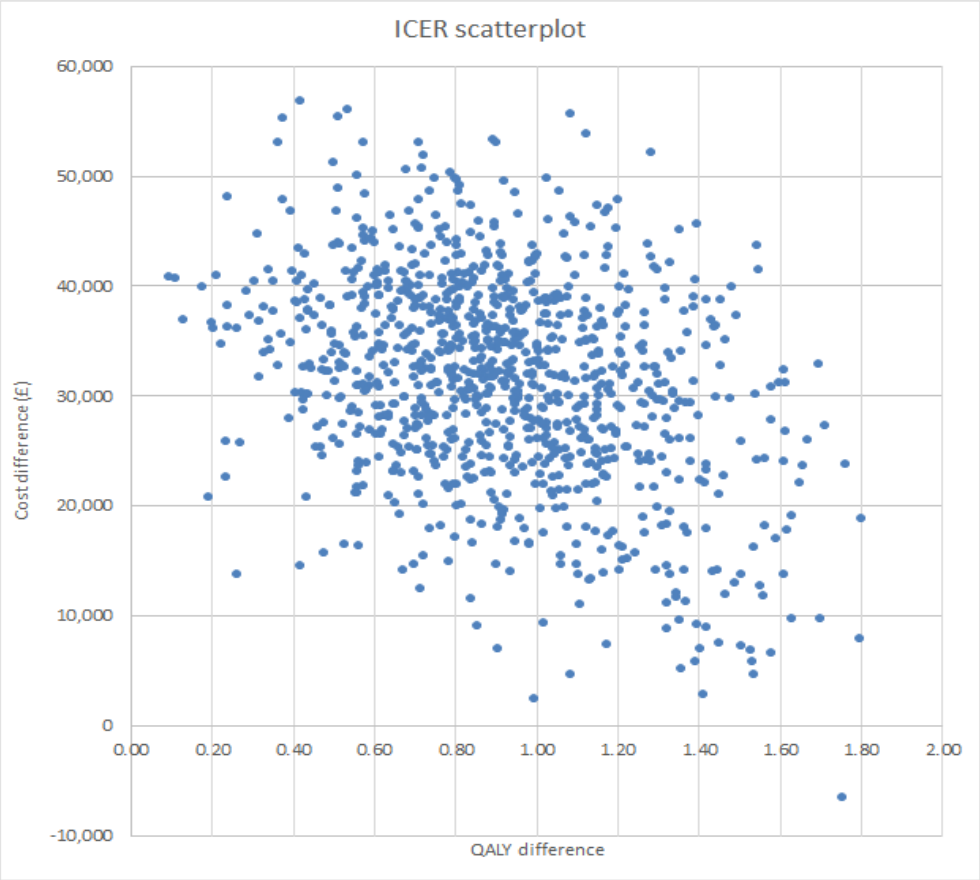
The cost-effectiveness acceptability curve is presented in Figure B22 (excluding the PAS) and Figure B23 (including the PAS). Including the PAS the probability of cost-effectiveness at a willingness-to-pay threshold of £30,000, £35,000 and £40,000 per QALY gained was 36%, 47% and 58%, respectively.

The variability of the ICER estimates as the number of probabilistic simulations was increased is presented in Figure B24 and B25. The ICER became stable after approximately 200 simulations. 1,000 simulations were performed for all analyses.

Figure B20. Probabilistic ICER estimates presented on the cost-effectiveness plane [excluding PAS)

[redacted]

Figure B21. Probabilistic ICER estimates presented on the cost-effectiveness plane [including PAS]



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

Figure B22. Cost-effectiveness acceptability curve [excluding PAS}

[redacted]

Figure B23. Cost-effectiveness acceptability curve [including PAS}

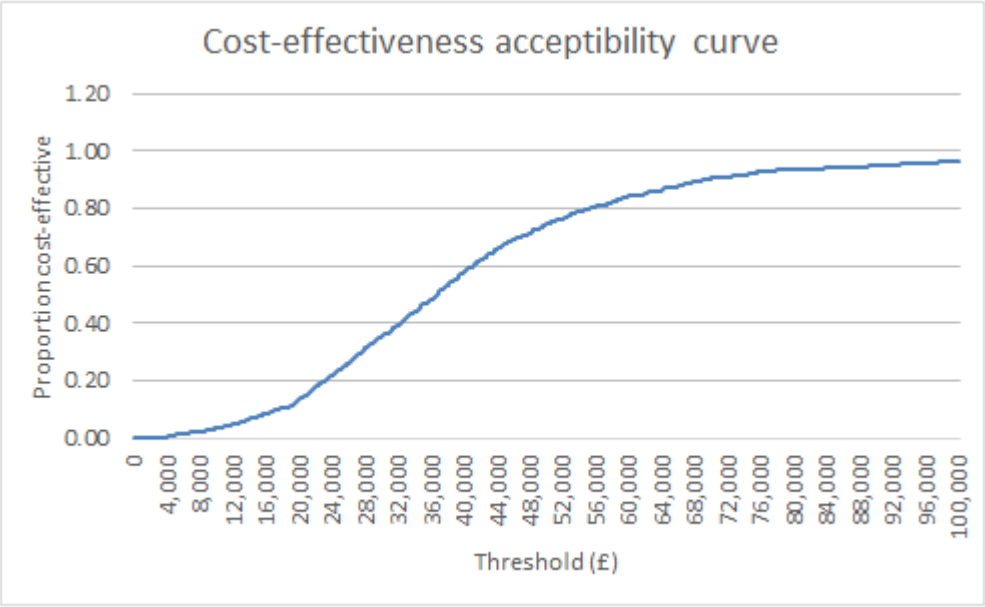
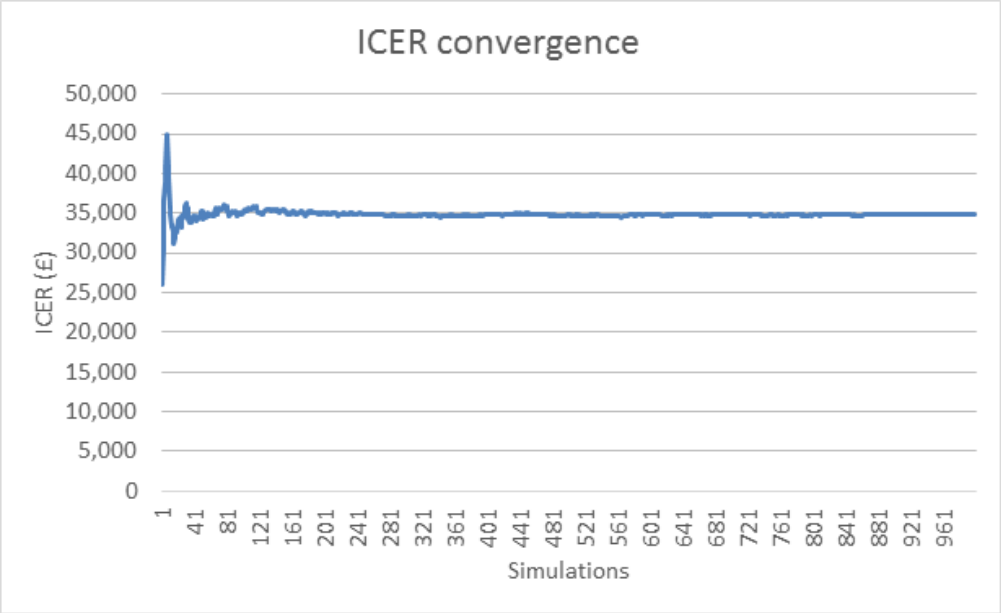


Figure B24. ICER estimates with increasing number of probabilistic simulations [excluding PAS]

[redacted]

Figure B25. ICER estimates with increasing number of probabilistic simulations [including PAS]



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

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results of the structural sensitivity analyses outlined in section 7.6.1 and the scenario analyses outlined in section 7.6.2 are presented in Table B54 and Table B55.

Table B54. Summary of probabilistic mean per-patient results of structural sensitivity and scenario analyses performed in the economic evaluation of tolvaptan versus no active treatment [excluding PAS]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
Base-case analysis	£[redacted]	£[redacted]	17.58	16.76	13.54	12.63	£[redacted]	0.82	0.91	£[redacted]
Structural sensitivity analyses										
Clinically significant pain excluded	£[redacted]	£[redacted]	17.56	16.73	13.56	12.64	£[redacted]	0.83	0.91	£[redacted]
Scenario analyses										
ESRD therapy eGFR <6	£[redacted]	£[redacted]	17.68	16.87	13.59	12.68	£[redacted]	0.81	0.91	£[redacted]
ESRD therapy eGFR <10	£[redacted]	£[redacted]	17.56	16.70	13.52	12.60	£[redacted]	0.86	0.93	£[redacted]
Discount rates = 0%	£[redacted]	£[redacted]	27.90	26.36	20.33	18.82	£[redacted]	1.54	1.51	£[redacted]
Discount rates = 1.5%	£[redacted]	£[redacted]	22.49	21.32	16.81	15.59	£[redacted]	1.18	1.22	£[redacted]
Treatment effect CKD-EPI	£[redacted]	£[redacted]	17.44	16.76	13.38	12.63	£[redacted]	0.68	0.75	£[redacted]
Treatment discontinuation year 4+ (0% SE 0%)	£[redacted]	£[redacted]	17.60	16.74	13.56	12.62	£[redacted]	0.86	0.95	£[redacted]
Treatment discontinuation year 4+ (2.0% SE 0.8%)	£[redacted]	£[redacted]	17.51	16.76	13.45	12.63	£[redacted]	0.75	0.83	£[redacted]
Disease progression	£[redacted]	£[redacted]	17.53	16.70	13.48	12.57	£[redacted]	0.83	0.91	£[redacted]
Conservative care (5%)	£[redacted]	£[redacted]	17.79	17.02	13.65	12.78	£[redacted]	0.77	0.88	£[redacted]
Conservative care (15%)	£[redacted]	£[redacted]	17.39	16.50	13.43	12.47	£[redacted]	0.89	0.96	£[redacted]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
CKD 3-4 HSUVs (Wu & Yang, 2014)	£[redacted]	£[redacted]	17.58	16.76	13.73	12.83	£[redacted]	0.82	0.90	£[redacted]
ESRD HSUVs decrements (Minimum Values)	£[redacted]	£[redacted]	17.58	16.76	14.19	13.41	£[redacted]	0.82	0.77	£[redacted]
ESRD HSUVs decrements (Maximum Values)	£[redacted]	£[redacted]	17.58	16.76	13.27	12.26	£[redacted]	0.82	1.01	£[redacted]
Disutility with treatment	£[redacted]	£[redacted]	17.58	16.75	13.42	12.62	£[redacted]	0.83	0.79	£[redacted]
European population Subgroup	£[redacted]	£[redacted]	17.92	16.89	13.92	12.77	£[redacted]	1.03	1.15	£[redacted]

HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year; SC, standard care (no active treatment)

Table B55. Summary of probabilistic mean per-patient results of structural sensitivity and scenario analyses performed in the economic evaluation of tolvaptan versus no active treatment [including PAS]

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
Base-case analysis	£[redacted]	£[redacted]	17.58	16.76	13.54	12.63	£31,583	0.82	0.91	£34,769
Structural sensitivity analyses										
Clinically significant pain excluded	£[redacted]	£[redacted]	17.56	16.73	13.56	12.64	£31,496	0.83	0.91	£34,480
Scenario analyses										
ESRD therapy eGFR <6	£[redacted]	£[redacted]	17.68	16.87	13.59	12.68	£30,617	0.81	0.91	£33,627
ESRD therapy eGFR <10	£[redacted]	£[redacted]	17.56	16.70	13.52	12.60	£31,263	0.86	0.93	£33,707
Discount rates = 0%	£[redacted]	£[redacted]	27.90	26.36	20.33	18.82	£41,897	1.54	1.51	£27,668
Discount rates = 1.5%	£[redacted]	£[redacted]	22.49	21.32	16.81	15.59	£36,242	1.18	1.22	£29,791
Treatment effect CKD-EPI	£[redacted]	£[redacted]	17.44	16.76	13.38	12.63	£35,755	0.68	0.75	£47,722
Treatment discontinuation year 4+ (0% SE 0%)	£[redacted]	£[redacted]	17.60	16.74	13.56	12.62	£32,222	0.86	0.95	£34,040
Treatment discontinuation year 4+ (2.0% SE 0.8%)	£[redacted]	£[redacted]	17.51	16.76	13.45	12.63	£30,282	0.75	0.83	£36,651
Disease progression	£[redacted]	£[redacted]	17.53	16.70	13.48	12.57	£31,803	0.83	0.91	£34,909
Conservative care (5%)	£[redacted]	£[redacted]	17.79	17.02	13.65	12.78	£29,855	0.77	0.88	£33,992
Conservative care (15%)	£[redacted]	£[redacted]	17.39	16.50	13.43	12.47	£33,529	0.89	0.96	£35,105

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
CKD 3-4 HSUVs (Wu & Yang, 2014)	£[redacted]	£[redacted]	17.58	16.76	13.73	12.83	£31,583	0.82	0.90	£35,211
ESRD HSUVs decrements (Minimum Values)	£[redacted]	£[redacted]	17.58	16.76	14.19	13.41	£31,583	0.82	0.77	£40,819
ESRD HSUVs decrements (Maximum Values)	£[redacted]	£[redacted]	17.58	16.76	13,27	12.26	£31,583	0.82	1.01	£31,208
Disutility with treatment	£[redacted]	£[redacted]	17.58	16.75	13.42	12.62	£31,668	0.83	0.79	£39,959
European population	£[redacted]	£[redacted]	17.92	16.89	13.92	12.77	£26,524	1.03	1.15	£22,993

HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year; SC, standard care (no active treatment)

7.7.10 What were the main findings of each of the sensitivity analyses?

In the PSA, the base-case mean ICER (including the PAS) was £34,769 per QALY gained and 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. In the structural sensitivity analysis (including the PAS), 'clinically significant pain state excluded' the ICER was £34,480. In the scenario analysis (including the PAS), the ICER ranged from £22,993 to £47,722.

Table B56. Main findings from the scenario analyses performed in the economic evaluation of tolvaptan versus no active treatment (including PAS)

	Main findings
Structural sensitivity analyses	
Clinically significant pain excluded	This scenario showed that excluding clinically significant pain events from the model has a small negative effect on the cost-effectiveness results. The ICER decreases by £289 to £34,480.
Scenario sensitivity analyses	
ESRD therapy eGFR <6	This scenario showed that lowering the eGFR threshold so that patients need to have more advanced disease to receive treatment for ESRD has a small positive effect on the cost-effectiveness results. The ICER declines by £1,142 to £33,627.
ESRD therapy eGFR <10	This scenario showed that increasing the eGFR threshold so that patients need to have less advanced disease to receive treatment for ESRD has a small positive effect on the cost-effectiveness results. The ICER declines by £1,062 to £33,707.
Discount rates = 0%	This scenario showed that removing discount rates for costs and QALYs has a moderate effect on the results of the cost-effectiveness. Both the incremental cost and QALYs increased versus the base-case analysis but the incremental QALYs increased by a proportionally larger amount which caused the ICER estimate to decrease to £27,668.
Discount rates = 1.5%	Reducing the discount rate to 1.5% had a similar effect as the previous scenario and caused the ICER estimate to decrease to £29,791. The choice of discount rates has a moderate effect on the cost-effectiveness results.
Treatment effect CKD-EPI	This scenario showed that slope of kidney function upon which treatment effect is based has a moderately large effect on the cost-effectiveness results. The ICER rose to £47,722.
Treatment discontinuation year 4+ (0% SE 0%)	This scenario showed that removing discontinuation from treatment had a small positive effect on the cost-effectiveness results. The ICER decreased by £729 to £34,040.
Treatment discontinuation year 4+ (2.0% SE 0.8%)	Increasing the discontinuation rate had a small negative effect on the cost-effectiveness results. The ICER increased to £36,651
Disease progression	This scenario showed that the choice of whether to fix the disease progression equation for the first 3 years of the model to reflect the outcomes seen in the TEMPO 3:4 study has a negligible effect on the cost-effectiveness results. The ICER increased to £34,909

	Main findings
Conservative care (5%)	This scenario showed that decreasing the proportion of patients that receive conservative care has a negligible effect on the cost-effectiveness results. The ICER declined to £33,992
Conservative care (15%)	This scenario showed that increasing the proportion of patients that receive conservative care has a negligible effect on the cost-effectiveness results. The ICER rose to £35,105
CKD 3-4 HSUVs (Wu & Yang, 2014)	This scenario showed that altering the CKD stage 3-4 utility decrements to match those reported by Wu and Yang (2014) has a negligible effect on the cost-effectiveness results. The ICER increased by £442 to £35,211.
ESRD HSUVs decrements (Minimum Values)	This scenario showed that altering the CKD stage 5 and dialysis decrements to reflect the minimum decrements resulted in a moderate effect on the cost-effectiveness results. The ICER increased to £40,819
ESRD HSUVs decrements (Maximum Values)	This scenario showed that altering the CKD stage 5 and dialysis decrements to reflect the maximum decrements resulted in a moderate effect on the cost-effectiveness results. The ICER decreased to £31,208
Disutility with treatment	This scenario showed that including an annual disutility associated with treatment has a small effect on the cost-effectiveness results. The ICER rose to £39,959
European population	This scenario showed that selecting a subgroup based on EU/ROW patients has a moderately large effect on the cost-effectiveness results, causing the incremental cost to decrease and the incremental QALYs to increase. The ICER declined to £22,993
HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year; SC, standard care (no active treatment)	

7.7.11 What are the key drivers of the cost-effectiveness results?

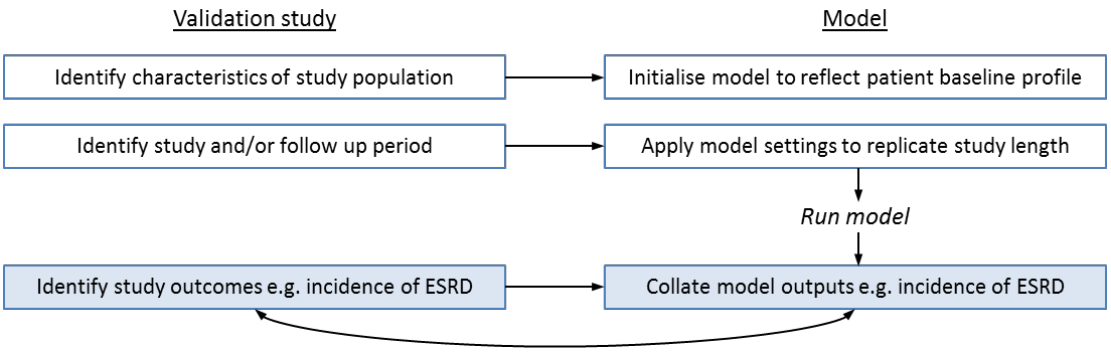
The largest component of the incremental cost was the cost associated with treating ESRD, followed by cost of tolvaptan. In the scenario analyses, assuming a disutility for the duration of tolvaptan treatment resulted in the highest ICER estimate. We expect this to be a highly conservative analysis as additive disutility is possibly not appropriate over patients' lifetime, and those unable to tolerate tolvaptan are likely to discontinue treatment. The following parameters were also key drives of the results: the discount rates, the treatment effect (using CKD-EPI and data for the European population in TEMPO 3:4), the HSUVs for ESRD and the disutility associated with treatment.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Validation was assessed using two primary criteria: face validity (evaluation of model structure, data sources and assumptions by clinical and health economic experts), and external consistency (validation of model predictions against data sources not used to build the model). A schematic of the external validation process is presented in Figure B26.

Figure B26. The validation process



The key validation exercises that were performed during the development of the model are described in section 7.8.1.1 to 7.8.1.5.

7.8.1.1 Face Validity

Clinical steering group co-development

Throughout its development, this disease and cost-effectiveness model has been co-developed with a steering group of European ADPKD expert clinicians, to evaluate its face validity and ensure that the model structure, data sources, problem formulation and results accurately reflect their experience of patients with ADPKD in clinical practice.

In particular, predictions of disease progression as simulated by the model were assessed by the clinicians and compared to their expectations. The expert clinicians concluded that this model performed favourably as a simulation of ADPKD disease progression.

The expert steering group consisted of six clinical experts, two of whom practice in the UK, with the remainder practising in Denmark, Italy, Germany and Spain.

UK clinical and HTA validation

The model was presented at two advisory board meetings to guide the development of the model and validate the assumptions within it.

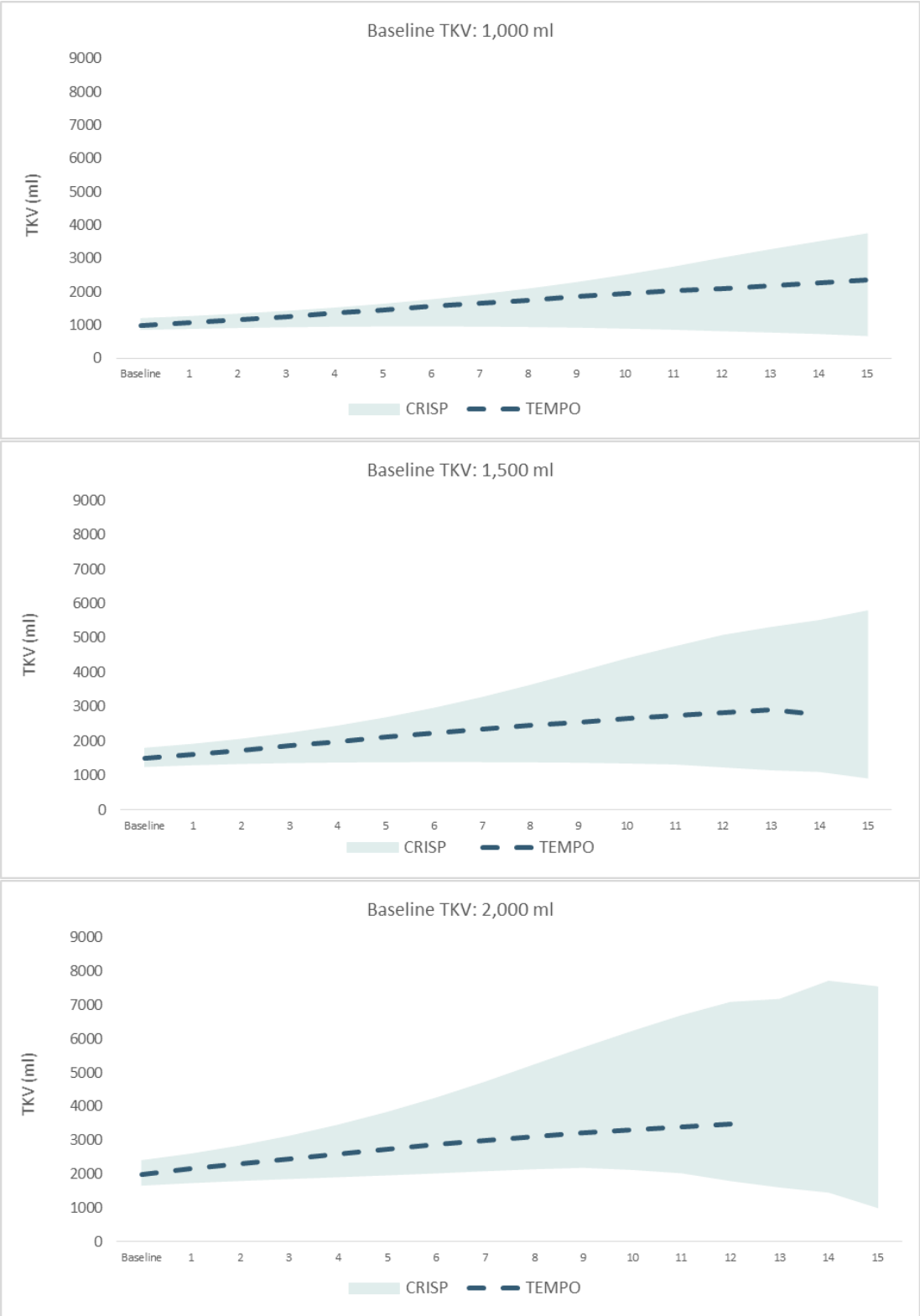
An advisory board meeting was held on 1 September, 2014 and was attended by five UK clinical experts and four UK health economics and HTA experts.

An HTA advisory board meeting was held on 3 September, 2014 and was attended by eight clinical and HTA experts from the UK (one HTA expert), and continental Europe.

7.8.1.2 External consistency with predictions using equations estimated from alternative study data

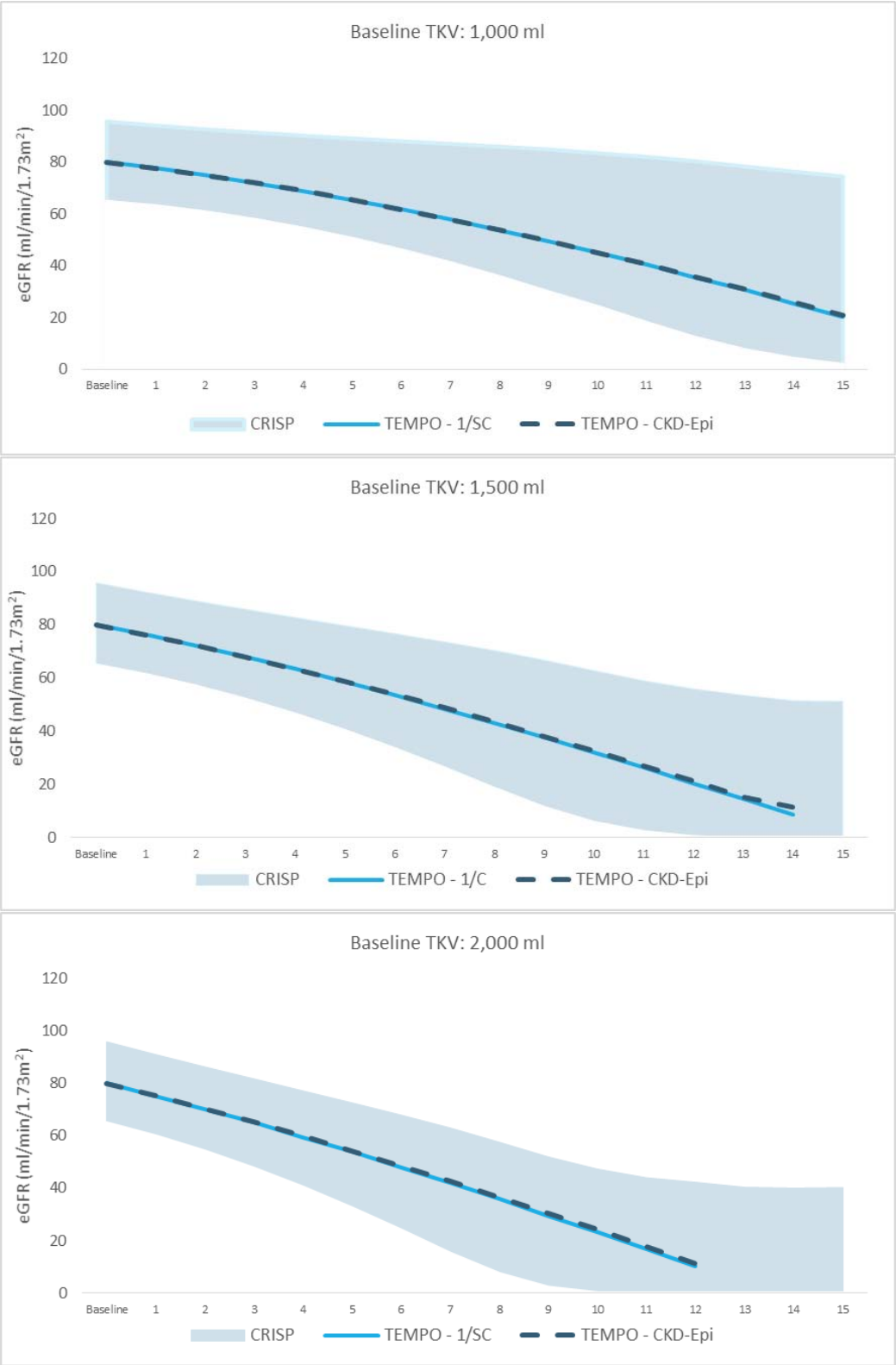
The validity of the model predictions for disease progression was assessed by computing equations based on the aggregated results of CRISP I (Grantham *et al*., 2006). Figure B287 and B28 present the comparison of underlying disease progression for TKV and eGFR from our model, compared with equations specified through CRISP I data. Table B57 consolidates this information into one endpoint, time to ESRD for various baseline patients. Disease progression rates predicted by the model are relatively similar to those predicted using CRISP I data.

Figure B27. Comparison of ADPKD disease progression as predicted by CRISP and TEMPO TKV regression equations



TKV trajectories estimated using TEMPO PLD (dashed line; derived from point estimates) and CRISP (shaded region; derived from standard deviations). Baseline patient profile: age: 40 years; eGFR: 80 mL/min/1.73m^2; TKV: 1000 mL, 1,500 mL and 2,000 mL.

Figure B28. Comparison of ADPKD disease progression as predicted by CRISP and TEMPO eGFR regression equations



eGFR trajectories estimated using TEMPO PLD equations (CKD-EPI equation: dashed line; 1/SC: solid line; derived from point estimates) and CRISP equation (shaded region; derived from standard deviations). Baseline patient profile: age: 40 years; eGFR: 80 mL/min/1.73m^2; TKV: 1000 mL, 1,500 mL and 2,000 mL

Table B57. Time to ESRD onset as predicted by alternative regression equations

	TEMPO 3:4 PLD (1/serum creatinine)	TEMPO 3:4 PLD (CKD-EPI)	CRISP
TKV: 1,000 mL	16 years	17 years	19 years
TKV: 1,500 mL	14 years	14 years	13 years
TKV: 2,000 mL	12 years	12 years	10 years

ESRD, end-stage renal disease; TKV, total kidney volume.
Baseline patient profile: age: 40 years; eGFR: 80 mL/min/1.73m^2; TKV: 1000 mL, 1,500 mL and 2,000 mL.
ESRD onset at 15 mL/min/1.73m^2.

7.8.1.3 Consistency of predicted progression rates with real world data

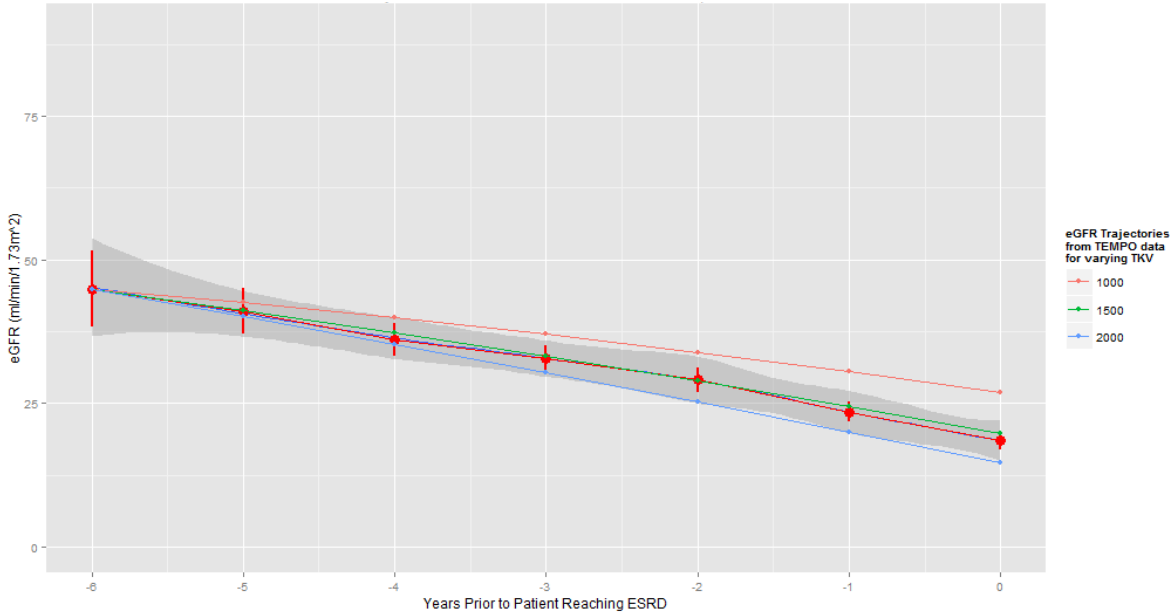
To assess how well the model replicates the progression observed in clinical practice, disease progression was simulated by the model, and outcomes were compared against data from the THIN database, which holds data from UK clinical practice.

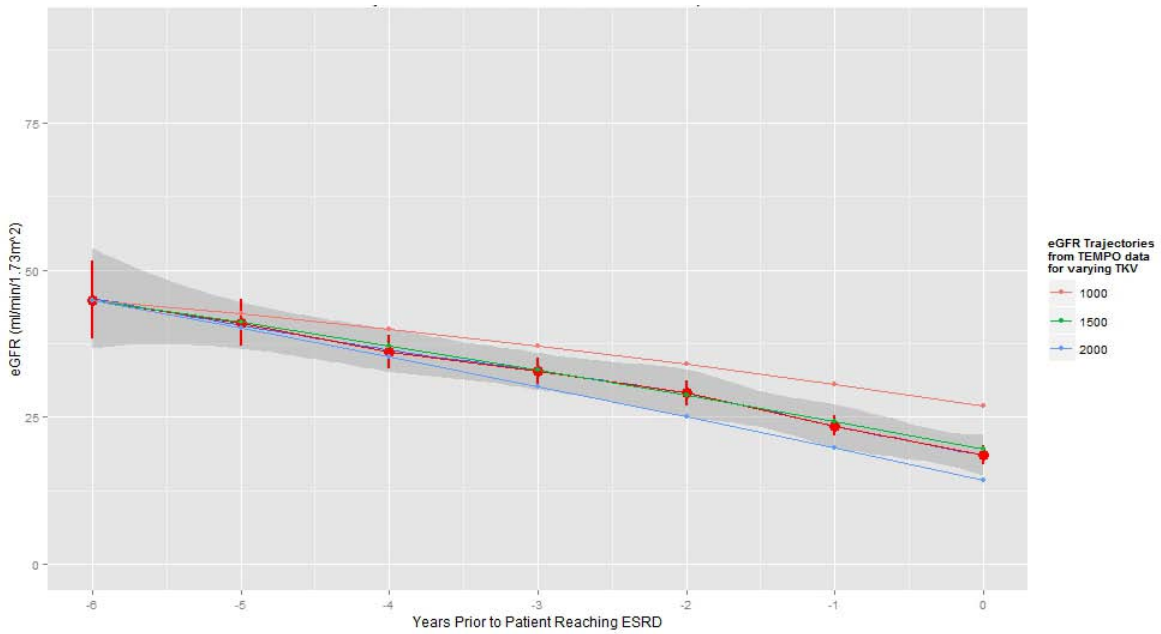
Anonymised patient-level primary care data, including age, gender and eGFR measurements, were obtained from THIN; no TKV measurements were available from this routinely collected dataset. Patients with ESRD were identified using read codes for RRT.

Observed eGFR trajectories prior to ESRD, among 64 patients, were compared to predictions made using the TEMPO PLD equations, with matched mean age (50.97), gender distribution (43.75% female) and mean eGFR (44.95 mL/min/1.73m^2) at 6 years prior to ESRD. Predicted trajectories were evaluated for TKV of 1,000, 1,500 and 2,000 mL.

Figure B30 show the TEMPO PLD trajectories compared with mean THIN observations. The predicted trajectories varied according to baseline TKV, but were consistent with the observations from clinical practice.

Figure B29. Comparison of ADPKD disease progression as predicted by CRISP and TEMPO eGFR regression equations



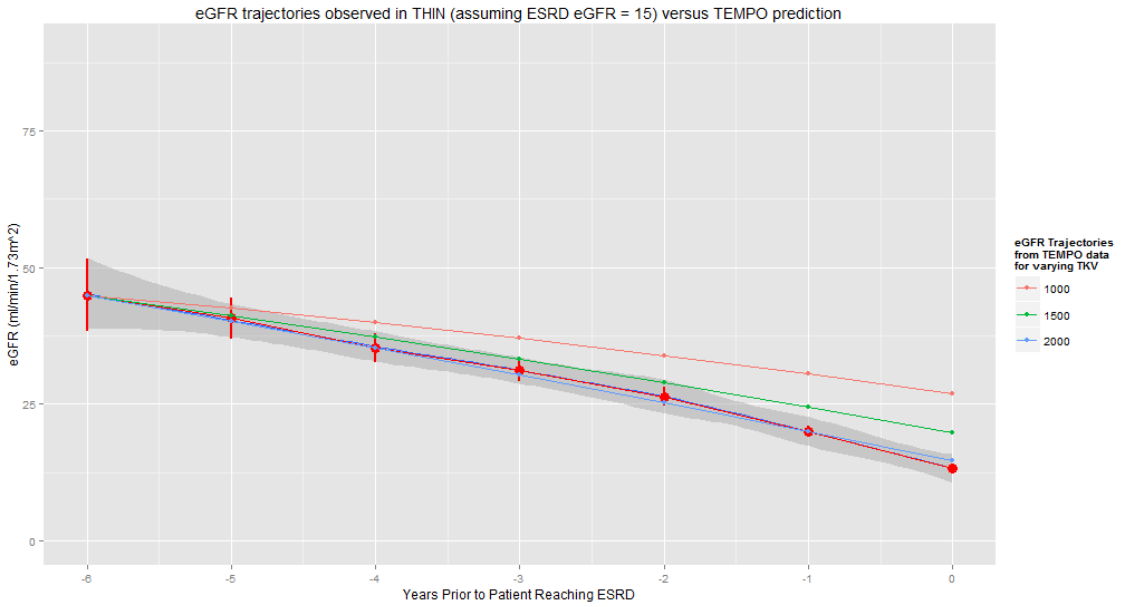


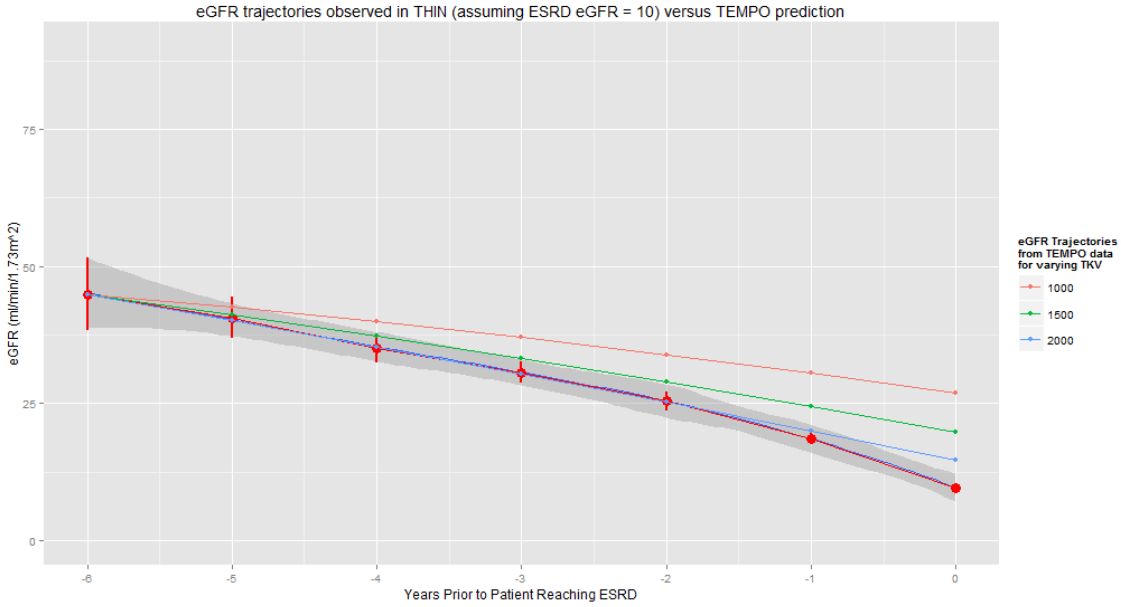
eGFR decline observed in THIN database patient (n = 64) who progressed to ESRD at time 0, with mean (SE; large red dots with SE bars) and smooth (blue shaded area). Associated trajectories calculated using TEMPO PLD equation based on CKD-EPI eGFR data (A) and reciprocal of serum creatinine eGFR data (B); baseline TKV 1000 mL (red), 1500 mL (green) and 2000 mL (blue); matched mean age (50.97), gender distribution (43.75% female) and mean eGFR (44.95 mL/min/1.73m^2) at 6 years prior to ESRD.

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. Despite a general trend in decline of eGFR, a minority of patients had high eGFR recordings at the time of ESRD, potentially relating to receipt of transplant in response to renal failure. By definition, patients with

ESRD have eGFR <15 mL/min/1.73m^2, and patients receiving RRT are likely to have eGFR measurements of 10 mL/min/1.73m^2 or lower. In order to take this into account, further analyses were conducted, imputing eGFR values at ESRD, under the assumption that eGFR was no higher than 15 mL/min/1.73m^2 and 10 mL/min/1.73m^2 at the time of ESRD, using both the TEMPO PLD CKD-EPI and reciprocal of serum creatinine equations (Figure B30 and Figure B31). As can be seen from Figure B30 and Figure B31, predictions from both equations remain consistent with real world primary care data.

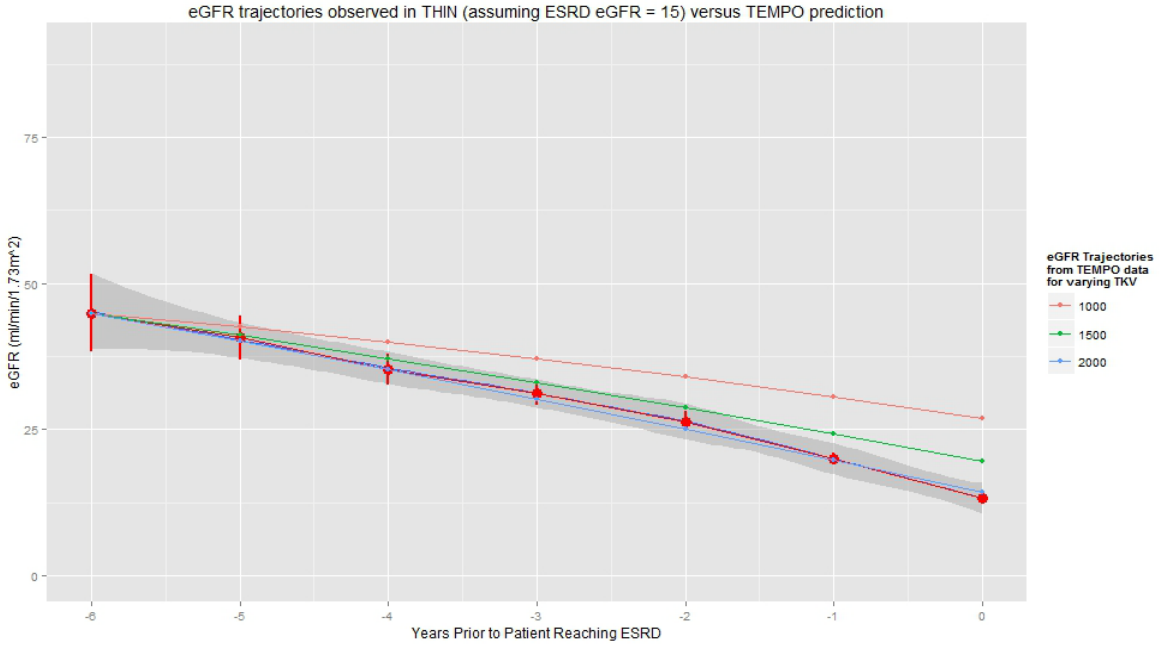
Figure B30. eGFR decline predicted by the model compared to THIN database data, using TEMPO PLD equation based on eGFR (CKD-EPI) data

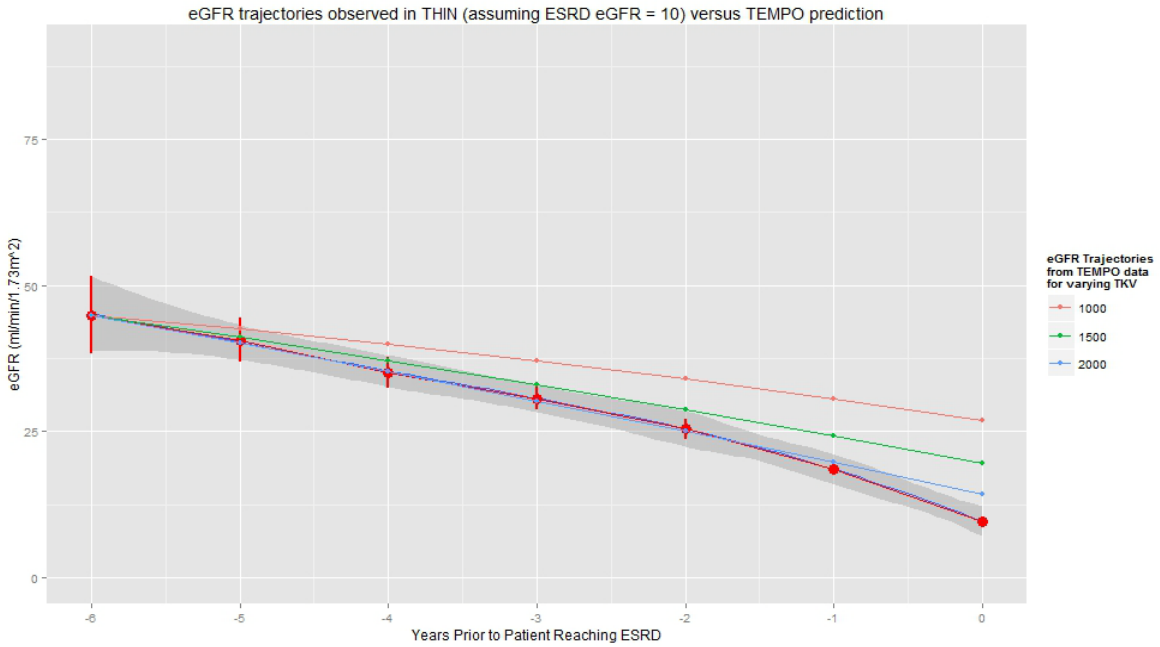




eGFR decline observed in THIN database patient (n = 64) who progressed to ESRD at time 0, with mean (SE; large red dots with SE bars) and smooth (blue shaded area) adjusted to the assumption that eGFR was equal to 15 mL/min/1.73m^2 or 10 mL/min/1.73m^2 at the time of ESRD, unless a lower eGFR record was available in THIN. Associated trajectories calculated using TEMPO PLD equations based on eGFR (CKD-EPI) data for baseline TKV 1000 mL (red), 1500 mL (green) and 2000 mL (blue); matched mean age (50.97), gender distribution (43.75% female) and mean eGFR (44.95 mL/min/1.73m^2) at 6 years prior to ESRD.

Figure B31. eGFR decline predicted by the model compared to THIN database data, TEMPO PLD equation based on eGFR (reciprocal of serum creatinine) data





eGFR decline observed in THIN database patient (n = 64) who progressed to ESRD at time 0, with mean (SE; large red dots with SE bars) and smooth (blue shaded area) adjusted to the assumption that eGFR was equal to 15 mL/min/1.73m^2 or 10 mL/min/1.73m^2 at the time of ESRD, unless a lower eGFR record was available in THIN. Associated trajectories calculated using TEMPO PLD equations based on eGFR (reciprocal of serum creatinine) data for baseline TKV 1000 mL (red), 1500 mL (green) and 2000 mL (blue); matched mean age (50.97), gender distribution (43.75% female) and mean eGFR (44.95 mL/min/1.73m^2) at 6 years prior to ESRD.

7.8.1.4 Age at ESRD

To assess the accuracy of the model's predictions for the time to ESRD, a review of the literature was conducted to identify studies reporting age of ESRD onset in ADPKD patients. Studies identified by the literature review are summarised in section 10.16, appendix 15. Ages reported by identified studies ranged from 45 to 80 years. Age at ESRD onset varied by study period, with more recent studies reporting more advanced age at ESRD onset, frequently within the range of 60–65 years. Additionally, age at ESRD varied with baseline characteristics, and patients with more advanced disease at baseline entered ESRD at any earlier age (there was paucity of data specifically looking at ADPKD).

Based on the amount of available patient demographic information, five studies were assessed in depth with the intention of using the model to replicate the observed progression (Table B58). Four studies did not report TKV at baseline, and so could not be used to validate disease progression equations; only one study (Schrier *et al*., 2003) reported TKV at baseline. However, the study did not report eGFR, limiting the extent to which analyses can be undertaken. Additionally, baseline TKV was too low (< 750 mL) for TEMPO equations to be used in the two patient groups comprised of female patients.

Model predictions for ESRD onset are dependent on specific population characteristics; the mean age of ESRD onset as predicted by the model was between 51 and 53 years when using either the CRISP-derived or TEMPO PLD (CKD-EPI or reciprocal of serum creatinine) disease progression equations, respectively. However, model predictions suggest that ESRD is typically expected at ages in the range of 50-60 years. This is broadly comparable to the age of ESRD onset reported in the identified literature, especially those studies using more recent data.

Table B58. Studies reporting age of ESRD onset in ADPKD patients

Study				Patient characteristics						ESRD outcomes	
Author (year)	**Title**	**Location**	**Dates**	**n (m/f)**	**Age (years)**	**Serum creatinine (mg/dl)**	**eGFR (mL/min/1.73m^2)**	**TKV (cm^3)**	**Hypertension N (%)**	**Age at onset**	**No at ESRD (%)**
Schrier *et al* (2003)	Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease	US	1985-1992	97 (97/0)	38 ± 10	2.0 ± 1.4	NR	826 ± 584	NR	53	NR
			1992-2001	80 (80/0)	36 ± 11	1.6 ± 1.1		834 ± 839		63	
			1985-1992	158 (0/158)	37 ± 10	1.4 ± 1.1		576 ± 537		57	
			1992-2001	178 (0/178)	39 ± 11	1.4 ± 1.1		575 ± 396		61	
Chang (2013)	Novel PKD1 and PKD2 mutations in Taiwanese patients with autosomal dominant polycystic kidney disease	Taiwan	2008-2011	23 (14/9)	43.4 ± 10.81	NR	54.8 ± 41.5	14.9 ± 2.4 (TKL cm)	17 (74%)	52 yrs [40 – 58]	NR
				7 (2/5)	52.9 ± 13	NR	58.6 ± 39.4	14.7 ± 1.9 (TKL cm)	5 (71%)	65.5 yrs [64 – 67]	
				16 (9/7)	51.1 ± 14.8	NR	68.61 ± 53.2	14.8 ± 2.3 (TKL cm)	9 (56%)	67 yrs [41 – 79]	
Romao (2006)	Renal and extra renal manifestations of autosomal dominant polycystic kidney disease	Brazil	1985-2003	92 (34/58)	35.1 ± 14.9	2.4 ± 2.8	NR	NR	NR	45.4 ± 9.5	27 (29.3%)
Haynes (2014)	Evaluating the Contribution of the Cause	UK	2003-2010	675 (360/315)	56 ± 10	NR	22.8 ± 11.1 (annual change -	NR	NR	NR	23% annually

Study				Patient characteristics						ESRD outcomes	
Author (year)	**Title**	**Location**	**Dates**	**n (m/f)**	**Age (years)**	**Serum creatinine (mg/dl)**	**eGFR (mL/min/1.73m^2)**	**TKV (cm^3)**	**Hypertension N (%)**	**Age at onset**	**No at ESRD (%)**
	of Kidney Disease to Prognosis in CKD: Results From the Study of Heart and Renal Protection (SHARP)						3.8 ± 2.5)				
Cornec-Le Gall (2013)	Clinical factors predicting renal outcome in autosomal dominant polycystic kidney disease (ADPKD): results of the Genkyst registry	France	2009-2012	1017 (466/551)	53.9 ± 14.2	NR	13.1% CKD 1, 15.8% CKD 2, 19.4% CKD3, 10.7% CKD4, and 41% CKD 5	NR	NR	65 [62.7-67.2]	NR
ADPKD, autosomal dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NR, not reported.											

7.8.1.5 Factors influencing progression rates

A systematic literature review was conducted to identify factors influencing the rate of disease progression reported in the literature. The cost-effectiveness model predicts varying rates of progression according to the following patient variables, depending on which approach for modelling disease progression is used: age, TKV, gender, age to ADPKD diagnosis, and kidney length. Analysis of patient eGFR trajectories predicted by the model showed great variation in rates of disease progression according to these factors, similar to those reported in the literature.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

The proposed licensed indication is in adults with ADPKD who have stage 1 to 3 CKD at initiation of treatment and evidence of rapidly progressing disease (as presented in section 1). In the TEMPO 3:4 trial, the treatment effect on renal function appeared to be consistent across the subgroups studied (see section 6.5.3). Therefore, all patients within the licensed indication are presumed to benefit from treatment. The base-case analysis uses the overall baseline characteristics of TEMPO 3:4, which is the best representation of patients under the licensed indication (see section 7.2.1). However, there is a wide variety of starting eGFR, TKV, and age combinations that could co-exist within this indication, and consequently a large variation is expected in the rate of disease progression. The starting values of eGFR, TKV, and age have a direct impact on the underlying disease progression and duration of treatment, which will in turn impact the long-term clinical outcomes and costs. Therefore, it is important to explore how varied combinations of baseline characteristics within the licensed indication impact the cost-effectiveness of tolvaptan.

Subgroup analyses were performed for patients in each CKD stage at treatment initiation (stage 1, stage 2, stage 3a and stage 3b). These groups represent defined subgroups of patients within the expected indication with different degrees of renal impairment and at different stages of ADPKD progression.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

The characteristics of each group at treatment initiation are presented in Table B59. Two sets of analyses were performed, using the baseline data from TEMPO 3:4 trial and data from the OVERTURE observational study (Otsuka data on file, 2012b).

Table B59. Summary of the characteristics of patients in the subgroup analyses

CKD Stage	TKV (mL)	eGFR (mL/min/ 1.73m^2)	Age (years)	Gender (% F)
All stages (base case)	1,692.30	81.61	38.70	48.40%
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				
Stage 1	[redacted]	[redacted]	[redacted]	[redacted]

Stage 2	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3a	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3b	[redacted]	[redacted]	[redacted]	[redacted]

7.9.3 Please describe how the statistical analysis was undertaken.

Analyses were performed by setting the initial patient characteristics in the model to the values noted in the Table above. 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 (see section 6.5).

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

The results are presented in Table B60 and Table B61 excluding and including PAS respectively.

Table B60. Summary of the results of the subgroup analyses (probabilistic mean estimates, per-patient, excluding PAS)

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
Base-case analysis	**£[redacted]**	**£[redacted]**	**17.58**	**16.76**	**13.54**	**12.63**	**£[redacted]**	**0.82**	**0.91**	**£[redacted]**
Subgroup analyses based on TEMPO 3:4 baseline characteristics										
CKD stage 1	**£[redacted]**	**£[redacted]**	**18.60**	**17.87**	**14.81**	**13.89**	**£[redacted]**	**0.73**	**0.92**	**£[redacted]**
CKD stage 2	**£[redacted]**	**£[redacted]**	**17.26**	**16.44**	**13.13**	**12.28**	**£[redacted]**	**0.82**	**0.86**	**£[redacted]**
CKD stage 3a	**£[redacted]**	**£[redacted]**	**15.36**	**14.67**	**11.01**	**10.34**	**£[redacted]**	**0.69**	**0.67**	**£[redacted]**
CKD stage 3b	**£[redacted]**	**£[redacted]**	**14.93**	**14.26**	**10.60**	**9.96**	**£[redacted]**	**0.68**	**0.64**	**£[redacted]**
Subgroup analyses based on OVERTURE baseline characteristics										
CKD stage 1	**£[redacted]**	**£[redacted]**	**20.09**	**19.34**	**16.45**	**15.53**	**£[redacted]**	**0.74**	**0.92**	**£[redacted]**
CKD stage 2	**£[redacted]**	**£[redacted]**	**16.03**	**15.39**	**11.98**	**11.17**	**£[redacted]**	**0.64**	**0.80**	**£[redacted]**
CKD stage 3a	**£[redacted]**	**£[redacted]**	**12.87**	**12.49**	**8.92**	**8.39**	**£[redacted]**	**0.38**	**0.53**	**£[redacted]**
CKD stage 3b	**£[redacted]**	**£[redacted]**	**11.58**	**11.25**	**7.57**	**7.14**	**£[redacted]**	**0.33**	**0.43**	**£[redacted]**

Table B61. Summary of the results of the subgroup analyses (probabilistic mean estimates, per-patient, including PAS)

Scenario	Total costs (£)		Total LYs		Total QALYs		Incremental costs (£)	Incremental LYs	Incremental QALYs	Cost/ QALY (£)
	Tolvaptan	SC	Tolvaptan	SC	Tolvaptan	SC				
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**

The overall clinical benefit in terms of QALYs and life-years increases when treating patients in an earlier stage of disease progression. However, the increasing uncertainty in underlying disease progression and treatment duration cause the incremental cost and ICER to increase when treating patients in an earlier stage of disease progression. It is most clinically effective to treat patients in CKD stage 1, whereas it is most cost-effective to treat patients in CKD stage 3 (omitting CKD stage-specific treatment effects). None of the subgroups are representative of the overall population within the licensed indication; the base-case analysis therefore strikes the most appropriate balance and is most representative of cost-effectiveness across the whole licensed indication.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

The subgroups defined by CKD stage represent clinically relevant subpopulations exhibiting a range of baseline TKV and expected rate of decline in renal function, as requested in the final scope (section 5). It should be noted that whilst CKD stages are recognised in clinical practice, they are not necessarily deemed to be appropriate on their own for determining patient management and treatment.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The systematic review detailed in section 7.1 identified one economic evaluation of the cost-effectiveness of tolvaptan in ADPKD (Erickson *et al*., 2013). The aim of the study was to establish the long term health outcomes and cost-effectiveness of tolvaptan based on TEMPO3:4 data) for a US population.

Base case results of Erickson *et al*. vs. evaluation

		Life years	**QALYs**	**Mean age at death**	**Costs**	**ICERs**
Erickson *et al*. (2013)	Tolvaptan	28.4	15.3	68.4	$1,231,400	$744,100
	Placebo	25.9	14.2	65.9	$387,200	
This evaluation	Tolvaptan	17.58	13.54	67.1	£[redacted]	
	Placebo	16.76	12.63	65.6	£[redacted]	£34,496

In terms of incremental QALYs the results of the evaluation are similar to those of Erickson *et al.* (2013); 0.91 QALYs (3.5% discount rate) versus 1.1. QALYs (Erickson *et al*., 3% discount rate). The mean age of death was similar with tolvaptan patients in the Erickson *et al*. study (68.4 years) compared to 67.1 years in this base case evaluation. The incremental life years recorded by Erickson *et al*. were larger than those in our evaluation; 2.6 years (Erickson *et al*.) versus 1.5 years. It should be noted that in all cases the estimation of incremental clinical benefit is lower in the economic evaluation presented in this submission compared to those in Erickson *et al*.

7.10.2 The results generated in the submission evaluation should be given greater credence than the published results as they reflect clinical practice in England and Wales and have made more conservative efficacy claims. Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

On average, patients seen in routine clinical practice have more advanced disease than the patients in the TEMPO 3:4 trial (Otsuka data on file, 2014c; Thong *et al*., 2013). This may result in underestimation of the real-world cost-effectiveness of tolvaptan in routine practice since the base case represents the licensed indication, which necessarily incorporates some patients eligible for tolvaptan without substantial renal function decline (sub-group analyses which explored patients defined by baseline CKD stage are described in Section 7.9).

Tolvaptan is expected to be indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults who have chronic kidney disease (CKD) stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. The economic evaluation was performed on this group of patients and is in accordance with the proposed product label. Thus, the economic evaluation is relevant for all patients who would potentially use tolvaptan.

No RCTs were presented in Section 6 to which the trial population in TEMPO 3:4 could be compared. However, the Sheffield natural history study cited by Thong and Ong (2013) described a population in routine clinical practice. The mean baseline age of the patients in the TEMPO 3:4 study was approximately 39 years, which was lower than the mean age of 45.59 years in the Sheffield study. An inverse correlation (r = –0.44) between the rate of decline in eGFR and the age at diagnosis was reported in the Sheffield study, which suggests that the average rate of decline in eGFR may have been higher in the TEMPO 3:4 population than in clinical practice. However, more patients in the tolvaptan (79.6%) and placebo (78.9%) arms of the TEMPO 3:4 study had hypertension at baseline than in the Sheffield study (70%). Patients with hypertension had a significantly lower median eGFR at baseline than normotensive patients (47 mL/min/1.73m2 vs. 84 mL/min/1.73m2) in the Sheffield study; this suggests that the TEMPO 3:4 population had a lower median eGFR at baseline and subsequently a lower rate in decline of eGFR than a population would be expected to have in clinical practice.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

- The efficacy and safety evidence for the evaluation is based on TEMPO 3:4, a large global, phase 3 clinical trial (N>1,400) with 3 years of follow-up.
- The TEMPO 3:4 inclusion criteria reflect the proposed license population.
- The appropriate comparator was utilised in the TEMPO 3:4 trial and no indirect comparisons were required. The full details of the strengths of the efficacy and safety data are reported in section 6.10.2.
- A patient level fixed-time increment stochastic simulation model was developed which can easily accommodate time dependent and individual patient history/baseline characteristics data.
- The ADPKD progression for untreated patients is based on individual patient data.
- The model encompasses the key health states in ADPKD (CKD stages and ESRD).
- The model has been co-developed with ADPKD clinical experts and externally validated against published naturalistic data

Limitations

- TEMPO 3:4 assessed an intermediate disease marker (TKV) as primary efficacy endpoint, however the correlation between TKV and eGFR is well established
- The model examines the key renal outcomes of ADPKD progression. However other renal and extra-renal complications have not been modelled. This is not thought to be of significant impact given the lack of evidence that tolvaptan has an effect on these other outcomes.
- The model does not account for any differences in ADPKD disease progression stratified by genetic mutation. TKV is thought to be more

important in predicting ADPKD progression, regardless of underlying PKD mutation.

- The utilisation of life tables derived from the general population implies the assumption that mortality in ADPKD patients prior to CKD stage 5 is the equal to mortality in the general population. This is in the absence of ADPKD-specific mortality risk multipliers (pre-ESRD)

Interpretation

In summary, the economic evaluation presented here has addressed the decision problem set out in the final scope. The modelling approach is appropriate under the NICE Reference Case, model inputs have been sourced from high-quality studies and the presentation of results allow transparent interpretation.

The findings of the economic evaluation have been demonstrated to be robust across a range of scenarios. We conclude that tolvaptan is a step-change in the management of ADPKD that will yield significant long-term benefits for patients and the NHS. Accordingly tolvaptan, within its proposed licensed indication, can be confidently regarded as a cost-effective use of NHS resources under the terms of the PAS.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

None.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The patient population eligible for tolvaptan treatment is expected to be diagnosed ADPKD patients, age 18 or above, with stage 1-3 CKD and rapidly progressing disease.

Prevalence of ADPKD

The diagnosed prevalence of ADPKD in the UK is estimated as 3.9 per 10,000 (Patch *et al*., 2011). As tolvaptan is the first disease modifying therapy in ADPKD, it is possible that the diagnosis rate may increase after its introduction. The diagnosis rate has been estimated as 90% (Wiley, 2013); therefore, the total prevalence of ADPKD (diagnosed and undiagnosed) is estimated as 4.3 per 10,000 (3.9 / 0.9). This higher estimate was explored in sensitivity analysis.

The number of prevalent cases of ADPKD was estimated by applying the prevalence rate to population estimates for England and Wales, age 18 and above (mid-year population projections 2015 – 2019 by single year of age; ONS, 2013).

Patients eligible for tolvaptan treatment

The proportion of patients with stage 1-3 CKD was estimated as 17%, 17% and 23% for CKD stage 1, 2 and 3, respectively (Otsuka, data on file).

The proportion of patients with rapidly progressing disease was estimated as 16%, 23% and 44% for CKD stage 1, 2 and 3, respectively (Otsuka, data on file).

Patients averse to tolvaptan and those with impaired renal function or other renal complications would be considered inappropriate for treatment. The number of patients in these categories is unknown and anticipated to be small, therefore no adjustment was made in this respect.

The number of patients eligible for tolvaptan treatment is presented in Table C1.

Table C1. **Estimated patient numbers for England and Wales, by year**

	2015	**2016**	**2017**	**2018**	**2019**
Population of England and Wales, age 18 and above[a]	45,494,244	45,830,038	46,148,567	46,449,002	46,725,521
Diagnosed ADPKD patients, age 18 and above[b]	17,743	17,874	17,998	18,115	18,223
Diagnosed ADPKD age ≥ 18 with stage 1-3 CKD[c]	10,113	10,188	10,259	10,326	10,387
Diagnosed ADPKD age ≥ 18 with stage 1-3 CKD and rapidly progressing disease (eligible for tolvaptan treatment)[d]	**2,972**	**2,994**	**3,015**	**3,034**	**3,052**
CKD Stage 1[c,d]	483	486	490	493	496
CKD Stage 2[c,d]	694	699	704	708	713
CKD Stage 3[c,d]	1,796	1,809	1,821	1,833	1,844

[a] Mid-year population projections 2015 – 2019 by single year of age (ONS, 2013)

[b] Diagnosed prevalence of ADPKD in the UK is estimated as 3.9 per 10,000 (Patch *et al*., 2011)

[c] Proportion of patients with stage 1-3 CKD was estimated as 17%, 17% and 23% for CKD stage 1, 2 and 3, respectively (Otsuka, data on file).

[d] Proportion of patients with rapidly progressing disease was estimated as 16%, 23% and 44% for CKD stage 1, 2 and 3, respectively (Otsuka, data on file).

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that patients currently receive no active treatment. Treatments currently used to manage the symptoms and complications of ADPKD will be made available also to tolvaptan patients and are excluded from the analysis. This is a conservative assumption as a reduction in resource use associated with ADPKD complications such as hypertension and pain may be expected.

8.3 What assumption(s) were made about market share (when relevant)?

Otsuka anticipates that the percentage of eligible patients in each CKD stage who receive tolvaptan treatment will be between 0.9% and 1% in 2015 rising to 48.3% to 51.4% in 2019 (Otsuka data on file, 2014). These estimates are based on tolvaptan being the only disease modifying therapy available in the UK. The estimates by CKD stage are presented in Table C2.

Table C2. **Estimated market share for tolvaptan, by CKD stage and year[a]**

CKD Stage	**% of all eligible patients that receive any treatment**				
	2015	**2016**	**2017**	**2018**	**2019**
CKD Stage 1	1.0%	4.9%	11.2%	27.7%	51.4%
CKD Stage 2	0.9%	4.6%	10.5%	26.1%	48.3%
CKD Stage 3	1.0%	4.9%	10.9%	26.9%	49.9%

[a] Percentages account for treatment discontinuation. E.g., the numerator of the value for 2016 includes all patients who are currently receiving treatment in 2016, including those who started in 2015 and have continued treatment into 2016, and those who started treatment in 2016. It excludes patients who started treatment in 2015 and discontinued prior to 2016. The denominator includes all patients eligible for tolvaptan.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Patients receiving tolvaptan will require additional monitoring). A liver function test will be performed every month for the first 18 months and every 3 months thereafter. In addition to the consultant time to review the test results and issue the prescription, it is expected that tolvaptan patients will receive two additional consultant visits in their first year of treatment and one additional consultant visit in their second year of treatment.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on

national reference costs or the PbR tariff, which HRGs reflected activity?

The cost of tolvaptan per patient per day, based on the list price, is £43.15. A patient access scheme discount of [redacted] was applied to the list price resulting in a cost per patient per day of [redacted] and an annual cost per patient of [redacted]. This was applied for all patients receiving treatment in a given year (it was conservative assumption that no reduction was applied to account for treatment discontinuation within a given year).

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). The remaining costs were based on NHS Reference Costs (2012-13).

The resource use associated with current monitoring of ADPKD patients is presented in Table C3, and was based on NICE clinical guideline 182 (CG182) and clinical expert input. The additional resource use required for patients receiving tolvaptan is presented in Table C4. This represents the additional resources that are expected to be required, over and above those associated with current monitoring.

Table C3. **Resource use for ADPKD patients following referral**

Diagnosis, Monitoring and Management	**Unit Cost**	**Year 1**		**Year 2**		**Year 3+**	
		Frequency	**Cost**	**Frequency**	**Cost**	**Frequency**	**Cost**
Consultant visits (Nephrologist)	£139.00	1	£139.00	1	£139.00	1	£139.00
Consultation with a specialist nurse	£25.00	1	£25.00	1	£25.00	1	£25.00
Biochemistry test	£1.25	1	£1.25	1	£1.25	1	£1.25
Haematology test	£3.01	1	£3.01	1	£3.01	1	£3.01
Phlebotomy	£3.64	1	£3.64	1	£3.64	1	£3.64
Ultrasound (one time only)	£51.00	1	£51.00	0	£0	0	£0
TOTAL			£222.90		£171.90		£171.90

Table C4. **Additional resource use for ADPKD patients receiving tolvaptan**

Diagnosis, Monitoring and Management	**Unit Cost**	**Year 1**		**Year 2**		**Year 3+**	
		Frequency	**Cost**	**Frequency**	**Cost**	**Frequency**	**Cost**
Consultant visits (Nephrologist)	£139.00	2	£278.00	1	£139.00	0	£0
Consultant Review of LFT (10 minute review)	£23.17	11	£254.93	8	£185.33	4	£92.67
Biochemistry test (monthly for 18 months)	£1.25	11	£13.70	8	£9.97	4	£4.98
Phlebotomy (monthly for 18 months)	£3.64	11	£40.04	8	£29.12	4	£14.56
TOTAL additional cost			**£586.57**		**£363.42**		**£112.21**

The cost estimates for the additional monitoring (Table C4) are included in the budget impact estimates. These differ over the first 3 years of treatment (Year 1, £586.57; Year 2, £363.42; Year 3 £112.21); the cost in subsequent years was assumed to be equal to that in Year 3.

The number of patients receiving their first, second, and third year of treatment in each calendar year was estimated, taking treatment discontinuation into account (Table C5).

Table C5. **Patients receiving tolvaptan by year from treatment initiation**

Treatment Start Year	**Discontinuation Rates**		**Number of treated patients by calendar year**				
			2015	**2016**	**2017**	**2018**	**2019**
2015	Y1	15.3%	29	24	23	22	22
2016	Y2	6.5%		118	100	94	91
2017	Y3	2.9%			204	173	162
2018	Y4	0.5%				526	445
2019	Y5	0.5%					799
Total	**-**	**-**	**29**	**143**	**327**	**814**	**1,519**
Note: The total costs row is subject to rounding error.							

8.6 Were there any estimates of resource savings? If so, what were they?

No resource savings are anticipated in the 5 year timeframe of the budget-impact analysis.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The annual budget impact estimates excluding and including the PAS discount) are detailed in Table C6 and Table C7, respectively.

Table C6. **Annual budget impact[a] (excluding PAS)**

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Tolvaptan Drug Acquisition Cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Additional Monitoring Cost	£17,026	£78,272	£158,710	£384,185	£661,399
Total	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]

Table C7. **Annual budget impact[a] (including PAS)**

	Year 1	Year 2	Year 3	Year 4	Year 5
Tolvaptan Drug Acquisition Cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Additional Monitoring Cost	£17,026	£78,272	£158,710	£384,185	£661,399
Total	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]

[a] Based on diagnosed prevalence (3.9 per 10,000).

As tolvaptan is the first disease modifying therapy in ADPKD, it is possible that the diagnosis rate in adults may increase after the introduction of tolvaptan. The budget impact assuming all patients are diagnosed (applying a prevalence of 4.3 per 10,000) is presented in Table C8 and Table C9.

Table C8. **Annual budget impact assuming all patients are diagnosed (excluding PAS)**

	Year 1	Year 2	Year 3	Year 4	Year 5
Tolvaptan Drug Acquisition Cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Additional Monitoring Cost	£18,917	£86,969	£176,345	£426,872	£734,887
Total	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]

Table C9. **Annual budget impact assuming all patients are diagnosed (including PAS)**

	Year 1	Year 2	Year 3	Year 4	Year 5
Tolvaptan Drug Acquisition Cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Additional Monitoring Cost	£18,917	£86,969	£176,345	£426,872	£734,887
Total	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]	**£**[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As shown in the cost-effectiveness analysis, treatment with tolvaptan for a given population is expected to reduce the number of ADPKD patients with ESRD, time spent on dialysis and the number of kidney transplants required. In addition, a reduction in resource use associated with ADPKD complications (e.g., hypertension and pain) may be expected. The majority of these savings are expected to be realised in the long-term and have not been considered in the budget-impact analysis.

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