NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Patiromer for treating hyperkalaemia [ID877]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Patiromer for treating hyperkalaemia [ID877]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Patiromer for treating hyperkalaemia
Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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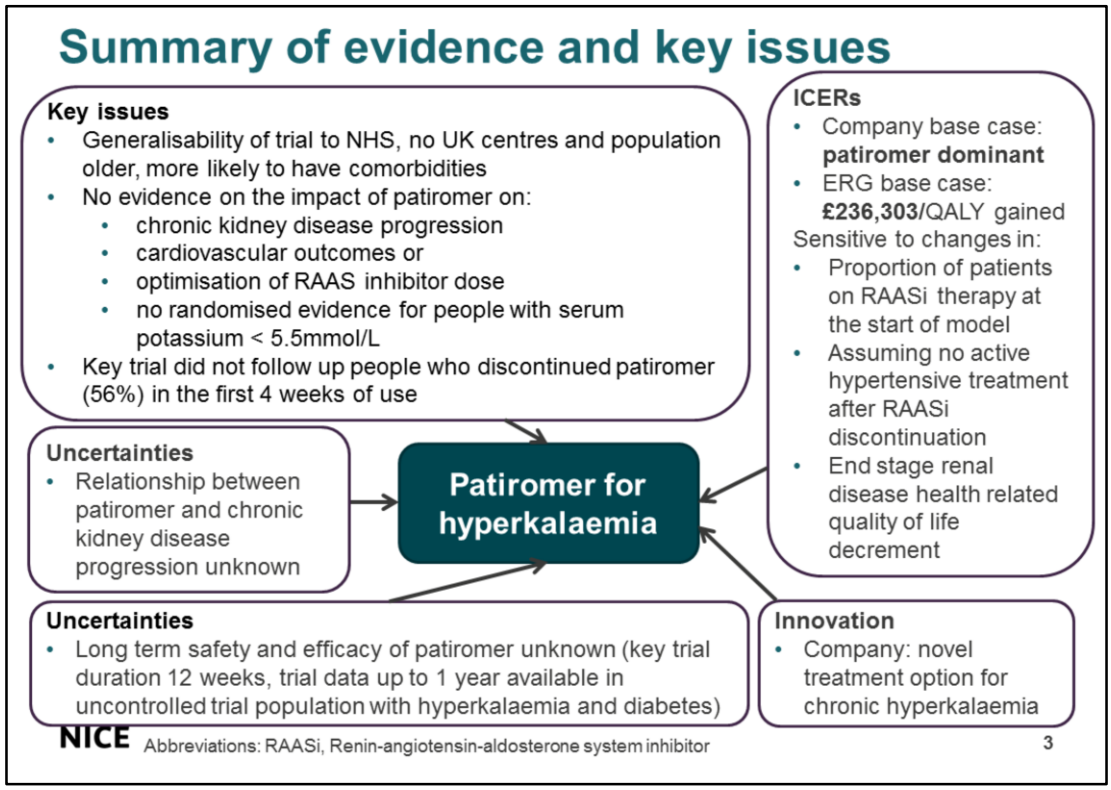
Summary of evidence and key issues
Key issues
• Generalisability of trial to NHS, no UK centres and population older, more likely to have comorbidities
• No evidence on the impact of patiromer on:
• chronic kidney disease progression
• cardiovascular outcomes or
• optimisation of RAAS inhibitor dose
• no randomised evidence for people with serum potassium < 5.5mmol/L
• Key trial did not follow up people who discontinued patiromer (56%) in the first 4 weeks of use
ICERs
• Company base case: patiromer dominant
• ERG base case: £236,303/QALY gained
Sensitive to changes in:
• Proportion of patients on RAASi therapy at the start of model
• Assuming no active hypertensive treatment after RAASi discontinuation
• End stage renal disease health related quality of life decrement
Uncertainties
• Relationship between patiromer and chronic kidney disease progression unknown
Patiromer for hyperkalaemia
Uncertainties
• Long term safety and efficacy of patiromer unknown (key trial duration 12 weeks, trial data up to 1 year available in uncontrolled trial population with hyperkalaemia and diabetes)
Innovation
• Company: novel treatment option for chronic hyperkalaemia
NICE
Abbreviations: RAASi, Renin-angiotensin-aldosterone system inhibitor
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Overview of key clinical relationships

	Source	RCT-based?	Use in model	Length of life	Quality of life
Association between serum K^+ and outcomes	Luo et al. (2016)	No	• Serum K^+ >5.5	↓	↓
Association between Renin-angiotensin-aldosterone (RAASi) use and outcomes	Landray et al. (2010)	Yes	• Lower rate of progression of chronic kidney disease to end stage disease	↑	↑
	Xie et al. (2016)	Yes	• Lower risk of death from chronic kidney disease • Lower rate of cardiovascular events	↑	↑
Association between patiromer and outcomes	OPAL-HK	No	• Lower serum potassium (hazard ratio of hyperkalaemia: 0.25) • Lower rate of stopping RAASi (hazard ratio: [redacted])	As above	

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Hyperkalaemia

- **Definition:** high levels of potassium in the blood (normal range 3.5 to 5.0 mmol/L). Definitions of high, moderate and mild levels vary
  - European Resuscitation Council definition:
    - **Mild** 5.5 to 5.9 mmol/L
    - **Moderate** 6.0 to 6.4 mmol/L
    - **Severe** >6.5 mmol/L
  - Company definition of hyperkalaemia in key trial:
    - **Mild** 5.1 to <5.5 mmol/L
    - **Moderate-to-severe** 5.5 to <6.5 mmol/L
    - Treatment initiation >5.1 mmol/L
- **Symptoms**: muscle weakness, muscle stiffness or fatigue. Many people have no symptoms
- **Severe hyperkalaemia**: can cause arrhythmias leading to cardiac arrest and death
- **Risk factors:**
  - Chronic kidney disease
  - Heart failure
  - Diabetes mellitus
  - Medicines such as renin–angiotensin–aldosterone system inhibitors used to treat high blood pressure and other indications

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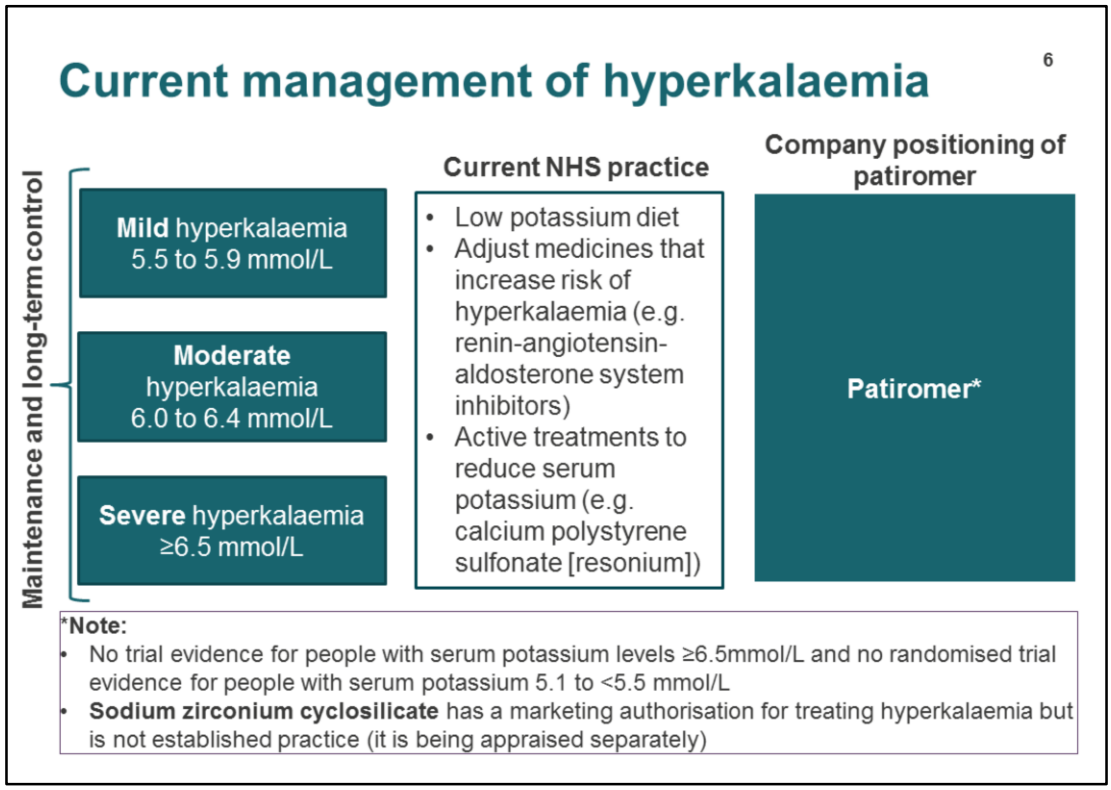
Source: European Resuscitation Council (2015) Guidelines for Resuscitation: 2015, Section 4. Cardiac arrest in special circumstances. https://ercguidelines.elsevierresource.com/european-resuscitation-council-guidelines-resuscitation-2015-section-4-cardiac-arrest-special



Source: Company submission document B p23

Patiromer (Veltassa®)

Marketing authorisation	For "the treatment of hyperkalaemia in adults"
Mechanism of action	• Non-absorbed, cation-exchange polymer • Binds to potassium in the gastrointestinal tract • Lowers potassium absorption and increases faecal excretion
Administration and dosage	• Powder for oral suspension (mixed with ≥80ml water) • **Starting dose: 8.4g once a day** • Increase or decrease dose by 8.4g based on blood potassium up to a **maximum dose: 25.2g once a day** • Taken with food and separated by 3 hours from other oral medications • Onset of action 4 to 7 hours after taking • Patiromer should not replace emergency treatment for life threatening hyperkalaemia
Cost	• **List price:** £10.00 per day for 8.4g and 16.8g sachets • Monthly treatment cost £304* • There is a commercial arrangement for patiromer **(simple discount patient access scheme)**

NICE *based on 30.44 days per months

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Source: Company submission document B table 2 p15-16

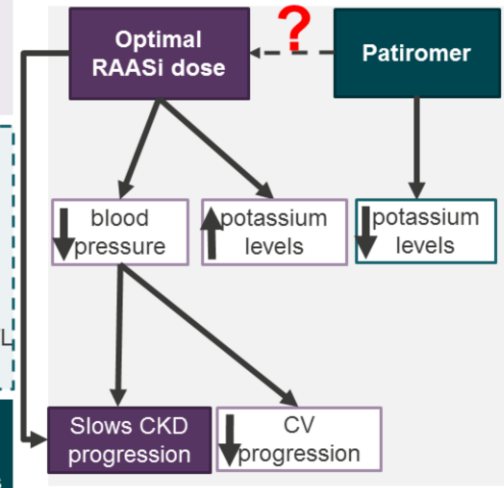
Relationship between patiromer, RAASi, potassium and outcomes

RAASi: (e.g. ACE inhibitors, ARBs etc.)
- **used to treat hypertension**
- **reduce progression of renal disease, heart failure and cardiovascular mortality**

NICE CG182 chronic kidney disease in adults:
- **offer a RAASi to people with CKD** and:
  - diabetes and ACR of ≥3mg/mmol
  - hypertension and ACR of ≥30 mg/mmol
  - an ACR of 70 mg/mmol or more

However, because **RAASi increases potassium**
- do not offer RAASi if serum potassium >5.0 mmol/L
- **stop RAASi if serum potassium ≥6.0 mmol/L**

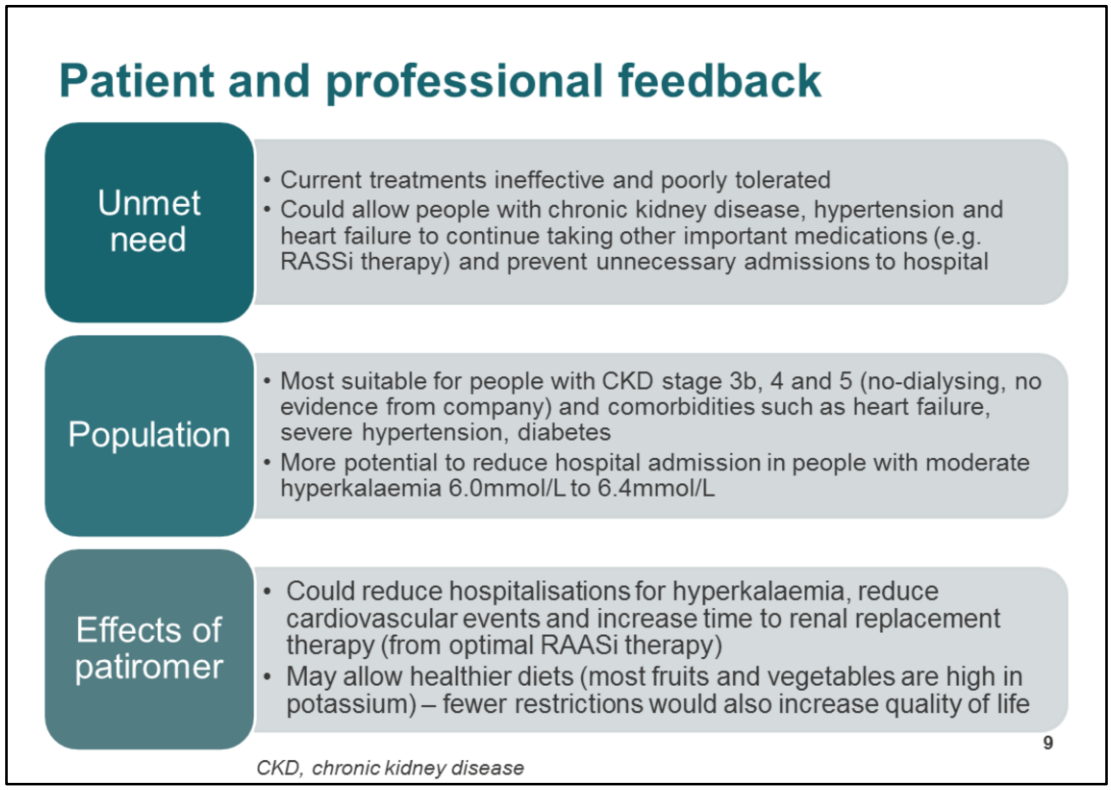
Patiromer claim:
- simple strategy to enable patients to continue optimal RAASi dose by regulating potassium levels



NICE Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin:creatinine ratio; ARB, angiotensin-receptor blockers; CKD, chronic kidney disease; CV, cardiovascular; RAASi, Renin-angiotensin-aldosterone system inhibitors 8

Source: NICE pathways Treatment steps for hypertension accessed August 2018: https://pathways.nice.org.uk/pathways/hypertension/treatment-steps-for-hypertension

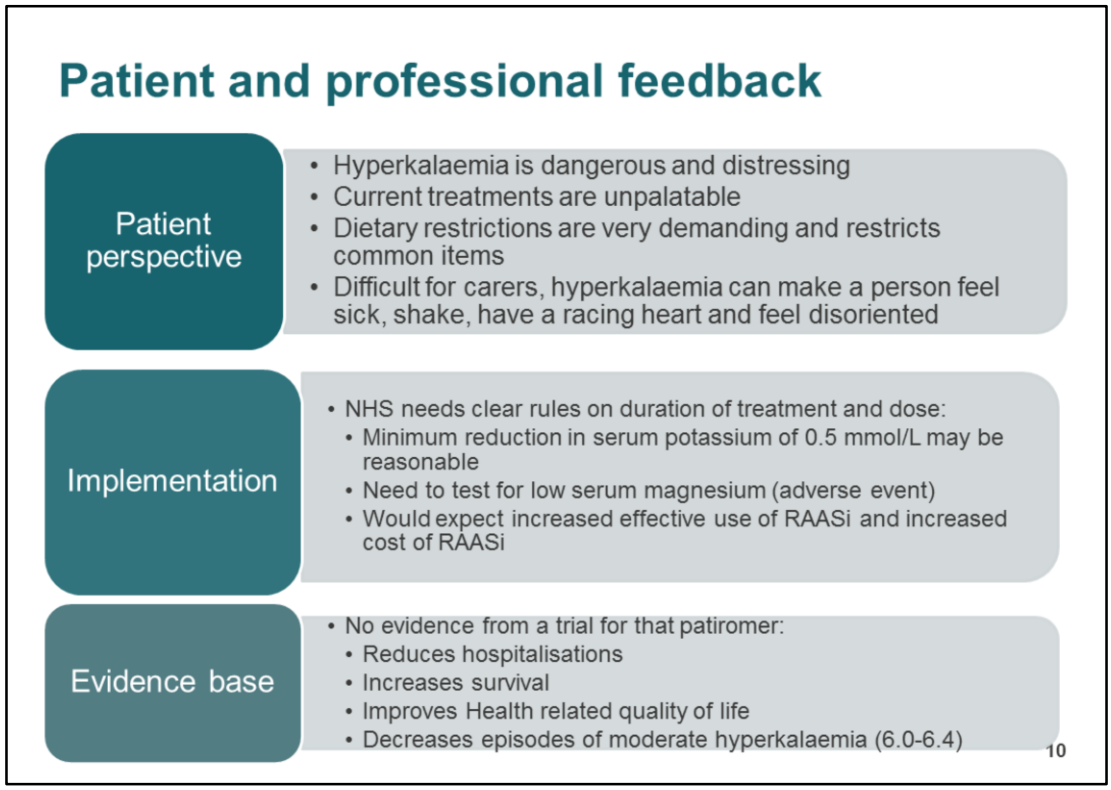
RAASi increased sodium elimination, resulting in potassium retention



Comments from consultees

This section summarises comments from:

- Renal association (endorsed by Royal College of Physicians)
- Royal College of Pathologists
- UK Renal Pharmacy Group



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Company's decision problem deviates from final scope

	Final NICE scope	Submission	Company rationale	ERG comments
Population	Adults with hyperkalaemia	Adults with stage 3 to 4 CKD **and** hyperkalaemia **and** taking RAASi therapy	Matches trial population	No clear rationale for restricting population to CKD and company does **NOT** provide evidence of effectiveness for broader population
Comparators	Standard care including a low potassium diet +/- agents that reduce potassium levels	Stopping RAASi or modifying its dose - no active comparators	No appropriate active comparator: • none in trial • sodium polystyrene sulfonate poorly tolerated	No evidence to justify excluding low potassium diet

Clinical expert feedback on current care

- Would expect patiromer to replace calcium polystyrene sulfonate (resonium)
- Adjusting doses of potassium increasing drugs such as Renin Aldosterone Angiotensin System inhibitors (angiotensin converting enzyme inhibitors)
- Restriction of high potassium foods

NICE Abbreviations: CKD, chronic kidney disease; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone inhibitor

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Please note in UK calcium polystyrene sulfonate may be used and it has a similar side effect profile to sodium polystyrene sulfonate

Key issues: clinical effectiveness

- OPAL-HK trial does not compare patiromer to treatment without patiromer; instead it treats everyone with patiromer, then randomises responders to stop or continue treatment
- OPAL-HK small trial, with n=107 randomised despite relatively common condition and restricted to:
  - people with serum potassium (5.5 to <6.4 mmol/L) and
  - people that responded to patiromer within 4 weeks
- OPAL-HK short trial, long term efficacy and safety of patiromer unclear because of short duration of trial (8 weeks) - AMETHYST provides 1 year of data but is in population with CKD and diabetes and is uncontrolled
- OPAL-HK results may not be generalisable to NHS
  - population in trial older, higher proportion have comorbidities than UK CPRD data (diabetes, hypertension, heart failure)
  - most centres in Eastern Europe (65%), no UK centres, 100% white ethnicity
  - no formal review of low potassium diet or hypertension medicines before trial
  - NHS may not treat people with an active therapy for mild hyperkalaemia
  - RAASi dose discontinuation protocol in OPAL-HK more aggressive than clinical practice
  - max dose is 50.4g daily in study; in marketing authorisation, 25.2g daily
- OPAL-HK not designed to demonstrate any direct health outcomes from continuing RAAS inhibition or target RAASi dose optimisation
  - no data for patiromer enabling optimum dose of RAASi
  - study excluded those with recent cardiovascular events and severe heart failure

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Clinical evidence

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	OPAL-HK n=243	AMETHYST-DN n=306	PEARL-HF n=120	TOURMALINE n=114
Population	• 18 to 80 years • Stage 3 to 4 CKD • Mild to moderate hyperkalaemia • On RAASi therapy* • Part B: already on patiromer	• 30 to 80 years • Stage 3 to 4 CKD • **Type 2 diabetes** • Mild hyperkalaemia • On RAASi therapy**	• ≥18 years • Stage 3 to 5 CKD • Chronic heart failure • Normal S-K (4.3 to 5.1 mmol/L) • Hyperkalaemia in last 6 months	• ≥18 years • Potassium >5.0 mmol/L
Intervention	Part A: patiromer **8.4g** to **50.4g** daily Par B Continuing patiromer	Patiromer **8.4g** to **33.6g** daily	Patiromer **30g** daily + spironolactone (RAASi)	Patiromer **8.4g** to **25.2g** daily without food
Comparator	**Placebo**	None	Placebo + spironolactone	Patiromer **8.4g** to **25.2g** daily with food
Outcomes	Change in S-K, proportion with target S-K	Change in S-K, proportion with target S-K	Change in S-K, proportion with target S-K	% with normal S-K levels, effects of food on patiromer
In economic model?	✓ Primary evidence source	✓ Source of data on stopping patiromer	✗	✗

ERG: [redacted]% had stage 2 CKD

Max licenced dose is 25.2g a day

Abbreviations: CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium

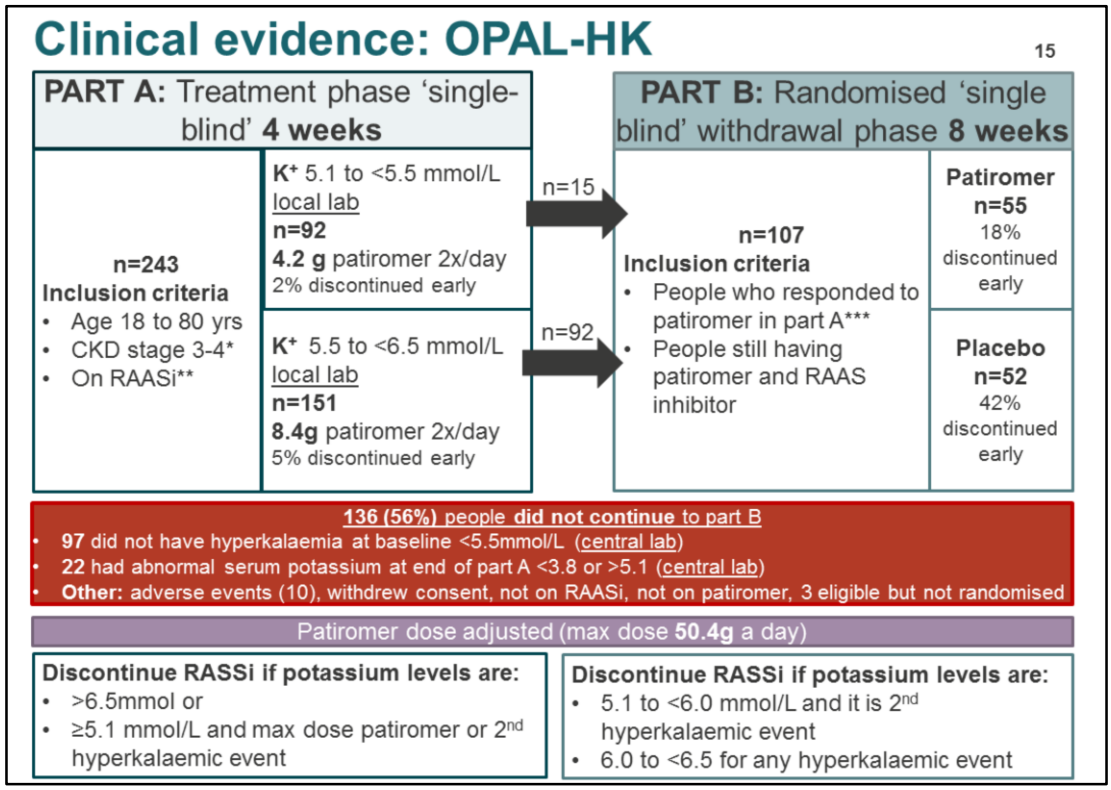
Source: Company submission document B p26 to 30

* Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, or renin antagonists.

** Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

OPAL HK summary

	Part A	Part B
Population	CKD 3 or 4 with K^+ above 5.5 mmol/l and below 6.5 mmol/l on RAAS outside of the UK	Patients who responded to patiromer during Part A
Intervention	Patiromer dosed depending on starting K^+ dosed to target range of 3.8 to <5.1 mmol/L	Continuing patiromer
Comparison	None	Placebo
Outcome	Mean change in the serum K^+ level from baseline to week 4	Change from part B baseline K^+ to either of: • week 4 visit, if patient's K^+ remained between ≥3.8 and <5.5 mmol/L up to the week 4 visit, or • earliest visit at which patient's K^+ between <3.8 and ≥5.5 mmol/L.
Exploratory Endpoint		• Time to RAAS inhibitor dose discontinuation • Proportion of patients receiving RAASi at the end of trial
Definition of 'single blind'	Consent form said patient would receive patiromer at some point, either during Part A or Part B	
Statistics	Adjusted for baseline K^+	Adjusted for diabetes and baseline K^+ (as a binary variable)



Source: company submission document B p31, p46 to 48.

OPAL-HK is a two-phase, single blind, phase III study of patiromer

*Estimated glomerular filtration rate 15 to 60 mL/min/1.73 m^2

**Angiotensin-Converting Enzyme (ACE) Inhibitor, an Angiotensin II receptor blocker (ARB), or an aldosterone antagonist (AA)

***Serum potassium ≥5.5 mmol/L at beginning Part A and 3.8 to 5.1mmol/L at the end of Part A (measured by local lab)

Discontinuation:

PART A - 219 out of 243 patients completed part A. Most common reasons for discontinuing were adverse events (n=10) and patient decision (n=5)

PART B – 74 out of 107 patients completed part B . Most common reasons for discontinuing therapy early in part B was because of high serum potassium levels (n=18) or low serum potassium levels.

Baseline characteristics: OPAL-HK and AMETHYST

- The overall baseline characteristics for part A non-responders not available
- Company use AMETHYST data (an uncontrolled dose ranging study) in economic model for patiromer discontinuation

	OPAL-HK			AMETHYST-DN
	Part A	Part B (responders)		Overall
	Overall (n=243)	Placebo (n=52)	Patiromer (n=55)	Patiromer (n=304)
Male sex, n (%)	140 (58)	30 (58)	28 (51)	192 (63.2)
Age, years*	64.2 ± 10.5	65.0 ± 9.1	65.5 ± 9.4	66.3 ± 8.6
White race, n (%)	239 (98)	52 (100)	55 (100)	304 (100)
Type 2 diabetes, n (%)	139 (57)	33 (63)	34 (62)	304 (100)
Heart failure, n (%)	102 (42)	22 (42)	27 (49)	105 (34.6)
Myocardial infarction, n (%)	60 (25)	14 (27)	18 (33)	Not reported
Hypertension, n (%)	236 (97)	50 (96)	54 (98)	304 (100)
Serum potassium (mmol/L)*	5.6 ± 0.5	5.9 ± 0.4**	5.9 ± 0.6**	5.3 ± 0.4
eGFR mL/min/1.73 m²*	35 ± 16	39 ± 20	39 ± 21	41 ± 16

*Mean ± standard deviation

**Serum potassium taken at baseline part A. At baseline part B serum potassium is 4.45 mmol/L placebo and 4.49 mmol/L for patiromer

- 100% of patients in AMETHYST-DN had diabetes, compared with 57% in OPAL-HK
- 100% of patients across both studies had white ethnic background
- 42% at OPAL-HK baseline also had heart failure in addition to chronic kidney disease

NICE Abbreviations: eGFR, estimated glomerular filtration rate

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Source: company response to clarification table 10 p13 to 14

RAAS inhibitor use was lower in AMETHYST than OPAL-HK

	OPAL-HK			AMETHYST
	Part A	Part B (responders)		Overall
	Overall (n=243)	Placebo (n=52)	Patiromer (n=55)	Patiromer (n=304)
RASSi use, n (%):	243 (100)	52 (100)	55 (100)	215 (70.7)
-ACE inhibitors, n (%)	170 (70)	38 (73)	37 (67)	150 (49)
-ARB II , n (%)	92 (38)	16 (31)	24 (44)	75 (25)
-aldosterone antagonists, n (%)	22 (9)	4 (8)	4 (7)	1 (0.3)
-renin inhibitors, n (%)	2 (1)	0	0	Not reported
-dual RASSi blockade, n (%)	41 (17)	6 (12)	10 (18)	Not reported
-receiving max doses, n (%)	106 (44)	21 (40)	21 (38)	Not reported

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Generalisability of OPAL-HK population to NHS practice

- No UK centres in OPAL-HK (24 centres in eastern Europe, 21 in the EU, 14 in USA)
- Company compared baseline characteristics in OPAL-HK with UK clinical practice research data link (CPRD) data
- The CPRD provides UK primary care data. Inclusion criteria for analysis: stage 3 to 4 chronic kidney disease OR heart failure and/or diabetes, hyperkalaemia, who were on at least one RAASi, between 2012 and 2016

	OPAL-HK Part B Placebo n=55	CPRD n=[redacted]
Male (%)	58	[redacted]
Mean age, years	65.0	[redacted]
Mean eGFR (mL/min/1.73m^2)*	39.0	[redacted]
RAASi, ACE (%)	73	[redacted]
RAASi, ARB (%)	31	[redacted]
RAASi, aldosterone (%)	8	[redacted]
Mean serum K+ (mmol/L) end of part B	5.17	[redacted]
Previous myocardial infarction (%)	27	[redacted]
Hypertension (%)	96	[redacted]
Diabetes mellitus (%)	63	[redacted]
Heart failure (%)	42	[redacted]

ERG: OPAL-HK is not representative of NHS population, CPRD patients are more likely to:
- be female
- be younger
- have fewer comorbidities (heart failure, diabetes, hypertension)

than patients in OPAL-HK

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* mL per minute per 1.73m^2 of body surface area

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor

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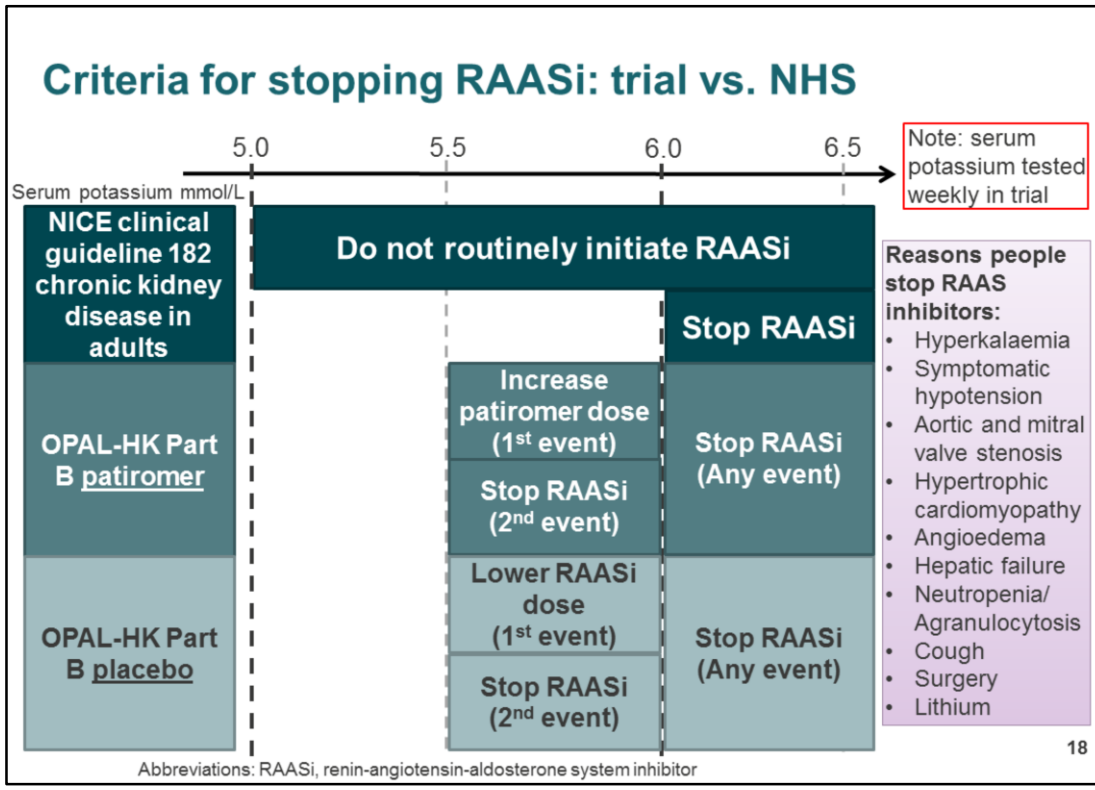
Source: Company's response to clarification p12, company submission document b p63, 90, ERG report p64


Criteria for stopping RAASi: trial vs. NHS
5.0
5.5
6.0
6.5
Serum potassium mmol/L
Note: serum potassium tested weekly in trial
NICE clinical guideline 182 chronic kidney disease in adults
Do not routinely initiate RAASi
Stop RAASi
OPAL-HK Part B patiromer
Increase patiromer dose (1st event)
Stop RAASi (2nd event)
Stop RAASi (Any event)
OPAL-HK Part B placebo
Lower RAASi dose (1st event)
Stop RAASi (2nd event)
Stop RAASi (Any event)
Reasons people stop RAAS inhibitors:
• Hyperkalaemia
• Symptomatic hypotension
• Aortic and mitral valve stenosis
• Hypertrophic cardiomyopathy
• Angioedema
• Hepatic failure
• Neutropenia/ Agranulocytosis
• Cough
• Surgery
• Lithium
18
Abbreviations: RAASi, renin-angiotensin-aldosterone system inhibitor

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OPAL-HK: ERG comments

OPAL-HK population may not be generalisable to NHS:

- [redacted]% of eligible patients had stage 2 chronic kidney disease (eligibility criteria stage 3 to 4), NHS population potentially later stage
- no formal review of hypertension management or low potassium diet before recruitment
- [redacted]% on angiotensin-converting-enzyme inhibitor and angiotensin receptor blockers, now contraindicated

→ may mean that NHS population are harder to treat than those in trial

- Majority of patients from Eastern Europe (65%), no UK sites (see slides 23/24)
- 100% white patients, no evidence for other ethnic groups
- Low concordance between local and central lab results. Central lab results showed 15 patients in mild hyperkalaemia arm (5.1 to <5.5 mmol/L as reported by local lab) had serum potassium ≥5.5 mmol/L

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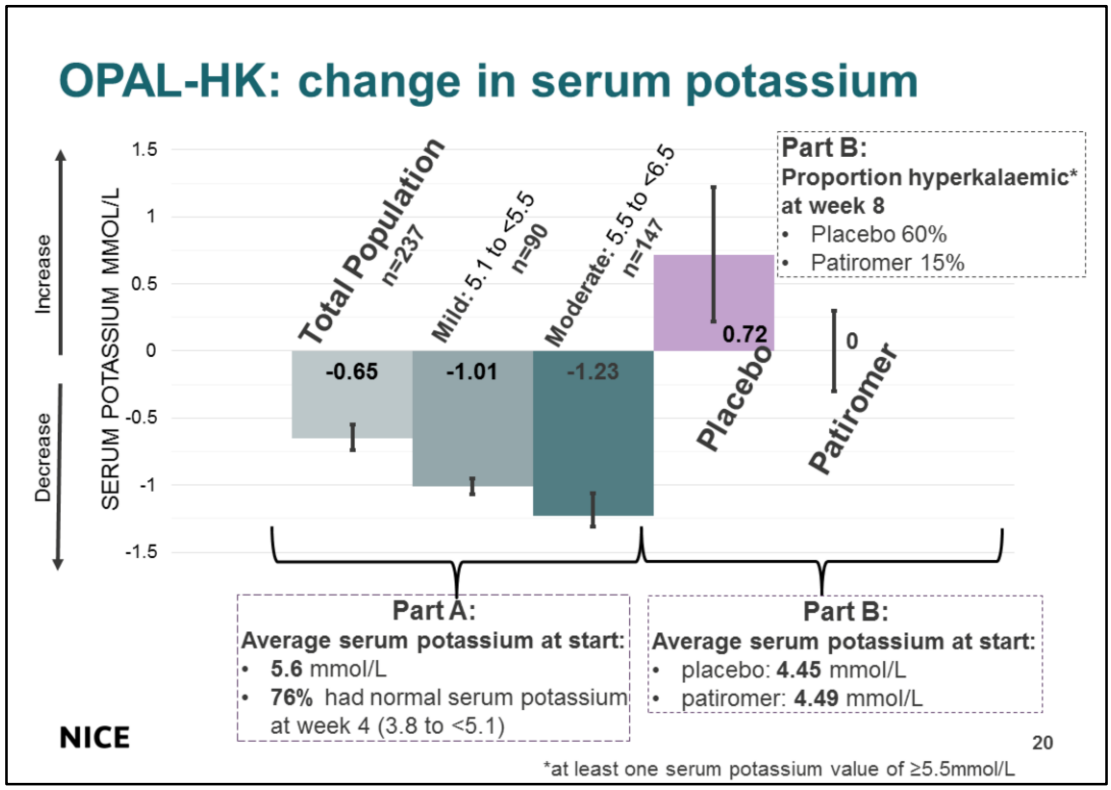

Source: Company submission document B p51

	Mild hyperkalaemia 5.1 to<5.5 mmol/L n=90	Moderate hyperkalaemia 5.5 to<6.5 mmol/L n=147	Total population n=237
Change in serum potassium from baseline to week 4, mmol/L (95% confidence interval)	-0.65 (-0.74 to -0.55)	-1.23 (-1.13 to -1.16)	-1.01 (-1.07 to -0.95)

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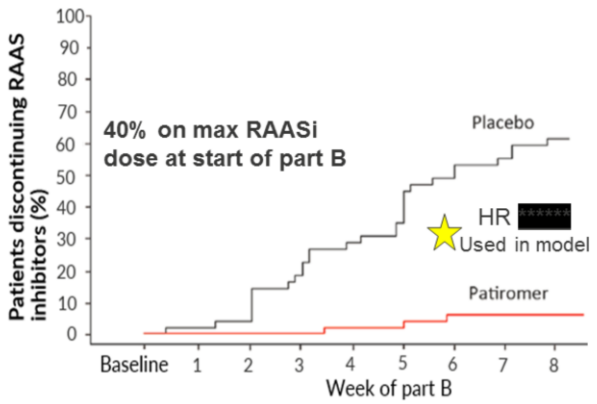
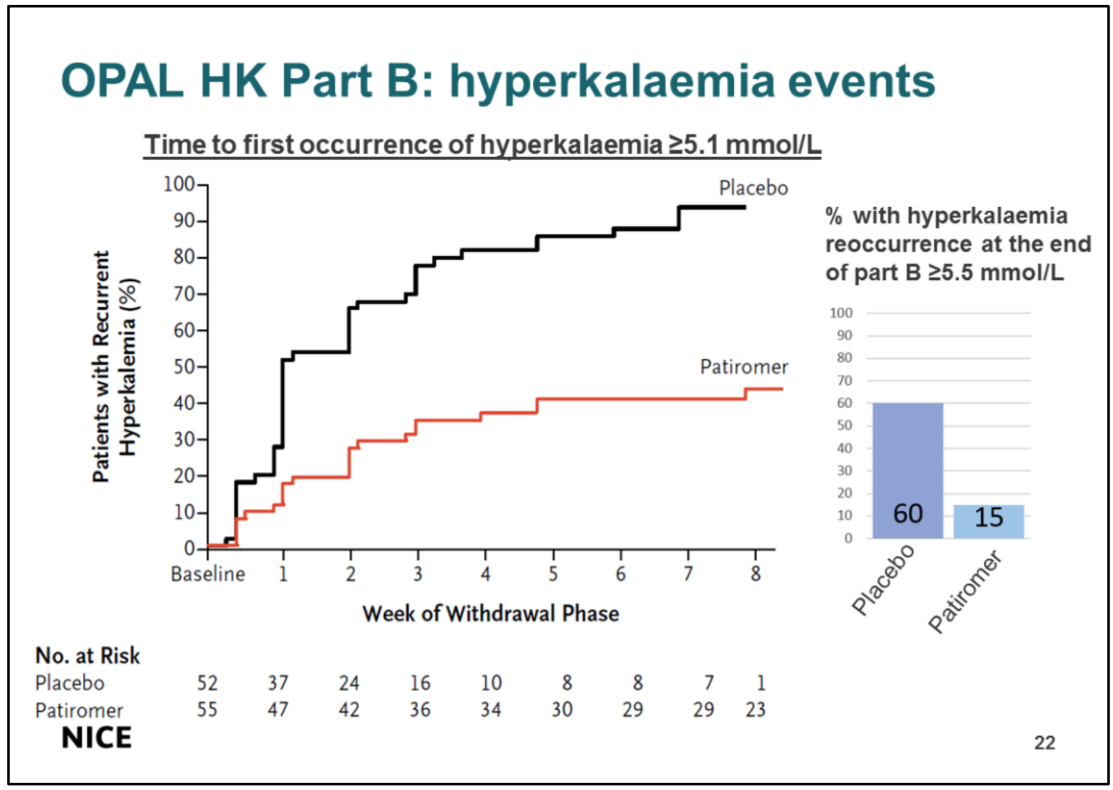
OPAL-HK Part B: % who stop RAASi exploratory endpoint



	Placebo (n=52)	Patiromer (n=55)
RAASi discontinuation because of hyperkalaemia	56%	6%
Requiring management of recurrent hyperkalaemia i) **placebo arm**: RAAS inhibitor dose reduction or discontinuation ii) **patiromer arm**: increase dose of patiromer or discontinue RAAS inhibitor.	62%	16%
Modifying dose of RAASi because of recurrent hyperkalaemia	66%	6%
Still receiving RAASi therapy at the end of Part B ☆	MODEL 44%	MODEL 94%

Source: Company submission document B p58 to 62

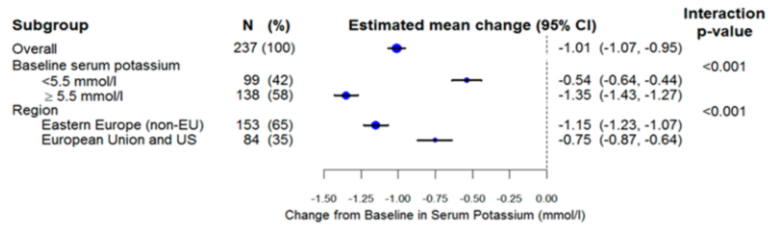


Source: Company submission document b page 57 figure 6b

OPAL-HK subgroups: change in serum potassium

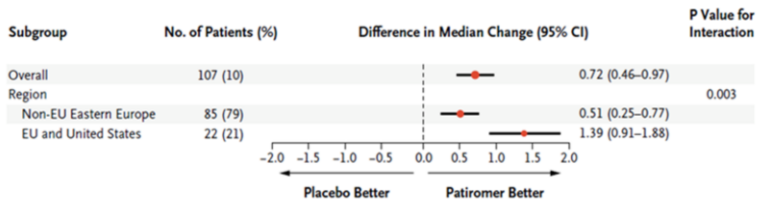
Part A: change in serum potassium from baseline to week 4

- No statistically significant difference: diabetes, heart failure, max RAASi, sex, age >65
- **Statistically significant difference for baseline serum potassium <5.5 and by region**



Part B change in serum potassium from baseline to week 4

- No statistically significant difference: diabetes, heart failure, serum potassium >5.8 mmol/L, max RAASi, sex, age >65
- **Statistically significant difference by region**



ERG: OPAL-HK had majority (65%) Eastern European patients who had a different health profile to Europe and US and showed a significantly higher reduction in K^+ levels (see next slide)

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Source: Company submission appendices p47 and p52, company submission document b p63 to 64

Pre-specified subgroups in OPAL-HK

- Patients with chronic heart failure
- Patients with type 2 diabetes
- Baseline serum potassium <5.5 mmol/L and ≥5.5 mmol/L
- Patients receiving maximal or submaximal RAASi dose
- Male or female
- Age <65 or ≥ 65 years
- Geographical region (EU and USA versus non-EU and Eastern Europe)
- No randomised evidence for people with mild hyperkalaemia (5.1 to <5.5mmol/L) or non-responders (56% of recruited population)

Chronic heart failure –

- 100% receiving patiromer in part B were receiving RAASi therapy at week 8 compared with 94% in the total trial population

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Baseline characteristics: OPAL-HK by region

- Myocardial infarction, hypertension, type of RAAS inhibitor and type of non-RAAS inhibitor diuretic were not reported by region
- Proportions were similar for gender, age and type 2 diabetes
- Estimated glomerular filtration rate higher in Eastern Europe than EU and US
- More patients received maximum RAASi dose in EU and US than Eastern Europe

	Placebo EU/US n=**	Patiromer EU/US n=**	Placebo E. Europe n=**	Patiromer E. Europe n=**
Heart failure, n (%)	*****	*****	*****	*****
Serum potassium (mmol/L)	*****	*****	*****	*****
Estimated GFR (mL/min/1.73 m²)	*****	*****	*****	*****
Receiving maximal RAASi, n (%)	*****	*****	*****	*****

ERG comments:

- Time to hyperkalaemia is faster for EU/US patients
  - likely to be due to differences in baseline characteristics, therefore relative effectiveness according to region is likely to be similar
- EU/US subgroup more generalisable to UK
- Use of estimates from whole population in company's economic model is likely to overestimate the benefit of patiromer

Source: Company response to clarification p13

Adverse event data - not used in economic model

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- **Company:** direct systemic toxicities not expected because patiromer is not absorbed
- Company pooled OPAL-HK and AMETHYST-DN adverse events data
- **ERG:** pooling of OPAL-HK and AMETHYST-DN safety data inappropriate because studies had different: designs, primary endpoints, patiromer doses, inclusion criteria, study length and hyperkalaemia cut-offs
  - safety findings are inconclusive because of short duration of study, low numbers of patients, high proportion with adverse events

	OPAL-HK			
	Part A	Part B (N=107)		
	Patiromer (n=243)	Placebo (n=52)	Patiromer (n=55)	Pooled data (N=547)
≥1 adverse event, n (%)	114 (47)	26 (50)	26 (47)	340 (62)
Adverse event leading to treatment discontinuation, n (%)	15 (6)	1 (2)	1 (2)	51 (9)
Constipation, n (%)	26 (11)	0	2 (4)	45 (8)
Diarrhoea, n (%)	8 (3)	0	2 (4)	27 (5)
Nausea, n (%)	8 (3)	0	2 (4)	14 (3)
Chronic renal failure, n (%)	7 (3)	1 (2)	1 (2)	35 (6)
Hypomagnesaemia, n (%)	8 (3)	2 (4)	1 (2)	35 (6)
Hypertension, n (%)	4 (2)	3 (6)	0	28 (5)
Anaemia, n (%)	7 (3)	0	1 (2)	18 (3)
Headache, n (%)	2 (1)	4 (8)	2 (4)	12 (2)
Supraventricular extrasystoles, n (%)	1 (<1)	1 (2)	2 (4)	10 (2)

Source: Company submission document B p64 to 73

100% of patients enrolled in AMETHYST-DN had diabetes and it was a dose ranging study

AMETHYST-DN was 52 weeks and OPAL-HK was 12 weeks

Ongoing study: AMBER

Study assessing the ability of patiromer to allow RAASi (spironolactone) dose optimisation

Estimated completion date May 2019, n~290

Study design	Phase II, randomised, placebo controlled, double-blind Screening period 4 weeks, treatment period 12 weeks, follow up 2 weeks
Population	• ≥18 years • **Uncontrolled high blood pressure**[a] • Taking ≥3 anti-hypertensives (one a diuretic) • Stage 3 to 4 chronic kidney disease[b] • Normal serum potassium levels[c]
Intervention	Patiromer 8.4g once daily + spironolactone (RAASi)
Comparator	Placebo + spironolactone (RAASi)
Outcomes	**Primary**: proportion remaining on spironolactone **Secondary**: change in systolic blood pressure

[a] Change in systolic blood pressure by automated office blood pressure measurements
[b] Estimated glomerular filtration rate of 25 to 45 ml/min/1.73m^2
[c] Serum potassium 4.3 to 5.1 mmol/L measured at least 3 times during screening

NICE Abbreviations: RAASi, renin-angiotensin-aldosterone system inhibitors

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Source: Company submission document B p73 to 74, clinicaltrials.gov [accessed: September 2018, https://clinicaltrials.gov/ct2/show/NCT03071263]

Key issues: cost effectiveness

- Company's economic model:
  - Assumes patients not on RAASi have no active treatment for hypertension
  - Applies initial RAASi discontinuation in line with OPAL trial, extrapolated using CPRD data
    - a greater proportion of patients discontinue RAASi in the placebo arm of OPAL-HK than expected in NHS practice
  - May overestimate the risk of developing end stage renal disease may, taken from data for people with CKD stage 3-5
  - May double count benefits of being on RAASi by including an effect for mortality as well as slower progression to end stage renal disease
  - Sensitive to changes in the assumption progression to end stage renal disease (different depending if on/off RAASi)
    - no evidence to show that patiromer delays progression to ESRD
    - no evidence to show that patiromer allows people to stay on optimal RAASi dose
  - Uses a hazard ratio estimate for RAASi discontinuation on patiromer based on data from OPAL-HK 8 week trial to extrapolate over a life time horizon
- Sensitive to changes in data source for patiromer discontinuation

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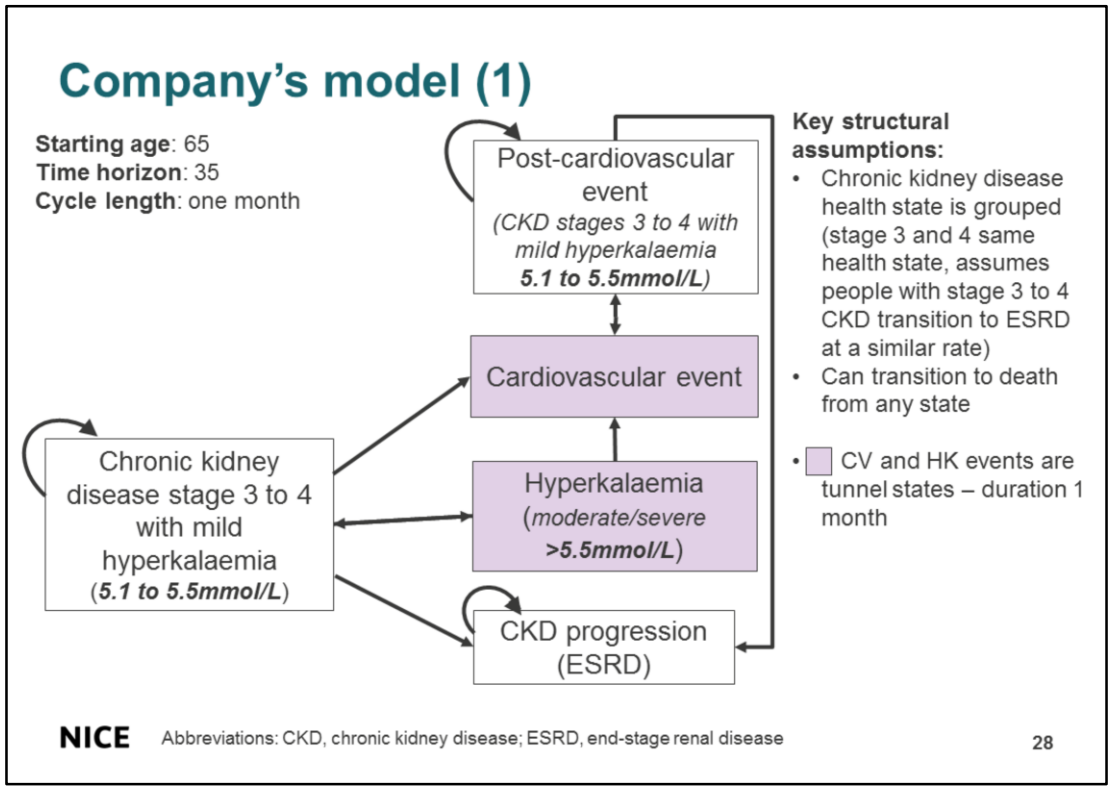
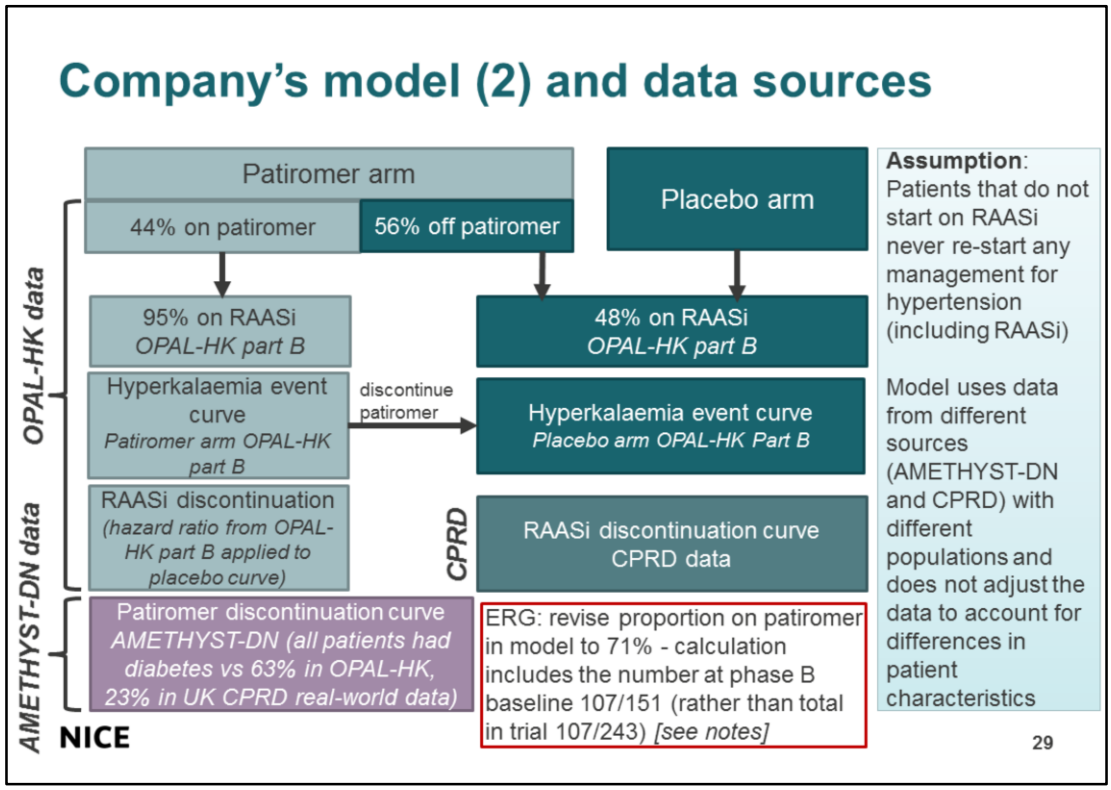


Source: Company submission document B p83



Part A of OPAL-HK included people with mild hyperkalaemia so it would be impossible for them to meet criteria for response and to enter part B. The effect of basing the proportion on patiromer as a percentage of participants at the part B baseline is that a higher proportion are on patiromer at start of model leading to higher QALYs and higher costs in patiromer arm, but both change proportionately, so this has little effect on ICER

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Key model inputs and assumptions (1)

Parameter	Company approach	ERG comment
Starting RAASi	From **OPAL-HK part B** • Patiromer arm: 69% (pooled value for patiromer responders/ non-responders) • Placebo arm: 48%	• RAASi management in trial does not reflect clinical practice (slide 18) • 56% on placebo discontinued in 8 weeks vs. 25% over 3 years in CPRD data • CPRD data better reflects NHS • 100% should start on RAASi, as in trial
Stopping RAASi	• Placebo arm: CPRD data extrapolated using Weibull curve	
	• Patiromer arm: Hazard ratio applied to **CRPD** data from **OPAL-HK** [redacted] (company justification – OPAL-HK only data in CKD 3 to 4)	• Patiromer arm: Calculate HR of [redacted] (see slide 32)
Hypertensive treatment after stopping RAASi	Company assume no anti-hypertensive treatment after stopping RAASi	• Unlikely to reflect NHS • People get another antihypertensive

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Key model inputs and assumptions (2)

Parameter	Company approach	ERG comment
Stopping patiromer	AMETHYST-DN data extrapolated using lognormal curve (best statistical fit). All patients in AMETHYST-DN have diabetes compared with 63% in OPAL-HK and 23% in CPRD	Prefer AMETHYST-DN extrapolated using **Weibull** curve. Results are sensitive to changes in data source, scenario analysis using data from OPAL-HK provided.
Time to hyperkalaemia	OPAL-HK extrapolated using log-normal curve (best statistical fit) Patients who stop patiromer have same risk as placebo arm	Explore scenario analyses looking at waning of treatment effect on time to hyperkalaemia
Adverse events	Not included in model	No long term safety data
Quality of life	ESRD quality of life decrement -**0.321** Lee et al 2005	Company overestimates decrement for ESRD, ERG base case -**0.263** Clarke et al. 2002

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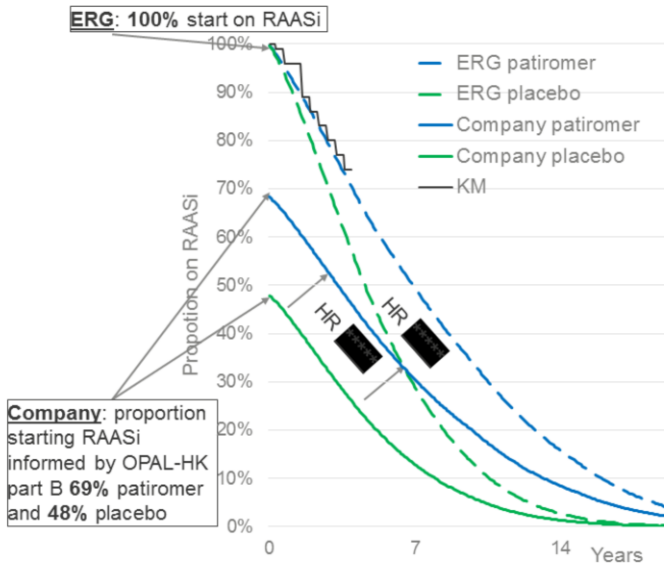
RAASi discontinuation



ERG & company:

- **Placebo** curve: **CPRD** data extrapolated using **Weibull**
- **Patiromer** curve: hazard ratio calculated using **OPAL-HK** data (n=30)
- **ERG comment**:
  - Company MAY have assumed informative censoring in the placebo arm and non-informative censoring in the patiromer arm
    - hazard ratio [redacted]
  - **ERG** calculated hazard ratio using non-informative censoring, assuming 3/30 patients who discontinued RAASi in placebo arm were censored.
    - ERG hazard ratio [redacted]

NICE Abbreviations: HR, hazard ratio

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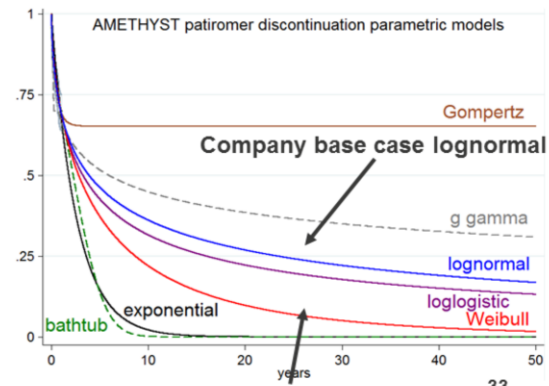
Patiromer discontinuation

- Company uses AMETHYST-DN instead of OPAL-HK for patiromer discontinuation because: larger number of patients, longer follow up
- ERG: substantial number continue taking patiromer until death using the lognormal model
  - **Weibull model more plausible**
- **ERG:** AMETHYST-DN is uncontrolled trial, with significant differences in trial population compared with OPAL-HK. Using data from OPAL-HK would reduce benefit from patiromer (ERG scenario analysis)

[redacted]



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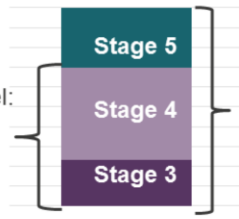
Baseline risk of events: off RAASi

Proportion of patients with CKD by stage



Used in **ERG** economic model: Probability of transitioning to ESRD **0.39%**

Used in **company** economic model: Probability of transitioning to ESRD **1.4%**

Landray et al. 2010	Chronic kidney disease			
	Stage 3	Stage 4	Stage 5	Pooled
Patients, n	88	178	116	382
End stage renal disease				
Patient years	560	837	173	1,571
ESRD, n	9	80	101	190
Annualised (%)	1.7	11.9	74.6	15.4
Monthly (%)	0.1	1.1	10.8	1.4

ERG comment:

- The company have over estimated the baseline transition probability from CKD to ESRD
  - did not adjust for differences in population characteristics - Landray et al. (CKD stage 3 to 5) OPAL-HK (CKD stage 2*, 3 and 4, ratio 11:48:41)
- Adjusting for differences in the populations changes the monthly probability from 1.4% to **0.39%** because rate from CKD5 to ESRD much higher than from other stages

- ERG correction: Company applied daily probabilities for hyperkalaemia events to a monthly cycle
- Company included baseline risk for a wide range of events. ERG restrict to stroke and myocardial infarction for consistency with quality of life and costs included in model

NICE Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease
* ERG assumed transition probability from stage 2 to ESRD of 0

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Source: ERG report p97 to 98

Relative risk of events: on RAASi

- Relative risks applied to baseline risk for people on RAASi taken from Xie et al.
  - Systematic review and network meta-analysis evaluating RAASi (ACE and ARBs) compared with placebo or active controls
  - 119 trials, 64,768 patients, patients with chronic kidney disease (any stage)
  - ERG comments:included trials mainly scored low for bias

ERG

- Including relative risks for all cause mortality introduces double counting
  - already includes benefit of being on RAASi by avoiding increased mortality risk from cardiovascular events and end stage renal disease
- ERG set to unity (1.00) to avoid double counting

		ESRD	Cardiovascular event	Cardiovascular death	Death
Company submission	vs Placebo	0.64	0.82	0.88	0.87
ERG	**vs Active**	0.68	0.92	0.82	0.74

ERG

- Patients with chronic kidney disease would have another treatment for hypertension when discontinuing RAASi
- More appropriate to calculate relative risks based on an active comparator

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Utilities

- No quality of life data in OPAL-HK, company uses values from different sources

ERG:

- Where possible use UK prospective diabetes study (UKPDS) quality of life values
  - prefer to take **utilities from a common source** that provides data for the relative effect of quality of life, so that effects of events are consistent for the population
    - high proportion of people in OPAL-HK had diabetes (63%)
    - used in previous NICE appraisals (TA418, 390, 336, 315, 288, 151)

	ERG	Company	
	UKPDS	Event	Post-event
No event	0.785	0.774	0.774
Decrements			
Myocardial infarction	-0.055 (-7%)	-0.204 (-26%)	-0.140 (-18%)
Stroke	-0.164 (-21%)	-0.285 (-37%)	-0.279 (-36%)
End stage renal disease	-0.263 (-34%)	-0.321 (-41%)	-0.321 (-41%)

- ERG revised quality of life for cardiovascular events
  - company uses 6 month values from Pockett et al. and weights stroke and myocardial infarction events based on Kerr et al. (35:65)
  - ERG prefer values from a later time point (24 months), more appropriate for extrapolation
  - balance between stroke and myocardial infarction events in line with company approach for 1st events, subsequent events use Pockett et al. (15:85)

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TA418 Dapagliflflozin in triple therapy for treating type 2 diabetes

TA390 Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes

TA336 Empagliflozin in combination therapy for treating type 2 diabetes

TA315 Canagliflflozin in combination therapy for treating type 2 diabetes

TA288 Dapagliflozin for the treatment of type 2 diabetes

TA151 Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus

Resource use

- ERG include prescribing cost for patiromer
  - £5, based on 10 minutes pharmacist time PPSRU unit cost for Band 6 staff
  - expert opinion suggested patiromer would be dispensed from a hospital pharmacy
- Company submission assumes 100% hyperkalaemic events result in hospitalisation at a cost of £1,386 (cost per event based on inpatient stay)

ERG:
•Apply probability of hospitalisation in line with cited paper 24.3%
•Revise costs of hospitalisation because of hyperkalaemic events to reflect expert opinion
  - 2 outpatient appointments (£153 per appointment from 2017 NHS reference costs, consultant led) and ongoing chronic kidney disease costs

- Company applies 56% discount for patiromer costs (to reflect 56% people discontinuing patiromer) twice

ERG:
- double application of the discount is invalid and underestimates patiromer costs by 56% - means only 20% of patients in patiromer arm incur cost of treatment

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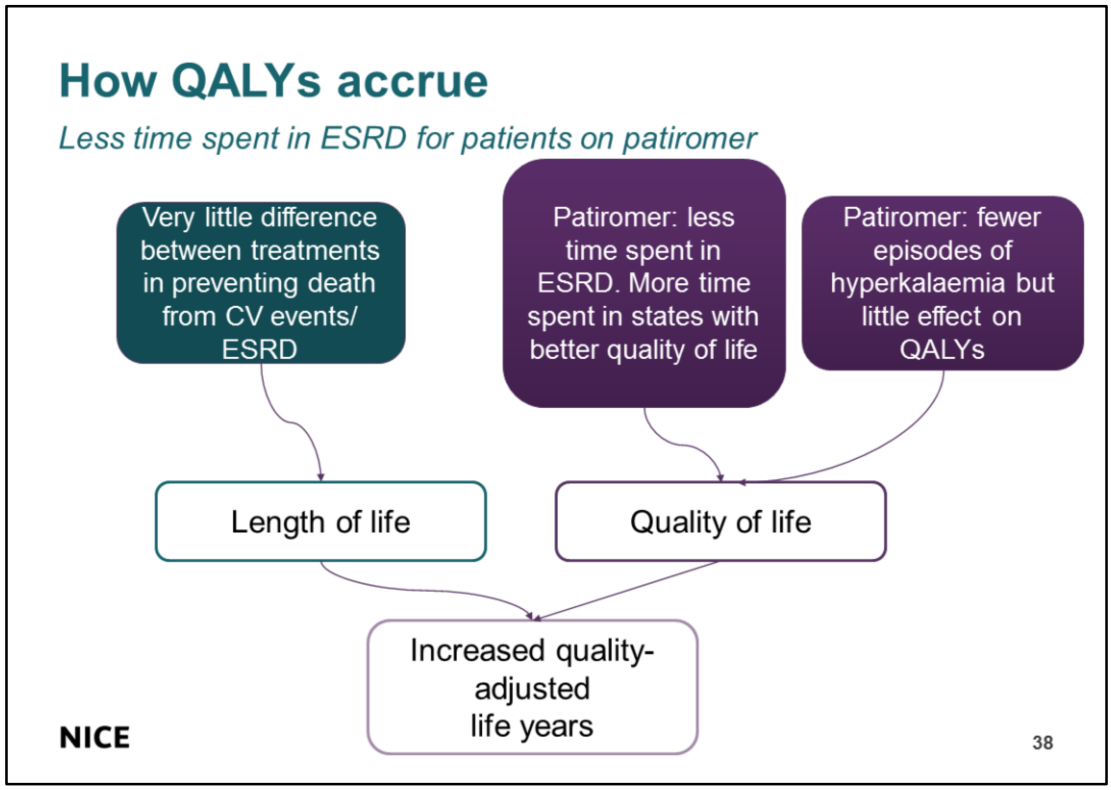
How QALYs accrue
Less time spent in ESRD for patients on patiromer
Very little difference between treatments in preventing death from CV events/ ESRD
Patiromer: less time spent in ESRD. More time spent in states with better quality of life
Patiromer: fewer episodes of hyperkalaemia but little effect on QALYs
Length of life
Quality of life
Increased quality-adjusted life years
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QALYs by health state

QALY gains in the patiromer arm are driven by additional time spent in the chronic kidney disease health state

NICE Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ESRD, end stage renal disease 39

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Company summary of costs by category

[redacted]

Differences in cost are mostly driven by end stage renal disease health state costs (CKD progression)

NICE Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ESRD, end stage renal disease; HK, hyperkalaemia

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Company base case (deterministic)^

	Treatment	Total			Incremental			ICER (£/QALY)
		LYG	Cost	QALY	LYG	Cost	QALY	
Company base case	Placebo	[redacted]	[redacted]	[redacted]	-	-	-	**Patiromer dominant**
	Patiromer	[redacted]	[redacted]	[redacted]	0.11	-£1,505	0.10	
Company base case corrected for errors identified by ERG*	Placebo	[redacted]	[redacted]	[redacted]	-	-	-	**Patiromer dominant**
	Patiromer	[redacted]	[redacted]	[redacted]	0.11	-£572	0.10	

*Errors:
1) 56% patiromer price discount
2) Probabilities applied for hyperkalaemia incorrect (daily applied instead of monthly)

^probabilistic and deterministic estimates broadly aligned but ERG notes there are some uncertainties in the probabilistic modelling, so only deterministic results are reported here

NICE Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

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Source: ERG report p119, company submission document b p122

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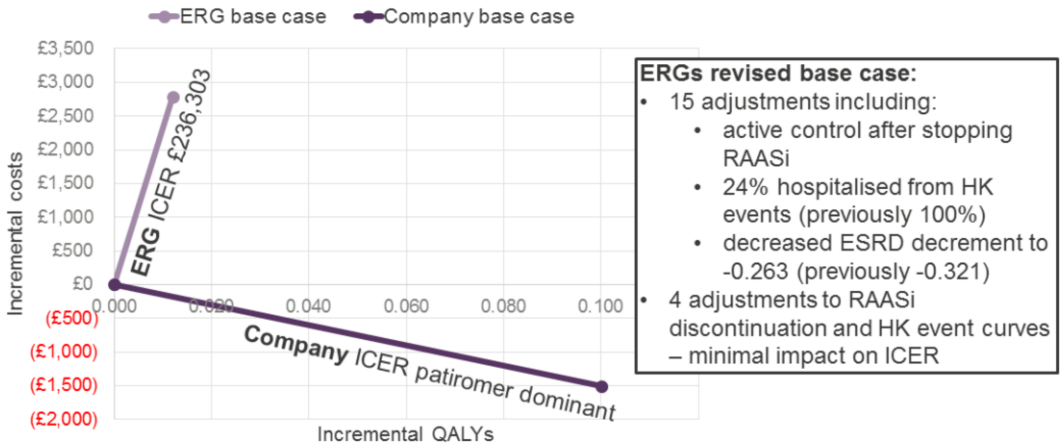
ERG base case (deterministic)

	Treatment	Total			Incremental			ICER (£/QALY)
		LYG	Cost	QALY	LYG	Cost	QALY	
ERG	Placebo	[redacted]	[redacted]	[redacted]	-	-	-	£236,303
	Patiromer	[redacted]	[redacted]	[redacted]	0.009	£2,787	0.01	



ERGs revised base case:

- 15 adjustments including:
  - active control after stopping RAASi
  - 24% hospitalised from HK events (previously 100%)
  - decreased ESRD decrement to -0.263 (previously -0.321)
- 4 adjustments to RAASi discontinuation and HK event curves – minimal impact on ICER

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Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

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Source: ERG report p119, company submission document b p122

ERG's base case adjustments (deterministic)

	Δ QALYs	Δ Costs	ICER
Company base case (corrected for 2 major errors slide 41)	0.10	-£572	Dominant
1) Active control after stopping RAASi (slide 35)	0.12	£2,310	£18,659
2) RAASi discontinuation: ERG's HR (slide 32)	0.10	-£565	Dominant
3) RAASi does not impact 'other cause' mortality (slide 35)	0.07	-£1,285	Dominant
4) CKD and ESRD cost revisions (as per clarification response)	0.10	-£328	Dominant
5) Baseline probability of ESRD reflects CKD 2 to 4 (slide 34)	0.09	£1,092	£11,796
6) Baseline CV event probability matches cited paper	0.10	-£608	Dominant
7) CV event probability reflects MI/stroke (slide 34)	0.10	-£588	Dominant
8) Proportion hospitalised for HK = 24.3% (slide 37)	0.10	-£62	Dominant
9) ESRD quality of life decrement to -0.263 (slide 36)	0.09	-£572	Dominant
10) Corrected error in CV events quality of life value (slide 36)	0.10	-£572	Dominant
11) Quality of life values relative to general population	0.10	-£572	Dominant
12) No half cycle correction for patiromer cost and added prescribing cost (£5) (slide 37)	0.10	-£250	Dominant
13) Phase A response proportion (slide 29)	0.16	-£1,060	Dominant
All the above revisions	0.07	£2,594	£38,905
Apply ERG curves*	0.06	£640	£10,520
Proportion on RAASi at start of model = 100%* (slide 32)	0.02	£4,806	£246,862
ERG base case (all above revisions)	0.01	£2,787	£236,303

NICE *includes 13 revisions from above

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ERG scenario analyses (deterministic)

- **ERG scenarios:**
  1. RAASi discontinuation curves estimated using OPAL-HK data (previously CPRD)
     - Analysis uses individual curves from OPAL (no need to apply a hazard ratio)
  2. Patiromer discontinuation curve estimated using OPAL-HK data (previously AMETHYST)
     - reduces benefit from patiromer because reduces time on patriomer
  3. ERG: unreasonable to apply hazard ratio for RAASi discontinuation from an 8 week trial to a 35 year time horizon in the model, explores scenarios on waning of treatment effect
     a) treatment effect wanes over 3 years
     b) treatment effect wanes over 5 years

	Δ QALYs	Costs	ICER
ERG revised base case	0.01	£2,787	£236,303
1) ERG estimated OPAL-HK RAASi discontinuation curves	0.01	£2,761	£227,403
2) ERG estimated OPAL-HK patiromer discontinuation curve	0.002	£1,074	£681,235
3a) Waning of treatment effect on hyperkalaemia events linearly over 3 years	0.01	£3,712	£371,095
3b) Waning of treatment effect on hyperkalaemia events linearly 5 years	0.01	£3,466	£330,461

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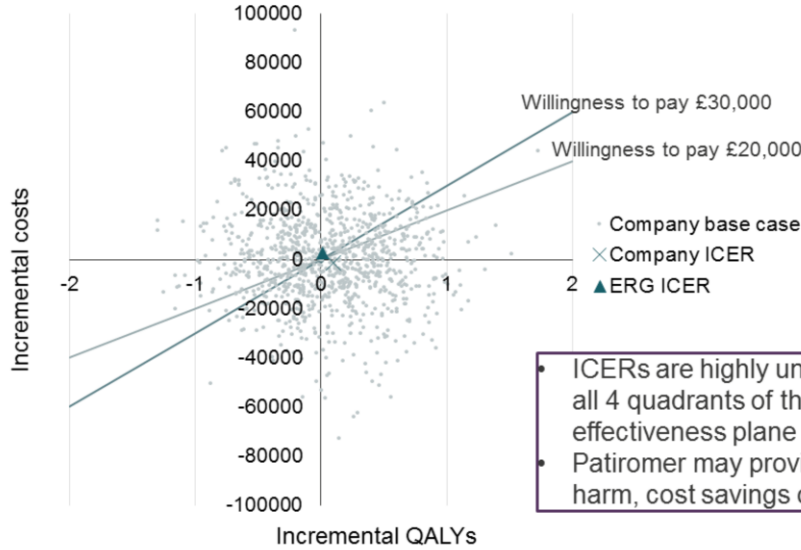
Probabilistic results company and ERG base case



- ICERs are highly uncertain and span all 4 quadrants of the cost-effectiveness plane
- Patiromer may provide benefit or harm, cost savings or additional costs

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Innovation

- Company: first commercialised medicine from Relypsa's polymer technology platform
- Novel treatment option for chronic hyperkalaemia
- Renal association: 'ability to relax diet from a patient perspective is a potential gain not captured by the QALY, including benefits from less malnutrition'

Equality and diversity

- ERG identified that OPAL-HK includes 100% white patients
- Initial view is that this is not an equalities issue, but about whether results of the trial are generalisable to the NHS (see slides 16 and 17)

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Authors

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with input from the Lead Team: Mona Johnson, Christopher O'Regan, Nigel Westwood and Chair, Amanda Adler

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Patiromer for treating hyperkalaemia (ID877)

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
Patiromer_ID877_B1-4_02Sep18	**3.0**	**Yes**	**3rd September 2018**

Contents

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Abbreviations

Abbreviation	
AA	Aldosterone antagonist
ACE	Angiotensin-converting-enzyme
ACEIs	Angiotensin-converting enzyme inhibitors
AEs	Adverse effects
AIC	Akaike information criterion
ANOVA	Analysis of variance
AOBP	Automated office blood pressure
ARBs	Angiotensin II receptor blockers
BIC	Bayesian information criterion
BID	Twice daily
BNF	British national formulary
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CHF	Comorbid chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
CPI	Consumer price index
CPRD	Clinical Practice Research Datalink
CPS	Calcium polystyrene sulphonate
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EPAR	The European Public Assessment Report
EPO	Erythropoietin
EQ-5D	EuroQol-5D
ESA	Erythropoiesis-stimulating agent
ESC	European Society of Cardiology
ESRD	End-stage renal disease
EU	European Union
GBP	British Pound
GFR	glomerular filtration rate
GI	Gastrointestinal
HD	Haemodialysis
HK	Hyperkalaemia
HR	Hazard ratios
HRQL	Health-related quality-of-life
HSU	Health state utilities

ICER	Incremental cost-effectiveness ratio
IP	Investigational product
IPD	Individual patient level data
ITT	Intention-to-treat
IWRS	Interactive Web Response System
K+	Potassium
KM	Kaplan-Meier
LYG	Life years gained
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MIMS	Monthly Index of Medical Specialties
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
PAS	Patient access scheme
PD	Peritoneal dialysis
PH	Proportional hazards
PP	Per protocol
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
Q1	25th percentile
Q2	50th percentile
Q3	75th percentile
QALYs	Quality-adjusted life years
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin-angiotensin-aldosterone system inhibitors
RR	Relative risk
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SOC	System organ class
SPS	Sodium polystyrene sulphonate
SRB	Safety Review Board
STA	Single technology appraisal
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event

UK	United Kingdom
US	United States
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The technology, patiromer (Veltassa®), is a novel, next-generation, non-absorbed, sodium-free, cation-exchange polymer that binds excess potassium in the lumen of the gastrointestinal tract and increases faecal potassium excretion for the treatment of hyperkalaemia in adult patients. Veltassa is indicated in Europe for the treatment of hyperkalaemia in adults.

The submission is focused on the use of patiromer in patients with stage 3–4 chronic kidney disease (CKD) on renin–angiotensin–aldosterone system (RAAS) inhibitor treatment with hyperkalaemia. This proposed patient population is narrower than the marketing authorisation because the evidence base on patiromer is focused on this population. The decision problem is summarised in Table 1.

Table 1. The decision problem

		Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population		Adults with hyperkalaemia	Adult patients with stage 3-4 chronic kidney disease (and other co-morbidities such as heart failure and diabetes) and hyperkalaemia treated with RAASi therapy	The safety and efficacy of patiromer were demonstrated in hyperkalaemic patients with chronic kidney disease (CKD) on stable doses of at least one renin–angiotensin–aldosterone system (RAAS) inhibitor.
Intervention		Patiromer	Patiromer (Veltassa)	N/A
Comparator		Standard care. This includes a low-potassium diet with or without agents that reduce levels of potassium in the body	The main comparator in the submission is discontinuation or dose modification of RAAS inhibitor therapy. The final matrix lists no other companies with relevant comparators. The 'response to consultee and commentator comments on the draft remit and draft scope (pre-referral)' document also confirms that NICE have amended the comparators to "take out reference to pharmacological treatments" in defining comparators to Veltassa®	There is currently no appropriate pharmacological comparator for the long-term treatment of recurrent hyperkalaemia in adults. In consultation with the Regulatory Authorities, it was agreed that the pivotal OPAL-HK study would not include an active comparator for ethical and clinical practice reasons. A variety of measures are used to manage hyperkalaemia clinically, including discontinuation of hyperkalaemia-inducing drugs such as RAAS inhibitors, diuretics, diet change, bicarbonates and potassium (K^+) binders (1-4). The cation exchange resins, sodium polystyrene sulphonate [SPS; Kayexalate®] and calcium polystyrene sulphonate [CPS; Sorbisterit®] are known to lower K+ levels in the acute setting, however, their transient effect on serum K+, limited long-term data (5), risk of serious gastrointestinal adverse events (AEs) and sodium load precautions (6)

				prevent their use for the management of chronic hyperkalaemia. Indeed, calcium and sodium polystyrene sulfonate are contraindicated for treating patients with a serum potassium < 5.0 mmol/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing (5). As a result of these issues, it is unlikely that either diet or SPS/CPS would be used in the key population of interest i.e. CKD patients managed on RAASi therapy. In addition, the Summary of Product Characteristics (SmPC) for Resonium A and Calcium Resonium state the licenced indication as for "the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis"(6, 7). In addition, low K+ diet is included in the scope as a comparator, however, is unlikely to be used widely because its value in the management of potassium levels is limited due to the difficulties in changing dietary habits and the prevalence of K+-rich foods making long-term adherence problematic (2). A comparison with sodium bicarbonate will not be addressed in the submission as this sub-group population was not included in

				patiromer trials. Vifor request that this comparison is removed from the scope. The European Public Assessment Report (EPAR) for Veltassa confirms the approach taken to determine relevant comparators in this submission. It highlights that for patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of RAASi therapies, the traditional approach has relied on dietary restriction and RAASi dose reduction or discontinuation, diuretics, oral bicarbonate or cation exchange resins (SPS/CPS) (5). However, it also states the difficulties in diet modification due to the ubiquitous presence of potassium in foods and the lack of rigorous long-term safety and efficacy data for SPS/CPS. Issues with poor tolerance and life-threatening side effects including intestinal necrosis with the cation-exchange resins are also of concern. Further SPS should be administered with caution in patients who cannot tolerate even small increases in sodium load due to the effect of appreciable sodium load. These issues make long-term use of these agents difficult. The favourable effects observed with Veltassa were considered important as currently there is an unmet need for safe and efficacious treatment of hyperkalaemia.

Outcomes		The outcome measures to be considered include: • serum potassium level • use of renin–angiotensin–aldosterone system inhibitor therapy • mortality • time to normalisation • adverse effects of treatment • health-related quality of life.	Serum potassium levels: • **Mean change in serum potassium levels from baseline to week 4.** • **Proportion of patients who achieved target potassium levels (3.8–<5.1 mmol/L)** • Difference between patiromer and placebo in the median change in serum K+ level at the start of the phase to week 4 or the earliest visit at which the K+ level was <3.8 mmol/L or ≥5.5 mmol/L • Proportion of patients with a recurrence of hyperkalaemia (≥5.1 or ≥5.5 mmol/L) • Following exploratory endpoints are reported: 1) time to 1st recurrent hyperkalaemia; 2) proportion of patients requiring an intervention due to recurrent hyperkalaemia at any time; 3) **time to RAAS inhibitor dose discontinuation** Use of renin-angiotensin-aldosterone system inhibitor therapy: • Proportion of patients who required RAAS inhibitor dose reduction or discontinuation due to recurrent hyperkalaemia. • Exploratory endpoints included: time to RAASi dose discontinuation; and	Time to normalisation and health-related quality of life (HRQoL) were not measured in the included trials. However, the impact HRQoL was included in the economic model by a systematic literature search of relevant utilities.

			proportion of patients receiving any dose of RAASi at the end of this phase. Mortality is reported as a safety endpoint Adverse effects are also reported. Events of interest were: • Hypokalaemia (serum K+ < 3.5 mmol/L) • Serum K+ ≥ 5.5 mmol/L • Hyperkalaemia-associated ECG changes • Hypokalaemia-associated ECG changes • Gastrointestinal AEs • Potential allergic reactions • Changes in serum calcium, magnesium, phosphorous and fluoride • AEs resulting in change of dose • AEs resulting in addition of concomitant therapy (e.g., magnesium supplement for hypomagnesemia) • Worsening renal function: o ≥ 100% increase in serum creatinine from baseline; or o >50% decrease in eGFR	

			from baseline • AE profile in subjects maintained on RAASi therapy versus those who have stopped RAASi therapy	
Subgroups to be considered		If the evidence allows the following subgroups will be considered: • people with acidosis • people with acute hyperkalaemia • people with chronic kidney disease • people with heart failure	Pivotal OPAL-HK trial enrolled patients with chronic kidney disease with hyperkalaemia. Pre-specified sub-groups in OPAL-HK are: • Type 2 diabetes mellitus (n=67) • Heart failure • Serum potassium level o <5.8mmol/L o ≥5.8mmol/L • Maximal dose of RAAS inhibitor • Sex • Age o <65 years o ≥65 years • Region o Non-EU Eastern Europe o EU and United States	Patients with acidosis were not included in the patiromer trials. Given the small number of patients entering the Withdrawal phase in OPAL-HK (patiromer n=55, placebo n=52) sub-group analysis were not performed and the economic analysis is based on the whole trial population

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Patiromer (Veltassa)
Mechanism of action	Veltassa is a non-absorbed, sodium-free, cation-exchange polymer that contains a calcium-sorbitol counterion. Veltassa increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. Binding of potassium reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction in serum potassium levels.
Marketing authorisation/CE mark status	Marketing authorisation for patiromer was received from the European Medicines Agency on 18 July 2017. The marketing authorisation for the UK is centralised through the European Medicines Agency. Patiromer was launched in the UK on 5 October 2017.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The treatment of hyperkalaemia in adults. Medicinal product subject to medical prescription. As a precautionary measure, it is preferable to avoid the use of Veltassa during pregnancy. There is limited data on the use of Veltassa in patients on dialysis. No special dose and administration guidelines were applied to these patients in clinical studies. Elderly population (≥65 years of age): no special dose and administration guidelines are recommended for this population. The safety and efficacy of Veltassa in children aged under 18 years have not yet been established. No data are available.
Method of administration and dosage	Patiromer is available as individual sachets containing 8.4 g, 16.8 g, or 25.2 g patiromer sorbitex calcium powder for oral suspension. The 25.2g sachet will not be commercially available in the UK. The recommended starting dose is 8.4 g patiromer once daily, with food. The daily dose may be adjusted at intervals of one week or longer, based on the serum potassium level and the desired target range. The daily dose may be increased or decreased by 8.4 g as necessary to reach the desired target range, up to a maximum dose of 25.2 g daily. If serum potassium falls below the desired range, the dose should be reduced or discontinued. If a dose is missed, the missed dose should be taken as soon as possible on the same day. The

	missed dose should not be taken with the next dose. Administration of Veltassa should be separated by 3 hours from that of other oral medicinal products.
Additional tests or investigations	The introduction of patiromer would result in new monitoring requirements: In clinical studies, serum magnesium values <1.4 mg/dL (0.58 mmol/L) occurred in 9% of patients treated with patiromer. Mean decreases in serum magnesium were 0.17 mg/dL (0.070 mmol/L) or less. Serum magnesium should be monitored for at least 1 month after initiating treatment, and magnesium supplementation considered in patients who develop low serum magnesium levels. Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. RAAS inhibitors or diuretics) and after the patiromer dose is titrated.
List price and average cost of a course of treatment	The list price for patiromer is £10.00 per day (£300.00 per 30-sachet pack) for both 8.4g and 16.8g sachets, as flat pricing is applied. The monthly treatment cost (based on 30.44 days per month) equates to £304.
Patient access scheme (if applicable)	The PAS price for patiromer is £[redacted] per day (£[redacted] per 30-sachet pack) for both 8.4g and 16.8g sachets, as flat pricing is applied. The monthly treatment cost (based on 30.44 days per month) equates to £[redacted].

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1. Hyperkalaemia

The normal range of extracellular potassium (K^+) is usually defined as 3.5–5.0 mmol/L (8). Hyperkalaemia is an abnormally high level of potassium in the blood and is a potentially life-threatening emergency (9). Although there is no universal definition, a serum level of ≥5.5 is widely used (9). Hyperkalaemia may be categorised as mild, moderate or severe:

- Mild: 5.5–5.9mmol/L
- Moderate: 6.0–6.4mmol/L
- Severe: ≥6.4mmol/L or if ECG changes or symptoms present

These definitions are based on the European Resuscitation Council Guidelines for Resuscitation (10) which other guidelines also adopt, including the UK Renal Association (9) and English NHS Trusts (11). However there is also some variation in these definitions, for example The National Institute for Health and Care Excellence (NICE) 'Treatment summary for fluids and electrolytes' defines acute severe hyperkalaemia as >6.0mmol/L (12) while mild hyperkalaemia is often defined as ≥5.1mmol/L (13).

While hyperkalaemia can be acute or chronic in nature, UK guidelines focus only on the management of acute elevations in potassium levels (1, 9, 14). Since there are no UK guidelines specifically on the management of chronic hyperkalaemia, it is often treated based on clinical judgement (15-17). Therefore, there are no guidelines for the management of chronic hyperkalaemia to inform trial design in this therapy area.

Analysis of primary care data show that in England the prevalence of hyperkalaemia (i.e. serum K^+ ≥5.1 mmol/L) in patients with CKD (stage 3-4) in 2016 was [redacted] rising to [redacted] for those with CKD (stage 3-4) and comorbid chronic heart failure (CHF) (18). This same study has also established that for the period between 2013-2016, the

incidence of hyperkalaemia in patients with CKD (stage 3-4) in England was [redacted] per person-year which also rose to [redacted] per person-year for patients with CKD (stage 3-4) and CHF (18). Another database study showed that among adult patients seeking healthcare services in the UK, the overall incidence of a first hyperkalaemic event (i.e. serum potassium ≥5.0 mmol/L; N=195,178) is 2.9/100 patient-years (19).

The clinical presentation of hyperkalaemia is variable such that many people are asymptomatic, while others experience muscle weakness, muscle stiffness or fatigue (9). Severe hyperkalaemia can cause life-threatening arrhythmia and sudden cardiac death (4, 20, 21). Hyperkalaemia usually occurs in people with impaired kidney function, which may be caused by acute kidney injury or CKD. Patients with CKD are at particular risk of hyperkalaemia, especially when CKD is coincident with other risk factors that increase potassium concentrations, such as co-morbid cardio-renal conditions, including CHF and diabetes mellitus (4, 20, 22, 23). Such co-morbid conditions have been shown to increase mortality rates to 18.4% when serum potassium concentration reaches 5.5 mmol/L compared with 9.0% in controls (22).

B.1.3.2. RAAS inhibitor therapy and hyperkalaemia

The risk of hyperkalaemia is increased by the use of potassium supplements, dietary choices and medicines including RAAS inhibitors such as angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and potassium-sparing diuretics (24) which are used to treat high blood pressure and heart failure in patients with CKD. In the case of RAAS inhibitors, hyperkalaemia is caused by the drugs mechanism of action where sodium elimination is induced resulting in potassium retention.

The enablement of RAAS inhibition is particularly relevant for slowing the progression of kidney disease as well as the prevention of cardiovascular events in CKD, improving morbidity and mortality. However, in the UK, the risk of a hyperkalaemic event rises by up to 17-fold in patients taking RAAS inhibitors (19).

A meta-analysis by UK-based authors has demonstrated that in CHF patients, RAAS inhibition reduced the risks of hospitalisation due to heart failure by 20%, cardiovascular mortality by 14% and all-cause mortality by 11% (25). Patients with

advanced CKD or CHF prescribed the maximum recommended doses of RAAS inhibitors have been shown to incur lower annual total costs than those prescribed lower-than-recommended doses or that discontinue RAAS inhibitor treatment (26).

Further, a US analysis found that the rate of AEs or mortality increased significantly ($p<0.05$) in CKD/CHF patients with hyperkalaemia who discontinued or received submaximal doses of RAAS inhibitors versus those who continued to receive the maximum dose (27). Suboptimal treatment with RAASi is associated with poorer clinical outcomes and high economic burden (26, 28-34) primarily driven by the costs of hospitalisation (e.g. >$1.1 billion in 2013 in the US) (4, 20, 21, 35). This treatment option for hyperkalaemia therefore compromises the clinical and pharmacoeconomic benefits of RAAS inhibition in CKD (27).

A UK study showed that among patients with CKD and hyperkalaemia, 6.5% had CHF, 59.2% were taking RAAS inhibitors, and 9.9% had previous exposure to RAAS inhibitors (36). Real-world evidence suggests that hyperkalaemia is the primary reason for not starting or discontinuing RAAS inhibition in stage 3–5 CKD patients (37).

UK, European and international guidelines for the treatment of CKD consistently recommend the use of RAAS inhibitors at the maximum recommended dose to preserve kidney function and delay progression of renal failure (30, 31, 38) thereby leading to significant reductions in progression of CKD, fewer cardiovascular events, reduced mortality, morbidity and hospitalisation for comorbid CHF and lower rates of post-myocardial infarction (29, 39-41). However, real world data shows that 47% of patients discontinue or receive submaximal doses of RAASi (27) and that hyperkalaemia is the primary reason for not starting or discontinuation of RAASi in stage 3-5 CKD patients (37).

B.1.3.3. Treatment guidelines for management of hyperkalaemia in CKD

Despite guidelines for the use of RAASi therapy in CKD, the only current recommendations for managing chronic hyperkalaemia is the discontinuation of RAASi, thereby foregoing the benefits these drugs provide:

- NICE guidelines for the management of CKD state that RAAS inhibitor treatment should not be initiated in patients with CKD with serum K^+ >5.0 mmol/L and in those receiving RAAS inhibitors, treatment should be discontinued if the serum K^+ reaches ≥6.0 mmol/L(31)

- NICE guidelines also advise that patients with pre-treatment K+ >5.0 mmol/L should not routinely be offered RAAS inhibitor therapy

- European Society of Cardiology (ESC) guidelines for the treatment of CHF indicate that K^+ >6.0 mmol/L necessitates short-term cessation of RAAS inhibitors (38)

- SIGN guidelines for the treatment of CHF indicate that small and asymptomatic increases in K^+ to <5.5 mmol/L are acceptable after initiation of RAAS inhibitor treatment. However, if K^+ rises to >5.5 mmol/L, ACE inhibitor/ARB treatment should be stopped (42)

This situation therefore creates a clinical dilemma as RAAS inhibition is a globally recommended management approach with demonstrably significant clinical and pharmacoeconomic benefits (28, 29, 32, 43) but hyperkalaemia prevents optimal use.

B.1.3.4. Treatment pathway for hyperkalaemia

A variety of measures are used to manage hyperkalaemia clinically, including discontinuation of hyperkalaemia-inducing drugs such as RAAS inhibitors, diuretics, diet change, bicarbonates and potassium (K+) binders. However, there is insufficient evidence for mid- to long-term hyperkalaemia treatment, or for maintaining hyperkalaemic patients on RAAS inhibitor therapy by the use of drugs licensed for the acute setting. Therefore, enabling optimal RAAS inhibitor therapy in adult CKD patients with hyperkalaemia is challenging.

NICE guidelines on the management of CKD in adults recommend non-initiation of RAAS inhibitors in cases where serum potassium is >5 mmol/L, and discontinuation of RAAS inhibitors where serum potassium increases to ≥6 mmol/L (31). In patients receiving RAAS inhibitors with hyperkalaemia, it has been shown that the most

common strategy for management of chronic hyperkalaemia is RAAS inhibitor dose reduction or discontinuation, occurring in 16-21% and 22-27% of patients, respectively (27). This treatment option exposes the patient to an increased risk of disease progression, morbidity and mortality (39-41, 44).

Another treatment option includes the use of potassium binders, such as CPS/sodium polystyrene sulphonate[1] (SPS; Kayexalate, Resonium A). These cation exchange resins are known to lower K+ levels in the acute setting, however, their transient effect on serum K+, limited long-term data, issues with tolerance, risk of serious gastrointestinal adverse events (AEs) including life threatening intestinal necrosis and sodium load precautions prevent their use for the management of chronic hyperkalaemia (5, 6). Both are contraindicated for treating patients with a serum potassium < 5.0 mmol/L and both require frequent stop and start cycles of drug administration, further complicating chronic dosing (5). Further, SPS should also be administered with caution in patients who cannot tolerate even small increases in sodium load due to the effect of appreciable sodium load. As a result of these issues, it is unlikely that SPS/CPS would be used in the chronic setting and according to UK key opinion leaders, the use of CPS/SPS for chronic hyperkalaemia is insufficiently evidence-based and is subsequently not commonly used (5, 16, 17). In addition, the Summary of Product Characteristics (SmPC) for Resonium A and Calcium Resonium state the licenced indication as for “the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis”(6, 7).

An additional strategy to manage chronic hyperkalaemia is a low K+ diet. However, is unlikely to be used widely because its value in the management of potassium levels is limited due to the difficulties in changing dietary habits and the prevalence of K+-rich foods making long-term adherence problematic (2). Limited evidence

[1]An ion-exchange resin recommended for the treatment of hyperkalaemia associated with anuria or severe oliguria. Also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis.

exists on both the efficacy of and adherence to a low K^+ diet (17). In addition, dietary habits can be difficult to change and K^+-rich foods are pervasive (2).

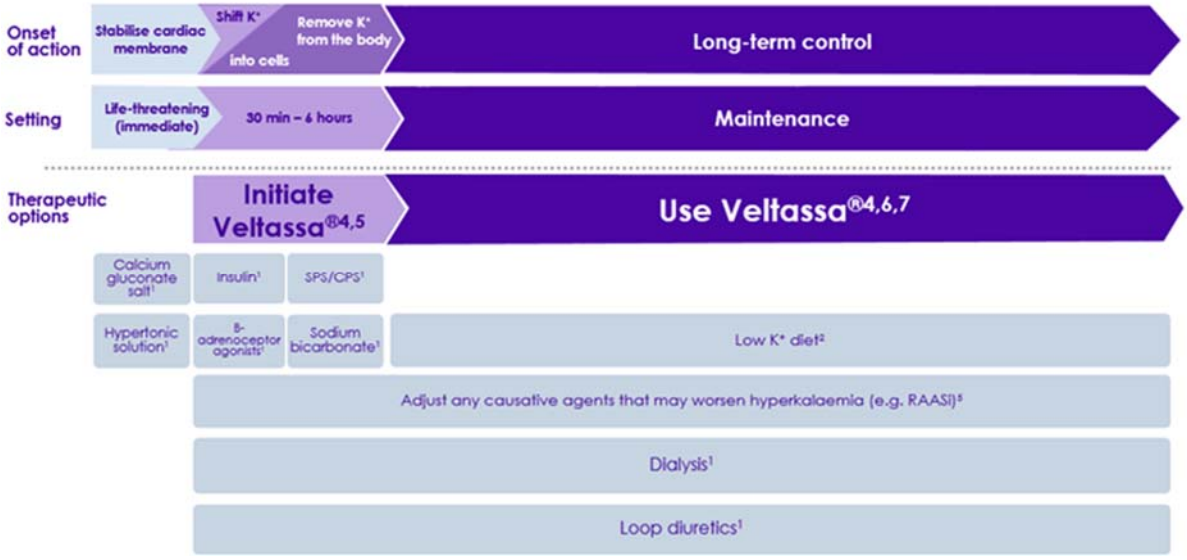
Other treatments approved for acute hyperkalaemia also have limited effectiveness. Loop diuretics induce volume contraction, which can lead to reduced distal nephron flow and potassium excretion.

Currently no treatment is available to CKD patients with hyperkalaemia who are also receiving RAAS inhibitors that protects from recurring life-threatening hyperkalaemia and enables optimal RAAS inhibitor therapy continuation. Therefore, an unmet need exists for treatment of chronic hyperkalaemia in patients with CKD where continuation of RAAS inhibitor therapy would have clear prognostic benefit.

B.1.3.5. Positioning of patiromer in hyperkalaemia treatment pathway

Patiromer (Veltassa®) is a novel, next-generation, non-absorbed, sodium-free, cation-exchange polymer that binds excess K^+ in the lumen of the gastrointestinal (GI) tract and increases faecal potassium excretion for the treatment of hyperkalaemia in adult patients (5). Furthermore, patiromer offers an innovative solution for maintenance of normokalaemia and enablement of optimal RAAS inhibitor therapy that in turn preserves the benefits related to RAAS inhibition in CKD (and CHF) patients.

Figure 1. Positioning of patiromer (Veltassa®) in the treatment pathway



CPS, calcium polystyrene sulphonate; SPS, sodium polystyrene sulphonate.

1. Weisberg et al, 2008 (45); 2. Palmer et al, 2004 (46); 3. National Kidney Foundation, 2004 (47); 4. Veltassa® EU SmPC, 2017 (48); 5. Bushinsky et al, 2015 (49); 6. Weir et al. (2015) (50); 7. Bakris et al., 2015 (3); 8. Raebel, 2012 (51)

B.1.4 Equality considerations

Patiromer is not expected to raise any equality issues. In clinical practice, the majority of patients treated with patiromer have been aged 65 years or older. The safety and efficacy of patiromer in paediatric patients has not been established.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

This submission is based primarily upon clinical data from a pivotal two-part, single-blind, phase III study evaluating the efficacy and safety of patiromer for the treatment of hyperkalaemia (OPAL-HK; NCT01810939) in patients with stage 3-4 chronic kidney disease (CKD) and hyperkalaemia receiving renin–angiotensin–aldosterone system (RAAS) inhibitor therapy (50). Safety data are supplemented, from the findings of the phase II study of patiromer in the treatment of hyperkalaemia in patients with hypertension and diabetic nephropathy (AMETHYST-DN; NCT01371747) of patients with diabetic kidney disease and hyperkalaemia who were receiving RAAS inhibitors (3). Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are provided in Appendix D. The OPAL-HK study is outlined in Table 3 (Section B.2.2).

The systematic search for clinical evidence (Appendix D) identified the following trials in addition to two systematic literature searches and meta-analyses:

- OPAL-HK
- AMETHYST-DN
- TOURMALINE
- PEARL-HF

AMETHYST was not considered relevant for informing efficacy for this submission given all patients were required to have a diagnosis of diabetes in addition to CKD. TOURMALINE was conducted to investigate food effects associated with patiromer and did not require patients to have a CKD diagnosis. Finally, PEARL-HF required a diagnosis of chronic heart failure in addition to either CKD or a history hyperkalaemia. Therefore, OPAL-HK was the only study considered to capture the population of interest.

B.2.2 List of relevant clinical effectiveness evidence

The OPAL-HK (50) study was conducted in two phases in adult patients with CKD and hyperkalaemia who were receiving at least one RAAS inhibitor (ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, or renin antagonists). The initial treatment phase was a four-week single-arm treatment period, during which all patients were assigned to one of two patiromer starting doses according to the severity of the hyperkalaemia: patients with a potassium level of 5.1 mmol/L to less than 5.5 mmol/L (mild hyperkalaemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 mmol to less than 6.5 mmol/L (moderate-to-severe hyperkalaemia) received 8.4 g of patiromer twice daily. Patients were eligible for the randomised withdrawal phase if they had had a serum potassium level of 5.5 mmol per litre or higher at baseline of the initial treatment phase and if their potassium level at the end of the initial treatment phase was within the target range (3.8 to <5.1 mmol per litre) while they were receiving patiromer and RAAS inhibitors. Qualifying patients were randomly assigned, in a 1:1 ratio, to continue receiving patiromer (at the same daily dose they were receiving at week 4 of the initial treatment phase) or to receive placebo. The withdrawal phase was a randomised, placebo-controlled 8-week phase during which pre-specified treatment algorithms (Appendix N) were developed to manage a recurrence of hyperkalaemia, either by an increase in the dose of patiromer (patiromer group) or by modification of the RAAS-inhibitor regimen (placebo group) at the time of the first event of hyperkalaemia. The primary endpoint in the initial treatment phase was the mean change in serum potassium concentrations from baseline to week 4; in the randomised withdrawal phase, the primary endpoint was the difference between patiromer and placebo in the median change in serum potassium at the start of the randomised withdrawal phase to week 4, or the earliest visit at which serum potassium was <3.8 mmol/L or ≥5.5 mmol/L.

Details of the OPAL-HK study are presented in Table 3.

Table 3: Clinical effectiveness evidence in OPAL-HK study (50)

Study design	• Initial treatment phase: non-randomised, single-arm. • Randomised withdrawal phase: randomised, placebo-

<table>
<tr><td></td><td colspan="5">controlled.</td></tr>
<tr><td>Population</td><td colspan="5">• Initial treatment phase:
o n=243
o age 18–80 years
o CKD (eGFR 15–<60 mL/min/1.73 m^2)
o serum K^+ of 5.1–<6.5 mmol/L at screening
o on any stable dose of at least one RAAS inhibitor for at least 28 days prior to screening.
• Randomised withdrawal phase:
o n=107
o serum K^+ value ≥5.5 mmol/L at initial treatment phase baseline and:
▪ serum K^+ of 3.8–<5.1 mmol/L at initial treatment phase week 4
▪ still on patiromer
▪ still on RAAS inhibitor*.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">• Initial treatment phase: patiromer 4.2 g (mild hyperkalaemia†) or 8.4 g (moderate to severe hyperkalaemia†) twice daily.
• Randomised withdrawal phase: patiromer daily dose administered during week 4 of initial treatment phase.</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">• Initial treatment phase: none.
• Randomised withdrawal phase: placebo.</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">• A placebo-controlled trial is considered appropriate for this submission, because there is currently no single clinically relevant comparator treatment for adult patients with CKD and hyperkalaemia.
• The OPAL-HK study has demonstrated the efficacy of patiromer in patients with CKD and hyperkalaemia. The OPAL-HK trial is the only completed randomised controlled trial with a comparison of relevance to the scope of this submission and with data on clinical effectiveness of patiromer in stage 3–4 CKD patients using RAAS inhibitor therapy and experiencing hyperkalaemia. These results support a favourable risk:benefit profile of patiromer as a treatment for hyperkalaemia in both the acute and chronic treatment settings.</td></tr>
<tr><td>Reported outcomes specified in the decision problem‡</td><td colspan="5">• Serum potassium levels:
o mean change in serum K^+ levels from baseline to week 4
o proportion of patients who achieved target K^+</td></tr>
</table>

	levels (3.8–<5.1 mmol/L) o difference between patiromer and placebo in the median change in serum K^+ level at the start of the phase to week 4 or the earliest visit at which the K^+ level was <3.8 mmol/L or ≥5.5 mmol/L o **proportion of patients with a recurrence of hyperkalaemia (two definitions: ≥5.1 mmol/L or ≥5.5 mmol/L)** o the following exploratory endpoints are reported: 1) time to first recurrence of hyperkalaemia; 2) proportion of patients requiring an intervention due to recurrent hyperkalaemia at any time. • Use of RAAS inhibitor therapy: o proportion of patients who required RAAS inhibitor dose reduction or discontinuation due to recurrent hyperkalaemia o exploratory endpoints included: time to RAAS inhibitor dose discontinuation, and proportion of patients receiving any dose of RAAS inhibitor at the end of this phase. • Mortality was reported as a safety endpoint. • AEs were also reported; events of interest were: o hypokalaemia (serum K^+ <3.5 mmol/L) o serum K^+ ≥5.5 mmol/L o hyperkalaemia-associated ECG changes o hypokalaemia-associated ECG changes o gastrointestinal AEs o potential allergic reactions o changes in serum calcium, magnesium, phosphorous and fluoride o AEs resulting in change of dose o AEs resulting in addition of concomitant therapy (e.g. magnesium supplement for hypomagnesemia) o worsening renal function: ▪ ≥100% increase in serum creatinine from baseline or ▪ >50% decrease in eGFR from baseline. • AE profile in subjects maintained on RAAS inhibitor therapy versus those who have stopped RAAS inhibitor therapy.
All other reported outcomes‡	Randomised withdrawal phase: 1. Time to first recurrent hyperkalaemia. 2. Proportion of patients requiring an intervention due to

	recurrent hyperkalaemia at any time. **3. Time to RAAS inhibitor dose discontinuation.** 4. Proportion of patients receiving any dose of RAAS inhibitor at the end of this phase.
*RAAS inhibitor dose modification or discontinuation was performed according to protocol-specified titration algorithms based on serum K^+ levels. †Mild hyperkalaemia defined as K^+ 5.1–<5.5 mmol/L; moderate-severe hyperkalaemia was defined as K^+ 5.5–<6.5 mmol/L. ‡See Table 7 for a comprehensive list of all study outcomes. AEs, adverse events; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system.	

Some outcomes from the phase II AMETHYST-DN study were used to populate the economic model, and the safety results from that study are included in Section B.2.10. The results of this study included assessment of the frequency and severity of adverse events as the safety endpoint and the safety data presented in this submission are based on a pooled analysis of the OPAL-HK and AMETHYST-DN studies. The design of the AMETHYST-DN study is summarised in Table 4

Table 4: Design of the AMETHYST-DN study

Trial	Intervention	Comparator	Population	Endpoints	Primary study reference
RLY5016-205 (AMETHYST-DN); NCT01371747 [(3)]	Patiromer 4.2 g, 8.4 g or 12.6 g twice daily (mild hyperkalaemia*), or patiromer 8.4 g, 12.6 g or 16.8 g twice daily (moderate hyperkalaemia*)	Single arm study	• N=306 • 30–80 years • CKD (eGFR 15–<60 mL/min/1.73 m^2) • T2D • Serum K^+ of 5.0–<6.0 mmol/L at screening • Receiving at least one RAAS inhibitor (ACE inhibitor or ARB) for at least 28 days prior to screening	• Primary: mean change in central laboratory serum K^+ level from baseline to week 4 or prior to the initiation of dose titration • Secondary: mean changes in serum K^+ level from baseline to other post-baseline visits	Bakris et al. JAMA 2015;314:151–61 (3)

*Mild hyperkalaemia defined as K^+ >5.0–5.5 mmol/L; moderate hyperkalaemia defined as K^+ >5.5–<6.0 mmol/L.

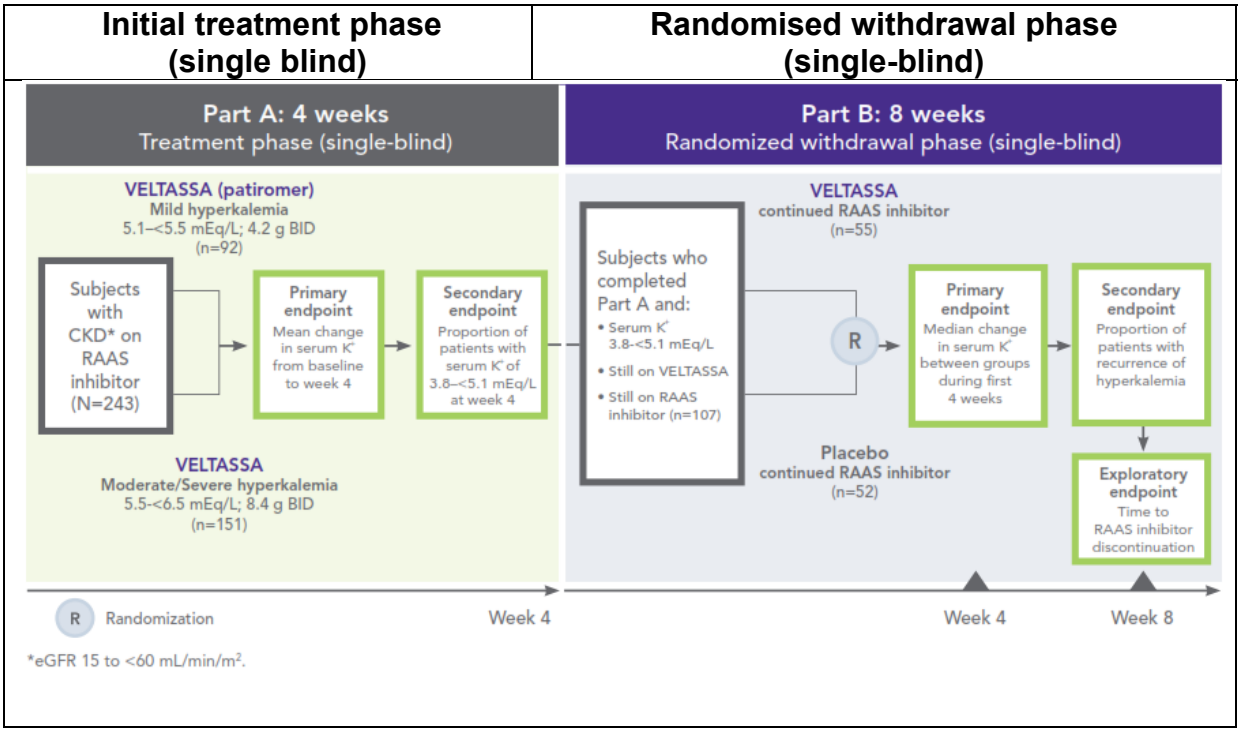
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system; T2D, type 2 diabetes mellitus.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. The OPAL-HK study (NCT01810939)

The OPAL-HK study (NCT01810939) was an international, multi-centre, single-blind study that was designed to evaluate the safety and efficacy of patiromer in CKD patients with hyperkalaemia who were receiving treatment with at least one RAAS inhibitor (50). The methods are described below in accordance with the CONSORT Statement. An overview of the study design is shown in Figure 2.

Figure 2: Design of the OPAL-HK study [(50)]



*eGFR 15–<60 mL/min/m^2.

BID, twice daily; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system.

Trial design

International, multi-centre, single-blind, two-phase study of patiromer in CKD patients with hyperkalaemia who were receiving at least one RAAS inhibitor:

- initial treatment phase: 4-week single arm, initial treatment phase
- randomised withdrawal phase: 8-week placebo-controlled, single-blind, randomised withdrawal phase.

The initial treatment phase was a 4-week, single-arm trial in which patients were stratified to two subgroups according to the severity of hyperkalaemia. Patients with mild hyperkalaemia (n=92) were defined as having serum potassium levels of 5.1 mmol/L to <5.5 mmol/L, and patients with moderate to severe hyperkalaemia (n=151) were defined as having serum potassium levels of 5.5 mmol/L to <6.5 mmol/L. Patients with serum potassium levels outside this range (<5.1 mmol/L or ≥6.5 mmol/L) were excluded from the study (Section B.2.3.2). All patients included in the study received patiromer for the duration of the initial treatment phase, the

dose of which was dependent on the severity of hyperkalaemia. Patients who withdrew early from the study during the initial treatment phase or those who were excluded from the randomised withdrawal phase entered a one- to two-week follow-up period during which patiromer treatment was discontinued and serum potassium levels were monitored.

The randomised withdrawal phase was an 8-week, randomised, single-blind, placebo-controlled phase. In this part of the study, 107 patients were randomised by an Interactive Web Response System (IWRS) in a 1:1 ratio to receive patiromer (n=55) or placebo (n=52). The IWRS was a centralised system whereby patients were assigned to randomised treatment during the randomised withdrawal phase sequentially, by time of the randomisation request to the IWRS, across all sites, regions and countries. Randomisation was stratified to ensure equal distribution to the patiromer and placebo arms within four strata formed by the combination of the following two baseline characteristics:

- initial treatment phase baseline central laboratory serum potassium (moderate hyperkalaemia [<5.8 mmol/L] versus severe hyperkalaemia [≥5.8 mmol/L])
- the presence or absence of type 2 diabetes at initial treatment phase baseline.

In both the initial treatment phase and the randomised withdrawal phase, all patients received patiromer in a single-blind fashion. Patients were blinded as to their treatment assignment during the study (they were informed that all participants would receive patiromer at some time either during the initial treatment phase or the randomised withdrawal phase). Investigators were unblinded, allowing appropriate management of patients' serum potassium, titration of patiromer and decision-making about RAAS inhibitor medication.

In the randomised withdrawal phase, patients randomised to the patiromer arm continued to receive patiromer at the dose dispensed during the initial treatment phase, and those randomised to the placebo arm were switched to receive placebo instead of patiromer which was received in initial treatment phase. RAAS inhibitor treatment was continued throughout the study, unless discontinuation was necessary

due to the development or exacerbation of hyperkalaemia. A detailed description of the study interventions can be found in Section B.2.3.3.

Patients who completed the randomised withdrawal phase or who discontinued the study early entered a one- to two-week follow-up period during which neither patiromer nor placebo was administered and serum potassium levels were monitored.

Protocol amendments

The phrase 'Other reasons for withdrawal may include: was added immediately preceding 'AE' in the bulleted list of (non-mandatory) criteria, which could have resulted in subject withdrawal from the study (but were not mandatory). This phrase had been inadvertently omitted from the original protocol. This omission did not affect the conduct of the study.

Participants

Adults with CKD and hyperkalaemia who were receiving treatment with at least one RAAS inhibitor at stable doses were eligible for enrolment in the OPAL-HK Study. The patient population evaluated in this study was selected based on comorbidities commonly associated with hyperkalaemia in a real-world clinical setting. Hyperkalaemia is a common occurrence in patients with CKD, and was therefore included in the inclusion criteria. Many patients with CKD have concomitant hypertension, type 2 diabetes, congestive heart failure (CHF) or established coronary heart disease; these comorbidities were not included in the study inclusion criteria, but patients presenting with these comorbidities were not excluded. History of CHF, date of diagnosis and New York Heart Association (NYHA) class were recorded for all patients enrolled in the OPAL-HK study.

RAAS inhibitors have been proven to slow the progression of CKD and to reduce the risk of cardiovascular morbidity and mortality; however, their use can often result in hyperkalaemia which may be treated by limiting the use of RAAS inhibitors. A key objective of the study was to demonstrate that patiromer enabled the prolonged use of RAAS inhibitors in patients with CKD and hyperkalaemia, and hence patients were required to be undergoing RAAS inhibitor therapy at enrolment. Key inclusion and

exclusion criteria are summarised in Table 5. A full description of the inclusion/exclusion criteria is provided in Appendix D.

Adults with a serum potassium concentration ≥5.5 mmol/L at the initial treatment phase baseline and potassium level at the end of the initial treatment phase within the target range (3.8 to <5.1 mmol/L) while receiving patiromer (8.4 to 50.4 g/d) and still receiving RAAS inhibitor therapy at the initial treatment phase week 4 visit were eligible for enrolment in the randomised withdrawal phase.

Table 5: Key inclusion and exclusion criteria* for selection of the trial population in the OPAL-HK study (RLY5016-301; NCT01810939)

Initial treatment phase	
Inclusion criteria	• Age 18–80 years old at screening. • Hyperkalaemia (serum K^+ level that was between 5.1 mmol/L and <6.5 mmol/L at two screenings). • Stage 3 or stage 4 CKD (eGFR of 15–<60mL/min/1.73 m^2 of BSA at screening). • Patients must have been treated with a stable dose of at least one RAAS inhibitor (an ACE inhibitor, ARB or AA) for at least 28 days prior to screening. • If on anti-hypertensive medications, had been receiving a stable dose for the 28 days prior to screening.
Exclusion criteria	• K^+-related electrocardiographic changes. • Severe gastrointestinal disorders. • Cardiac defects such as acute coronary syndrome, clinically significant ventricular arrhythmias, and uncontrolled or unstable arrhythmias within two months prior to study participation. • Cardiac surgery within two months prior to study participation. • Heart or kidney transplantation within two months prior to study participation. • Transient ischaemic attack or stroke within two months prior to study participation. • Confirmed systolic blood pressure of 180 mmHg or higher, or lower than 110 mmHg; or confirmed diastolic blood pressure of 110 mmHg or higher, or lower than 60 mmHg.
Randomised withdrawal phase	
Inclusion criteria	• Serum K^+ level of 5.5 mmol/L or higher at baseline of the initial treatment phase. • Serum K^+ level at the end of the initial treatment phase within the target range (3.8–<5.1 mmol/L) while patients were receiving patiromer and RAAS inhibitors.

Exclusion criteria	• Serum K^+ level outside of the target range (3.8–<5.1 mmol/L). • Discontinuation of either patiromer or RAAS inhibitor treatment during the initial treatment phase.

*For full details of eligibility criteria see Appendix D.

AA, aldosterone antagonist; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system.

Settings and locations where the data were collected

Patients (N=243) were enrolled from 20 February 2013 across 71 study centres in 10 countries (Croatia, Czech Republic, Denmark, Georgia, Hungary, Italy, Serbia, Slovenia, Ukraine, and the USA). The study was carried out in two sequential parts over 12 weeks. The last study visit took place on 6 August 2013.

Interventions

Study interventions are summarised in Table 6. For the initial treatment phase, eligible patients were allocated to one of two patiromer starting doses according to hyperkalaemia severity. Each dose was administered as an oral suspension in 40mL of water with breakfast and dinner.

During the initial treatment phase, the patiromer dose could be adjusted to reach and maintain a target potassium level of 3.8 to <5.1 mmol/L, according to the algorithm shown in Appendix N. Adjustments could be made 48 hours after treatment initiation and at weekly intervals through to week 3 of the initial treatment phase. The RAAS inhibitor doses were not adjusted, although they were discontinued if the potassium level was ≥6.5 mmol/L (≥5.1 mmol/L in patients receiving the maximum dose).

Patients were eligible for inclusion in the randomised withdrawal phase were randomly assigned (1:1) to continue receiving patiromer at the same daily dose they were receiving at week 4 of the initial treatment phase, or to switch to placebo. Randomisation was stratified according to the initial treatment phase baseline serum potassium level (moderate [serum potassium 5.5 to <5.8 mmol/L] vs severe [serum potassium ≥5.8 mmol/L] hyperkalaemia) and the presence or absence of type 2 diabetes.

During the randomised withdrawal phase, pre-specified treatment algorithms (summarised in Appendix N) were followed to manage a recurrence of

hyperkalaemia, either by increasing the patiromer dose (patiromer group) or by modification of the RAAS inhibitor therapy (placebo group). Subsequent events required discontinuation of RAAS inhibitor therapy.

Table 6: Interventions in the OPAL-HK study (RLY5016-301; NCT01810939)

Initial treatment phase	
Patients with mild hyperkalaemia (5.1–<5.5 mmol/L)	• Initial dose of 4.2 g patiromer administered twice daily with breakfast and dinner (oral suspension of patiromer powder in 40 mL water). • Initial dose of patiromer could be adjusted after 48 hours from the initiation of patiromer treatment and at weekly intervals through to week 3 to achieve and maintain a serum K^+ level of 3.8–<5.1 mmol/L. Dose modifications were made according to a treatment algorithm (Appendix N).
Patients with moderate to severe hyperkalaemia (5.5–<6.5 mmol/L)	• Initial dose of 8.4 g patiromer administered twice daily with breakfast and dinner (oral suspension of patiromer powder in 40mL water). • Initial dose of patiromer could be adjusted after 48 hours from the initiation of patiromer treatment and at weekly intervals through to week 3 to achieve and maintain a serum K^+ level of 3.8–<5.1 mmol/L. Dose modifications were made according to a treatment algorithm (Appendix N).
Randomised withdrawal phase	
Patiromer group	• Continuation of patiromer administration at the equivalent daily dose dispensed in week 4 of the initial treatment phase. Dose modifications were made during weeks 1–4 and weeks 5–8 of the randomised withdrawal phase according to a treatment algorithm (Appendix N).
Placebo group	• Placebo was administered at a dose of 4 g/day twice daily with breakfast and dinner. The dose was not titrated in response to changes in serum K^+ levels.

K^+, potassium.

Pre-specified primary and secondary outcome measures

Endpoints in the initial treatment and randomised withdrawal phases of OPAL-HK are summarised in Table 7. Serum potassium levels were assessed at beginning of the initial treatment phase in a central laboratory, thereafter at a local laboratory. Whereas in the withdrawal phase of the trial, serum potassium was measured at both local and central laboratory.

Table 7: Primary, secondary, exploratory and safety endpoints in the OPAL-HK study (RLY5016-301; NCT01810939)

Initial treatment phase	
Primary efficacy endpoint	• Mean change in serum K^+ level from baseline to week 4 (assessed in patients who received at least one dose of patiromer and had at least serum K^+ measurement at a scheduled visit after day 3). o Change from baseline at visits other than week 4 summarised but not considered formal endpoints.
Secondary efficacy endpoint	• Proportion of patients who had a serum K^+ level of 3.8–<5.1 mmol/L at week 4.
Randomised withdrawal phase	
Primary efficacy endpoint	• Difference between patiromer and placebo groups in the median change in serum K^+ level from the start of the randomised withdrawal phase to week 4 of the phase, or to the earliest visit at which the patient's serum K^+ level was <3.8 mmol/L or ≥5.5 mmol/L.
Secondary efficacy endpoint	• Proportion of patients with a recurrence of hyperkalaemia according to two definitions: o serum K^+ levels of ≥5.1 mmol/L o serum K^+ levels of ≥5.5 mmol/L
Exploratory endpoints	• Time to first recurrence of hyperkalaemia. • Proportion of patients requiring an intervention (i.e. RAAS inhibitor dose reduction or discontinuation in the placebo group, or patiromer dose increase or RAAS inhibitor discontinuation in the patiromer group) due to recurrent hyperkalaemia at any time. • Time to RAAS inhibitor dose discontinuation. • Proportion of patients receiving any dose of RAAS inhibitor at the end of this phase.
Safety endpoints	• AEs (including events of interest, such as gastrointestinal events and allergic reactions). • Renal events (e.g. worsening renal failure, acute kidney injury, specified changes in eGFR and serum creatinine). • Clinical laboratory test results (including cases of hyper- and hypokalaemia, clinically significant changes in serum calcium, serum magnesium, phosphorus and fluoride). • Vital signs (including blood pressure), clinically significant ECG findings, potassium-related ECG changes, and newly observed physical examination abnormalities.
AEs, adverse events; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system.	

No changes were made to trial outcomes after the trial commenced.

A comparative summary of the methodology of the trials

A summary of the methodology for the OPAL-HK study is given in Table 8**.**

Table 8: Summary of the methodology for the OPAL-HK study (RLY5016-301; NCT01810939)

Location	• 71 study centres in 10 countries: Croatia, Czech Republic, Denmark, Georgia, Hungary, Italy, Serbia, Slovenia, Ukraine, and USA.
Design	• International, multicentre, single-blind, two-phase study of patiromer in CKD patients with hyperkalaemia who were receiving at least one RAAS inhibitor: o initial treatment phase: four-week single-arm o randomised withdrawal phase: eight-week placebo-controlled, single-blind.
Duration of study	20 February 2013 (first patient enrolled) to 06 August 2013 (last study visit).
Method of randomisation	• In the randomised withdrawal phase, qualifying patients were randomly assigned by IWRS in a 1:1 ratio to either continue receiving patiromer (at the same daily dose they were receiving at week 4 of the initial treatment phase) or to receive placebo. • Randomisation was stratified to ensure equal distribution to the patiromer and placebo arms within the four strata formed by the combination of the following two baseline characteristics: o T2DM (yes/no) o initial treatment phase baseline central laboratory serum K^+ (<5.8 mmol/L versus ≥5.8 mmol/L). • The IWRS was a centralised system in which patients were assigned to randomised withdrawal phase randomised treatment sequentially, by time of the randomisation request to the IWRS, across all sites, regions and countries.
Method of blinding	• In both the initial treatment phase and the randomised withdrawal phase, patients were blinded to their assigned treatment (N.B. the informed consent form stated that all individuals would receive patiromer at some time during the study, either during the initial treatment phase or the randomised withdrawal phase.) • Site staff involved with collection, handling, and processing of blood specimens were also blinded. To manage serum K^+ appropriately and to facilitate titration of patiromer and decision-making about RAAS inhibitor medication, study investigators were aware that all patients were treated with patiromer during the initial treatment phase. They were also aware of whether patients had been randomised to patiromer or placebo during the randomised withdrawal phase.

Intervention and comparator	**Interventions: initial treatment phase: N=243** • Patients with a screening serum K^+ of 5.1–<5.5 mmol/L were assigned to a starting dose of 8.4 g/day patiromer administered as 4.2 g BID (n=92). • Patients with a screening serum K^+ of 5.5–<6.5 mmol/L were assigned to a starting dose of 16.8 g/day patiromer administered as 8.4 g BID (n=151). • Patiromer dose titrated according to the serum K^+ level assessed, starting at the initial treatment phase day 3 visit and continuing through weekly visits to the end of four weeks, with the aim of achieving serum K^+ in a target range of 3.8–<5.1 mmol/L. • RAAS inhibitor dose was unchanged during initial treatment phase unless medically necessary.
	Interventions: randomised withdrawal phase: N=107 • Patients with a baseline serum K^+ of ≥5.5 mmol/L at the beginning of the initial treatment phase and who responded to patiromer during that phase were randomly assigned to treatment with: o patiromer 16.8 g/day (plus continued RAAS inhibitor; n=55) o placebo (plus continued RAAS inhibitor; n=52). • Patiromer and RAAS inhibitor dose modification or discontinuation was performed according to protocol-specified titration algorithms based on serum K^+ levels assessed starting at the randomised withdrawal phase day 3 visit and continuing through weekly visits to the end of the eight weeks of the patiromer withdrawal phase.
	Comparators: • Initial treatment phase: none. • Randomised withdrawal phase: placebo.
Primary endpoint (including scoring methods and timings of assessments)	• **Initial treatment phase.** Mean change in the serum K^+ level from baseline to week 4 o Assessed in enrolled patients who received at least one dose of patiromer and had at least one post-baseline weekly serum K^+ measurement o assessments of efficacy and safety were performed at day 3, week 1, week 2, week 3 and week 4
	• **Randomized withdrawal phase.** The change from randomized withdrawal phase baseline serum K^+ to the corresponding level at either of: o the randomized withdrawal phase week 4 visit, if the patient's serum K^+ remained ≥3.8 mmol/L and <5.5 mmol/L up to the randomised withdrawal phase week 4 visit, or o the earliest randomised withdrawal phase visit at which the patient's serum K^+ was <3.8 mmol/L or ≥5.5 mmol/L. • Assessments of efficacy and safety were performed at visits

	scheduled on randomised withdrawal phase day 3, and at weekly visits for the entire eight-week withdrawal phase.
Secondary endpoint	**Initial treatment phase** • The proportion of patients with controlled hyperkalaemia, specifically a centrally measured serum K^+ level that was in a target range of 3.8–<5.1 mmol/L after four weeks of treatment with patiromer.
	Randomised withdrawal phase • Secondary endpoints were the proportion of patients with recurrent hyperkalaemia, specifically, at any time (post-randomised withdrawal phase baseline) through the randomised withdrawal phase to the week 8 visit: o the proportion of patients with a serum K^+ ≥5.5 mmol/L o the proportion of patients with a serum K^+ ≥5.1 mmol/L.
Exploratory efficacy endpoints	**Randomised withdrawal phase** • Time to first recurrent hyperkalaemia. • Proportion of patients requiring an intervention (i.e. RAAS inhibitor dose reduction or discontinuation in the placebo group, or patiromer dose increase or RAAS inhibitor discontinuation in the patiromer group) due to recurrent hyperkalaemia at any time. • Time to RAAS inhibitor dose discontinuation. • Proportion of patients receiving any dose of RAAS inhibitor at the end of this phase.
Follow-up period	• Patients who withdrew early from the study during the four weeks of the initial treatment phase or who, at the end, were not eligible for the randomised withdrawal phase, entered a one- to two-week follow-up period during which patiromer was not administered and serum K^+ was monitored. • Upon completion of the randomised withdrawal phase, or discontinuation from the eight-week randomised withdrawal period, patients entered a one- to two-week follow-up period during which neither patiromer nor placebo was administered and serum K^+ was monitored.
Pre-planned subgroups	• Patients with and without CHF • Patients with and without type 2 diabetes • Baseline serum potassium <5.5 mmol/L and ≥5.5 mmol/L • Patients receiving RAAS inhibitor treatment at maximal or submaximal doses • Male or female • Age <65 years or ≥65 years • Geographical region (EU and USA versus non-EU Eastern Europe)

BID, twice daily; CKD, chronic kidney disease; IWRS, interactive web response system; K^+, potassium; RAAS, renin–angiotensin–aldosterone system; T2DM, type 2 diabetes mellitus.

B.2.3.2. Overview of the AMETHYST-DN study (NCT01371747)

The AMETHYST-DN study (NCT01371747) was a phase II, multicentre, open-label, dose-ranging RCT conducted at 48 sites in Europe from June 2011 to June 2013 that evaluated patiromer in outpatients with type 2 diabetes (3). All patients received RAAS inhibitors prior to and during study treatment. Patients were stratified by baseline serum potassium level into mild or moderate hyperkalaemia groups, and received one of three randomised starting doses of patiromer (4.2 g, 8.4 g, or 12.6 g twice daily). Patiromer doses were titrated to achieve and maintain serum potassium levels of 5.0 mmol/L or lower (3).

B.2.3.3. Baseline characteristics of patients enrolled in OPAL-HK and AMETHYST-DN

Baseline demographic characteristics of patients enrolled in OPAL-HK are summarised in Table 9. In general, the two treatment groups in the randomised withdrawal phase of the study were comparable except for a higher proportion of patients receiving angiotensin II receptor blockers and loop diuretics in the patiromer group, compared with the placebo group.

Table 9: Demographic characteristics of patients enrolled in OPAL-HK

	Initial treatment phase	**Randomised withdrawal phase**	
	Overall (N=243)	**Placebo (n=52)**	**Patiromer (n=55)**
Male sex, n (%)	140 (58)	30 (58)	28 (51)
Age, years*	64.2 ± 10.5	65.0 ± 9.1	65.5 ± 9.4
White race, n (%)	239 (98)	52 (100)	55 (100)
Type 2 diabetes, n (%)	139 (57)	33 (63)	34 (62)
Heart failure, n (%)	102 (42)	22 (42)	27 (49)
Myocardial infarction, n (%)	60 (25)	14 (27)	18 (33)
Hypertension, n (%)	236 (97)	50 (96)	54 (98)
Serum potassium (mmol/L)*	5.6 ± 0.5	5.9 ± 0.4	5.9 ± 0.6
Estimated GFR (mL/min/1.73 m^2)*	35.4 ± 16.2	39.0 ± 20.4	38.6 ± 20.7
RAAS inhibitor use, n (%):	243 (100)	52 (100)	55 (100)
ACE inhibitors, n (%)	170 (70)	38 (73)	37 (67)
angiotensin II receptor blockers, n (%)	92 (38)	16 (31)	24 (44)
aldosterone antagonists, n (%)	22 (9)	4 (8)	4 (7)

renin inhibitors, n (%)	2 (1)	0	0
dual RAAS blockade, n (%)	41 (17)	6 (12)	10 (18)
receiving maximal doses, n (%)	106 (44)	21 (40)	21 (38)
Non-RAAS inhibitor diuretic use, n (%):	132 (54)	27 (52)	28 (51)
thiazides, n (%)	70 (29)	11 (21)	16 (29)
loop diuretics, n (%)	77 (32)	20 (38)	16 (29)

*Mean ± standard deviation.

ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system.

In the AMETHYST-DN trial, mean baseline age of the study population was 66.3 years; 63.2% were men and 100% were white. All patients had hypertension and type 2 diabetes; 65% had stage 3 CKD and 22% had stage 4 CKD; 35%had heart failure. Median ratio of albumin to creatinine was 300 (interquartile range, 50-1490) mg/g. Mean serum potassium level at baseline was 5.3mmol/L. Baseline characteristics by starting-dose group were generally balanced within each stratum. All patients received RAAS inhibitor medications during the treatment and maintenance phases of the study (3).

B.2.3.4. Analysis sets

Summary descriptions of the analysis sets are provided below, with full details in Table 10.

Intention-to-treat

The intention-to-treat (ITT) population for the efficacy analyses in initial treatment phase consisted of all subjects enrolled, defined as any subject who has met all eligibility criteria for initial treatment phase and who had taken at least one dose of patiromer.

The ITT population for the efficacy analyses in the randomised withdrawal phase included all subjects randomised, defined as any subject who has met all eligibility criteria for the randomised withdrawal phase and who had been randomised to either the active or placebo group.

Primary analyses of the primary and secondary efficacy outcomes, as well as some sensitivity and exploratory analyses were performed using the ITT population.

Per protocol

For the initial treatment phase and the randomised withdrawal phase, the respective per protocol population was comprised of those in the ITT populations who have been compliant with study drug, defined as taking 80–120% of the dispensed dose, and who do not have any important protocol deviations.

Safety

In initial treatment phase, the safety population included all enrolled subjects who had received at least one dose of patiromer. Thus, for initial treatment phase, the safety and ITT populations are identical.

In the randomised withdrawal phase, the safety population included all randomised subjects who had received at least one dose of randomised investigational product (IP). Subjects who received at least one dose of patiromer after randomisation were classified in the patiromer group; subjects who received at least one dose of placebo and no patiromer after randomisation were classified in the placebo group.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Statistical analyses

Primary and secondary efficacy endpoints in both parts of the study were analysed in the intention-to-treat (ITT) population, which included all patients who received at least one dose of patiromer or placebo (Table 10). Selected efficacy endpoints were also analysed in the per protocol (PP) population, which included all patients included in the ITT population who received [redacted]% of the dispensed dose and had no important protocol deviations (Table 10).

Table 10: Definitions of analysis groups in the OPAL-HK study (RLY5016-301; NCT01810939)

Initial treatment phase	
ITT population	• All patients who received at least one dose of patiromer.
PP population	• Patients within the ITT population who received [redacted] of the dispensed dose and did not have any important protocol deviations. • Important protocol deviations included: o enrolled in violation of the entry criteria for either initial treatment phase or randomised withdrawal phase o violations of informed consent o on prohibited K^+-affecting medication during study participation o patients not withdrawn from study when patient met withdrawal criterion o patiromer or placebo incorrectly dispensed.
Safety population	• All patients who received at least one dose of patiromer.
Randomised withdrawal phase	
ITT population	• All patients who met the eligibility criteria for the randomised withdrawal phase and were randomised to either the patiromer or placebo group* and received at least one dose of patiromer or placebo.
PP population	• Same as for initial treatment phase.
Safety population	• All randomised subjects who received at least one dose of either the patiromer or placebo group.

*One patient from the randomised withdrawal phase ITT population was excluded from the analysis and the ITT population because the patient was mistakenly randomised into a treatment group as the result of a clerical error. The patient did not receive study medication.

ITT, intention-to-treat; K^+, potassium; PP, per protocol.

Analysis of primary endpoints

In the initial treatment phase of the study, the mean change in serum potassium from baseline to week 4, and the corresponding 95% confidence interval, were calculated using a longitudinal repeated-measures model with treatment phase baseline potassium concentration, presence of absence of CHF at baseline, and presence or absence of type 2 diabetes at baseline as covariates. In the randomised withdrawal phase, comparisons between the two groups were performed using analysis of variance (ANOVA) of rank-transformed data with covariates corresponding to the randomisation strata:

- treatment phase baseline serum potassium as a binary covariate (<5.8 mmol/L [moderate hyperkalaemia], ≥5.8 mmol/L [severe hyperkalaemia])
- presence of T2DM at initial treatment phase baseline (yes/no).

Rank-transformed data were used because the post-baseline value used to compare primary efficacy endpoint in the two treatment groups was constrained by clinical intervention if serum potassium was high (≥5.5 mmol/L) or low (<3.8 mmol/L), which may have occurred at any time during the study; hence, changes in serum potassium from baseline could not be assumed to have a common distribution. The ranking procedure used for the ANOVA used the last observed rank carried forward (52), and accounted for the use of serum potassium values prior to week 4 of the randomised withdrawal phase (i.e. for subjects whose local serum potassium value was outside the range 3.8 to < 5.5 mmol/L prior to week 4 of this phase).

Methods for imputing missing serum potassium data

Imputation of missing serum potassium measurements was applied when central, local, or both laboratory potassium values were missing for a specific patient and visit. If only the central laboratory value was missing, a regression model using the local laboratory value was used to impute the missing central value. During the randomised withdrawal phase, if both the central and local values were missing, multiple imputation was used to impute the missing central value.

Analysis of secondary endpoints

The study was prospectively designed to have sufficient power to analyse the secondary endpoints if the primary endpoint

as significant. For the secondary efficacy endpoint in the initial treatment phase (proportion of patients with serum potassium between 3.8 and <5.1 mmol/L), the estimated proportion of patients, standard error, and 95% confidence interval were calculated with stratification by the presence or absence of CHF and type 2 diabetes, and baseline serum potassium <5.5 mmol/L or ≥5.5 mmol/L.

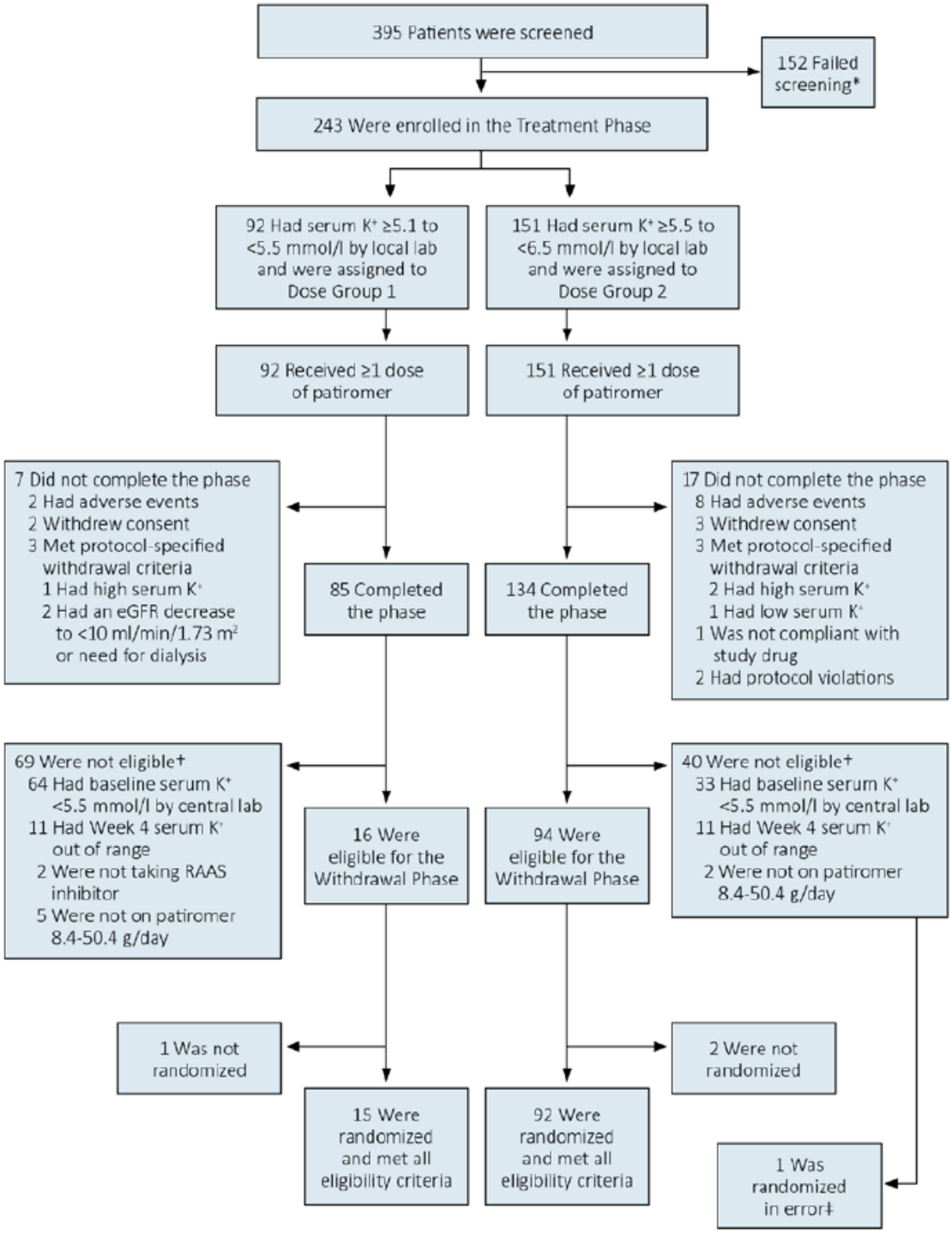
The two secondary efficacy endpoints in the randomised withdrawal phase (proportion of patients with recurrence of hyperkalaemia, defined as serum

potassium ≥5.1 mmol/L or ≥5.5 mmol/L) were tested with a Hochberg correction at an overall Type I error rate of 0.05. For each secondary endpoint, between-group comparisons were performed by means of a Mantel-Haenszel test, stratified according to the randomisation variables (serum potassium <5.8 mmol/L versus ≥5.8 mmol/L; presence or absence of type 2 diabetes). Exploratory efficacy endpoints were summarised descriptively without formal statistical testing. The time to the first event was evaluated using the Kaplan–Meier technique.

B.2.4.2. Participant flow in the relevant randomised controlled trials

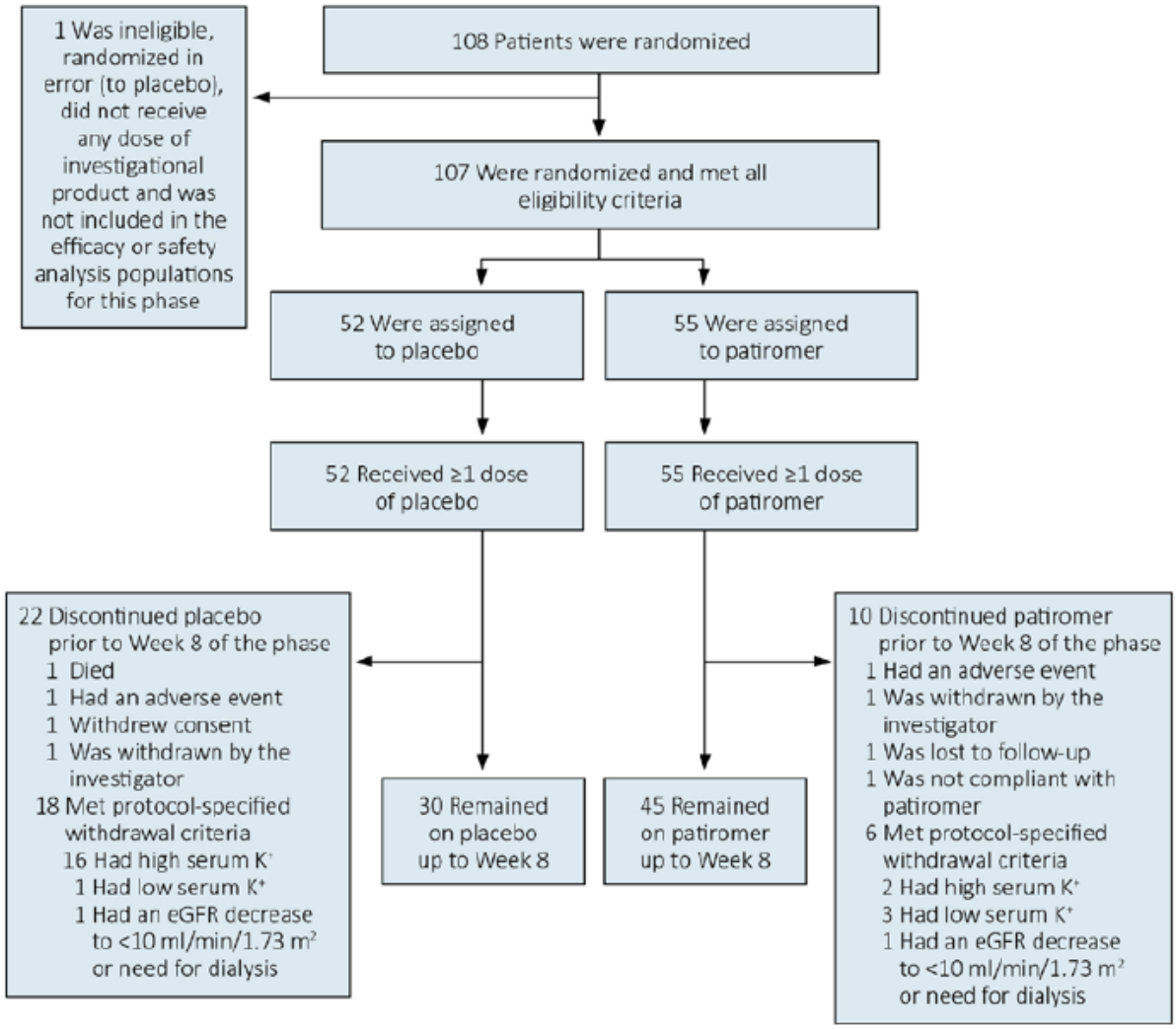
Patient disposition in the OPAL-HK study in summarised in Figure 3 and Figure 4. A total of 243 patients were enrolled into the treatment phase, of whom 219 completed the four-week treatment period and 107 were randomised to receive patiromer or placebo during the withdrawal phase. The most common reasons for discontinuation from the initial treatment phase were adverse events (2 [2%] in dose group 1 and 8 [5%] in dose group 2) and patient decision (2 [2%] in dose group 1 and 3 [2%] in dose group 2). All of the patients entering the withdrawal phase received at least one dose of study medication. Overall, 10 patients (18%) in the patiromer group and 22 (42%) in the placebo group discontinued prematurely during the randomised withdrawal phase; the most common reasons for discontinuation were elevated potassium levels that met pre-specified withdrawal criteria (2 patients [4%] in the patiromer group and 16 [31%] in the placebo group) and potassium levels of <3.8 mmol/L (3 patients [5%] in the patiromer group and 1 [2%] in the placebo group). The first patient was enrolled in February 2013, and the last patient completed follow-up in August 2013.

Figure 3: Patient disposition in the OPAL-HK study (initial treatment phase)



eGFR, estimated glomerular filtration rate; K^+, potassium; RAAS, renin–angiotensin–aldosterone system.

Figure 4: Patient disposition in the OPAL-HK study (randomised withdrawal phase)



eGFR, estimated glomerular filtration rate; K+, potassium

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The randomisation and blinding procedures used in this study are considered to be adequate and appropriate. A complete quality assessment of the OPAL-HK study can be found in Appendix D.

Was randomisation carried out appropriately?

Randomisation for the randomised withdrawal phase was performed centrally by IWRS, according to the time of the randomisation request across all sites.

Was the concealment of treatment allocation adequate?

During both parts of the study, patients were blinded to their assigned treatment; the Informed Consent form signed by each patient stated that the patient would receive patiromer at some point during the study, either during the initial treatment phase or the Randomised Withdrawal Phase.

Were the groups similar at the outset of the study in terms of prognostic factors?

The baseline characteristics of patients in the two randomised groups were similar during the initial treatment phase, and were balanced at the randomised withdrawal phase baseline (50).

Were the care providers, participants and outcome assessors blind to treatment allocation?

At each site, personnel involved in the collection, handling, and processing of blood specimens were blinded. To manage serum potassium appropriately, and to facilitate titration of patiromer and decision-making about RAAS inhibitor dosing, study investigators were aware that all patients were treated with patiromer during the initial treatment phase. They also knew which patients had been randomised to patiromer or placebo during the randomised withdrawal phase.

Were there any unexpected imbalances in drop-outs between groups?

There appeared to be no unexplained differences in drop-out rates between the two groups during the randomised withdrawal phase of the study.

Is there any evidence to suggest that the authors measured more outcomes than they reported?

There is no evidence to suggest that there were any unreported outcomes in the study.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Statistical analyses of the primary endpoint in both parts of the study were performed on an ITT basis, and appropriate imputation methods were used to replace missing data.

The majority of enrolled patients were male, and the mean age was 64.2 years. Overall, 46% of patients had stage 3 CKD, and 45% had stage 4 disease; 9% were considered to have stage 2 CKD on the basis of central laboratory measurements, but were included in the study because they met entry criteria on the basis of local measurements (50). Hypertension was present in 97% of patients, and type 2 diabetes in 57%; 42% had CHF and 25% had experienced a myocardial infarction. The proportions of patients with these comorbidities were similar in both randomised treatment groups.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1. OPAL-HK Initial treatment phase

The mean daily dose of patiromer during the initial treatment phase was 12.8 g in patients with mild hyperkalaemia, and 21.4 g in those with moderate-to-severe hyperkalaemia. Overall, 147 of 243 patients (60%) who received patiromer during the OPAL-HK initial treatment phase reported at least one dose titration. Of these, 91 (62%) required only one adjustment. The majority of titrations occurred in day 3 (33% of patients) or at the week 1 visit (25%). Dose increases were reported by a larger proportion of patients than were dose reductions.

Reduction in serum potassium (initial treatment phase primary endpoint)

For the overall OPAL-HK study cohort, the mean (± standard error [SE]) change in serum potassium levels from baseline to week 4 was −1.01 ± 0.03 mmol/L (95% confidence interval [CI], −1.07 to −0.95; $p<0.001$) (Table 11). Corresponding changes for patients with mild or moderate to severe hyperkalaemia are given in Table 11. Observed mean serum potassium levels over time for the overall cohort during the initial treatment phase are shown in Figure 5.

Table 11: Estimated change in serum potassium (mmol/L): initial treatment phase, ITT population*

	Dose group 1: 5.1–<5.5 mmol/L (n=90)		Dose group 2: 5.5–<6.5 mmol/L (n=147)		Total: 5.1–<6.5 mmol/L (N=237)		
Visit†	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	**Mean ± SE**	**95% CI**	**p-value‡**
Initial treatment phase day 3§	-0.34 ± 0.042	(−0.43, −0.26)	−0.51 ± 0.038	(−0.58, −0.43)	−0.45 ± 0.030	(−0.51, −0.39)	
Initial treatment phase week 1	-0.47 ± 0.047	(−0.56, −0.37)	−0.87 ± 0.042	(−0.95, −0.78)	−0.71 ± 0.032	(−0.78, −0.65)	
Initial treatment phase week 2	-0.63 ± 0.051	(−0.73, −0.53)	−1.09 ± 0.039	(−1.17, −1.01)	−0.91 ± 0.031	(−0.97, −0.85)	
Initial treatment phase week 3	-0.68 ± 0.057	(−0.79, −0.57)	−1.23 ± 0.039	(−1.30, −1.15)	−1.02 ± 0.032	(−1.08, −0.95)	
Initial treatment phase week 4	-0.65 ± 0.049	(−0.74, −0.55)	−1.23 ± 0.040	(−1.31, −1.16)	**−1.01 ± 0.031**	**(−1.07, −0.95)**	**<0.001**

*This analysis includes subjects in the ITT population of the initial treatment phase who have either a local or central serum potassium result at baseline and at least one weekly post-baseline visit (i.e. the initial treatment phase week 1 or later) and excludes six subjects who had no result collected after the initial treatment phase day 3. Column header counts are subjects included in the cohort described above. Subjects are classified according to their dosing group assignment reported on the eCRF. The primary efficacy outcome for the initial treatment phase is the change in serum potassium at the initial treatment phase week 4. The estimate of change and corresponding p-value are indicated by the bolded results. The estimates for the initial treatment phase week 1 through to the initial treatment phase week 4 come from a longitudinal model with:

1. Weekly post-baseline measurements from the initial treatment phase as the response variables.
2. Three categorical covariates:
   a) time as defined by weekly initial treatment phase visits
   b) presence of type 2 diabetes mellitus at the initial treatment phase baseline
   c) presence of heart failure at the initial treatment phase baseline.
3. The initial treatment phase baseline central serum potassium as a continuous covariate.
4. An unstructured covariance structure.

Estimates for the starting dose groups come from running the longitudinal model separately on the cohort of subjects in each dosing group. If a central serum potassium result was missing at a visit, it was imputed by the regression model and the local laboratory result from that particular visit. No other imputation was used.

†Visits are determined by windows defined in terms of days relative to first dose of patiromer during the initial treatment phase.

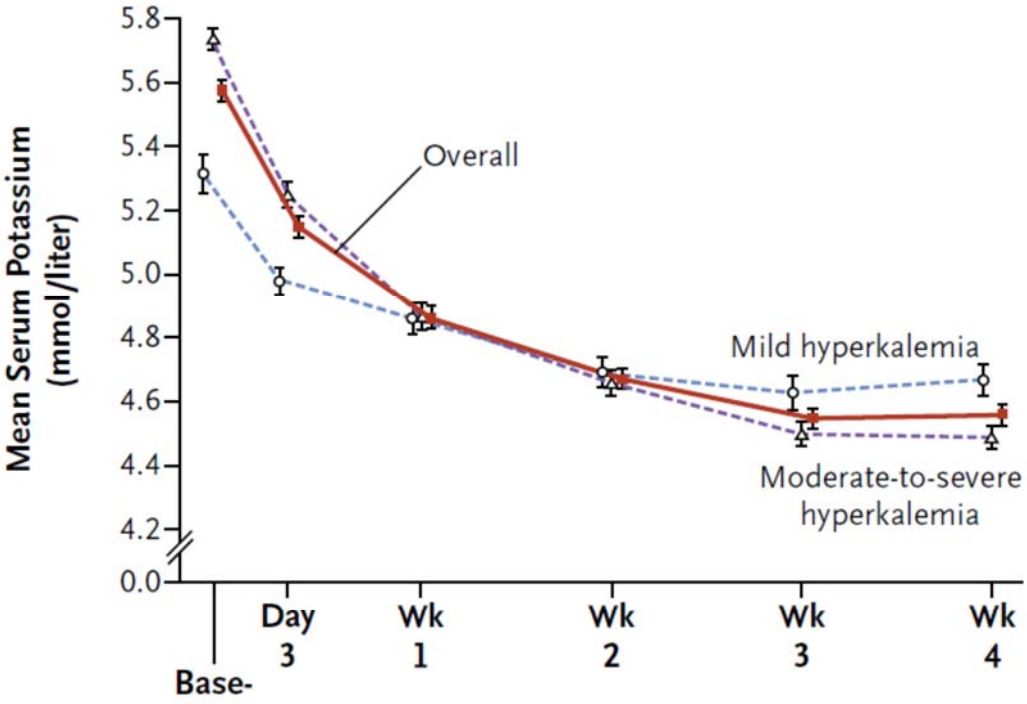
‡The p-value comes from a test comparing the mean change in serum potassium at the initial treatment phase week 4 to zero.

§The estimates for initial treatment phase day 3 come separately from an ANCOVA model with initial treatment phase day 3 measurement as the response variable and the same covariates listed for the longitudinal model. Estimates for the starting dose groups come from running the ANCOVA model separately on the cohort of subjects in each dosing group. This analysis includes the total ITT population of the initial treatment phase with a baseline and a day 3 result.

ANCOVA, analysis of covariance; CI, confidence interval; eCRF, electronic case report form; ITT, intention-to-treat; SE, standard error.

Source: Table 14.2.1.1.1 from Clinical Study Report.

Figure 5: Change in serum potassium levels during the initial treatment phase of OPAL-HK



No. at Risk						
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

Values are the observed mean values as measured in a central laboratory. During the four-week initial treatment phase, all patients received treatment with patiromer; patients with a potassium level of 5.1–<5.5 mmol/L (mild hyperkalaemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5–<6.5 mmol/L (moderate-to-severe hyperkalaemia) received 8.4 g of patiromer twice daily. Bars indicate standard error. Data points are staggered to make them more legible.

Wk, week.

Source: Figure 1 from Weir et al. 2015.

Proportion of patients with controlled hyperkalaemia (initial treatment phase secondary endpoint)

The proportion of patients with serum potassium levels within the target range (3.8–<5.1 mmol/L) at week 4 was 76% (95% CI, 70 to 81), with similar results in patients with mild hyperkalaemia (74% [95% CI, 65 to 82]) and those with moderate-to-severe hyperkalaemia (77% [95% CI, 70 to 83]).

Fifty-nine patients (24%) did not have serum potassium levels in the target range at week 4. Of these 27 completed the phase with serum potassium levels of 5.1 mmol/L or higher, but only three (1%) never had a serum potassium value below 5.1 mmol/L during the initial treatment phase (Table 12).

Table 12: Estimated percentage of subjects with serum potassium values within the target range of 3.8–<5.1 mmol/L at initial treatment phase week 4 (ITT population)

	Dose group 1: 5.1– <5.5 mmol/L (n=90)	Dose group 2: 5.5– <6.5 mmol/L (n=147)	Total: 5.1– <6.5 mmol/L (N=237)
Raw percentage, n (%)			
Success: initial treatment phase week 4 serum K^+ 3.8 to < 5.1 mmol/L	[redacted]	[redacted]	184 (76)
Failure: either reason	[redacted]	[redacted]	59 (24)
Did not complete the initial treatment phase	[redacted]	[redacted]	24 (10)
Initial treatment phase week 4 serum K^+ <3.8 mmol/L or ≥5.1 mmol/L	[redacted]	[redacted]	35 (14)
<3.8 mmol/L	[redacted]	[redacted]	8 (3)
≥5.1 mmol/L	[redacted]	[redacted]	27 (11)
Stratified percentage, % (95% CI)			
Success: initial treatment phase week 4 serum K^+ 3.8–<5.1 mmol/L	[redacted]	[redacted]	76 (70, 81)
Failure: either reason (see above)	[redacted]	[redacted]	24 (19, 30)

Column header counts are subjects in the ITT population of the initial treatment phase classified according to their dosing group assignment reported on the eCRF. Initial treatment phase secondary efficacy result is shown in bolded text: the stratified percentage and 95% CI of subjects who had an initial treatment phase week 4 serum K^+ result within the range of 3.8–<5.1 mmol/L. The estimated percentage and standard errors are stratified by the presence or absence of heart failure, the presence or absence of type 2 diabetes mellitus, and central initial treatment phase baseline serum K^+ (<5.5 mmol/L or ≥5.5 mmol/L). The raw percentages presented at the top of this table are simple percentages calculated using the column header counts as denominators. Subjects who completed initial treatment phase week 4 but are missing a central laboratory result had their missing week 4 value imputed by the regression model and the initial treatment phase week 4 local laboratory result.

CI, confidence interval; eCRF, electronic case report form; ITT, intention-to-treat; K^+, potassium.

B.2.6.2. OPAL-HK Randomised withdrawal phase

Reduction in serum potassium (randomised withdrawal phase primary endpoint)

The randomised withdrawal phase included patients whose serum potassium was well controlled during the initial treatment phase; mean potassium levels at randomised withdrawal phase baseline in the placebo and patiromer groups were 4.45 mmol/L and 4.49 mmol/L, respectively. The estimated median change from the start of the randomised withdrawal phase to week 4 was 0.72 mmol/L in the placebo group and 0 mmol/L in the patiromer group (Table 13). The between-group difference of 0.72 mmol/L was statistically significant (p<0.001) (50).

Table 13. Change in serum potassium in the randomised withdrawal phase from baseline to week 4 or the first local laboratory serum potassium result of <3.8 mmol/L or ≥5.5 mmol/L (ITT population)

Estimated median change in serum K^+ (mmol/L) (quartiles)		Difference in median change (mmol/L)	
Placebo (n=52)	**Patiromer (n=55)**	**Estimate (95% CI)**	**p-value**
0.72 (0.22, 1.22)	0.00 (−0.30, 0.30)	0.72 (0.46, 0.99)	<0.001

Column header counts are subjects in the ITT population of the randomised withdrawal phase classified by their randomised treatment assignment recorded in the IWRS data. Missing serum potassium values were imputed as described in Appendix 2 of the Statistical Analysis Plan. Multiple imputation yielded 10 complete observation datasets for this analysis.The primary efficacy outcome for the randomised withdrawal phase is change from baseline serum potassium to the central laboratory serum potassium measured at either: i) randomised withdrawal phase week 4, for subjects whose local serum potassium remains in the range of 3.8–<5.5 mmol/L up to randomised withdrawal phase week 4 or ii) an earlier time point when the subject first has a local serum potassium <3.8 mmol/L or ≥5.5 mmol/L. Changes from baseline serum potassium were ranked, and the treatment groups were compared using an ANOVA model with strata used at randomization (initial treatment phase baseline serum potassium [<5.8 mmol/L or ≥5.8 mmol/L] and presence of type 2 diabetes mellitus [yes/no]) included as covariates in the model and a variable for treatment group. To compare patiromer with placebo, the difference between the mean ranks was tested using a two-sided t-test. The difference and 95% CI between the treatment groups in median change from baseline was estimated using a Hodges-Lehmann estimator. The statistical tests and estimates were calculated for each of the 10 complete observation datasets and combined using multiple imputation methods. The estimates of median change and quartiles in the patiromer group were calculated as the median of patiromer medians and median of the quartiles from the 10 complete observation datasets created through multiple imputation. The placebo median was calculated by adding the Hodges-Lehmann difference to the patiromer median. The quartile changes of the placebo group were calculated as the median quartiles shifted by the difference (0.08) between the Hodges-Lehmann estimate (0.72) and the median of the medians of the placebo group (0.80).

ANOVA, analysis of variance; CI, confidence interval; ITT, intention-to-treat; IWRS, interactive web response system; K^+, potassium.

Source: Table 14.2.1.2.1 from Clinical Study Report.

Proportion of patients with recurrent hyperkalaemia at any time (randomised withdrawal phase secondary endpoint)

During the 8-week randomised withdrawal phase, 60% of patients in the placebo group, and 15% of those in the patiromer group had at least one potassium value ≥5.5 mmol/L (p<0.001 for the between group difference). In the placebo group, 91% of patients, versus 43% in the patiromer group, had at least one potassium value ≥5.1 mmol/L (p<0.001) (50) (Table 14).

Table 14. Secondary efficacy outcome results (randomised withdrawal phase, ITT population)

	Stratified percentages (95% CI)			
Secondary outcome	**Placebo (n=52)**	**Patiromer (n=55)**	**Difference***	**p-value**
Having a serum K^+ ≥5.5 mmol/L	60 (47, 74)	15 (6, 24)	45 (29, 61)	<0.001
Having a serum K^+ ≥5.1 mmol/L	91 (83, 99)	43 (30, 56)	48 (33, 63)	<0.001

Column header counts are subjects in the ITT population of the randomised withdrawal phase classified by their randomised treatment assignment recorded in the IWRS data. The estimated percentages and standard errors are stratified by the presence or absence of type 2 diabetes mellitus and central initial treatment phase baseline serum potassium level (<5.8 mmol/L or ≥5.8 mmol/L). The treatment groups were compared with a Mantel-Haenszel test stratified by the four randomization strata. Missing centrally-measured serum potassium results were imputed using either the local laboratory values and the regression model or multiple imputation. Multiple imputation yielded 10 complete observation datasets for this analysis. The statistical tests and estimates were calculated for each of the 10 complete observation datasets and combined using multiple imputation methods.

*Difference is calculated as placebo minus patiromer.

CI, confidence interval; ITT, intention-to-treat; IWRS, interactive web response system; K^+, potassium.

Source: Table 14.2.2.2.1 from Clinical Study Report.

B.2.6.3. OPAL-HK Randomised withdrawal phase exploratory endpoints

Exploratory efficacy outcomes used in the economic model that incorporated aspects of RAAS inhibitor dosing and dose adjustments in the randomised withdrawal phase are summarised below.

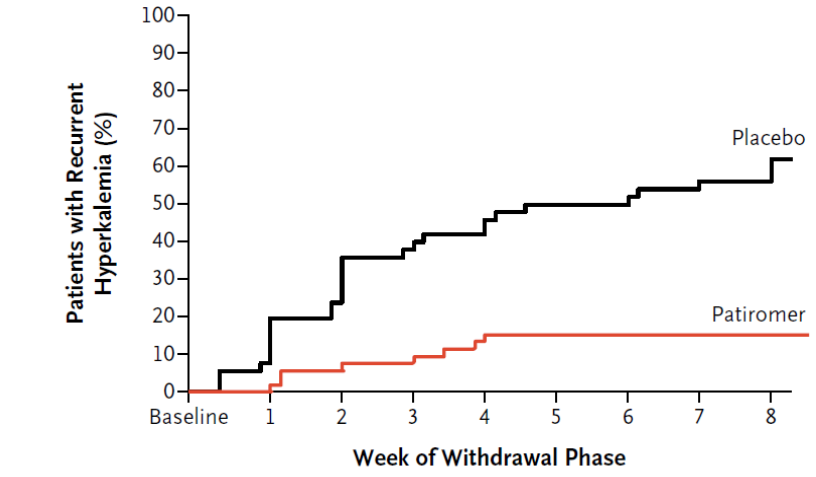
Time to first occurrence of hyperkalaemia

The cumulative proportions of patients in the patiromer and placebo groups with a first occurrence of serum potassium ≥5.5 mEq/L and ≥5.1 mEq/L over the eight weeks of the randomised withdrawal phase are shown in Figure 6. For both thresholds, the estimated proportion of patients in the placebo group was higher than

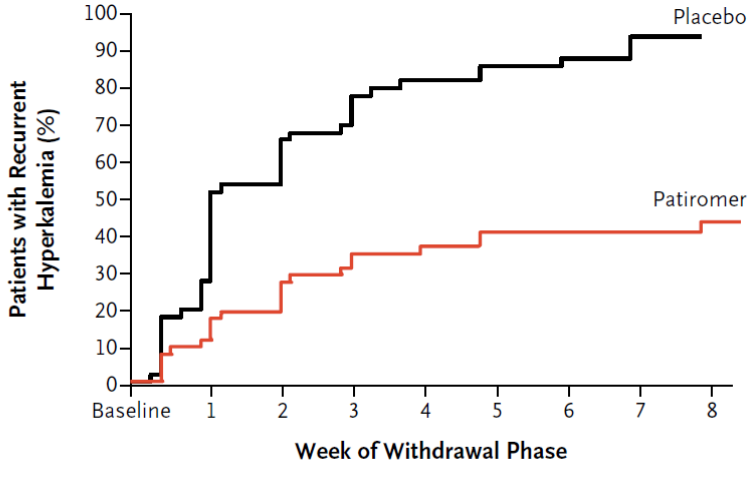
that in the patiromer group from the first follow-up visit (day 3), and the difference between the groups increased with time (50).

Figure 6. Time to first occurrence of hyperkalaemia during the randomised withdrawal phase: (a) serum potassium ≥5.5 mEq/L; (b) serum potassium ≥5.1 mEq/L

(a)



No. at Risk									
Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32



No. at Risk									
Placebo	52	37	24	16	10	8	8	7	1
Patiromer	55	47	42	36	34	30	29	29	23

(b)

Time to the first occurrence of a serum potassium level of ≥5.5 mEq/L (a) and of ≥5.1 mEq/L (b) among patients who were randomly assigned to continue patiromer treatment and those who were assigned to switch to placebo for the randomised withdrawal phase. Baseline refers to week 0 of the randomised withdrawal phase. The dose of the study drug was intended to be kept stable, and the doses of renin–angiotensin–aldosterone system inhibitors were not to be changed during the first four weeks of the randomised withdrawal phase. After week 4 of the randomised withdrawal phase, an increase in the dose of patiromer was allowed at first occurrence of a serum potassium level of ≥5.1 mEq/L.

Source: Figure 2 from Weir et al. 2005.

Enablement of optimal RAAS inhibitor therapy

Pre-specified treatment algorithms for the management of recurrent hyperkalaemia were followed during the randomised withdrawal phase. A first hyperkalaemia event was managed by increasing the dose of patiromer (patiromer group) or modifying the RAAS inhibitor dose (placebo group), as described below. Subsequent hyperkalaemia events mandated discontinuation of RAAS inhibitor therapy.

During the first four weeks of the randomised withdrawal phase, the potassium threshold used for mandating changes to RAAS inhibitor treatment was 5.5–<6.0 mEq/L. During the second four weeks of the randomised withdrawal phase, RAAS inhibitors were discontinued in patients who experienced two events of potassium 5.1–<6.0 mEq/L, or in patients who had any event of potassium 6.0–<6.5 mEq/L. In the placebo group, the RAAS inhibitor dose was also decreased by 50% or to the next available dose below 50% upon the first event of potassium 5.1–<6.0 mEq/L.

RAAS inhibitor dose adjustment or discontinuation due to hyperkalaemia

During the randomised withdrawal phase, 32 patients (62%) in the placebo group, compared with 9 (16%) in the patiromer group, required a protocol-specified intervention (i.e. RAAS inhibitor dose reduction or discontinuation in the placebo group; patiromer dose increase or RAAS inhibitor discontinuation in the patiromer group) in order to manage a recurrence of hyperkalaemia; 8 patients (15%) reported a dose increase (Table 15 and Figure 7) (50).

Table 15. Management of recurrent hyperkalaemia during the randomised withdrawal phase

Placebo (n=52)		Patiromer (n=55)	
RAAS inhibitor dose reduction by 50%,* n (%)	5 (10)	Patiromer dose increase,† n (%)	6 (11)
RAAS inhibitor discontinuation,‡ n (%)	27 (52)	RAAS inhibitor discontinuation, n (%)	3 (5)
Neither and completed the randomised withdrawal phase, n (%)	17 (33)	Neither and completed the randomised withdrawal phase, n (%)	40 (73)
Neither and discontinued prior to week 8, n (%)	3 (6)	Neither and discontinued prior to week 8, n (%)	6 (11)

*Subjects who reduced their RAAS inhibitor dose by 50% or to the next dose available below 50% without discontinuing their RAAS inhibitor completely.

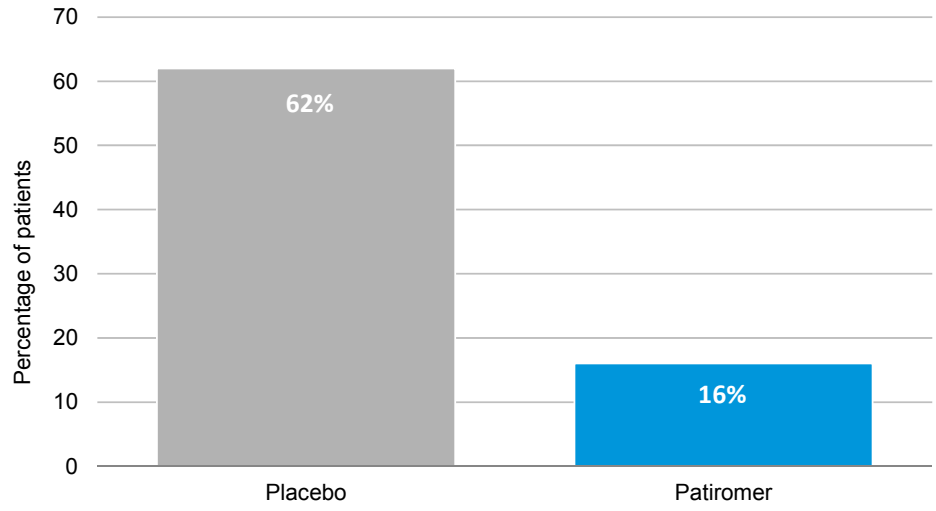
†Subjects who increased their patiromer dose without discontinuing their RAAS inhibitor completely.

‡Subjects who discontinued all RAAS inhibitor medication for any reason.

RAAS, renin–angiotensin–aldosterone system.

Source: Table 48, OPAL rly5016-301-study-report-body.pdf.

Figure 7. Patients requiring protocol-specified intervention for management of recurrent hyperkalaemia during the randomised withdrawal phase



Interventions in the placebo group include subjects who reduced their RAAS inhibitor dose by 50% or to the next dose available below 50% without discontinuing their RAAS inhibitor completely, and patients who discontinued all RAAS inhibitor medication for any reason. Interventions in the patiromer group include patients who increased their patiromer dose without discontinuing their RAAS inhibitor completely, and patients who discontinued all RAAS inhibitor medication for any reason.

RAAS, renin–angiotensin–aldosterone system.

Source: Table 48, OPAL rly5016-301-study-report-body.pdf; Weir et al. 2015.

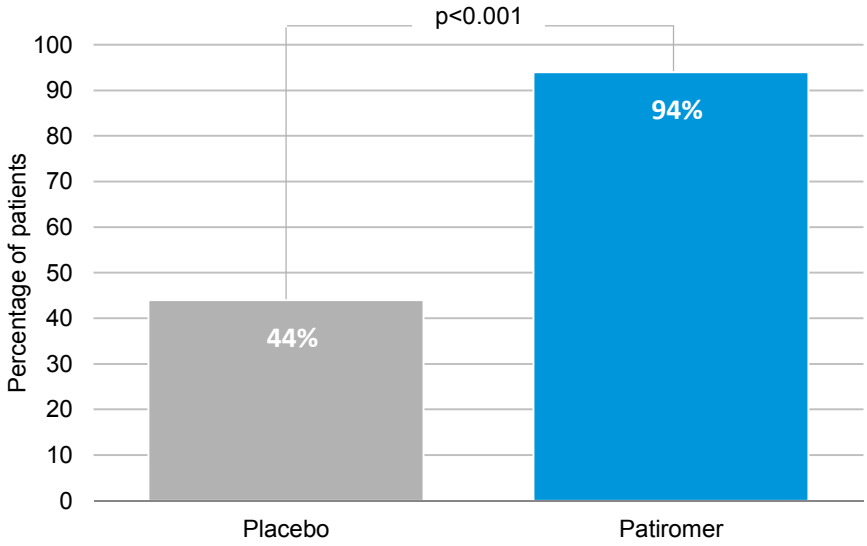
Irrespective of patiromer dose modification, the proportion of patients that required RAAS inhibitor dose modification (dose reduction, discontinuation, or both) as a result of recurrent hyperkalaemia during the eight-week randomised withdrawal phase was 66% (95% CI, 52, 79) in the placebo group and 6% (95% CI, 2, 18) in the patiromer group.

The estimated proportion of patients who discontinued RAAS inhibitor therapy because of hyperkalaemia during the eight-week randomised withdrawal phase was 56% (95% CI, 42, 71) in the placebo group and 6% (95% CI, 2, 18) in the patiromer group.

Patients receiving any dose of RAAS inhibitor at end of the randomised withdrawal phase

By the end of the randomised withdrawal phase, more patients in the patiromer group were still receiving RAAS inhibitor therapy compared with those in the placebo group (94% versus 44%, respectively) (Figure 8) (50).

Figure 8. Patients receiving RAAS inhibitors at the end of the randomised withdrawal phase



The Kaplan–Meier (product-limit) estimates are shown. The estimates use time to first occurrence of an outcome for outcomes that can occur more than once. Time is defined relative to first dose of study treatment in the randomised withdrawal phase. RAAS inhibitor modifications included in these exploratory outcomes used the data from the medication modification eCRF. Subjects who reduced

their RAAS inhibitor dose or completely discontinued RAAS inhibitor because of hyperkalaemia while on study treatment are considered to have had an event at the time of the first RAAS inhibitor reduction or discontinuation. Subjects who neither reduced their RAAS inhibitor dose nor completely discontinued RAAS inhibitor because of hyperkalaemia while on study treatment are censored at the last site visit on or before their last dose of study treatment. Subjects who completely discontinued RAAS inhibitor for reasons other than hyperkalaemia while on study treatment and who did not modify their RAAS inhibitor in any way prior to discontinuing are censored at their last RAAS inhibitor dose. Subjects who reduced their RAAS inhibitor dose for reasons other than hyperkalaemia while on study treatment and who did not reduce their RAAS inhibitor dose because of hyperkalaemia prior to that reduction are not considered to have had an event at the time of that reduction. Instead, their RAAS inhibitor exposure while on study treatment after that initial reduction will determine whether they are considered to have had an event or are censored, as noted earlier.

RAAS, renin–angiotensin–aldosterone system.

Source: Section 11.4.2.4.3, Table 14.2.5.2.2, OPAL rly5016-301-study-report-body.pdf.

In patients with CHF, 100% of patients receiving patiromer were receiving RAAS inhibitor treatment at week 8 of the randomised withdrawal phase compared with 55% of patients in the placebo group (53).

A greater proportion of patients in the patiromer group (78%) than in the placebo group (37%) remained on the study treatment **and** were taking any RAAS inhibitor dose at the end of the randomised withdrawal phase (Table 16) (53).

Table 16. Proportion of patients taking study treatment and RAAS inhibitors at the end of the randomised withdrawal phase

Exploratory outcome	Placebo (n=52) n (%)	Patiromer (n=55) n (%)
Taking any RAAS inhibitor dose*	19 (37)	43 (78)
Taking maximum RAAS inhibitor dose†	6 (12)	14 (25)

Randomised withdrawal phase ITT population: investigators indicated with a yes/no checkbox on the medication modification eCRF at the initial treatment phase baseline visit whether the subject was on maximal RAAS inhibitor dose. Subsequent RAAS inhibitor dose adjustments were identified on the prior/concomitant medication repeating form data. Randomised withdrawal phase week 8 visit window is defined as day 54 (i.e. 53 days after first dose of IP) until last dose of IP. Therefore, these exploratory outcomes use day 54 as the reference timepoint.

*Subjects who remained on study treatment until day 54 (relative to first dose of IP) and who were taking any RAAS inhibitor dose on day 54 are counted in the numerators of this row. Subjects who discontinued RAAS inhibitor on day 54 or who discontinued study treatment prior to day 54 are not considered as having remained on RAAS inhibitor by randomised withdrawal phase week 8. All subjects in the ITT population of the randomised withdrawal phase are included in the denominators.

†Subjects who remained on study treatment until day 54 and who were still taking a maximum RAAS inhibitor dose on day 54 are counted in the numerator of this row. Subjects who reduced or discontinued their RAAS inhibitor dose on or before day 54 or who discontinued study treatment prior to day 54 are not considered to be still taking maximum RAAS inhibitor dose at randomised

withdrawal phase week 8. All subjects in the ITT population of the randomised withdrawal phase are included in the denominators.

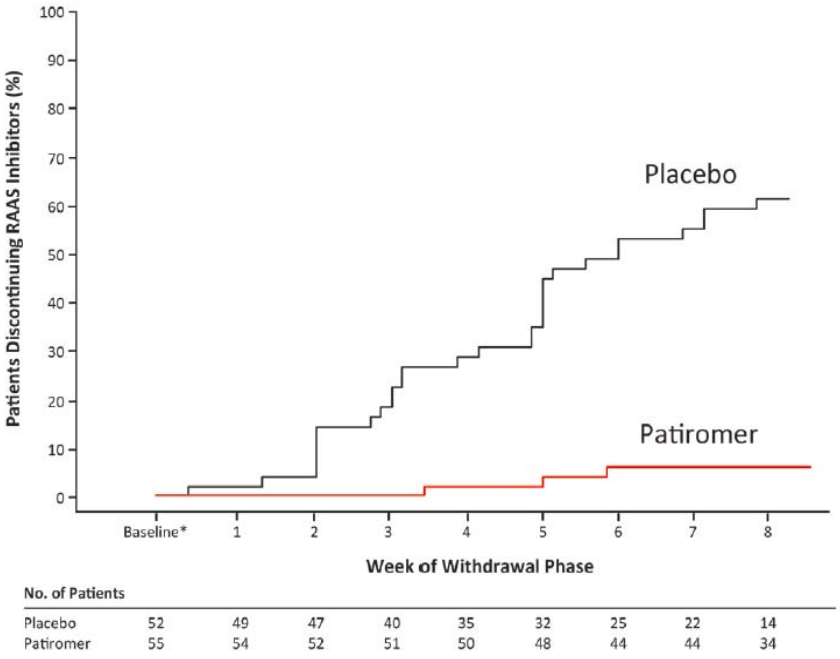
eCRF, case report form; IP, investigational product; ITT, intention-to-treat.

Source: Table 14.2.5.2.3, OPAL rly5016-301-study-report-body.pdf.

Time to discontinuation of RAAS inhibitor

The time to RAAS inhibitor discontinuation in patients receiving placebo and patiromer is shown in Figure 9. Patients who were randomised to receive placebo required RAAS inhibitor discontinuation more often than patients who continued to receive patiromer (50).

Figure 9: Time to RAAS inhibitor discontinuation during the randomised withdrawal phase



*Baseline refers to week 0 of the randomised withdrawal phase.

RAAS, renin–angiotensin–aldosterone system.

Source: Figure S4 from Weir et al. 2005.

B.2.6.4. AMETHYST-DN Clinical Effectiveness Overview

Among 306 randomised patients, the least squares mean reduction from baseline in serum potassium level at week 4 or time of first dose titration in patients with mild hyperkalemia was 0.35 (95%CI, 0.22-0.48) mmol/L for the 4.2 g twice daily starting-

dose group, 0.51 (95%CI, 0.38-0.64) mmol/L for the 8.4 g twice daily starting-dose group, and 0.55 (95%CI, 0.42-0.68) mmol/L for the 12.6 g twice daily starting-dose group. In those with moderate hyperkalemia, the reduction was 0.87 (95%CI, 0.60-1.14) mmol/L for the 8.4 g twice daily starting-dose group, 0.97 (95%CI, 0.70-1.23) mmol/L for the 12.6 g twice daily starting-dose group, and 0.92 (95%CI, 0.67-1.17) mmol/L for the 16.8 g twice daily starting-dose group (P < .001 for all changes vs baseline by hyperkalemia starting-dose groups within strata). From week 4 through week 52, statistically significant mean decreases in serum potassium levels were observed at each monthly point in patients with mild and moderate hyperkalemia (3).

B.2.7 Subgroup analysis

Pre-specified subgroup analyses were conducted in the following subgroups in OPAL-HK:

- patients with and without CHF
- patients with and without type 2 diabetes
- baseline serum potassium <5.5 mmol/L and ≥5.5 mmol/L
- patients receiving RAAS inhibitor treatment at maximal or submaximal doses
- male or female
- age <65 years or ≥65 years
- geographical region (EU and USA versus non-EU Eastern Europe)

These analyses were conducted to investigate the efficacy of patiromer in patients with common comorbidities of CKD, and other potential risk factors such as age and sex. The number of patients in these subgroups are shown in Appendix E.

The subgroup analysis by geographical region was conducted because almost half of the participating centres (n=24) were in Eastern Europe, while 21 were in the EU and 14 were in the USA. Compared with EU and US sites, patients at Eastern European sites had higher mean serum potassium levels at baseline (EU:

5.4 mmol/L; USA: 5.3 mmol/L; Eastern Europe: 5.7 mmol/L) and lower proportions were on maximal doses of RAAS inhibitor (62%, 82%, and 31%, respectively).

The results of the subgroup analyses during the initial treatment phase are summarised in Appendix E. In general, reductions in serum potassium were consistent in patients with or without CHF or type 2 diabetes, in males and females, older or younger patients, and in patients receiving maximal or submaximal doses of RAAS inhibitors. However, reductions in serum potassium were significantly greater in patients with baseline potassium ≥5.5 mmol/L, in women, and in patients from Eastern Europe, compared with the respective comparator subgroups.

B.2.8 Meta-analysis

No meta-analyses were undertaken for the efficacy endpoints in this submission but safety endpoints from both OPAL-HK and AMETHYST-DN were pooled (see section B.2.10).

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were undertaken for this submission.

Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

The OPAL-HK study (1) included collection of safety data, and the AMETHYST-DN study (2) included assessment of the frequency and severity of adverse events as the safety endpoint. In order to provide the most robust appraisal of the safety data, this submission is based on safety and tolerability data for OPAL-HK, and a pooled analysis of safety and tolerability data for patients who received patiromer in OPAL-HK and AMETHYST-DN. The AMETHYST-DN phase 2 multicentre, open-label, dose-ranging randomised clinical trial was conducted to inform dose selection for a phase III study using data from patients evaluated through four weeks, as well as to evaluate the 52-week safety and efficacy of patiromer in patients with diabetes and CKD receiving therapy with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin-receptor blocker (ARB), or both, with or without spironolactone. The

inclusion of the AMETHYST-DN safety data is considered relevant to this submission as the consistent findings relating to the primary safety endpoint (adverse events through 52 weeks) supports the long-term safety profile of patiromer.

B.2.10.1. Treatment exposure in OPAL-HK and AMETHYST-DN

In the initial treatment phase of the OPAL-HK study, 243 patients received at least one dose of patiromer (50). Patients received a mean total of 486.9 g of patiromer: the mean daily dose was 18.2 g, and the mean treatment duration was 27.0 days. During the randomised withdrawal phase, 55 patients received patiromer, over a mean treatment duration of 51.4 days. The mean daily dose during this period was 21.2 g (54).

The pooled dataset for the OPAL-HK and AMETHYST-DN studies included 547 patients, who received at least one dose of patiromer. The mean duration of treatment was 166.7 days, and the mean daily dose was 20.1 g. The duration of treatment with patiromer, duration of exposure to patiromer and mean daily dose for the initial treatment and randomised withdrawal phases of OPAL-HK and the pooled analysis of patiromer-treated patients in OPAL-HK and AMETHYST-DN, are shown in Table 17.

Table 17: Patiromer exposure in OPAL-HK and AMETHYST-DN

	OPAL-HK		**OPAL-HK and AMETHYST-DN pooled data (N=547) [(55)]**
	Initial treatment phase: ITT population (N=243)	**Randomised withdrawal phase: ITT population (N=55)**	
Patiromer treatment duration,* days			
Mean (SD)	27.0 (6.3)	51.4 (13.5)	166.7
Q1; Q2; Q3	28.0; 29.0; 29.0	56.0; 57.0; 57.0	29.5; 85.5; 365.0
Range (min; max)	1.0; 34.0	6.0; 61.0	1.5; 385.0
Total patiromer received,† g			
Mean (SD)	486.9 (215.6)	1,065.3 (502.1)	3,632.4 (4,161.3)
Q1; Q2; Q3	294.0; 479.0; 655.0	571.0; 941.0; 1,411.0	478.8; 1,419.6; 6,132.0
Range (min; max)	8.0; 958.0	126.0; 2,117.0	8.4; 18,295.2
Mean daily dose,‡ g/day			
Mean (SD)	18.2 (6.6)	21.2 (8.1)	20.1 (9.4)
Q1; Q2; Q3)	15.0; 17.0; 23.0	17.0; 21.0; 25.0	14.2; 17.6; 25.1
Range (min; max)	8.0; 37.0	8.0; 40.0	3.0; 55.5

ITT, intention-to-treat; Q1, 25th percentile; Q2, 50th percentile; Q3, 75th percentile; SD, standard deviation.

*The number of days spanning the first and last patiromer dose dates in OPAL-HK and AMETHYST-DN was calculated as date of last dose minus date of first dose plus 1. This calculation did not account for partial or missed doses. For subjects randomised to patiromer in the OPAL-HK randomised withdrawal phase, the total duration is the sum of the duration of the initial treatment phase plus the duration of the randomised withdrawal phase. The date of the last dose of patiromer was identified by the investigator; duration of exposure may include days in which a 0 g/day patiromer dose was prescribed.

†The total amount of patiromer in the OPAL-HK treatment phase accounted for subjects: i) taking the first dose while at the study site and the second dose at home in the evening of the same day; ii) taking morning and evening doses each day without study site visits; iii) taking the morning dose from kits dispensed at the prior visit on the day of a study site visit and an evening dose from the kits dispensed that same day; and iv) taking only the morning dose on the date of the last dose. The total dose received in the pooled dataset was calculated based on study drug dispensing and return records from each study visit.

‡Mean daily dose for each subject is the total amount of patiromer taken divided by the period of time during which the subject took patiromer. The period of time for taking the total amount of patiromer equals the duration of exposure as defined in the first footnote (*): 0.5 to account for the last dose being only a morning dose.

Source: OPAL-HK treatment phase: Table 52, OPAL rly5015-301-study-report-body.pdf; OPAL-HK randomised withdrawal phase: Table 14.5.1.2.1, rly5016-301-end-of-text-tables-and-figures.pdf; pooled data: Table 6, 2.7.4 summary-clin-safety.pdf.

B.2.10.2. Overview of adverse events in OPAL-HK and AMETHYST-DN

The incidence of adverse events (AEs) in the OPAL-HK and AMETHYST-DN trials, and the pooled dataset, is summarised in Table 18. In the OPAL-HK treatment phase, 47% of patients experienced any adverse event (AE), with 1% of patients experiencing a serious AE (50). Treatment-related AEs, none of which were serious, were reported in 22% of patients (54). In the randomised withdrawal phase of OPAL-HK, the proportions of patients experiencing any AE were similar in the patiromer group (47%) and the placebo group (50%) (50). Treatment-related AEs occurred in 7% and 4% of patients, respectively. One patient in each treatment group experienced a AE leading to treatment discontinuation (54).

The pooled dataset from OPAL-HK and AMETHYST-DN showed that 21.2% of patients receiving patiromer experienced AEs considered to be treatment-related (Table 18): no SAEs were assessed by the investigator or sponsor as being related to patiromer. Approximately 9% of patients discontinued treatment due to an AE with patiromer; this figure included those patients who received patiromer for up to two months in the AMETHYST-DN study (56).

Table 18: Summary of AEs in OPAL-HK and AMETHYST-DN

	OPAL-HK*			Pooled data (N=547) [(56)]
	Initial treatment phase (N=243)	Randomised withdrawal phase (N=107)		
		Placebo (n=52)	Patiromer (n=55)	
AEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥1 AE	114 (47)	26 (50)	26 (47)	340 (62)
≥1 SAE	3 (1)	1 (2)	0	47 (9)
AE leading to treatment discontinuation†	15 (6)	1 (2)	1 (2)	51 (9)
SAE leading to treatment discontinuation†	2 (1)	1 (2)	0	24 (4)
AE leading to dose modification‡	22 (9)	1 (2)	1 (2)	NA
SAE leading to dose modification	2 (1)	1 (2)	0	NA
Treatment-related AE	53 (22)	2 (4)	4 (7)	116 (21)
Treatment-related SAE	0	0	0	0
Severe AE	2 (1)	1 (2)	0	41 (8)
Severe SAE	2 (1)	1 (2)	0	38 (7)
AE resulting in death	0	1 (2)§	0	15 (3)

Data are presented as number of subjects (percent of subjects). Column header counts and denominators are patients in the ITT population of either phase who received at least one dose of study treatment.

*Treatment phase results includes the initial treatment phase treatment period plus the follow-up period; the randomised withdrawal phase results include the randomised withdrawal phase period plus the follow-up period. For subjects who did not enter the randomised withdrawal phase, events collected on the AE eCRF with onset on or after the first dose of patiromer in the initial treatment phase are included in the initial treatment phase column. For subjects who did enter the randomised withdrawal phase, only events collected on the AE eCRF with onset on or after the first dose of patiromer in the initial treatment phase, and on or before the first dose of study treatment in the randomised withdrawal phase, are included in the initial treatment phase column. Only events recorded on the AE eCRF with onset after first dose of IP in the randomised withdrawal phase are included in the randomised withdrawal phase column.

†In the pooled analyses, events leading to discontinuation include all events with a fatal outcome that occurred while the subject was taking study treatment, regardless of whether the event was reported as leading to discontinuation.

‡AEs with any of the following outcomes are considered events leading to patiromer dose modification: permanent or temporary discontinuation of patiromer; or increase or decrease of the patiromer dose.

§Mesenteric vessel thrombosis leading to death occurred in one patient.

AE, adverse event; eCRF, electronic case report form; IP, investigational product; ITT, intention-to-treat; NA, not applicable; SAE, serious adverse event.

Source: OPAL-HK treatment phase: Table 14.3.1.1.2, rly5016-301-end-of-text-tables-and-figures.pdf; OPAL-HK randomised withdrawal phase: Table 14.3.1.2.2, rly5016-301-end-of-text-tables-and-figures.pdf; pooled data: Table 11, clinical-overview.pdf.

B.2.10.3. Most commonly reported AEs in OPAL-HK and AMETHYST-DN

A summary of the most common AEs – defined as occurring in ≥3% of patients in any patiromer treatment group in OPAL-HK and the pooled dataset from OPAL-HK and AMETHYST-DN – is shown in Table 19. The threshold of 3% was selected because, due to the low patient numbers in each treatment group, all AEs occurring in a single patient during the randomised withdrawal phase were recorded as occurring in 2% of patients.

During the OPAL-HK initial treatment phase and its follow-up period, mild-to-moderate constipation was the most common AE, occurring in 11% of patients. During the randomised withdrawal phase, mild-to-moderate constipation, diarrhoea and nausea were the most common gastrointestinal events; each of these events occurred in 4% of patients receiving patiromer and in none of the patients receiving placebo (50, 54). Hypomagnesaemia occurred in 3% of patients in the OPAL-HK initial treatment phase, and magnesium replacement therapy was initiated in 4% of patients in the patiromer group during that phase. None of these patients had serum magnesium levels <1.2 mg/dL (50).

Pooled safety data for patients who received at least one dose of patiromer in the OPAL-HK and AMETHYST-DN studies showed similar rates of AEs to the initial treatment phase of OPAL-HK, even though the duration of study treatment (4–52 weeks) and follow-up (one to four weeks) differed across the studies. Constipation was the most common AE, occurring in 8.2% of patients, and chronic renal failure and hypomagnesaemia each occurred in 6.4% of patients (55).

Table 19: TEAEs occurring with an incidence of ≥3% of patients in any patiromer treatment group

	OPAL-HK			Pooled data (55)
	Initial treatment phase	Randomised withdrawal phase		
System organ class preferred term	Patiromer (N=243)	Placebo (n=52)	Patiromer (n=55)	Patiromer (N=547)
	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders				
Constipation	26 (11)	0	2 (4)	45 (8)

Diarrhoea	8 (3)	0	2 (4)	27 (5)
Nausea	8 (3)	0	2 (4)	14 (3)
Renal and urinary disorders				
Chronic renal failure	7 (3)	1 (2)	1 (2)	35 (6)
Metabolism and nutrition disorders				
Hypomagnesaemia	8 (3)	2 (4)	1 (2)	35 (6)
Vascular disorders				
Hypertension	4 (2)	3 (6)	0	28 (5)
Blood and lymphatic system disorders				
Anaemia*	7 (3)	0	1 (2)	18 (3)
Nervous system disorders				
Headache	2 (1)	4 (8)	2 (4)	12 (2)
Cardiac disorders				
Supraventricular extrasystoles	1 (<1)	1 (2)	2 (4)	10 (2)

Data are presented as number of subjects (percent of subjects). OPAL-HK TEAEs reported over the study period and through the safety follow-up period for each phase. The safety follow-up period was one to two weeks after discontinuation of study treatment in each case. Events are listed if they occurred in ≥3% of patients in any patiromer treatment group.

*The case of anaemia reported in the randomised withdrawal phase of OPAL-HK was nephrogenic anaemia.

TEAE, treatment-emergent adverse event.

Source: OPAL-HK treatment phase: Table 14.3.1.1.4, rly5016-301-end-of-text-tables-and-figures.pdf; OPAL-HK randomised withdrawal phase: Table 14.3.1.2.8, rly5016-301-end-of-text-tables-and-figures.pdf; pooled data: Table 19, 2.7.4 summary-clin-safety.pdf.

B.2.10.4. AEs of interest in OPAL-HK

AEs of interest in the OPAL-HK trial include renal, cardiovascular, or gastrointestinal events, and events representing possible hypersensitivity reactions. A summary of AEs of interest is provided in Appendix F.

B.2.10.5. Serious AEs in OPAL-HK and AMETHYST-DN

Treatment-emergent SAEs that occurred in patients receiving patiromer in OPAL-HK and AMETHYST-DN are listed in Table 20. Three patients (1%) experienced a total of six SAEs during the OPAL-HK initial treatment phase and its follow-up period. None of the SAEs were fatal, and all were considered by the investigators to be unrelated to patiromer treatment. One fatal SAE occurred during the OPAL-HK randomised Withdrawal Phase, as described below.

In the pooled dataset, treatment-emergent SAEs occurred in 8.6% of patients treated with patiromer. Adverse events are described using the Medical Dictionary for Regulatory Activities (MedDRA) 'preferred term', which describes a single medical concept. Each MedDRA system organ class (SOC) is associated with a number of MedDRA preferred terms. At the SOC level, the most common SAEs were cardiac disorders (2.4%), general disorders and administration site conditions (1.6%), and renal and urinary disorders. At the preferred term level, no SAE occurred in ≥2% of patients, and the only SAE occurring in ≥1% of patients was chronic renal failure (1.3%) (7).

Table 20: Treatment-emergent SAEs in OPAL-HK and AMETHYST-DN

	OPAL-HK			
	Initial treatment phase	Randomised withdrawal phase		Pooled data
	Patiromer (N=243)	Placebo (n=52)	Patiromer (n=55)	Patiromer (N=547) [(55)]
System organ class	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total number of SAEs	6	1	0	63
Patients with SAEs	3 (1)	1 (2)	0	47 (9)
Cardiac disorders	1 (<1)	0	0	13 (2)
General disorders and administration site conditions	0	0	0	9 (2)
Renal and urinary disorders	1 (<1)	0	0	9 (2)
Infections and infestations	1 (<1)	0	0	6 (1)
Metabolism and nutrition disorders	0	0	0	4 (1)
Vascular disorders	0	0	0	5 (1)
Nervous system disorders	0	0	0	4 (1)
Gastrointestinal disorders	0	1 (2)	0	3 (1)
Investigations	1 (<1)	0	0	2 (<1)
Eye disorders	0	0	0	1 (<1)
Hepatobiliary disorders	0	0	0	1 (<1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (<1)

Data are presented as number of events (percent of subjects). OPAL-HK TEAEs reported over the study period and through the safety follow-up period for each phase. The safety follow-up period was one to two weeks after discontinuation of IP in each case. AEs are coded to SOC using MedDRA Version 12.0. At each level of summarisation (any SAE, SOC), subjects reporting >1 event are counted only once.

AE, adverse event; IP, investigational product; SAE, serious adverse event, SOC, system organ class.

Source: OPAL treatment phase: Table 14.3.2.1.2, rly5016-301-end-of-text-tables-and-figures.pdf; OPAL withdrawal phase: Table 14.3.2.2.2, rly5016-301-end-of-text-tables-and-figures.pdf; pooled data: Table 32, 2.7.4 summary-clin-safety.pdf.

B.2.10.6. Fatal AEs in OPAL-HK and AMETHYST-DN

No patients died while participating in the initial treatment phase of OPAL-HK, or the post-treatment follow-up (50). One death was reported during the randomised withdrawal phase, which occurred in a patient receiving placebo who died due to

mesenteric vessel thrombosis that was considered to be unrelated to patiromer (the patient had previously received patiromer during the initial treatment phase) (50). In the pooled dataset, 16 deaths occurred; one (<1%) in the placebo group and 15 (2.7%) in the patiromer groups (56). All deaths were considered by investigators to be unrelated to study treatment (55).

None of the deaths that occurred, including cardiovascular deaths, were considered by the Safety Review Board (SRB) to be related to hypokalaemia or hyperkalaemia. All cardiovascular deaths occurred in patients with underlying heart disease, including CHF or coronary artery disease with or without a history of cardiac arrhythmias. The major risk factors for death, particularly cardiovascular death, in the populations studied included age ≥65 years, male sex, CKD, diabetes, CHF, hypertension and prior myocardial infarction. All 16 patients who died had ≥4 of these risk factors (56).

A summary of all AEs leading to death in the OPAL-HK and AMETHYST-DN studies is shown in Table 21.

Table 21: Fatal AEs in OPAL-HK and AMETHYST-DN

	OPAL-HK			**OPAL-HK and AMETHYST-DN pooled data [(55, 56)]**
	Initial treatment phase	**Randomised withdrawal phase**		
	Patiromer (n=243)	**Placebo (n=52)**	**Patiromer (n=55)**	**Patiromer (n=547)**
Fatal AEs	0	1* (2)	0	15 (3)
SRB-adjudicated cause of death				
Cardiovascular	0	0	0	12 (2)
Sudden cardiac death	0	0	0	7 (1)
Acute myocardial infarction	0	0	0	4 (<1)
Stroke	0	0	0	1 (<1)
Non-cardiovascular	0	1 (2)	0	3 (<1)
Gastrointestinal	0	1 (2)	0	1 (<1)
Infection	0	0	0	1 (<1)
Neurological (non-cardiovascular)	0	0	0	1 (<1)
Fatal AEs not attributed	0	1 (2)	0	15 (3)

to study treatment				
Fatal AEs attributed to study treatment	0	0	0	0

*One subject received four weeks of treatment with patiromer in the OPAL-HK treatment phase, followed by placebo in the randomised withdrawal phase of OPAL-HK. The subject was receiving placebo at the time of the fatal event.

AE, adverse event; SRB, scientific review board.

Source: OPAL-HK treatment phase: Table 14.3.1.1.2, rly5016-301-end-of-text-tables-and-figures.pdf; OPAL-HK withdrawal phase: Table 70, OPAL rly5015-301-study-report-body.pdf; pooled data: Table 14, clinical-overview.pdf.

B.2.11 Ongoing studies

B.2.11.1. Spironolactone with patiromer in the treatment of resistant hypertension in chronic kidney disease (AMBER) study

The spironolactone with patiromer in the treatment of resistant hypertension in chronic kidney disease (AMBER; NCT03071263) study (Table 22) is an outcomes trial currently in progress to determine whether patiromer treatment in CKD patients receiving spironolactone (an aldosterone antagonist) for the treatment of resistant hypertension will facilitate optimal spironolactone dosing by preventing hyperkalaemia and lead to improved blood pressure control, compared with treatment with spironolactone alone. The results of this study are expected in 2019 (57).

Table 22: AMBER study design

Trial	Intervention	Comparator	Population	Endpoints	Primary study reference
RLY5016-207 (AMBER): NCT03071263 [(57)]	Spironolactone 25 mg once daily (increased to 50 mg once daily at week 3 [or after] for all subjects with AOBP SBP ≥120 mmHg and K^+ ≤5.1 mmol/L) plus patiromer 8.4 g once daily	Spironolactone 25 mg once daily (increased to 50 mg once daily at week 3 [or after] for all subjects with AOBP SBP ≥120 mmHg and K^+ ≤5.1 mmol/L) plus placebo	• Estimated enrolment 300 patients • ≥18 years • Uncontrolled hypertension as documented by AOBP SBP • Taking ≥3 antihypertensive medications, one of which is a diuretic, for ≥28 days at a stable dose • eGFR of 25–≤45 mL/min/1.73 m^2 during screening period • Three K^+ measurements of 4.3–5.1 mmol/L during screening period	• Primary: treatment group difference (spironolactone plus patiromer vs spironolactone plus placebo) in proportion of subjects remaining on spironolactone • Secondary: treatment group difference in change in SBP by AOBP measurements from baseline to week 12 or last available AOBP measurement prior to addition of any new blood pressure medications or changes to any baseline blood pressure medications	Relypsa, Inc. Data on file: Clinical study report for RLY5016-207 (report date 04 November 2016)

AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

B.2.12 Innovation

Patiromer is a non-absorbed, sodium-free, cation-exchange polymer; a potassium binder developed and approved for the treatment of hyperkalaemia. The active moiety (a crosslinked polymer anion of patiromer) binds potassium in the lumen of the colon and increases faecal potassium excretion, leading to removal of potassium from the body, thus lowering serum potassium levels. It is the first commercialised medicine resulting from Relypsa's polymer technology platform.

Patiromer is an alternative treatment to dose modification or discontinuation of RAASi therapy, which is the most routinely used approach to managing the risk of hyperkalaemia. Patiromer offers a novel treatment option for chronic hyperkalaemia in patients with CKD, type 2 diabetes or CHF for whom there are currently no well tolerated and effective therapies available. The addition of patiromer is particularly welcomed by nephrologists and cardiologists who now can administer RAAS inhibitors continuously for cardiorenal protection without worrying about life-threatening hyperkalaemia. However, patiromer should not be used as an emergency treatment for life-threatening hyperkalaemia because of its delayed onset of action.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Hyperkalaemia represents a serious condition that can result in life-threatening cardiac arrhythmias and is associated with increased mortality risk (20). The incidence of hyperkalaemia varies between 1.1% and 10% of hospital patients, of which 77% of cases are thought to be due to renal failure, 63% to prescribed drugs, and 49% to hyperglycaemia. Hyperkalaemia is the reason for emergency haemodialysis in 24% of haemodialysis patients, and accounts for 3–5% of deaths in this patient group. In 2013–14, there were 7,214 hospital admissions for hyperkalaemia in England, resulting in 20,725 bed days and 9,942 finished consultant episodes (58).

Patients most at risk are those with compromised renal excretion of potassium, primarily patients with CKD and/or patients being treated with drugs that inhibit renal potassium excretion, particularly RAAS inhibitor medications. Hyperkalaemia can be

a recurring condition in such patients. However, the utility of current options for chronic management of hyperkalaemia (e.g. dietary potassium restriction, diuretics, sodium bicarbonate, sodium and calcium polystyrene sulphonate) is limited. Also, while there are compelling data supporting the use of RAAS inhibitor therapy to reduce adverse cardiovascular and renal outcomes in certain high-risk patient populations, the chronic use of RAAS inhibitor therapy has been limited, partly because RAAS inhibitor medications reduce renal potassium excretion and may result in hyperkalaemia, with accompanying risks of cardiac arrhythmia and death (23, 37, 44, 59-61).

There is limited good quality evidence on the role of drug treatment in hyperkalaemia. Aside from reducing potassium intake, treatment options largely focus on reducing cardiac cell membrane excitability, shifting of potassium from the extracellular to the intracellular domain, and reducing total body potassium. The OPAL-HK phase III clinical trial compares the effect of patiromer on serum potassium against treatment with placebo.

The OPAL-HK study was a two-phase, single-blind, phase III study of patiromer in 243 subjects with hyperkalaemia and CKD that serves as two pivotal studies supporting the efficacy and safety of patiromer for the treatment of hyperkalaemia. The initial treatment phase of the study (four weeks) was designed to evaluate the efficacy of patiromer in the treatment of hyperkalaemia by demonstrating a clinically meaningful reduction in serum potassium levels in hyperkalaemic subjects. The randomised withdrawal phase was designed to confirm the serum potassium lowering effect observed in the initial treatment phase and to evaluate the efficacy of continued treatment with patiromer in the treatment of hyperkalaemia by demonstrating clinically meaningful control of serum potassium compared with withdrawal of treatment.

The characteristics of the study population facilitated the evaluation of efficacy and safety in a population similar to the target population.

The results from the four-week initial treatment phase demonstrated that treatment with patiromer at a starting dose of 8.4 g/day or 16.8 g/day, followed by a titration regimen according to the serum potassium response (when necessary), significantly

reduced serum potassium levels and maintained serum potassium within the target range of 3.8–<5.1 mmol/L. From initial treatment phase baseline to week 4, mean (SE) serum potassium was reduced by 1.010 ± 0.031 mmol/L (primary endpoint, p<0.001), with clinically meaningful and statistically significant reductions observed in both starting dose groups.

Eligible subjects entered the eight-week randomised withdrawal phase after having controlled serum potassium during the initial treatment phase. An increase from baseline in serum potassium was observed in the placebo group (median change of 0.72 mmol/L) relative to no increase (median change of 0.0 mmol/L) in the patiromer group, resulting in an estimated difference of 0.72 mmol/L between the two groups in median change from randomised withdrawal phase baseline (primary endpoint, p<0.001). As a result, significantly more patients who received placebo developed recurrent hyperkalaemia in the randomised withdrawal phase. The results of the randomised withdrawal phase therefore provide confirmatory evidence of the potassium-lowering effect of patiromer shown in the initial treatment phase and demonstrate the need for chronic potassium-lowering treatment in hyperkalaemic patients with CKD.

The safety findings in both phases of the study are consistent with the hypothesis that, because patiromer is not absorbed, direct systemic toxicities are not expected. The most common adverse event in the study was mild to moderate constipation, reported in 11% of subjects in the initial treatment phase and in 4% of subjects in the patiromer group in the randomised withdrawal phase, which was generally not treatment-limiting. Hypokalaemia and hypomagnesaemia were uncommon.

In conclusion, the OPAL-HK study demonstrated clinically meaningful and statistically significant reductions in serum potassium levels resulting in the majority of subjects reaching the target serum potassium range, and illustrated the need for chronic treatment with patiromer to maintain control of serum potassium. Patiromer, a non-absorbed, polymeric potassium binder was well tolerated and no direct systemic toxicities were noted. These results support a favourable risk:benefit profile of patiromer as a treatment for hyperkalaemia.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify all relevant economic evaluations and quality-of-life studies for the purposes of informing the economic assessment of patiromer for the treatment of hyperkalaemia in adult patients with stage 3-4 CKD (and other co-morbidities such as heart failure and diabetes), treated with RAASi therapy. Studies were included where the intervention or comparator included any of patiromer, RAASi discontinuation, SPS, CPS, zirconium cyclosilicate, diuretics, diet or dialysis. Few studies of relevant economic evaluations were identified given the current lack of treatment options. Further information about the methods and results of the SLR can be found in Appendix G. Of the 9 studies identified and data extracted; 3 studies were cost-effectiveness analysis studies. A summary of these studies is provided in Table 23.

Table 23. Summary list of published cost-effectiveness studies

Study	Year	Type of model	Patient population	QALYs	Costs (currency) (intervention, comparator)	ICER (per QALY gain)
Sutherland (62)	2017	Markov model	CKD patients, some with co-morbid chronic heart failure and diabetic nephropathy.	Including patiromer within RAASi regimen for HK population yielded net gains 0.33 to 0.54 QALYs.	Including patiromer within RAASi regimen for HK population yielded net gains of £9,540 to £9,950 (2017 cost year)	NR. Cost effective within thresholds of £20,000-30,000.
Smith (63)	2011	Probabilistic decision model	Patients receiving RAASi treatment to prevent hyperkalaemia and acute renal failure.	Laboratory monitoring via pharmacy led outreach program: 7.717834 Usual care: 7.717649	Cost year: 2007. Probability that monitoring program is cost saving: 95%. Probability cost-effective at WTP thresholds of $30k per QALY: 95%, $100k per QALY: 99%	NR
Little (64)	2014	Decision analytic model with Monte Carlo probabilistic sensitivity analyses – cost-utility design	Hyperkalaemic outpatients with Chronic Heart Failure, proteinuric CKD or both	SPS: 0.7193 Patiromer: 0.7197	Base case scenario (2011 cost year) Total cost SPS: $3,926.82 Total cost Patiromer: $14,616.96	$26,088,369
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; HK, hyperkalaemia; SPS, Sodium polystyrene sulfonate; CKD, Chronic Kidney Disease; RAASi, Renin-Angiotensin-Aldosterone System inhibitors; WTP, Willingness-to-pay						

B.3.2 Economic analysis

An economic evaluation was conducted to assess the cost-effectiveness of patiromer versus RAASi discontinuation in the treatment of hyperkalaemia in patients with stage 3–4 CKD. Use of patiromer allows for RAASi enablement which in turn impacts both the probability of experiencing cardiovascular events and progression of renal disease.

The current economic model is based on a model developed by Sutherland et al. (2014) which performed a cost-effectiveness analysis in a population matching the current decision problem – chronic hyperkalaemia in stage 3–4 CKD. The model includes major elements of CKD (stage 3–4 disease, end-stage disease, cardiovascular events) and considers the impact of patiromer on both prevention of hyperkalaemia and RAASi discontinuation. The analysis took a Scottish NHS perspective using the OPAL-HK trial data to model patiromer vs. RAASi discontinuation. The economic evaluation SLR described above was used to confirm the model developed by Sutherland et al was the only one relevant to the current decision problem.

3.2.1. Patient population

The patient population in the cost-effectiveness analysis, stage 3–4 CKD on RAASi therapy with hyperkalaemia, was selected to be identical to the population from the pivotal OPAL-HK trial. In the Initial Treatment Phase (n=243), the average age of the cohort was 64.2 years with 58% of patients were male. The proportion of patients with Type II diabetes, heart failure, previous myocardial infarction and hypertension were 57%, 42%, 25% and 97%, respectively. At baseline, the average serum potassium was 5.6mmol/L with an estimated GFR of 35.4 ml/min. All patients were on at least one RAAS inhibitor (the majority using ACE inhibitors, followed by ARBs and a small proportion on aldosterone) and 54% on non-RAASi diuretics. In the randomised Withdrawal Phase, baseline characterises in the patiromer and placebo arms were comparable (65). The OPAL-HK trial population is summarised in **Table 24**.

Table 24. Population demographics, OPAL HK - Part B

	Treatment phase (part A)		**Source**
Mean serum K^+ (initial)	5.6 ±0.5 mmol/L		Weir 2015 (66)
	Randomised withdrawal phase (part B)		
	Placebo	**Patiromer**	**Source**
Male	58%	51%	Weir 2015 (66)
Mean age	65.0 ± 9.1	65.5 ± 9.4	Weir 2015 (66)
NYHA class		I – 20% II – 64-65% III – 15-16% IV – 0%	Post-hoc analysis, OPAL-HK 301 Part B
Mean eGFR	39.0 ± 20.4	38.6 ± 20.7	
RAASi (ACE)	73%	67%	
RAASi (ARB)	31%	44%	
RAASi (aldosterone)	8%	7%	
Mean serum K+ (end)	5.17 mmol/L	4.5 mmol/L	

The patient population in the cost-effectiveness analysis is narrower than the scope issued by NICE and the Marketing Authorisation for patiromer, which is the treatment of hyperkalaemia in adults. This is because the evidence base for patiromer from the OPAL-HK trial is limited to hyperkalaemia in stage 3–4 CKD which is aligned to the population for which this appraisal is seeking reimbursement.

There have been no previous NICE technology appraisals for this specific indication (adult stage 3-4 CKD patients on RAASi therapy with HK).

3.2.2. Model perspective

The perspective for this analysis is that of the NHS and Personal and Social Services (PSS) in England and Wales (in line with current NICE guidelines). The cost-effectiveness analysis therefore excluded patients' out-of-pocket expenses, carers' costs, and lost productivity costs. All costs are reported in pounds sterling (May 2018).

3.2.3. Model structure

A Markov model was developed in Microsoft Excel 2016 ® (Redmond, WA). The structure followed the design of the OPAL-HK trial such that all patients enter the model in an initial treatment phase followed by a randomised phase where treatment

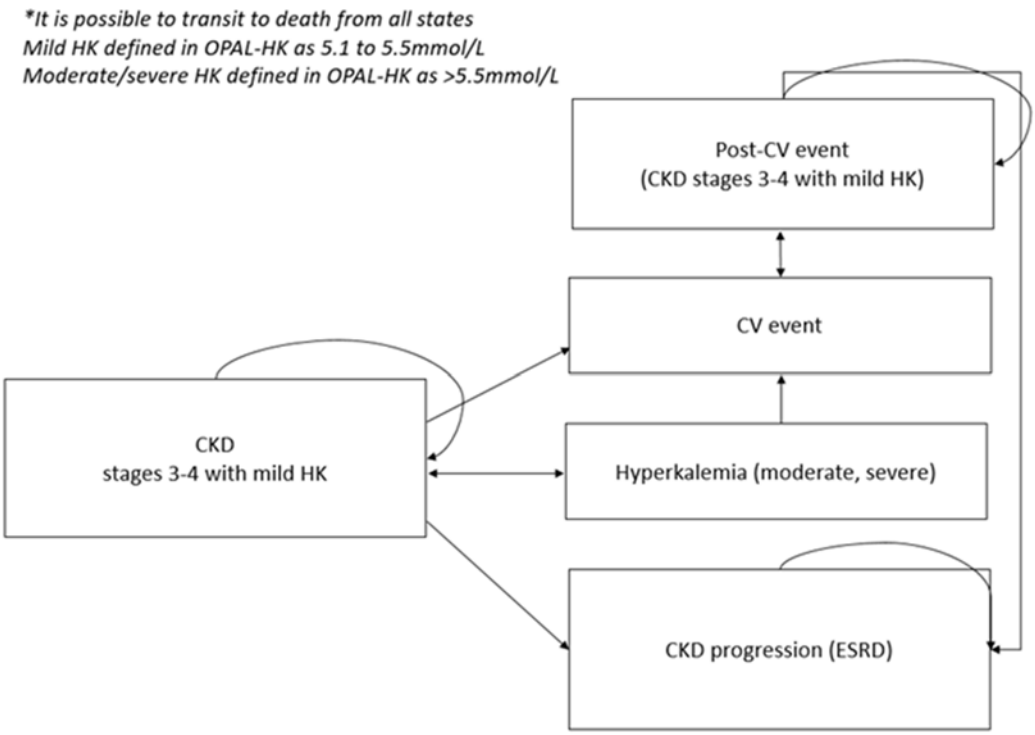
of hyperkalaemia is either with patiromer or RAASi discontinuation. The model includes CKD health states (e.g. CKD, end-stage renal disease, death) through which patients may progress. Cardiovascular event health states (e.g. MI, stroke) and hyperkaliaemic are also included to model the benefits and adverse events associated with RAASi therapy. Incorporation of health states including CV and hyperkalaemia were discussed and validated with UK clinical experts (further information can be found in 3.3.6).

The model utilises cycle lengths of one month, as one month is considered appropriate to adequately model the progression of disease while allowing for the development (and resolution, where relevant) of key events including hyperkalaemia and CV events.

In line with the reference case, the model simulates a life time horizon. Although the model allows for a maximum time horizon of 35 years (maximum age 100 years old), the mean life span of individuals in the model (7.5 years) is comparable to estimates of life expectancy for stage 3–4 CKD patients observed in real world practice (average 7 to 8 years) (67) and validated by clinical expert opinion.

The Markov model incorporates five main health states, which captures the progression of CKD and associated events, as described in section 1.3. It is possible to transit to an absorbing death state from any other health state. Figure 10 provides a schematic of the model structure.

Figure 10. Markov model for patiromer



CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HK, hyperkalaemia

A description of each health states is provided below:

HK with CKD (stages 3-4)

- All patients begin in this health state with the possibility of progression to:
  - "CKD progression (ESRD)"
  - Having a cardiovascular event ("CV event") which consists of either MI or stroke
  - Having a HK event that requires hospitalisation ("hyperkalaemia")
  - Death resulting from an age-related mortality

Hyperkalaemia

- After a hyperkalaemic event, patients either:
  - Return to the "CKD stages 3-4" state
  - Have a CV event
  - Progress to ESRD

- Have a possibility of death

- It should be noted that the memoryless Markov does not take the cumulative morbidity of recurring HK events for an individual, this is a conservative approach

CV event

- Patients in the "CV event" state either:
  - Transit to a "post-CV event"
  - Have a possibility of death related to cardiovascular events

Post-CV event

- This health state is used to model CKD 3–4 patients who have experienced a CV event
- The difference compared with the CKD 3–4 state is the inclusion of additional disutility and costs that a patient may incur after needing a CV intervention
- Patients can either:
  - Have another CV event (i.e. recurrent CV)
  - Progress to ESRD
  - Have a possibility of death

CKD progression

- This health state encompasses patients in stage 5 and ESRD, with options for renal replacement therapy (RRT) including peritoneal dialysis (PD), haemodialysis (HD) and renal transplant
- Patients remain in this state until death related to ESRD mortality
- It was assumed that the morbidity, cost and disutility of ESRD take into account hyperkalaemic events and potential CV events for this population, as the sources of the inputs used incorporate these aspects already (this is a conservative approach)

Within the economic model both the intervention and comparator arms comprise of two sub-arms – one where patients continue on RAASi therapy and the other where RAASi therapy is discontinued. These sub-arms are identical in structure however

contain variations in the relative risk of events related to RAASi treatment (i.e. CKD progression, cardiovascular events, hyperkalaemia and mortality) and patiromer treatment continuation (i.e. hyperkalaemia). The proportion of patients allocated to each varies between the patiromer and no patiromer arms as informed by Part A and Part B of OPAL-HK.

In the patiromer arm of the model, the proportion of patients who were responders in Part A of OPAL-HK (44%) enter the 'RAASi continued' sub-arm of the model while the remainder enter the 'RAASi discontinued' sub-arm. In the comparator 'no patiromer' arm, all patients discontinue RAASi therapy. This approach incorporates Part A of OPAL-HK. Thereafter patients discontinue RAASi therapy in accordance with either real world data from the CPRD or the proportion of discontinuers at the end of Part B of OPAL-HK. The application of either option is described below.

Given the 8-week duration of the OPAL-HK trial, extrapolation of clinical outcomes to a lifetime horizon would result in inevitable uncertainty in the estimates of efficacy. Therefore, additional sources of data other than OPAL-HK have been used in the base case analysis to improve the robustness of effectiveness estimates, including real world data from the Clinical Practice Research Datalink (CPRD) to model the long term rate of RAASi discontinuation.

3.2.4. Intervention technology and comparators

Patiromer is a non-absorbed, sodium-free, cation exchange polymer that contains a calcium-sorbitol counterion. Patiromer increases faecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract. This reduces the concentration of free potassium in the gastrointestinal lumen, resulting in a reduction in serum potassium levels in adult patients (5). Patiromer offers a solution for the maintenance of normokalaemia and enablement of optimal RAAS inhibitor therapy which in turn preserves the benefits related to RAAS inhibition in CKD and CHF patients.

Bicarbonates or potassium binders are useful in the acute setting but not suitable in the management of chronic hyperkalaemia. There is insufficient clinical trial evidence for mid- to long-term hyperkalaemia treatment, or for maintaining hyperkaliaemic patients on RAAS inhibitor therapy, with CPS or SPS. According to UK key opinion

leaders (KOLs) the use of CPS/SPS for chronic hyperkalaemia is insufficiently evidence-based and subsequently not commonly used (68). In addition, the European Public Assessment Report for Patiromer states that SPS and CPS do not serve as a treatment option for long-term/chronic management of hyperkalaemia (5).

UK guidelines for hyperkalaemia focus only on the management of acute elevations of K^+ levels (69, 70). Thus, management of chronic hyperkalaemia is based on physicians' clinical judgement. During early advice meetings with The Vifor Group, the German G-BA (Gemeinsamer Bundesausschuss; Federal Joint Committee) defined the appropriate comparator therapy for patiromer as a "*patient-individualised therapy at the discretion of the treating physician under consideration of aetiology, severity and symptoms*" (71). In consultation with the Regulatory Authorities, it was agreed that the pivotal OPAL-HK study, investigating the efficacy of patiromer for the treatment of hyperkalaemia and ability to maintain RAASi therapy in patients with CKD 3-4 and hyperkalaemia (50), would not include an active comparator for ethical and for clinical practice reasons. The absence of an active pharmacological comparator in OPAL-HK, and thus the economic model supporting this submission therefore reflects current UK practice and the intervention and comparator in the decision problem (Table 1).

A treatment continuation rule has been assumed in the model in order to align with clinical practice and the OPAL-HK trial protocol. It was assumed that if a patient hyperkalaemia was not managed by patiromer after 4 weeks of therapy (i.e. were non-responders in the initial treatment phase of OPAL-HK), then they would discontinue patiromer. There are no cost or health consequences of implementing this treatment continuation rule, as hyperkalaemia is carefully monitored in clinical practice regardless.

B.3.3 Clinical parameters and variables

3.3.1. Efficacy

The Markov model differentiates patients that continue on RAAS inhibitors versus those who do not (no RAAS inhibitor/discontinue RAAS inhibitor) in both the "no patiromer" and "patiromer" arms. Annual event rates were taken from the literature and converted to monthly transition probabilities as per Briggs et al (72).

$$rate = -ln\ (1 - p)/t$$

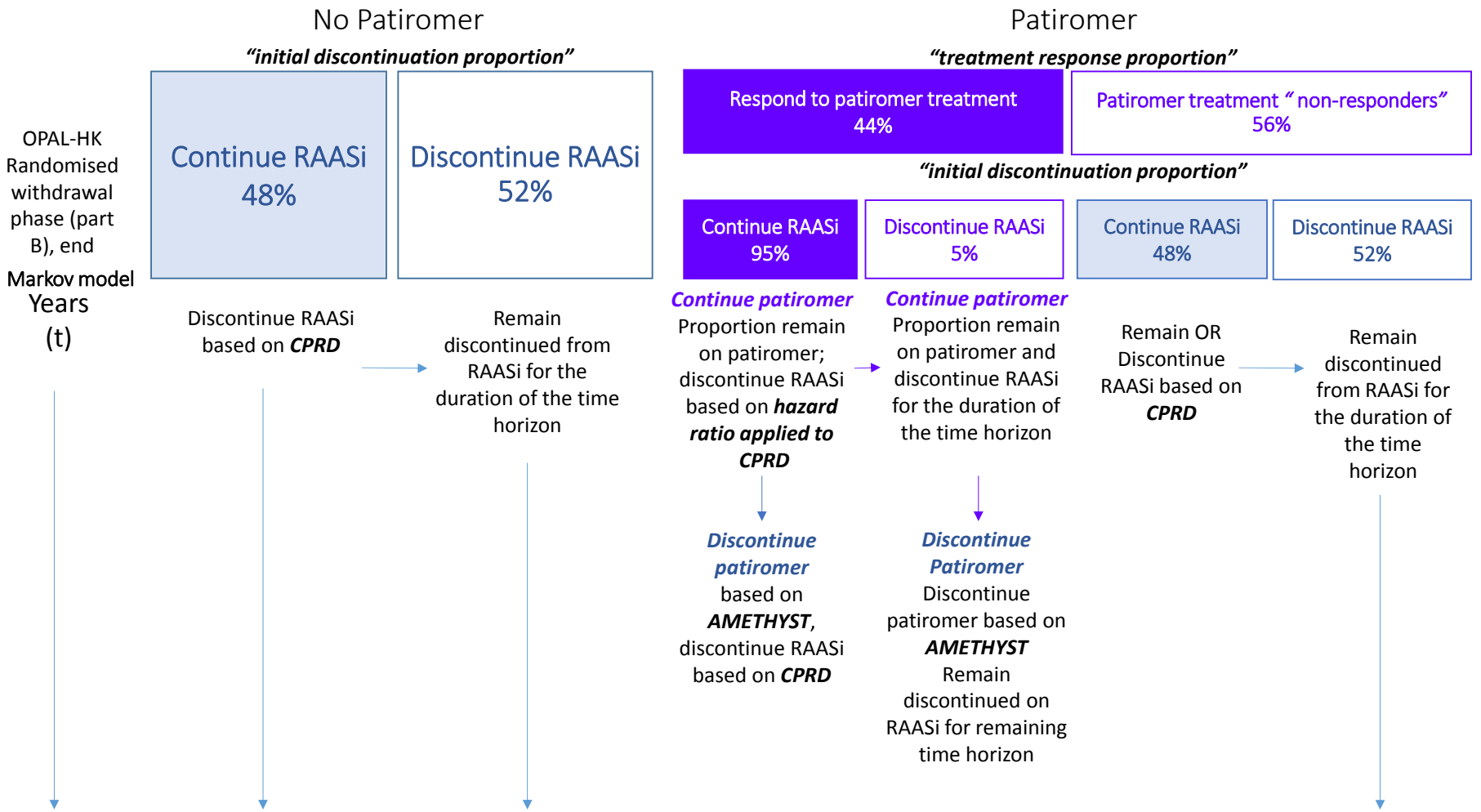
$$probability = 1 - Exp\ (-rate * t)$$

Where p = probability, t=time in years

Time to RAASi discontinuation

The economic model was developed to mirror the design of OPAL-HK. Patients with stage 3–4 CKD and hyperkalaemia (5.1mmol/L to <6.5mmol/L) receiving stable doses of at least one RAAS inhibitor were eligible for inclusion. Part A was a single-group, single-blind initial treatment phase where all patients received patiromer where the dose was dependent upon the severity of hyperkalaemia. Doses could be adjusted to reach target K^+ level but RAASi dose modification was not permitted although withdrawal was permitted if K^+ exceeded 6.5mmol/L. At the end of Part A, patients were eligible to enter Part B if their K^+ was within target range (3.8–<5.1mmol/L). The model schematic is provided in Figure 11.

Figure 11. Model schematic



RAASi, renin-angiotensin-aldosterone system inhibitors; CPRD, Clinical Practice Research Datalink

Short term discontinuation

The economic model incorporates Part A of OPAL-HK by initially stratifying patients in the patiromer arm of the model into patients who either responded (K^+ target range achieved) or did not respond in Part A. Those who respond enter the 'RAASi continued' sub-arm of the model and those who do not enter the 'RAASi discontinued' sub-arm. Response was calculated as the proportion of patients entering Part B of OPAL-HK (n=107) versus the initial cohort who entered Part A (n=243). This determines the distribution of patients entering the long-term Markov trace of the economic model.

Long term discontinuation

At the initiation of the long-term Markov model Part B of OPAL-HK is incorporated where the proportion of patients continuing and discontinuing RAASi at the end of this phase enter the 'RAASI continued' or 'RAASi discontinued' sub-arms of the Markov trace. In order to determine the proportion of patients that would enter into the Markov model as either "continued" or "discontinued" a post-hoc analysis of the data was completed by Relypsa, Vifor Pharma Group. The results, which are listed in Table 25, show that when on "patiromer", 95% of patients continued RAASi at 8 weeks in comparison to 48% in the "no patiromer" arm. This distributes patients into each sub-arm of the Markov within the patiromer and no patiromer model arms.

Table 25. Proportion of patients that continue/discontinue RAAS inhibition based on post-hoc analysis of OPAL-HK Part B

	CKD general population	Source
Patiromer, continued RAASi	95%	post-hoc analysis, OPAL-HK 301 Part B
Patiromer, discontinued RAASi	5%	post-hoc analysis, OPAL-HK 301 Part B
No patiromer (placebo), continued RAASi	48%	post-hoc analysis, OPAL-HK 301 Part B
No patiromer (placebo), discontinued RAASi	52%	post-hoc analysis, OPAL-HK 301 Part B

Given the 8-week duration of the OPAL-HK trial, extrapolation of clinical outcomes to a lifetime horizon would result in inevitable uncertainty in the estimates of efficacy. Therefore, additional sources of data other than OPAL-HK have been used in the base case analysis to improve the robustness of effectiveness estimates, including real world data from the Clinical Practice Research Datalink (CPRD) to model the long-term rate of RAASi discontinuation.

The CPRD is an electronic medical records database representative of the primary care patient population in the UK. The CPRD collects data from 714 contributing practices across the UK, covering approximately 8% of the total UK population. Patient data is maintained by GPs who record demographic, medical and prescription details at every encounter. The CPRD was used to identify CKD stage 3-4 adult patients with hyperkalaemia.

Adult CKD patients were identified in the database by the identification of appropriate Read codes between 1st January 2012 and on 31st December 2016 (73). The use of RAASi therapy was determined as patients having at least one prescription of a RAASi identified by Gemscript codes in the 90 days prior to hyperkalaemia diagnosis. Finally, RAASi discontinuation was considered in patients receiving RAASi therapy within the 90 days prior to a hyperkalaemia event. RAASi discontinuation was defined as no prescription of any of the RAASi medications within 90 days after the expected termination date of the RAASi prescription, where date of prescription occurs prior to the hyperkalaemia event. The main inclusion and exclusion criteria for the population are summarised in Table 26.

Table 26. Inclusion and exclusion criteria for CPRD

Inclusion	Exclusion
Patients with a diagnosis of CKD identified by a Read code in CPRD identified between 1st January 2012 and 31st December 2016 inclusive	Patients with a flag indicating non-continuous data records
Patients with a hyperkalaemia diagnosis (index date) identified by a Read code in CPRD after and including the date of CKD or a co-diagnosis of interest (HF, DM)	Patients < 18 years old at index date
Patients that are eligible for HES linkage	
Patients with at least 12 months of baseline data at index date	

Patients with a flag for 'Acceptable Quality Standards'	

The use of CPRD analysis was considered more robust than extrapolation of OPAL-HK since the latter provides discontinuation over an 8-week period only which would not be appropriate for extrapolation over a life time horizon. Further, management of chronic hyperkalaemia in both the OPAL-HK 'no patiromer' treatment arm and in clinical practice would be either RAASi dose modification or discontinuation and therefore RAASi discontinuation rates would be comparable. The CPRD analysis was considered to strengthen the analysis as it provided longer term real world data in a large population (N=[redacted]). Propensity score matching was not performed as individual patient level data was not available for analysis. A comparison of baseline patient characteristics between cohorts showed kidney function and serum K^+ to be similar, as was the use of various RAASi medication. A greater proportion of patients in OPAL-HK suffered with co-morbidities and while the mean age was different, the impact of this is explored as a scenario analysis. A summary of patient characteristics is provided in Table 27.

Table 27 Patient characteristics in CPRD and OPAL-HK Part B

	OPAL-HK Part B Placebo (N=55)	**CPRD (N=[redacted])**
Male	58% (30)	[redacted]
Mean age	65.0 (55)	[redacted]
Mean eGFR	39.0 (55)	[redacted]
RAASi (ACE)	73% (38)	[redacted]
RAASi (ARB)	31% (16)	[redacted]
RAASi (aldosterone)	8% (4)	[redacted]
Mean serum K+ (end)	5.17 mmol/L	[redacted]
Myocardial infarction	27% (14)	[redacted]
Hypertension	96% (50)	[redacted]
Diabetes mellitus	63% (33)	[redacted]
Heart Failure	42% (22)	[redacted]

The observed discontinuation of RAASi was used to perform a time-to-event analysis and thereafter parametric functions were fitted to estimate long-term RAASi discontinuation in real-world practice. The best statistical fitting curve, based on AIC and BIC statistics, was deemed to be the Weibull which was used in the base case

analysis to model time to RAASi discontinuation for the 'no patiromer' arm, where patients in the Markov trace discontinued RAASi in accordance with the parametric curve. Parametric extrapolations and best fit statistics are provided in Figure 12 and Table 28.

Figure 12. Parametric extrapolations for time to RAASi discontinuation ('no patiromer')

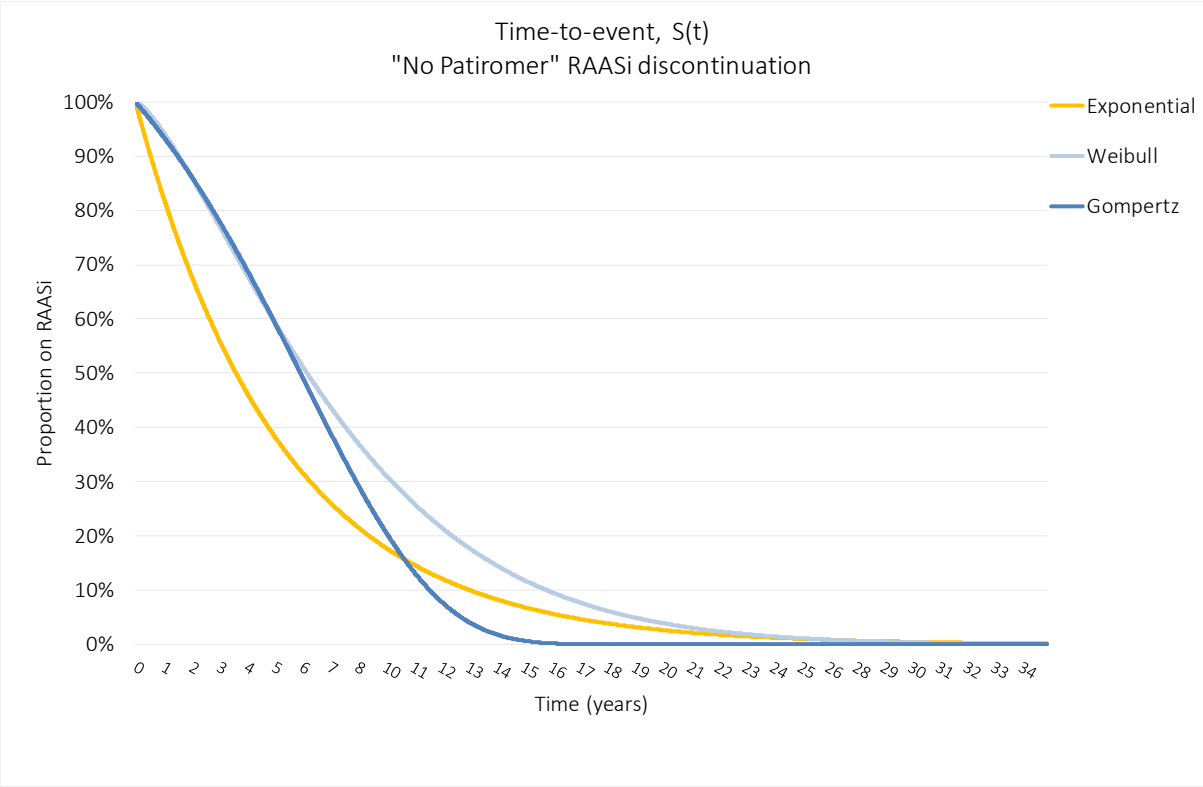


Table 28. Summary of best fit statistics: time to RAASi discontinuation

Distribution	AIC	BIC
Weibull	**4068**	**4079**
Exponential	4104	4110
Gompertz	4093	4105

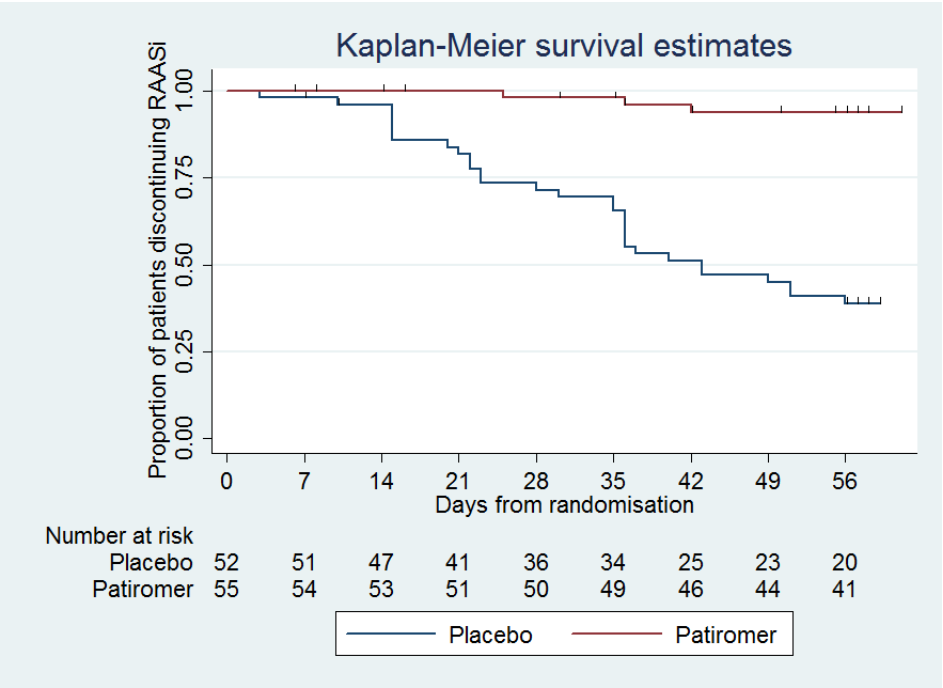
Estimation of RAASi discontinuation for patiromer arm

Since patiromer is not used in UK clinical practice the treatment effect compared with no patiromer on RAASi discontinuation is not clear. The hazard ratio from Part B of OPAL-HK was therefore calculated as this is the most robust available estimate of the efficacy of patiromer. The estimated HR was thereafter applied to the parametric

RAASi discontinuation curves generated for the CPRD to estimate RAASi discontinuation while on patiromer. The methods for determining the hazard ratio are explained below.

Individual patient level data (IPD) from the OPAL-HK trial was used to model time to RAASi discontinuation for patients randomised to the “patiromer” and “no patiromer” arms. This data was used to generate Kaplan Meier (KM) curves (Figure 13) for both treatment arms and shows that patiromer is likely to delay the time to RAASi discontinuation when compared with placebo. The curves were visually inspected and patient numbers at risk checked in both Stata and R to ensure accuracy.

Figure 13. Kaplan-Meier time to RAASi discontinuation estimates from OPAL-HK



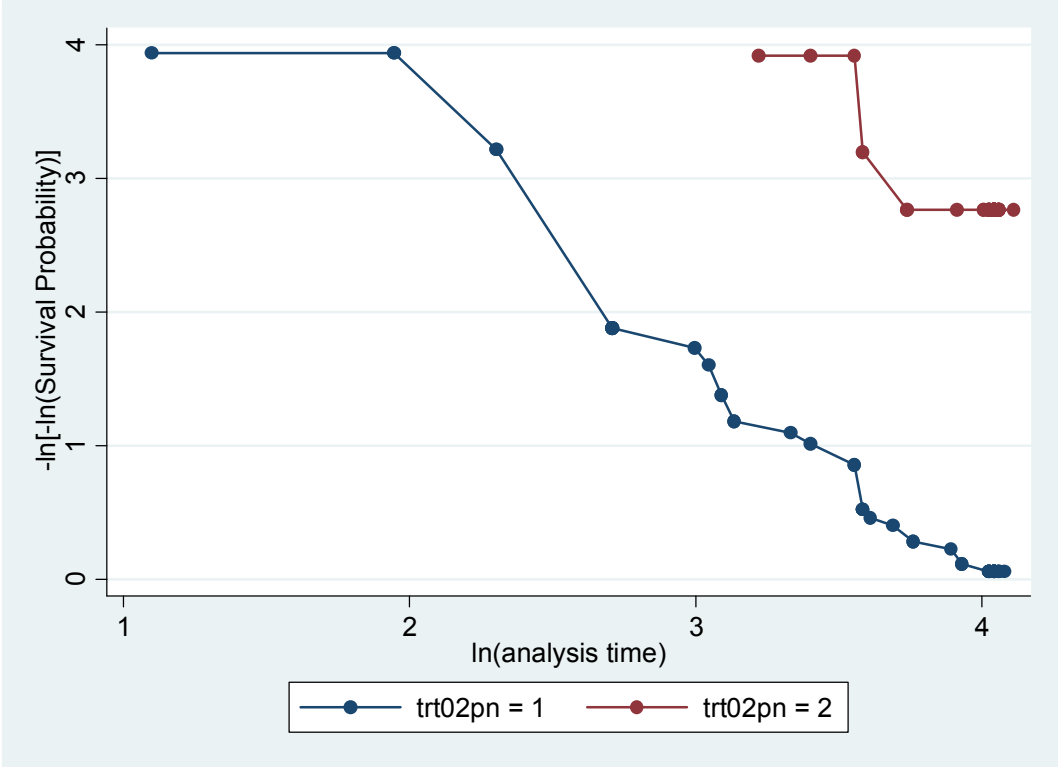
A series of statistical tests were thereafter performed.

The Log-rank test was used to test for a difference between the two survival curves, with a null hypothesis that the risk of progression is the same in both arms: $p>Chi^2=0.0000$, therefore there is a statistically significant difference.

The cox-proportional model was fitted and the proportional hazards (PH) assumption tested, with the null hypothesis that the proportional hazards assumption is not violated: p=0.7978 (>0.05) therefore the null cannot be rejected.

A log-log graph was also plotted to verify the PH assumption (Figure 14). As the lines are parallel and do not cross, this indicates that the proportional hazards assumption is valid.

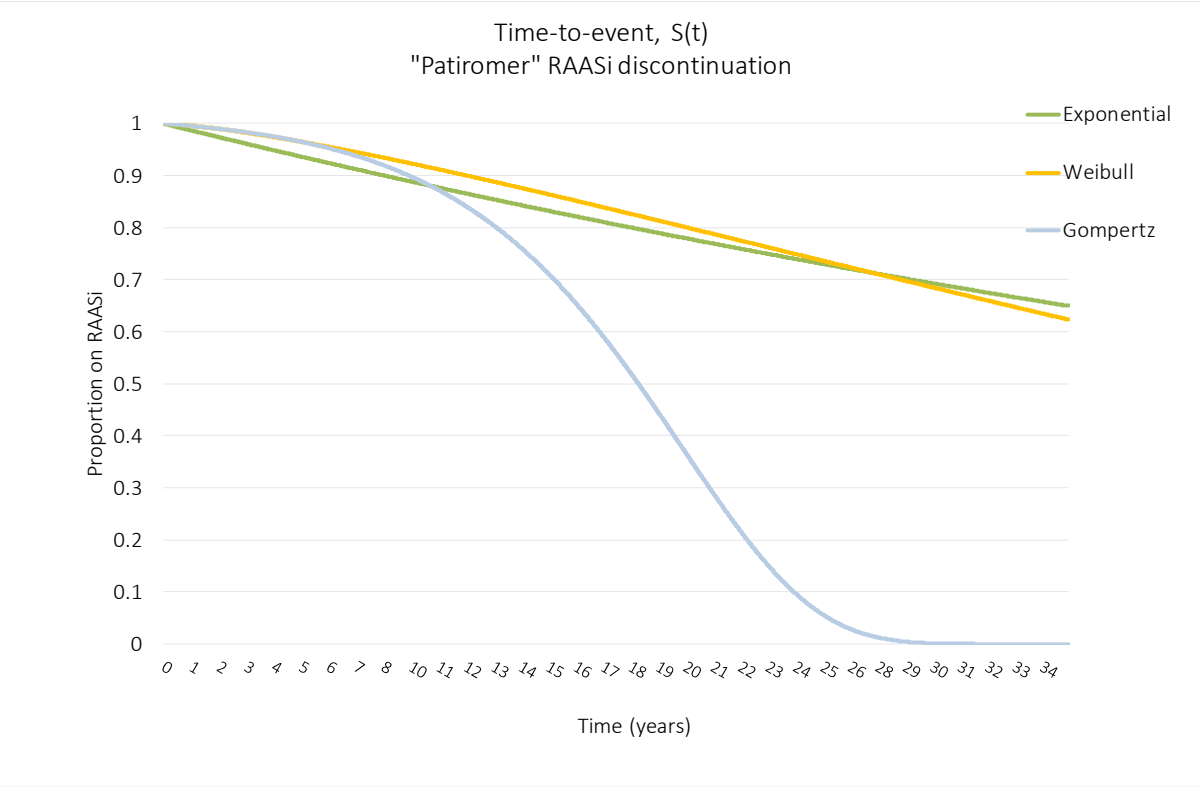
Figure 14. Log-log graph verifying the validity of the proportional hazards assumption



The hazard ratio was determined to be [redacted] (p<0.001), with a standard error of [redacted] (95% CI [redacted]).

The generated parametric curves for patiromer are provided in Figure 15.

Figure 15. Parametric extrapolations for time to RAASi discontinuation ('patiromer')



The economic model considers the impact of RAASi enablement in that the relative risk of events, for example stroke and myocardial infarction, changes as patients transition from 'on RAASi' to 'off RAASi'. The difference between treatment arms estimates the benefit of patiromer in relation to continuation of RAASi therapy and therefore a reduced risk of cardiovascular events and progression of renal disease.

Since patiromer is associated with RAASi enablement, alternative RAASi discontinuation rates are applied to patients on and off patiromer in the model. The Markov model differentiates patients that continue on RAAS inhibitors versus those who do not (no RAASi or discontinue RAASi) in both the "no patiromer" and "patiromer" arms. This is accounted for by weighting the relative risk of RAASi directly in the Markov transition matrix, by a proportion to account for those that have discontinued. For example, if in the 4th month, the estimated proportion of patients who discontinue RAASi is 1.1% (survival, continued treatment equivalent to 99%), then 1% of the patients in the CKD state will have no relative risk reduction (aRR=1) while 99% of the patients would receive the full relative risk reduction of RAASi (aRR=0.636). This essentially re-weights the RR to 0.640. The estimates of RAASi

discontinuation for the comparator (no patiromer) and intervention (patiromer) were generated using patient level data.

3.3.2. Patiromer discontinuation

The AMETHYST Phase II dose-selecting trial described in Section B.2.3.2. was used to model time on patiromer as it provides the longest-term data available for patients on patiromer (52 weeks). Individual patient level data (IPD) from AMETHYST was used to model patiromer discontinuation, as this was deemed to be a better alternative to extrapolating 8-week data from OPAL-HK. This approach is limited in that the AMETHYST trial population does not precisely match the population in the model; AMETHYST only included patients with diabetic kidney disease and hyperkalaemia as opposed to stage 3-4 CKD and hyperkalaemia. However, 63% of the OPAL-HK randomised withdrawal phase trial population had type-2 diabetes at baseline (Table 9). Moreover, since no estimates of efficacy are being used from AMETHYST, this approach was considered conservative and avoided using strong assumptions about the treatment duration of patiromer.

IPD from AMETHYST was used to model patiromer discontinuation using Kaplan-Meier (KM) curves (Figure 16).

Figure 16. Kaplan-Meier patiromer discontinuation estimates from AMETHYST

A lifetime horizon has been applied in the model in order to capture all costs and outcomes over a patient's life. Extrapolation of data was therefore used to model costs and outcomes within and beyond the observed data period of 52 weeks in AMETHYST. Parametric functions were fitted to the observed Kaplan-Meier curve for patiromer and selected according to the best fitting curve. The functional forms Exponential, Weibull, Gompertz, Log-logistic and Log-normal were tested to assess the best fit to the KM data (Figure 17).

Figure 17. Kaplan-Meier analysis of patiromer discontinuation

AIC and BIC statistics (Table 29) were also calculated, and from this the log-normal was determined to be the best statistical fit.

Table 29. AIC and BIC statistics for parametric curves

Parametric Curve	AIC	BIC
Exponential	590.24	593.86

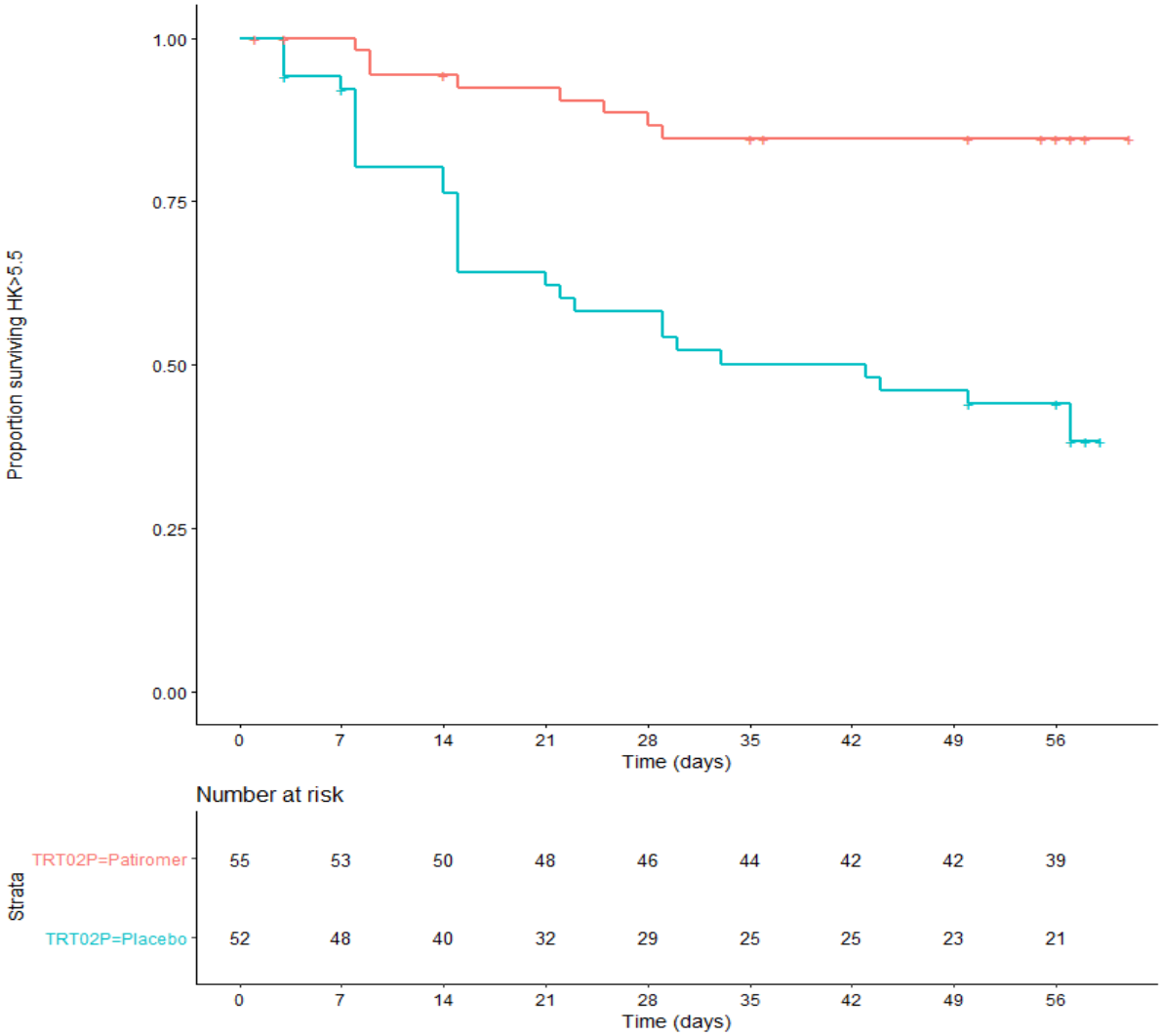
Weibull	570.57	577.80
Loglogistic	569.19	576.41
Gompertz	571.09	578.32
Lognormal	***565.48***	***572.70***

Since the clinical impact of patiromer (time to RAASi discontinuation and time to hyperkalaemia) is modelled separately, time on patiromer is used in order to estimate the expected costs of treatment.

3.3.3. Time to hyperkalaemia

In the base case analysis, the time to hyperkalaemia (defined as K^+ ≥5.5mmol/L) was modelled by using IPD from OPAL-HK. AMETHYST could not be used for this parameter, as the time to hyperkalaemia would be expected to be different in different patient populations. A survival analysis was performed in order to generate KM curves for the patiromer and no patiromer arms and thereafter statistical tests confirmed a difference between curves. The hazard ratio between the two curves was calculated as 0.187 ($p<0.001$) confirming statistical significance.

Figure 18. KM curves for time to hyperkalaemia



Thereafter, parametric functions were generated for each arm in order to allow extrapolation to the model lifetime horizon. The gompertz was the best statistical fit in the patiromer arm and log normal in the no patiromer arm. The log normal was selected in the base case given it was the second best statistical fit in the patiromer arm and because as the gompertz assumes patients do not experience a hyperkalaemia event after approximately 6 months, which may not be clinically plausible.

Figure 19. Parametric extrapolations for time to hyperkalaemia – patiromer

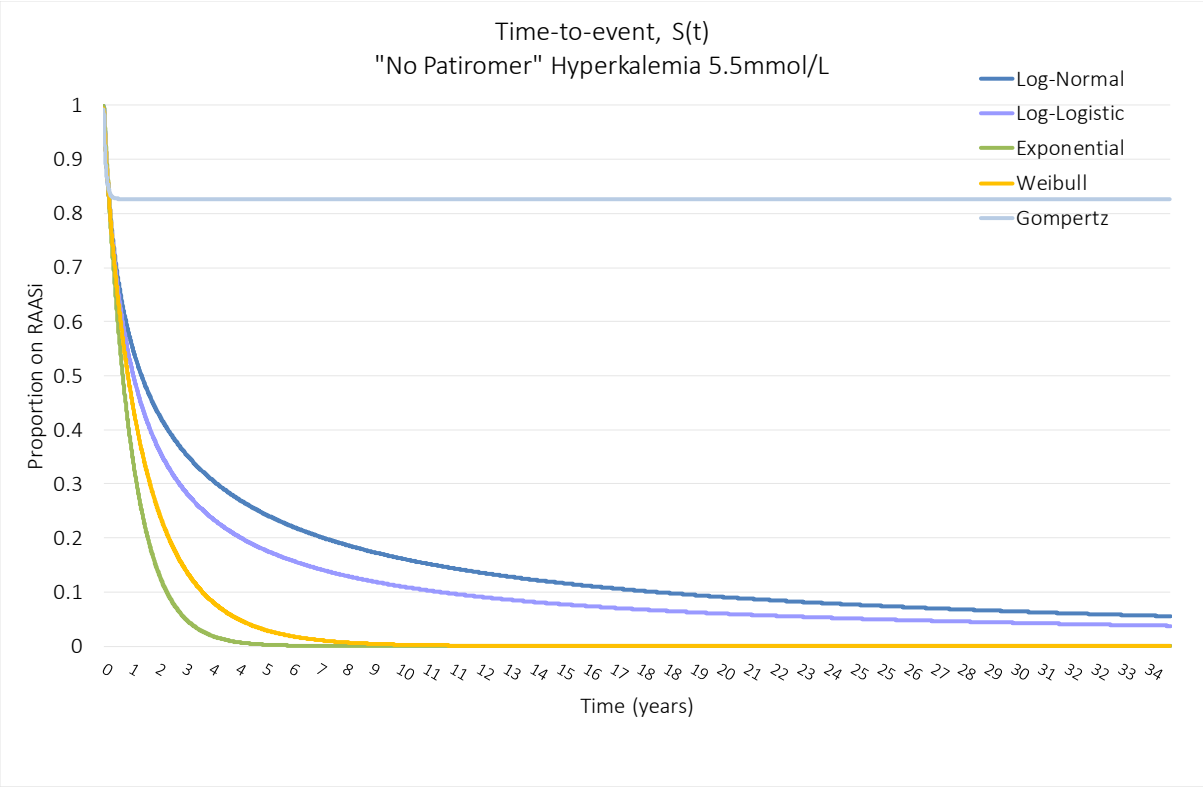


Table 30. Best statistical fit, time to hyperkalaemia: patiromer

Parametric Curve	AIC	BIC
Exponential	245.31	247.31
Weibull	244.83	248.84
Loglogistic	243.08	247.10
Gompertz	239.91	243.93
Lognormal	***240.92***	***244.94***

Figure 20. Parametric extrapolations for time to hyperkalaemia – no patiromer

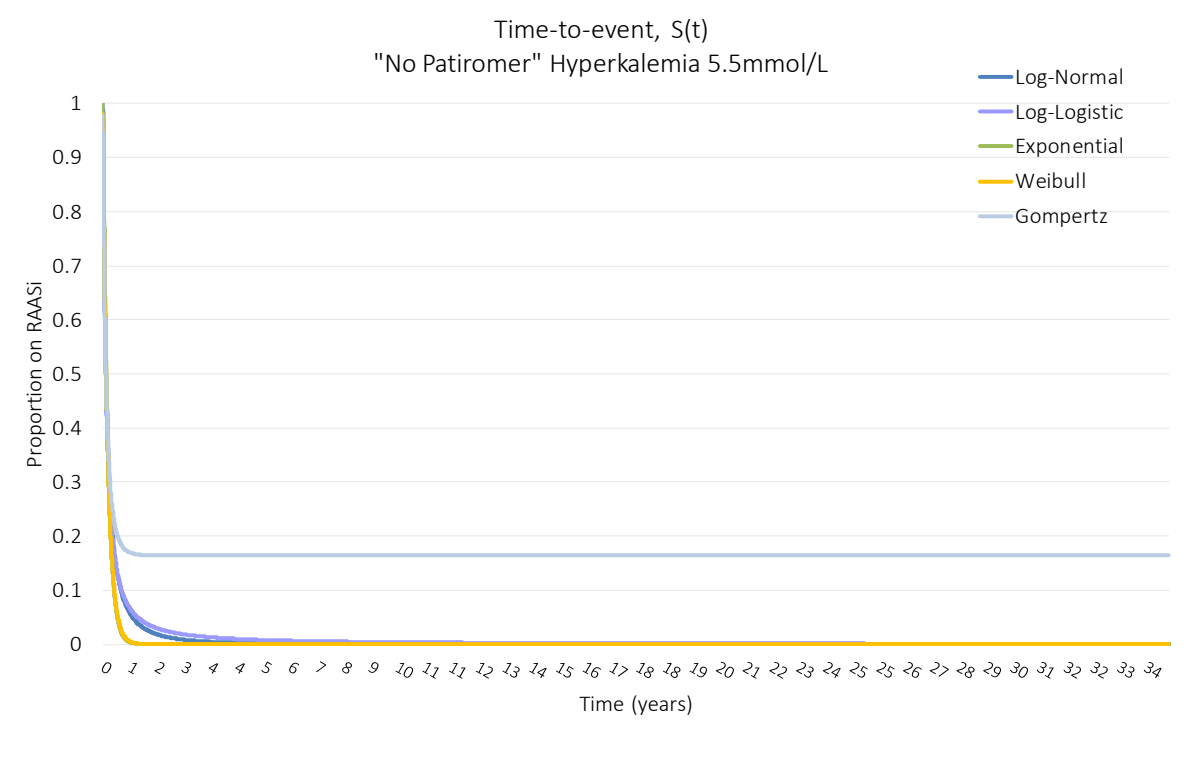


Table 31. Best statistical fit, time to hyperkalaemia: no patiromer

Parametric Curve	AIC	BIC
Exponential	376.09	378.03
Weibull	377.95	381.85
Loglogistic	369.95	373.86
Gompertz	377.19	381.09
Lognormal	***368.37***	***372.27***

While time to RAASi discontinuation and time to hyperkalaemia are modelled as independent events, the time to hyperkalaemia is utilised to model the increase in time to this event in patients using patiromer. This impacts the probability of transition to the hyperkalaemia health state in each arm and the resultant costs and decrement in utility.

3.3.4. Mortality

Patients can transition to death from any health state. Methods to determine the transition to death for health states is provided below. Transition probabilities to death from "CV event" and "Post-CV event" are described in section 3.3.5.

CKD stages 3-4

Death for the population with CKD stages 3-4 was taken from the National Life Tables in England and Wales (74). The probability of mortality in the model is based on annual age-related event rates derived from National Life Tables for England and Wales and were adjusted to monthly probabilities. To account for the additional morbidity related to CKD stages 3-4, Standardised Mortality Ratios (SMRs) were calculated. A large renal cohort study from Eriksen et al. (75) reported the SMRs of patients in CKD 3 for three age ranges: less than 69 years old, 70 to 79 years old and greater than 79 years old. A recent Canadian study demonstrated that in comparison to the mortality of a patient with CKD stage 3, a patient with CKD 4 had hazard ratios (HR) of 2.56 (76). Hence, it was assumed that the SMR for patients with CKD 4 could be calculated as a multiple of CKD stage 3 with the reported HR. The overall SMR for stages 3 and 4 was then weighted based on the distribution of these patients in OPAL-HK study (56% and 44% for CKD stages 3 and 4, respectively).

CKD progression (ESRD)

An age-related mortality rate for patients with ESRD was used from the recently published renal registry in the UK by Steenkamp et al. in 2016 (77) as shown in Table 32.

Table 32. Age-related event rates related to ESRD mortality

ESRD life table (Steenkamp 2016, Table 5.16)	Event per 1000	Annual rate	Monthly probability
Age 60-64	75	0.0750	0.0062
Age 65-69	114	0.1140	0.0095
Age 70-74	143	0.1430	0.0118
Age 75-79	200	0.2000	0.0165
Age 80-84	258	0.2580	0.0213

Age 85+	371	0.3710	0.0304

3.3.5. Event probabilities

A systematic literature review was performed to identify studies which reported Major Adverse Cardiovascular Events (MACE) in order to inform the risk of cardiovascular events (Appendix L). Identified studies were used to inform model parameters as described below.

An English prospective cohort study of patients in stage 3-5 CKD by Landray et al. predicting CKD progression estimated an annual event rate of 0.168, which was a converted to a monthly probability (0.0139) and used as the progression from the starting state of “CKD stages 3-4”, to ESRD, referred to as “CKD progression” in the model (78). The same probability was applied for patients that survived a CV event, moving to ESRD (i.e. moved from “post CV event” to “CKD progression”).

To derive the event probabilities in the renal population of MI, stroke, and, death after surviving a CV event, the pooled event rates in the placebo arms of trials in a published network meta-analysis by Xie et al. (79) were used. Myocardial infarction (MI) and stroke occurred at a monthly probability of 0.0064, and death after surviving a CV event at a monthly probability of 0.0030.

The annual probability of having a recurrent cardiovascular event (“post-CV” to “CV event”) was calculated as 0.0084 based on the MI and stroke outcomes reported in Ariyartne et al. (large registry data from Australia) (80), and the probability of death following a cardiovascular event was 0.0015 (81).

As described earlier, in the base case analysis, the time to hyperkalaemia is estimated by an IPD time-to event analysis using Part B of OPAL-HK. The model also includes an alternative option where the relative risk of hyperkalaemia is applied. Thomsen et al. (2011) provides data which was used to calculate a monthly probability of having a HK event requiring hospitalisation of 0.0397 (82).

A systematic literature search (full methods and results available in Appendix M) was undertaken to determine the association between hyperkalaemia and cardiovascular events such as heart failure, arrhythmias etc. and cardiovascular mortality or death.

This SLR identified a recent cohort study that evaluated K^+ levels in relation to eGFR and additional morbidity (Luo et al., 2016), which informed the probability of hyperkalaemic events for all cardiovascular events (MI, stroke) (83).

Adverse events related to patiromer were taken from the OPAL-HK trial at 8 weeks where mild-to-moderate constipation, diarrhoea and nausea each occurred at a rate of 3.6% in patients with patiromer (66). Since no grade 3–4 adverse events were observed with a frequency of ≥5%, they are not included in the base case analysis.

Relative risk of events

As described above, an SLR was performed to identify the risk of MACE events. This was supplemented with a non-systematic search (Appendix N) to identify studies which could inform the relative risk of renal progression and CV events when using RAASi therapy compared with placebo. This allows an estimation of the renal and CV benefit associated with RAASi enablement. Within the model, the relative risk (RR) of events for patients discontinuing RAAS inhibitors (shown in **Table 33**), came from the Xie et al. NMA (Appendix L). The values used in the base-case analysis assumed the effect of RAAS inhibitors to be equivalent to that of a weighted average of ACE inhibitors and ARBs, using proportions from CPRD where [redacted]%, [redacted]% and [redacted]% of CKD + RAASi patients received ACEi, ARBs and aldosterone antagonists, respectively (73). The impact of individual RRs of ACE inhibitors and ARBs are explored as a scenario analysis. The RR of having a HK event on patiromer was derived directly from the OPAL-HK study (post-hoc analysis, OPAL-HK 301 Part B).

Table 33. Summary of efficacy inputs

	CKD population	Sources
Monthly transition probabilities (placebo, "discontinued RAASi")		
CKD to CKD progression	0.0139	Landray 2010 (78)
CKD to CV event	0.0064	Xie 2016 (44)
CKD to HK hospitalisation	0.0397	Thomsen 2017 (84)
CV event (MI/stroke) to death	0.0015	Parving 2012 (85)
Post-CV event to CKD progression	0.0101	Landray 2010 (78)
Post-CV event to CV-event (recurrent)	0.0084	Ariyaratne 2013 (80)
Post-CV event to death	0.0030	Xie 2016 (44)

	CKD population	Sources
HK to MACE	0.0009	Luo 2016 (83)
HK to death	0.0009	Luo 2016 (83)
Age related mortality	Life tables, England and Wales	Office of National Statistics, UK (74)
CKD stage 3-4 related mortality (age related) Standardised mortality ratios (SMRs)		
Ages less than 69 years old	5.2257	Eriksen 2006 (75), Sud 2016 (76)
Ages 70 to 79 years old	3.3714	Eriksen 2006 (75), Sud 2016 (76)
Ages 79 or greater	3.7086	Eriksen 2006 (75), Sud 2016 (76)
ESRD related mortality (age related) - monthly		
Ages 60-64	0.0062	Steenkamp 2016 (77)
Ages 65-69	0.0095	Steenkamp 2016 (77)
Ages 70-74	0.0118	Steenkamp 2016 (77)
Ages 75-79	0.0165	Steenkamp 2016 (77)
Ages 80-84	0.0213	Steenkamp 2016 (77)
Ages 85+	0.0304	Steenkamp 2016 (77)
Relative risk (RR) (event with RAASi compared to placebo, "continued RAASi")		
CKD to CKD progression	0.64	Xie 2016 (44)
CKD to CV event (MI/stroke)	0.82	Xie 2016 (44)
CKD to HK	2.06	Xie 2016 (44)
CKD to HK with patiromer	0.25	OPAL-HK 301 Part B
CKD to death (non-CV)	0.87	Xie 2016 (44)
CKD progression to death	1.00	Assumption
CV event (MI/stroke) to death	0.88	Xie 2016 (44)
Clinical proportions		
% Proportion ESRD patients die hospital	0.33	Tuso, 2013 (86)
% Proportion of other patients dying in-hospital	0.53	Marie Curie, 2013 (87)
% ESRD - peritoneal dialysis (PD)	0.19	UK Renal Registry (88)
% ESRD - haemodialysis (HD)	0.73	UK Renal Registry (88)
% ESRD - kidney transplant	0.08	UK Renal Registry (88)
% CV event - MI	0.6468	Kerr 2012 (89)
% CV event - Stroke	0.3532	Kerr 2012 (89)

3.3.6. Use of expert opinion for clinical parameters

All parameters in the economic model were informed by way of literature searching, database analyses and relevant clinical trial data. Expert opinion was used for validation purposes only (17). A face-to-face presentation was used to provide a summary of results from OPAL-HK as well as the proposed positioning of patiromer and discussion of current need and clinical burden. Thereafter, the economic model structure, assumptions, preliminary results and proposed scenario analyses were discussed with two clinical experts (one nephrologist and one heart failure specialist) and two health economists. Expert input was thereafter used to confirm the final model structure and assumptions. Particular assumptions which were validated included:

- The risk of events in the patiromer arm reverts to that of the placebo arm upon discontinuation of patiromer
- ESRD health state includes the costs and disutilities associated with hyperkalaemia since the cost and disutility of dialysis and renal transplant are included

B.3.4 Measurement and valuation of health effects

3.4.1. Health-related quality-of-life data from clinical trials

Health-related quality of life data was not collected in OPAL-HK or AMETHYST.

3.4.2. Mapping

As no HRQL data was collected in the above trials, mapping was not possible.

3.4.3. Health-related quality-of-life studies

Two systematic literature reviews were conducted in order to identify relevant health-related quality-of-life data, i.e. studies directly quantifying and reporting health state utilities (HSU) for patients with CKD and CVD, in order to inform the utilities applied in the model. Appendix H describes the full methods and results of the SLRs. A total of 58 and 200 studies were retained for extraction in the CKD and CVD SLRs, respectively.

The following summary of the SLRs are limited to studies which reported EQ-5D values for patients in the UK alone, and reported HSU for health states which were relevant to the economic model.

Health states	Sample sizes	Range of utilities reported	Disutility
Renal transplant and dialysis	416 – 2250	0.443-0.860	NR
CKD stages 1-5	436 – 745	0.67-0.85	Disutility per 10 years of age: -0.034
ESRD	41	0.85	6-month decrement prior to death: -0.19
Stroke	80 – 2253	0.20-0.88	NR
Myocardial infarction	122 – 2876	0.58-0.837	NR
Heart disease and heart failure	50 – 857	0.54-0.56	-0.093

3.4.4. Adverse reactions

The most common adverse events in the OPAL-HK randomised withdrawal phase were constipation, diarrhoea, nausea, headache, and supraventricular extrasystole, which occurred in 3.6% of subjects in the patiromer arm. As these adverse events occurred in fewer than 5% of patients in the OPAL-HK randomised withdrawal phase, disutilities and costs were not included in the cost-effectiveness analysis.

3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

Utility in the model is calculated based on the individuals' age and derived from a general population utility equation developed by Ara & Brazier. This equation was derived from the UK National Health Survey 2012 cited in a previous NICE submission appraisal by Jones-Hughes et al. (1) as follows:

*Utility = C-coeffage*age-coeffage2*age2 +coeffsex *male*

The general population equation calculates the utility for a healthy person of 65 years of age as 0.8210. Thereafter utilities for CKD, model health states and

cardiovascular and hyperkalaemia events are taken and the relative utility compared with the general population utility is calculated. Thereafter, this relative utility is applied to the declining general population utility (as the cohort ages) as model events are experienced. This ensures the utility of events is always linked to the utility of a healthy person of any age in the model.

For example, the baseline population utility at 65 years is 0.8210 and the utility of Stage 3 CKD is 0.8000. Therefore, the relative utility of CKD is calculated as:

Relative utility = (0.8000/0.8210) = 0.9745

The results from the utility SLR (Appendix H) highlighted three key sources that reported utilities for patients with CKD by stage (2), cardiovascular events (3), and ESRD (4). These sources all reported EQ-5D values for patients in the UK specifically.

The utility associated with CKD was derived from Jesky et al where stage 3, 3b and 4 disease was associated with utilities of 0.8000, 0.8000 and 0.7400, respectively (90). These were weighted to the proportion of patients suffering from each disease stage in OPAL-HK to estimate an overall CKD stage 3–4 utility of 0.7736. This utility is 94% of that for the general population and, as described above, this factor is applied to the general population utility in each cycle to all patients to account for the declining age-related healthy population utility and because a CKD population is modelled. The same approach is taken for all event utilities described below.

The utilities for stroke (0.5189) and MI (0.6046) events were taken from Sullivan et al (91) to calculate an overall 'CV events' utility of 0.6996. Post MACE utilities (MI and stroke utilities were 0.6720 and 0.525, respectively) were taken from Pocket et al (92) to calculate an average utility of 0.6215. In both cases, weighted averages were taken based on the proportion of patients suffering from each event (89).

The utility due to disease progression to end-stage renal disease (ESRD) was calculated as 0.5852 based on estimates of utility associated with peritoneal dialysis (0.5300), haemodialysis (0.4430) and renal transplant (0.7120) which were taken from a comparative health related quality-of-life study from the University Hospital of Wales (93). As with MACE events, utilities were weighted in accordance to the

proportion of patients undergoing each type of treatment. Estimates were obtained from the UK Renal Registry Annual Report 2017 where estimates for PD, HD and transplant were 19%, 73% and 8%, respectively (88). The 0.11 annual disutility of hyperkalaemia based on emergency dialysis as per Wyld et al. 2012 was taken and converted to approximately two-weeks of disutility (15.7 days) as was reported in the real-world evidence study conducted in Germany (Xcenda, AmerisourceBergen 2017) (94).

Utilities used in the model are provided in Table 34.

Table 34. Summary of utility inputs

Utility	Point estimate	Source
Constant (C)	0.9680	Jones-Hughes 2016 (95)
Coefficient age ($coeff_{age}$)	0.0018	Jones-Hughes 2016 (95)
Coefficient age 2($coeff_{age2}$)	0.00001	Jones-Hughes 2016 (95)
Coefficient sex ($coeff_{sex}$)	0.0233	Jones-Hughes 2016 (95)
CKD stage 3	0.80 (0.69–1.0)	M. D. Jesky et al. 2016 (90)
CKD stage 3b	0.80 (0.68–1.0)	
CKD stage 4	0.74 (0.62–0.85)	
HK (2 weeks) utility	0.8159	Xcenda AmerisourceBergen 2017 (96), Wlyd 2012 (94)
Stroke	0.5189 (0.47–0.57)	Sullivan 2011 (91)
MI	0.6046 (0.54–0.67)	
Post-MACE MI	0.672 (0.60–0.74)	Pocket 2018 (92)
Post-MACE stroke	0.525 (0.47–0.58)	
Peritoneal dialysis	0.5300 (0.48–0.58)	A.J. Lee 2005 (93)
Haemodialysis	0.4430 (0.40–0.49)	
Renal transplant	0.7120 (0.64–0.78)	
CKD progression (functioning graft, transplant)	-0.0616 (-0.0591 to -0.0642)	A.J. Lee 2005 (93)

As described, above utilities were sourced via a systematic search of the literature. A general population base line utility is applied to all patients which decreases as the cohort ages. Thereafter, since the whole cohort suffers from stage 3–4 CKD a further utility decrement is applied to reflect the disease status. As explained above, relative utilities are applied such that the utility of the model population is 94% that of the

general population of the same age. Further decrements in utility are experienced by patients where they progress to end-stage disease, experience cardiovascular events or hyperkalaemia. The relative utility decrement associated with each event compared with the baseline general population utility is summarised in Table 35

Table 35. Summary change in utility

Health state	Proportional utility
CKD stage 3–4	0.9423
CV events	0.6996
Post-CV events	0.6201
ESRD	0.5852
Hyperkalaemia	0.9938

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR to identify costs associated with CKD, co-morbidities and RAASi therapy was performed to inform model cost inputs (Appendix I). The search was extended to countries where costs may be expected to be similar to the UK – EU-5 and Nordics although only four potentially relevant studies were identified. Therefore, the previously mentioned non-systematic search (Appendix N) was used in addition to the SLR.

A number of costs (CKD management, concomitant medications, end-stage renal disease and cardiovascular events) in the model were found in an economic study estimating financial costs in CKD from the NHS by Kerr et al. in 2012 (89). Its sources are derived from the NHS reference costs, NHS Kidney Care, Hospital Episode Statistics (HES) data, the UK Renal Registry, NHS Blood and Transplant, the Personal Social Services Research Unit (PSSRU) and other key sources from the United Kingdom. Specifically, the costs associated with testing of K^+ levels are captured within the two additional yearly General Practitioner visits (via urine tests), through Nephrology outpatient visits and CKD specific NHS Reference Costs codes (LA08A-C, LA08E-F and QZ13A-B) for admitted care. Therefore, to avoid double-counting, K^+ testing is not costed separately in this analysis.

Additional costs not mentioned in Kerr 2012 were taken from the British national formulary (BNF) (i.e. drug costs), peer-reviewed literature and grey literature reports. The current costs in the model are based on 2018 values, with values from previous years inflated to May 2018 UK GBP using the CPI from the Office for National Statistics, UK. Recurring costs are reported in monthly units to account for the model transition cycle length, while event costs were applied as a "one-time" cost. A complete list of all the costs included in the model is provided in Table 36.

Table 36. Summary of cost inputs

	Point Estimate	Source
Treatment costs (ongoing) - monthly		
Patiromer treatment without PAS (£10 per diem*30.44 days per month)	£304	List price, BNF (97)
Patiromer treatment with PAS (£[redacted] per diem*30.44 days per month)	£[redacted]	Vifor Pharma Ltd.
RAASi cost (ACE-I)	£3.60	BNF (97)
Cost of concomitant medication (Vitamin D, EPO/ESA and Phosphate)	£50.06	Kerr 2012 (89), BNF (97)
Disease costs (ongoing) - monthly		
CKD (stages 3-4) disease management	£162.39	Kerr 2012 (89)
CKD progression (ESRD)	£2,620.64	Kerr 2012 (89)
Cost of post-CV event concomitant medications (clopidogrel)	£1.16	BNF (97)
Event costs (one-time)		
Cardiovascular event	£11,893.89	Kerr 2012 (89)
HK hospitalisation	£1,386.24	NHS Reference Costs (98)
Death in-hospital	£4,884.49	Georghiou 2014 (99)

AE, adverse event; BNF, British National Formulary; CKD, chronic kidney disease; CV, cardiovascular; EPO, erythropoietin; ES, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; HK, hyperkalaemia; MI, myocardial infarction; MRSA, Methicillin-resistant Staphylococcus aureus; PAS, patient access scheme; RAASi, renin-angiotensin-aldosterone system inhibitors

3.5.1. Intervention and comparators' costs and resource use

Given that the model compares the use of patiromer with 'no patiromer' and that patiromer is not expected to be associated with any additional resource use outside of usual care received by CKD patients, differential resource use across strategies is not included in the model. Rather, cost (and benefit) differences originate from alternative rates of events including RAASi discontinuation (cost of therapy), cost of

patiromer, disease progression (to ESRD) and the rate of cardiovascular and hyperkalaemia events.

Cost of patiromer

In the base case analysis, the cost of patiromer was based on a dosage of 8.4g since evidence from the US demonstrates that, since August 2016, the 8.4g dose has been written for [redacted]% of patiromer enrolments (100), and over a 1-year follow-up period (i.e. January 2016 to February 2017), [redacted]% of patients who were treated for hyperkalaemia were maintained on the 8.4g/day patiromer dose (101). The WHO collaborating centre for drug statistics methodology have also issued a temporary define daily dose (DDD) for patiromer at 8.4g (102). The cost, as listed by the NHS, is a flat price for both 8.4g and 16.4g per diem at £10. Hence, the monthly cost for patiromer is calculated as follows:

Monthly cost per patient = 1 per day x £10 per day x 30.44 days per month = £304

A patient access scheme (PAS) has also been considered by the Vifor Pharma Group, for a price of £[redacted] per diem for patiromer. The monthly price of £[redacted] has also be modelled to evaluate its impact on cost-effectiveness and resource implications.

No additional administration, monitoring or test costs are expected to be incurred with commencement of treatment with patiromer.

Table 37. Unit costs associated with the technology in the economic model

Items	Patiromer	Reference in submission	No patiromer	Reference in submission
Technology cost (list)	£304	Table 2	£0	NA
Administration cost	£0	NA	£0	NA
Monitoring cost	£0	NA	£0	NA
Tests	£0	NA	£0	NA
Total	304	NA	£0	NA

3.5.2. Health-state unit costs and resource use

Cost of CKD (stages 3-4) disease management

Primary care costs were equivalent to £91.06 per year which included estimates for blood pressure monitoring control as well as albumin creatinine ratio/protein creatinine ratio testing on an average of two consultations throughout the year (89). This cost also included the resource time spent with clinicians or nursing staff. The annual cost of inpatient management of CKD, based on 6.78 hospital days per patient per annum on average and a per diem cost of £225, was estimated to be £1,525 in 2009/2010 GBP (89). In total, the monthly costs of CKD management with adjustments for inflation, is £162.39.

Cost of CKD progression (end-stage renal disease)

The costs of renal progression incorporates the distribution of renal replacement therapies according to the most recent UK Renal Registry report which showed use of haemodialysis (HD) in 73.1% of patients, peritoneal dialysis (PD) in 19.2% and pre-emptive transplantation in 7.7% (88). The study by Kerr et al, was used to estimate the cost of each type of renal replacement therapy (89). Peritoneal dialysis costs were based on NHS Reference Costs. The cost of HD incorporated patients attending the dialysis clinic/hospital three times a week per annum (including cost of NHS provided transport). Renal transplant costs include costs of the first year associated with the transplant that include: initial assessment, waiting list attendance, acute transplant episode, post-transplant visits and one-year post-immunosuppressive therapy. In addition, data from the UK renal registry shows that patients with renal replacement therapy start near the mean age of the OPAL-HK population live an additional 6 years (88) and hence the total pre- and post-transplantation costs were then divided over 6 years to provide an annual cost. The calculated, inflated, cost per month for PD, HD and transplant equated to £2,137, £2,857 and £1,587, respectively to provide a weighted cost of £2,621 for ESRD.

According to the literature derived from the NHS reference costing, stroke and MI events were estimated to cost £15,009 and, £9,515 respectively, with the weighted proportion of events in a CKD population occurring at 35.3% for stroke and 64.7% for MI (103).

3.5.3. Adverse reaction unit costs and resource use

Adverse events were not included in the economic evaluation given their low frequency.

3.5.4. Miscellaneous unit costs and resource use

Cost of RAAS inhibitors

Assuming 100% compliance, the average cost of RAAS inhibitors was based on the mean doses from a selection of 141 patients who were on ACE inhibitors in the OPAL-HK trial, part A. Based on the BNF and MIMS, the monthly cost is £3.60.

Cost of hyperkalaemia requiring hospitalisation

The cost of a hyperkalaemic hospitalisation was assumed equivalent to a weighted average of two HRGs codes ('Fluid or electrolyte disorders without interventions, critical care 2-3' KC05M and 'Fluid or electrolyte disorders without interventions, critical care 0-1' KC05N) in the 2016-17 NHS reference costs (98). These are associated with average lengths of stay of 3 days, which is consistent with internal expert opinion and gives an average cost of £1,386.24, using finished consultant episode weights of 4,821 and 1,220 for each code, respectively.

Cost of concomitant medications

CKD requires complex drug management and so the cost of primary care prescriptions for vitamin D, EPOs/ESAs, and phosphate binders were included. The usage of each drug was taken from the Kerr study and unit costs derived from MIMS. The cost of these concomitant medications was estimated at £50.06 per month based on the proportion of renal patients using each as reported in Kerr et al (89) Unit costs were taken from the BNF and MIMS.

Table 38. Summary of individual concomitant drug components

Drug	Number of patients	Unit cost
Vitamin D	662,006	£0.54
EPO/ESA	45,797	£11.85
Phosphate binders	59,225	£6.09

Cost of CV event

The cost of MI and stroke events were taken from Kerr et al and thereafter inflated to 2018. Cost of MI and stroke was estimated at £9,879 and £15,584. A weighted average cost was then calculated (£11,894) where proportions are based on the number of events in the same study – 6,734 (35%) strokes and 12,334 MIs (65%).

Post-CV concomitant medication was assumed to consist of clopidogrel which the MIMS reports has a cost of £1.16 per month.

Cost of death

A Nuffield Trust report that explored the costs of end of life care in the UK, provided the cost of hospital related death in the UK (99). This estimate was applied to 33% of patients with ESRD that are known to die in hospital (86) and that 53% of all patients in the UK that die in hospital (87). The inflated event cost is £4,884.

B.3.6 Summary of base-case analysis inputs and assumptions

3.6.1. Summary of base-case analysis inputs

A summary of base case settings applied in the model is provided in Table 39

Table 39. Summary of variables applied in the economic model

Variable	Value	High	Low	Source	Probabilistic distribution	Reference
Model settings						
Discount rate (costs)	3.5%	Not varied as in line with NICE Reference Case				NICE
Discount rate (benefits)	3.5%					
Time horizon	Lifetime (35 years)	Not varied as in line with NICE Reference Case				
Model cohort characteristics						
Age at start	65	NA	NA	NA	NA	OPAL-HK
Patiromer % non-responders	56%					OPAL-HK
Continue RAASi end of Part B	Patiromer: 95% No patiromer: 48%	0	1	Possible range	Beta	OPAL-HK
Patiromer discontinuation	Log Normal	Parameters varied as estimated by variance co-variance matrix				AMETHYST (best fit)
RAASi discontinuation	Weibull					CPRD and OPAL-HK (best fit)
Time to hyperkalaemia	Log normal	Log normal co-efficient				OPAL-HK (best fit)
CKD related events						
RR CKD to CKD progression - RAASi	0.6360	0.4704	0.7903	95% CI	Log Normal	(44)
RR CKD to CV event (MI/stroke) - RAASi	0.8210	0.7103	0.9201	95% CI	Log Normal	(44)
RR CKD to hyperkalaemia with RAASi	2.0648	1.2283	3.3257	95% CI	Log Normal	(44)
RR CKD to hyperkalaemia with Patiromer	0.2500	0.2250	0.2750	+/-10%	Log Normal	(66)
RR CKD to death (non-CV) - RAASi (all-cause mortality)	0.8705	0.7403	1.010	95% CI	Log Normal	(44)
RR CKD progression to death - RAASi	1.0000	0.9000	1.1000	+/-10%	Log Normal	Assumption
RR CV event (MI/stroke) to death - RAASi	0.8802	0.7203	1.0899	95% CI	Log Normal	(44)
prob CKD to CKD progression - no RAASi	0.0139	0.0125	0.0153	+/-10%	Beta	(78)
prob CKD to CV event (MI/stroke) - no RAASi	0.0019	0.0017	0.0021	+/-10%	Beta	(44)
prob CKD to hyperkalaemia hospitalisation	0.0397	0.00027	0.00033	+/-10%	NA	(82)
prob CKD to death (non-CV)- no RAASi	English life tables	NA	NA	NA	NA	(104)
prob CV event (MI/stroke) to death	0.0132	0.0170	0.0108	95% CI	Beta	(81)

- no RAASi						
prob Post-CV event to CKD progression - no RAASi	0.0139	0.0125	0.0153	+/-10%	Beta	(78)
prob Post-CV event to CV-event (recurrent) - no RAASi	0.0084	0.0076	0.0093	+/-10%	Beta	(80)
prob Post-CV event to death - no RAASi	0.0030	0.0027	0.0033	+/-10%	Beta	(44)
prob hyperkalaemia to MACE - no RAASi	0.0009	0.0007	0.0011	95% CI	Beta	(83)
prob hyperkalaemia to death - no RAASi	0.0009	0.0007	0.0011	95% CI	Beta	(83)
prob death to death	1.0000	NA	NA	NA	NA	Assumption
Cost of no patiromer (placebo (comparator)	0.0000	NA	NA	NA	NA	No cost
Cost of patiromer per month (PAS)	[redacted]	NA	NA	NA	NA	Assumption
Cost of patiromer per diem per 8.4g (PAS)	[redacted]	NA	NA	NA	NA	Vifor
Times patiromer taken per diem	1.0000	NA	NA	NA	NA	(5)
Dosage regimen for patiromer (daily = per month 365.25/12),	30.4	NA	NA	NA	NA	(5)
Costs of RAASi treatment (ACE inhibitor/ARB)	3.60	3.24	3.96	+/-10%	Gamma	BNF(69) and OPAL-HK 301 ACE inhibitors: enalapril, perindopril, lisonipril, ramipril
Cost of CKD management	162.39	146.15	178.62	+/-10%	Gamma	(89)
Cost of CKD progression (ESRD)	2620.64				NA	(89)
Cost of concomitant medications (CKD)	50.10	45.05	55.11	+/-10%	Gamma	(89) Vifor data on file (IHS Markit 2018, DataPharm Ltd 2018)
Cost of hospitalization, hyperkalaemia related (severe event)	1386	1248	1525	+/-10%	Gamma	(98)
Cost of CV event	11893.9	NA	NA	NA	NA	Calculated
Cost of in-hospital death	4884.49	4,396	5,373	+/-10%	Gamma	(99)
Cost of post-CV event concomitant medications (Clopidogrel)	1.16	1.04	1.28	+/-10%	Gamma	(97)
Probability of dying in hospital (CKD progression)	0.3344	0.3010	0.3678	+/-10%	Beta	(86)
Probability of dying in hospital (all non-CKD progression)	0.5300	0.4770	0.5830	+/-10%	Beta	(87)
Cost MI event per patient	9879.21	8,891	10,867	+/-10%	Gamma	(89)
Costs of stroke event per patient	15583.96	14,026	17,142	+/-10%	Gamma	(89)
% CV event - MI	0.6468	0.5822	0.7115	+/-10%	Fixed	(89)
% CV event - Stroke	0.3532	0.3178	0.3885	+/-10%	Fixed	(89)
Cost peritoneal dialysis (PD) per patient - monthly	2137.26	1,924	2,351	+/-10%	Log Normal	(89)
Costs ESRD - Haemodialysis (HD) per patient month	2856.53	2,571	3,142	+/-10%	Log Normal	(89)
Costs ESRD - ongoing post kidney transplant per patient - monthly	1586.56	1,428	1,745	+/-10%	Log Normal	(89, 105)
% ESRD - peritoneal dialysis (PD)	19%	0.1728	0.2112	+/-10%	Fixed	(88)
% ESRD - haemodialysis (HD)	73%	0.6579	0.8041	+/-10%	Fixed	(88)
% ESRD - kidney transplant	8%	0.0693	0.0847	+/-10%	Fixed	(88)
Baseline utility equation constant & coefficients						
male	0.5450	0.4905	0.5995	+/-10%	Fixed	(95)

Constant	0.9680	0.9679	0.9679	+/-10%	Fixed	
Coeff age	0.0018	0.0018	0.0018	+/-10%	Fixed	
Coeff age2	0.00001	0.00001	0.00001	+/-10%	Fixed	
Coeff sex (male)	0.0233	0.023289	0.023289	+/-10%	Fixed	
Standardised mortality ratio (SMR), weighted for CKD stage 3/4, based on age						
less than 69 years old	5.2257	NA				(75)
70 to 79 years old	3.3714					
greater than 79 years old	3.7086					
HR for mortality with CKD 4 vs CKD 3	2.5600	1.75	3.75	95% CI	Log Normal	(76)
Patiromer HR RAASi discontinuation from OPAL-HK	[redacted]	[redacted]	[redacted]	+/-10%	Log Normal	OPAL-HK
Utilities						
CKD utility						
Stage 3	0.8000	0.69	1	95% CI	Log Normal	(90)
Stage 3b	0.8000	0.68	1	95% CI	Log Normal	
Stage 4	0.7400	0.62	0.85	95% CI	Log Normal	
CKD stage 3-4 proportions						
Stage 3a (Moderate CKD (45-59mL/min/1.73m2)	24%	0.22	0.27	+/-10%	Log Normal	OPAL-HK
Stage 3b (Moderate CKD (30-44mL/min/1.73m2)	32%	0.29	0.35	+/-10%	Log Normal	
Stage 4 (Severe CKD (15-29mL/min/1.73m2)	44%	0.40	0.48	+/-10%	Log Normal	
CV event utility						
stroke	0.5189	0.47	0.57	+/-10%	Log Normal	(91)
MI	0.6046	0.54	0.67	+/-10%	Log Normal	
post MACE - MI	0.6720	0.60	0.77	+/-10%	Log Normal	(92)
post MACE- stroke	0.525	0.47	0.58	+/-10%	Log Normal	
ESRD utility						
PD	0.5300	0.48	0.58	+/-10%	Log Normal	(93)
HD	0.4430	0.40	0.49	+/-10%	Log Normal	
transplant	0.7120	0.64	0.78	+/-10%	Log Normal	
Hyperkalaemia	0.8159	0.73	0.90	+/-10%	Log-Normal	(94, 96)

3.6.2. Assumptions

Assumptions employed in the base-case analysis are described in Table 40.

Table 40. Model assumptions and justifications

Assumption	Justification
The rate of patiromer discontinuation was assumed to be equivalent to the rate of discontinuation in the AMETHYST trial (Phase II dose-selecting trial for patiromer, described in detail in Section B.2.3.2).	The AMETHYST trial provides the longest-term data available for patients treated with patiromer. Consequently, AMETHYST was used to determine time on patiromer as a better alternative to extrapolating 8-week data from OPAL-HK. While the AMETHYST trial population (who all had diabetic kidney disease) does not precisely match the population in the model, 63% of the OPAL-HK randomised withdrawal phase trial population

	had type-2 diabetes at baseline.
Rate of RAASi discontinuation for the 'no patiromer' arm based on real world analysis of CPRD	This was considered a more robust evidence source than extrapolation of 8 weeks of data from OPAL-HK (Part B)
Rate of RAASi discontinuation for patiromer arm based on applying the hazard ratio of Part B of OPAL-HK to CPRD 'no patiromer' curves.	This is the only data source for efficacy estimates in a stage 3–4 CKD population
It was assumed that after patiromer treatment is stopped, the rate of RAASi discontinuation reverts to that of the no RAASi treatment arm	Validated by UK expert opinion as the risk of hyperkalaemia reverts to that where the protective effects of patiromer are no longer applies The current known discontinuation rate comes from 4 years of UK data provided by CPRD ([redacted]%). The HR associated with patiromer is derived from the OPAL-HK study which is the only available evidence for this population using patiromer.
In the "no patiromer" comparator arm, it is assumed that the discontinuation rate of RAASi at the end of OPAL-HK remains constant for the duration of the model (if using 'fixed proportions' settings)	Alternative option if time-to-event analysis is not used
The short-term effects of reduction in hyperkalaemia after 8 weeks with patiromer (post-hoc analysis, OPAL-HK 301 Part B) were extended by parametric extrapolation	Parametric extrapolation was considered the strongest option given OPAL-HK is the only trial where the effect of patiromer on hyperkalaemia has been studied in the population of interest
RAAS inhibitor use in the CKD stage 3-4 population based on a weighted average of ACE-I and ARB use as per the CPRD. This was translated to relative risks used in the model.	Weighting of relative risks in accordance with real world usage of RAASi allows for a more accurate assessment of risks
For non-CV mortality estimates the all-cause mortality estimates were used, therefore non-CV mortality and related relative risks may be overestimated.	It was more common to report cardiovascular mortality and "all-cause mortality in the reviewed studies
Rate of progression from "CKD stage 3-4" to ESRD and "post-CV event CKD stage 3–4" to ESRD assumed to be equivalent.	This assumption was made given a lack of data providing differential rates. This approach assumes that experiencing a CV event would not impact renal disease progression as the two events are not considered to be related
The model does not mimic disease progression of CKD in stages, and hence assumes that patients in	The intention is not to model CKD progression, rather the impact of

"stages 3-4" move to "stage 5-end-stage renal disease (ESRD)" at a similar rate. This is referred to as ESRD in the model.	patiromer on hyperkalaemia and RAASi enablement. Given RAASi continuation is associated with reno-protective effects, this assumption is likely to favour the no patiromer arm of the model
It was assumed that 53% of all patients would eventually die in hospital.	Based on Marie Curie end of life care in the UK report (87).
Assumed CKD progressed patients do not transit to hyperkalaemia events, as the morbidity, costs and disutility estimates of ESRD include hyperkalaemia hospitalisations (i.e. emergency dialysis).	The morbidity, costs and disutility estimates of the ESRD state includes the impact hyperkalaemia hospitalisations (i.e. emergency dialysis and potential CV events) as the inputs used incorporate these aspects. The model also includes an option to include the impact of further CV events within the ESRD state
The rate of RAASi discontinuation in Part A non-responders is equivalent to that of the placebo arm in Part B of OPAL-HK trial.	The natural history is expected to match that of a population not treated with patiromer. This assumption was confirmed with clinical experts

B.3.7 Base-case results

3.7.1. Base case settings

Base case model settings are summarised in Table 41

Table 41. Base case model settings

Setting	Base case	Justification
Population	CKD stage 3–4 with hyperkalaemia and on RAASi	OPAL-HK population
Age at start	65 years	OPAL-HK
Intervention	Patiromer	OPAL-HK
Comparator	RAASi discontinuation	OPAL-HK
Discount rate (costs)	3.5%	NICE Reference Case
Discount rate (benefits)	3.5%	NICE Reference Case
Time horizon	Lifetime (35 years)	NICE Reference Case

Patiromer % non-responders	56%	OPAL-HK
Continue RAASi end of Part B	Patiromer: 95% No patiromer: 48%	OPAL-HK
Patiromer discontinuation	Log Normal	Best statistical fit
RAASi discontinuation	Weibull	Best statistical fit to which proportional hazards assumption can be applied
Time to hyperkalaemia	Log normal	Best statistical fit
Definition of hyperkalaemia	5.5mmol/L	Aligned to clinical practice
Patiromer dose	8.4g	Based on 2016 US prescription data where 94–96% of patients used this dose (100)

3.7.2. Base-case incremental cost-effectiveness analysis results

When applying a list price of £10 per day, the total costs in the base-case were lower with patiromer compared with the no patiromer strategy, £[redacted] and £[redacted], respectively which led to cost savings of £[redacted]. Total QALYs were higher in the patiromer arm, [redacted], compared with [redacted] in the no patiromer arm resulting in incremental QALYs of [redacted]. Since the analysis indicates patiromer is associated with overall cost savings and QALY gain the strategy is [redacted]. Detailed results are presented in Table 42.

Table 42. Base-case results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Patiromer	[redacted]	[redacted]	[redacted]				
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

At a PAS price of £[redacted] per day, the total costs in the base-case were lower with patiromer compared with the no patiromer strategy, £[redacted] and £[redacted], respectively which led to cost savings of £1,505. Total QALYs were higher in the patiromer arm, [redacted], compared with [redacted] in the no patiromer arm resulting in incremental QALYs of

0.10. Since the analysis indicates patiromer is associated with overall cost savings and QALY gain the strategy is dominant. Detailed results are presented in Table 43.

Table 43. Base-case results (PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Patiromer	[redacted]	[redacted]	[redacted]	-£1,505	0.11	0.10	Dominant (-£14,651)
No Patiromer	[redacted]	[redacted]	[redacted]				
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B.3.8 Sensitivity analyses

3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to test the impact of second order uncertainty by random, simultaneous variation of the input parameters in the model. This analysis was performed by assigning probability distributions to certain variables in the model and repeatedly sampling values from these distributions so propagating uncertainty to estimate the cost effectiveness ratios. One thousand iterations were run. The results of the probabilistic sensitivity analysis are illustrated on the cost effectiveness plane and in the cost effectiveness acceptability curve. The former shows the distribution of incremental costs and benefits under uncertainty and the latter the likelihood of being cost effective at given willingness to pay thresholds.

Parameters included in the PSA and the distributions applied to each are summarised in Table 39. The Cholesky decomposition was applied to simulate random draws for correlated parameters to vary the coefficients for parametric fits (RAASi discontinuation and patiromer discontinuation).

Results

PSA results suggest that the model is robust to parameter variation, with probabilistic results remaining consistent with the deterministic results presented in the base-case section. At list price, the probability that patiromer is cost-effective compared with no

patiromer is [redacted] and [redacted] at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.

Table 44. Base-case results, probabilistic (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Patiromer	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 21. Base case cost-effectiveness plane (list price)

Figure 22. Base case CEAC (list price)

At PAS price, the probability that patiromer is cost-effective compared with no patiromer is 56% and 57% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.

Table 45. Base-case results, probabilistic (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Patiromer	[redacted]	[redacted]	-£146	0.10	Dominant (-£1,403)
No Patiromer	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 23. Base case cost-effectiveness plane (PAS price)

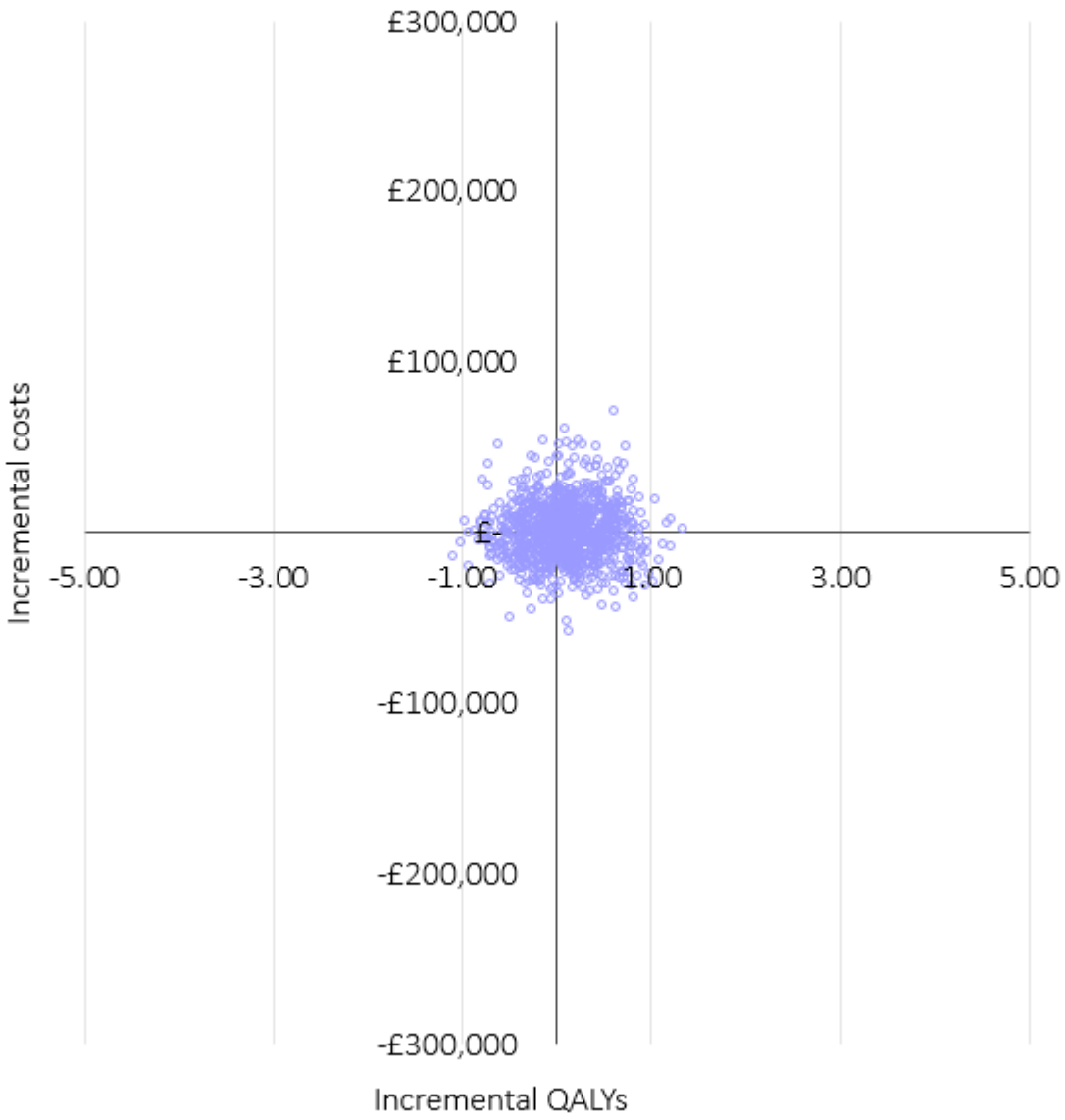
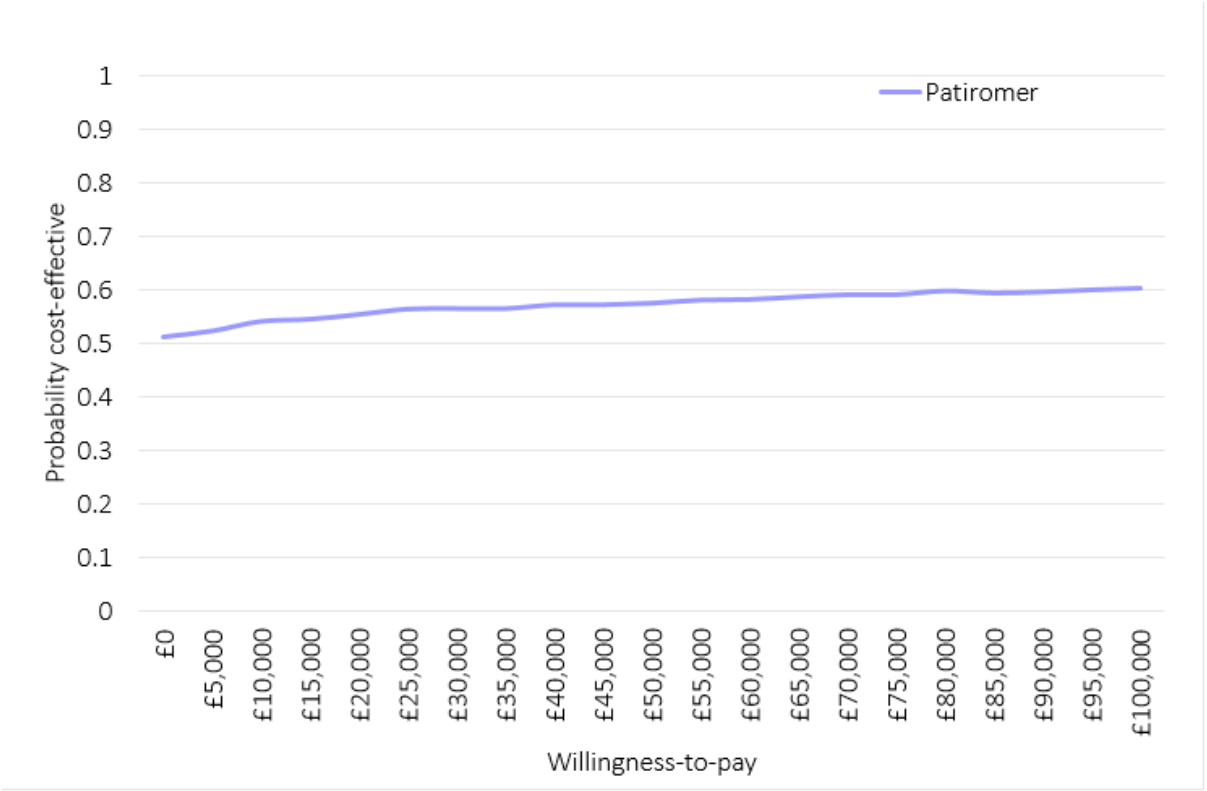


Figure 24. Base case CEAC (PAS price)



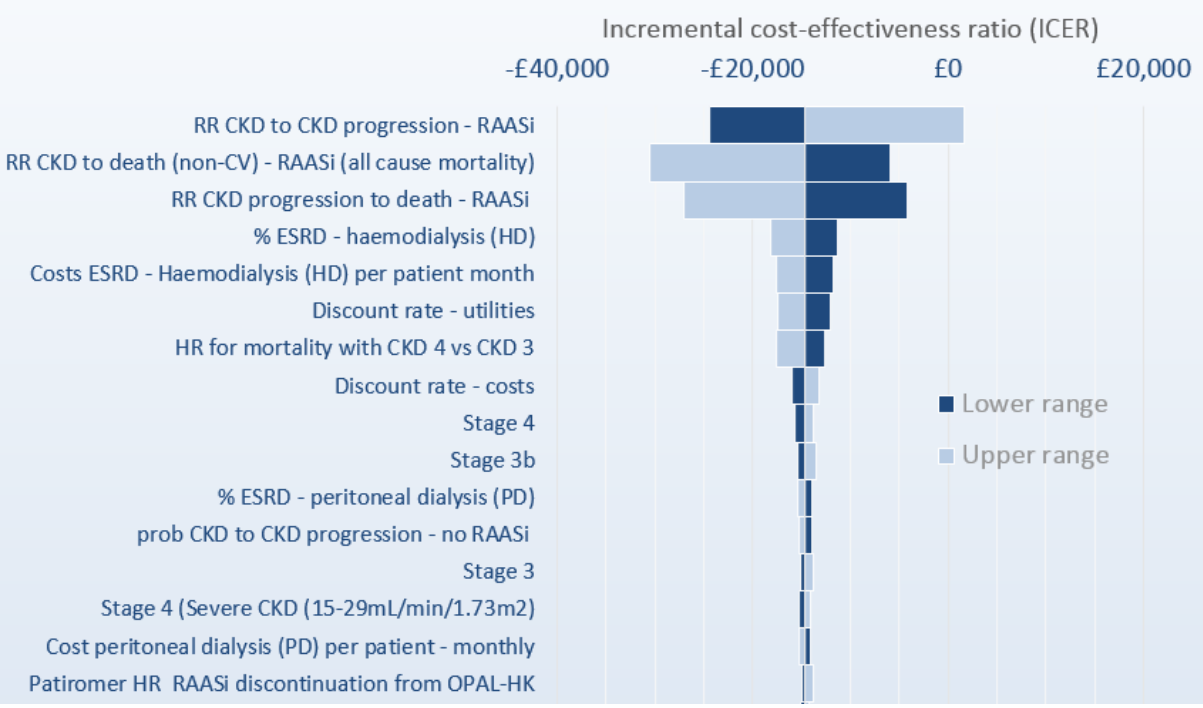
3.8.2. Deterministic sensitivity analysis

In order to determine the impact of single parameter variation, and identify key model drivers, one-way sensitivity analyses were performed. Base case parameters were varied through extreme values as provided in 95% confidence intervals. Where these were not available, an arbitrary 10% variation was applied. Results are presented in the tornado diagram (

and Figure 26) and show no individual parameter takes the ICER above £20,000 per QALY.

Figure 25. One-way sensitivity analysis (List)

Figure 26. One-way sensitivity analysis (PAS)



3.8.3. Scenario analysis

To assess the impact of variation in base case assumptions a number of key scenario analyses were conducted. Particular attention was given to parameters that the model is sensitive or where there was greatest uncertainty. A scenario that was not explored was an alternative definition for moderate to severe hyperkalaemia using a level of 6.0mmol/L. This was dictated by the pre-specified treatment algorithm in the withdrawal phase of OPAL-HK such that patiromer up-titration or RAASi dose modification was applied when serum potassium was ≥5.1mmol/L or 5.5mmol/L, depending on the time point in the trial.

Table 46. Rationale for scenario analyses

Scenario	Base case	Changes	Justification
RAASi discontinuation	CPRD analysis (Weibull) for no patiromer arm and application of the hazard ratio from OPAL-HK to generate patiromer arm	Alternative parametric curves Fixed proportions option where post-patiromer RAASi discontinuation rate assumed to be [redacted]% based on CPRD analysis	Alternatives explored in order to assess the impact of parametric distributions since a life time horizon is modelled

Time to hyperkalaemia	OPAL-HK	Alternative parametric curves	Long term extrapolations are made based on OPAL-HK. Therefore, the impact of various parametric curves was investigated
Time on patiromer	AMETHYST (log normal)	Alternative parametric curves	Long term extrapolations are made based on AMETHYST. Therefore, the impact of various parametric curves was investigated
Relative Risk of CKD progression	Weighted average of relative risk for ACE-I and ARB vs. placebo from the Xie NMA. The weights are based on a CPRD analysis showing that [redacted]% of CKD stage 3–4 patients on RAASi are prescribed ACE-I and [redacted]% ARBs (the remainder using aldosterone antagonists)	Use of ACE-I only (0.61) and ARB only (0.70) relative risks	To evaluate the impact of individual drug classes
Proportion of patients using daily patiromer dose of 25.2g	The base case assumes all patients use 8.4g or 16.8g of patiromer per day (flat pricing)	5%, 10%, 50% and 95% of patients use 25.2g	Maximum licenced dose of patiromer is 25.2g and so a proportion of patients may use the highest dose
ESRD cost	£2,621	Varied by 20%	This is a key model driver
Age at start of model	65 years based on baseline characteristics in OPAL-HK	Apply patient age from CPRD analysis ([redacted] years) and an older cohort (72)	To test cost-effectiveness in a real-world cohort
Hyperkalaemia hospitalisation cost	NHS Reference cost for ('Fluid or electrolyte disorders without interventions, critical care 2-3' KC05M and 'Fluid or electrolyte disorders without interventions, critical care 0-1' KC05N). Non-	Corresponding weighted HRG codes using the National Tariff (2017-18) (106), weighted using the finished consultant episode weights from NHS Reference Costs (2016-2017). This gives an average cost of a	Test impact of alternative cost method

	elective care codes used.	hyperkalaemia hospitalisation of £1,105.77. Further details are available in Appendix I.	
Probability of CV event to death (no RAASi)	Based on estimate from a randomised controlled trial	Alternative estimate from an observational study	To test cost-effectiveness in a real-world cohort
Include CV events within CKD progression (ESRD)	Assumed that cost and disutility of CV events are included within ESRD health state	Additional cost and disutility included in the model	Explicitly model the impact of CV events within ESRD

3.8.4. Summary of sensitivity analyses results

Table 47. Scenarios analyses

Scenario	Setting	ICER (List price)	ICER (PAS price)
RAASi discontinuation	Exponential	[redacted]	Dominant
	Gompertz	[redacted]	Dominant
	Fixed proportions	[redacted]	Dominant
Time to hyperkalaemia	Log logistic	[redacted]	Dominant
	Exponential	[redacted]	Dominant
	Weibull	[redacted]	Dominant
	Gompertz	[redacted]	Dominant
	Fixed proportions	[redacted]	Dominant
Time on patiromer	Log logistic	[redacted]	Dominant
	Exponential	[redacted]	Dominant
	Weibull	[redacted]	Dominant
	Gompertz	[redacted]	Dominant
	Fixed proportions (7 years)	[redacted]	Dominant
	Fixed proportions (30 years)	[redacted]	Dominant
	Fixed proportions (1 year)	[redacted]	Dominant
CKD progression RR	ACEI	[redacted]	Dominant
	ARB	[redacted]	Dominant
Use of 25.2g patiromer	5%	[redacted]	Dominant
	10%	[redacted]	Dominant
	50%	[redacted]	Dominant
	95%	[redacted]	£150
ESRD cost	+20%	[redacted]	Dominant
	-20%	[redacted]	Dominant

Age of cohort	72	[redacted]	Dominant
	50	[redacted]	Dominant
Hyperkalaemia hospitalisation cost	£1105.77	[redacted]	Dominant
Probability of CV death	Morel 2011 (107) (0.0132)	[redacted]	Dominant
Include CV events within CKD progression (ESRD)	Included	[redacted]	Dominant

B.3.9 Subgroup analysis

No sub group analyses were performed

B.3.10 Validation

3.10.1. Validation of cost-effectiveness analysis

The model structure and main assumptions were validated by two health economists, one renal consultant and a heart failure expert (17). Key inputs and data sources were provided for expert review to validate their use. The modelling approach was presented, including:

- Appropriateness of health states
- Methods for extrapolating data, for example RAASi discontinuation
- Key data sources

Initial results were presented and outputs confirmed – for example life expectancy in CKD 3–4 patients.

B.3.11 Interpretation and conclusions of economic evidence

The OPAL-HK trial has shown that patiromer provides demonstrable and statistically significant benefit in maintenance of serum potassium and prevention of recurrent hyperkalaemia compared with placebo (50).

Cost-effectiveness analyses show patiromer is likely to be a dominant strategy providing incremental QALY benefit while yielding cost savings in a stage 3–4 CKD population with hyperkalaemia and using RAASi therapy in England and Wales. Probabilistic sensitivity analyses were performed to test second order uncertainty by

assigning probability distributions to individual parameters and running 1000 iterations. The results confirmed base case results providing, at the PAS price, a probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY of 56% and 57%, respectively. The corresponding results at list price were [redacted]% and [redacted]%. One-way sensitivity analyses confirmed no individual parameter, varied by known confidence intervals or +/-10% resulted in an ICER above £20,000 per QALY. Finally, a series of plausible scenarios were performed with all analyses generating ICER values below £20,000 per QALY.

The introduction of patiromer in England and Wales for the treatment of chronic hyperkalaemia in patients with stage 3–4 CKD and on RAASi therapy provides a treatment option where there is currently an unmet need. Patiromer therefore offers an innovative solution for maintenance for serum potassium and enablement of optimal RAASi therapy.

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 only published economic evaluation identified in the SLR evaluating the management of hyperkalaemia and RAASi enablement in a comparable population is an abstract published by Sutherland et al (62). The abstract states patiromer to be cost-effective within the £20,000 per QALY threshold. The results of this analysis also indicate cost-effectiveness using both list and PAS price.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

The patient population in this cost-effectiveness analysis is narrower than the Marketing Authorisation for patiromer, which is the treatment of hyperkalaemia in adults. This is because the evidence base for patiromer from the OPAL-HK trial is

limited to hyperkalaemia in stage 3–4 CKD which is aligned to the population for which this appraisal is seeking reimbursement. A substantial proportion of the OPAL-HK population had co-morbidities for which treatment of hyperkalaemia may be relevant, for example diabetic and cardiovascular disease patients.

How relevant (generalisable) is the analysis to clinical practice in England?

The results from this analysis are derived from OPAL-HK which included sites in the US and European countries, however there were no UK sites. Therefore, study site location and treatment in the clinical trial setting may not always be generalisable to the UK setting. However, the economic analysis utilises OPAL-HK for initial stratification of patients only, by:

- Responders and non-responders
- RAASi discontinuation

Thereafter, long-term RAASi discontinuation (for 'no patiromer') is modelled using an analysis of CPRD of CKD stage 3–4 patients in England. Patient characteristics were considered similar to OPAL-HK for key metrics thus increasing the generalisability to UK practice with regards to use of RAASi.

The economic analysis uses OPAL-HK to model time to hyperkalaemia. A cut-off of 5.5mmol/L was used to define a hyperkalaemia event. This is aligned to treatment guidelines and was validated by clinical experts as the level at which management in primary care would be initiated – for example, discontinuation of RAASi medication and dietary modification.

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of this analysis are:

- Long term RAASi discontinuation for 'no patiromer' is modelled using real-world data in the UK from the CPRD

- Patiromer discontinuation rates are used modelled using longer term data from the AMETHYST trial (although all patients had diabetes)

- The economic analysis considers the impact of RAASi enablement on CKD progression, hyperkalaemia and the risk of CV events therefore incorporating the main clinical outcomes expected in CKD

Limitations of note include:

- The short duration of OPAL-HK

    - For example, the treatment effect from OPAL-HK had to be used to estimate the hazard ratio for long-term RAASi discontinuation since OPAL-HK is the only relevant trial

  Scenario analyses were performed to test the impact of alternative assumptions of long term RAASi discontinuation, including different parametric curves and long-term use of the proportion of discontinuers observed in OPAL-HK

- No UK patients in OPAL-HK

  Base line characteristics were comparable between CPRD and OPAL-HK

- Stage 3–4 CKD combined in the economic model

  Costs, benefits and the risk of progression may be different between these disease stages

What further analyses could be carried out to enhance the robustness or completeness of the results?

None

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Single technology appraisal

Patiromer for treating hyperkalaemia [ID877]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 5 July 2018 from Vifor Pharma UK. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **8 August 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Jessica Cronshaw, Technical Lead (Jessica.Cronshaw@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. PRIORITY Dietary reduction of potassium is excluded as an option from the company submission. Please provide evidence to support this, as 'low-potassium diet with or without agents that reduce levels of potassium in the body' was included as a comparator in the NICE scope (e.g. a systematic review).

A2. The main comparator in the submission is 'discontinuation or dose modification of RAAS inhibitor therapy' (document B table 1 pg 10), please clarify how hyperkalaemia and hypertension were managed for patients who discontinued or received dose modification of RAAS inhibitor therapy in the OPAL-HK trial.

A3. Document B: Table 1, pg. 10 and pg. 86: the company argues that certain comparators (active) were not included in the OPAL-HK trial because of "ethical and clinical practice reasons". Please clarify why these issues do not apply to the placebo arm of the OPAL-HK trial.

A4. Document B, pg. 36 of the company submission states: "*Serum potassium levels were assessed at beginning of the initial treatment phase in a central laboratory, thereafter at a local laboratory".* How well did local and central measures correlate? Was the central lab also one of the local labs?

A5. There were no UK centres in the OPAL-HK study. Please supply any supporting evidence that demonstrates that the randomised population is generalisable to UK patients.

A6. Document B, p41 Table 9: please provide further columns for:

- the overall baseline characteristics of the patients not randomised into the withdrawal phase in OPAL-HK
- the baseline characteristics data for the AMETHYST DN trial
- withdrawal phase subgroups $K^+<5.5$ at and $K^+\geq5.5$ and by region (Eastern Europe vs. EU/US group).

  Please also include additional rows in the revised Table 9 for the number (%) of patients receiving: (1) calcium channel blockers and (2) beta blockers.

A7. Document B: p63 states that: "almost half of the participating centres (n=24) were in Eastern Europe, while 21 were in the EU and 14 were in the USA.".

Please provide a histogram displaying Number of Patients (y) by Number of sites (x), i.e. number of sites with 1, 2, 3 etc participants in the withdrawal phase.

A8. Please present the numbers of patients receiving RAASi at Part A (Treatment phase) baseline and the numbers continuing and discontinuing RAASi at the end of Part A split as below.

	On RAASi at baseline	On RAASi at 4 weeks	No RAASi at 4 weeks
Non-EU patients			
Baseline K^+<5.5	N=?	N=?	N=?
Baseline K^+≥5.5	N=?	N=?	N=?
W.EU&US patients			
Baseline K^+<5.5	N=?	N=?	N=?
Baseline K^+≥5.5	N=?	N=?	N=?

A9. Did OPAL-HK measure proteinuria? If yes, then please provide details at the withdrawal phase and treatment phase by intervention.

A10. PRIORITY Guidelines on chronic kidney disease (CKD) (e.g. NICE CKD guideline 2014) require eGFR<60 on two separate occasions. Please clarify whether this was a requirement in the OPAL-HK or AMETHYST-DN trials.

A11. PRIORITY OPAL-HK includes 11% of patients who don't have CKD (i.e. eGFR 60+) at trial baseline (Table S5 Weir supplement). Why are these patients classified in the company submission as having CKD?

A12. PRIORITY Please provide analysis of patiromer effectiveness (change in serum potassium) and RAASi discontinuation by eGFR categories shown in Table S5 (Weir Supplement), 60 to ≤90; 45 to <60; 30 to <45; <30 ml/min/1.73 m^2; as well as by region (Eastern Europe vs. EU/US)

A13. Kidney function is known to decline with age, and clinical experts note age-unadjusted eGFR overdiagnoses of CKD (e.g. see Wetzels, Kidney International 2007;72:632–637; doi:10.1038/sj.ki.5002374). Would the company like to comment on how this may affect their model?

A14. **PRIORITY** Changes in level of use of diuretics and RAASi dual blockade are potential confounders for serum potassium levels. Please provide blood pressure control and use of each class of hypertension drugs at the beginning and end of the withdrawal phase by intervention group.

A15. PRIORITY A meta-analysis published at the beginning of 2013 showed dual RAASi blockade was harmful (raising HK and worsening CKD) and should be avoided. Why are these patients on dual RASSi blockade included in OPAL-HK? Please provide change in serum potassium and RAASi discontinuation by sub-group dual/no dual blockade. (see Makani H et al BMJ. 2013; 346: f360. https://doi.org/10.1136/bmj.f360.)

A16. Document B: Figure 6, pg.57: please supply figures with 95% CI for each arm.

A17. Page 63. Please define maximal and submaximal doses of RAASi.

A18. Please present the mean (95% CI) drop in K^+ from Part A baseline to Part B week 4 among those enrolled in Part B by arm, and also the equivalent means (95% CIs) for the Eastern Europe group (n=85) and the EU+US group (n=22) (6 mean values).

A19. B.5 In the appendices a list of excluded studies is provided (embedded word document). Please provide the list of the 16 studies excluded at the stage of full-text assessment.

A20. Please provide justification for excluding data from PEARL-HF from the submission, particularly for informing subgroup analyses for 'people with heart failure'.

A21. PRIORITY Please provide the PDFs of:

- AMETHYST DN Clinical Study Report
- TOURMALINE Clinical Study Report
- PEARL-HF Clinical Study Report
- B.5 Appendices: Please provide the full reference and PDFs of the three studies identified from the hand search as stated in Figure 1, p39.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY. The prognosis of patients with CKD is heavily dependent upon the stage of CKD (e.g. 3a, 3b or 4). Please explain the rationale for modelling these as one group (Document B, Figure 10, p83) and the impact of this assumption on the model results.

B2. Please explain why the numbers at risk in graphs of Document B Figure 9 and 13 are different.

B3. PRIORITY Please provide Document B Figures 12 and 15 showing the "observed" data (and 95% CI) that is being fitted as well as the modelled curves. Please provide the CPRD individual patient data that underlie Figure 12 and 15, or the CPRD Kaplan–Meier RAASi discontinuation data), in the following format.

T (Day)	N Risk	Event	Censored	S(t)
T=0	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…

B4. PRIORITY Please provide Document B Figures 19 and 20 showing the "observed" data (and 95% CI) that is being fitted as well as the modelled curves, with the time scale reduced to show the first 120 days.

B5. Within the CPRD data how was the expected termination date of the RAASi prescription calculated? Why was the period defining RAASi discontinuation limited to 90 days after the anticipated end of the RAASi prescription? Was there any analysis of the CRPD RAASi discontinuation data that examined whether patients ever (a) resumed RAASi after "discontinuing", as defined on page 89 of Document B or (b) switched to an alternative blood pressure treatment regime following RAASi discontinuation. If there was what were its conclusions?

B6. PRIORITY Please provide the Kaplan–Meier data by: (1) intervention arm that underlies Figure 6 of Document B (4 tables); (2) split by Part A Dose groups (8 tables); (3) split by $K^+<5.5$ or $K^+\geq5.5$ at Part A baseline, (8 tables) and (4) for the region subgroups (Eastern Europe vs EU/US) (8 tables) in the following

format. If the Kaplan–Meier data underlying Figure 18 of Document B differs from this, please outline how and provide the parallel data for Figure 18.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0	N=?	N=?	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…	etc…	etc…
EoT: End of trial, LTFU: Lost to Follow-Up						

.

B8. PRIORITY Please provide the OPAL-HK Kaplan–Meier patiromer/placebo discontinuation data for the withdrawal phase for all patients and separately for the region subgroups (Eastern Europe vs EU/US) (6 tables) in the following format. If it is felt more appropriate to include LTFU (lost to follow-up) as an event than as censoring, please outline the rationale for this and split Events into two columns of (a) observed discontinuations and (b) LTFU

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0	N=?	N=?	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…	etc…	etc…

B9. Please provide scenario analyses exploring the primary outcome stratified by Eastern Europe compared to US/EU.

B10. PRIORITY Please provide the OPAL-HK Kaplan–Meier RAASi discontinuation data for the withdrawal phase that underlies Document B Figure 13 for all patients and also separately for the EU/US subgroup in the following format. (4 Tables). If LTFU was treated as a RAASi discontinuation rather than as censoring, please split events into two columns of (a) observed RAASi discontinuations and (b) LTFU. If the data underlying Document B Figure 9 differs from Figure 13, please provide the rationale and the parallel Kaplan–Meier data underlying Document B Figure 9 in the same format.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0	N=?	N=?	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…	etc…	etc…
EoT: End of trial, LTFU: Lost to Follow-Up						

B11. PRIORITY Please provide the AMETHYST-DN Kaplan–Meier discontinuation data that underlies Figure 16 of Document B in the following format, preferably split by dose (3 doses in two strata) but if this is not possible then split by strata. If Figure 16 is derived from a subset of AMETHYST-DN please define this subset. Please confirm if this data relates to the latest data cut of AMETHYST-DN.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0	N=?	N=?	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…	etc…	etc…

B12. PRIORITY Did AMETHYST-DN collect RAASi discontinuation data? If it did, please provide the Kaplan–Meier RAASi discontinuation data in the following format, preferably split by dose but if this is not possible split by stratum. Please confirm if this discontinuation data is restricted to patients who discontinued RAASi and did not resume RAASi during AMETHYST-DN. Was switching to an alternative blood pressure medication after discontinuing RAASi permitted during AMETHYST-DN? Please confirm if this data relates to the latest data cut of AMETHYST-DN.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0	N=?	N=?	N=?	N=?	N=?	N=?
T=?	N=?	N=?	N=?	N=?	N=?	N=?
etc…	etc…	etc…	etc…	etc…	etc…	etc…

B13. Section 3.3.5 notes the use of Landray et al, Ariyartne et al, Parving et al, Thomsen et al and Eriksen et al for various inputs to the economic model. How were these studies identified and why were they chosen over the alternatives?

B14. It is not obvious why the probabilities calculated from Landray et al for CKD patients should be viewed as being 'No RAASi'. Has this been assumed and if so why? Similarly, please outline separately for each of the probabilities calculated from Thomsen 2017, Parving 2012, Ariyarantne 2013 and Luo 2016 if these are viewed as relating as being 'No RAASi', and if so why?

B15. Please provide the RAASi proportions data on file from Reference 73 and outline how it has been derived from the CPRD. Are the RAASi costs within the model aligned with these proportions?

B16. Please outline the reasons for exclusion of studies in Table 57 of the appendices. Why was Xie used in preference to Palmer in the economic model?

B17. PRIORITY Please clarify some of the calculations in the model:

- provide an excel spreadsheet that separately calculates the RAASi odds ratios of *Calculations* Y40:Y44 from the data of Xie et al 2016, with full table/text/figure referencing of the values taken from Xie et al 2016.
- clarify why the relative risk for CKD to ESRD of 0.61 calculated from Xie, *Calculations* AB40 is not used and why the value of 0.64, *Inputs* K23, is used.
- provide the full arithmetic of the calculation of the 0.64 value, together with full table referencing of the source data.
- provide an excel spreadsheet that calculates the No RAASi annual rate of 3.6% for post-MACE to Dead from the data of Xie et al 2016, with full table/text/figure referencing of the values taken from Xie et al 2016.

B18. Please present the equivalent of Calculations W72:AC77 for Part A of OPAL-HK.

B19. PRIORITY The probabilities of HK to Death and HK to MACE from Luo et al have two values for CKD 3b. Why is this? Please provide fuller referencing for the values of Luo et al that underlie each of *Calculations* cells X98, X100:Y103 and X108:Y111 together with the details of any additional calculations that are required to derived the values in *Calculations* cells X98, X100:Y103 and X108:Y111.

B20. The electronic model appears to include CHF, MI and stroke in the probability of secondary MACE events derived from Ariyarantne 2013. Please give a rationale for including CHF as a MACE event. Please clarify how the probabilities and relative risks are aligned with this. It can also be noted that Ariyarantne 2013 was for the 12-month period following PCI. Is there evidence that these probabilities apply beyond the 12-month period following PCI or is this a company assumption?

B21. PRIORITY Table 3 of Landray et al outlines all patient incidences of 12.1%/y ESRD and 6.5%/y Death. These are not obviously aligned with the values in the electronic model. Please provide an excel spreadsheet outlining how the values in the electronic model have been calculated and why they differ from those of table 3 of Landray et al.

B22. PRIORITY Please provide fuller referencing for the source of the Thomson et al data within the ((0.338*1.72)-0.338)/0.5 formula that underlies the calculated No RAASi 48.7% annual rate of CKD to HK hospitalisations. Explain the rationale underlying the formula**.**

B23. Please provide more explicit referencing for the source of the QoL values for MI and stroke from Sullivan et al 2011 and the details of any calculations to derive the values in Table 34. Please provide the link to the calculations if used, and outline what inputs were specified in it to arrive at the values of Table 34.

B24. Table 3 of Pocket et al 2018 gives quality of life values for a number of time points. At 6 months, the values are reported as all patients 0.672, MI 0.702, UA 0.637 and Stroke 0.525. Are the 6-month values those applied in the model? If they are why was this time point used and has the MI value been incorrectly transcribed? If not, please provide fuller referencing to which values from Pocket et al 2018 have been used and why. Given the NICE/DSU preference for sourcing quality of life values from a single coherent source, why have the 0 months QoL values of Pocket et al 2018 been ignored in preference to values from Sullivan et al 2011?

B25. Please provide a more explicit table/text/figure reference for the source the - 0.0616 value of Document B table 34 for CKD progression from Lee et al

2005 and if necessary outline how this value has been calculated from values within Lee et al 2005.

B26. Please provide the full calculation of the monthly costs of CKD of £162, full table/text/figure referencing to all values used and also the rationale underlying this cost. Does it include all annual costs likely to be incurred by CKD patients, given the differential overall survival estimates of the model? For the other costs within the model neither Thokla 2013 nor Seaton (year unspecified) appear to be within the reference pack. Please provide these. What is the source for the post-transplant average life expectancy of 5 years?

B27. Please provide more explicit table/text/figure referencing to the UK Renal Registry for the following data on ESRD: 19.2% on PD, 73.1% on HD and 7.7% receiving transplant.

B28. In document B p116 table 39 upper and lower limits are not given for the parameter '% of non-responders to patiromer', however the 95% CI is 42% to 71% (document B p60). Please provide the sensitivity analysis for this parameter or if not please provide justification.

Section C: Textual clarifications and additional points

C1. Please confirm the value for the post-CV event proportionate utility of Document B Table 35. It does not seem aligned with the values given in table 34.

C2. PRIORITY Please provide the arithmetic explaining how the health state utility values in Document B Table 35 have been calculated from specified and identified values within the relevant source papers.

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Single technology appraisal

Patiromer for treating hyperkalaemia [ID877]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 5 July 2018 from Vifor Pharma UK. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **8 August 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Jessica Cronshaw, Technical Lead (Jessica.Cronshaw@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. PRIORITY: Dietary reduction of potassium is excluded as an option from the company submission. Please provide evidence to support this, as 'low-potassium diet with or without agents that reduce levels of potassium in the body' was included as a comparator in the NICE scope (e.g. a systematic review).

A low potassium (K+) diet restricts consumption of healthy foods (e.g., the Dietary Approaches to Stop Hypertension - DASH diet recommended for the hypertension management) and it is unlikely to be widely used considering the difficulties in changing dietary habits (K+-rich foods are pervasive) and the prevalence of K+ rich foods makes long-term adherence problematic (1). Limited evidence exists on both the efficacy of and adherence to a low K+ diet (2).

The European Public Assessment Report (EPAR) for Veltassa confirms the approach taken to determine relevant comparators in this submission. It highlights that for patients in whom the aetiology of hyperkalaemia is not reversible but rather more chronic in nature from underlying CKD and/or use of RAASi therapies, the traditional approach has relied on dietary restriction and RAASi dose reduction or discontinuation, diuretics, oral bicarbonate or cation exchange resins (SPS/CPS) (3). However, it also states the difficulties in diet modification due to the ubiquitous presence of potassium in foods.

The clinical systematic literature review (SLR) performed for this submission also found that most studies included either dietary restrictions or counselling on the restriction of high K^+ foods. In OPAL-HK diet was not controlled; however, patients were counselled at each visit to restrict their intake of high-potassium foods (>250 mg per 100 g) and to maintain a low-potassium diet (potassium intake of ≤3 g per day). Similar criteria or potassium restriction were also applied in AMETHYST-DN and PEARL-HF. TOURMALINE was the only study where dietary restrictions were not applied.

Therefore, the company believe that diet should be considered as a background therapy to which active treatment treatments for hyperkalaemia can be added rather than a standalone option.

A2. The main comparator in the submission is 'discontinuation or dose modification of RAAS inhibitor therapy' (document B table 1 pg. 10), please clarify how hyperkalaemia and hypertension were managed for patients who discontinued or received dose modification of RAAS inhibitor therapy in the OPAL-HK trial.

In both Parts A and B of the study, no new RAASi medications were to be initiated and doses of RAASi medications were not changed unless the subject became hyperkalemic and the RAASi needed to be reduced or discontinued according to the titration guidelines. In order to control blood pressure (BP), all subjects were allowed to add or modify non-RAASi and antihypertensive drugs that did not affect serum potassium levels (e.g., calcium channel blockers, alpha blockers or alpha-2 agonists) per the investigator's discretion at any time during the study. Subjects BP was checked and closely monitored to determine the need for RAASi dose adjustment or discontinuation. If at any time during the study a subject developed symptomatic postural hypotension or SBP <100 mmHg or DBP <60 mmHg, non-RAASi antihypertensive treatments were to be removed or their doses reduced before adjustments were made to the RAASi medications. If hypotension persisted after reducing or discontinuing non-RAASi antihypertensive medications, RAASi medication could either be dose reduced or discontinued. For those subjects on an ACEI or ARB and an AA such as spironolactone or eplerenone, preference was given to modifying the AA first before any adjustments were made to the ACEI or ARB.

In Part A, the dose of patiromer could be adjusted based on the local laboratory serum potassium (at Part A Day 3, Week 1, Week 2 and Week 3 visits) and according to titration algorithms (Table 1) with the aim of achieving serum potassium in a target range (3.8 to < 5.1 mmol/L). In addition, the rate of change in serum potassium was also to be taken into account; that is, if the serum potassium was 5.1 to < 5.5 mmol/L and the reduction in serum potassium from the previous visit was ≥ 0.4 mmol/L, then no dose increase was required. Dose adjustments were made in increments of 8.4 g/day patiromer. However, per the investigator's discretion, in order to ensure subject safety, very high or very low serum potassium values could result in greater patiromer dose adjustments, up to the maximum daily dose of 50.4 g or down to 0 g patiromer. RAASi discontinuation was permitted at any time in the Part A period for those subjects

with a serum potassium ≥ 6.5 mmol/L and for those subjects on the maximum dose of 50.4 g/day patiromer with a serum potassium ≥ 5.1 mmol/L.

Table 1. Titration algorithm for Part A

Table 4 Titration Algorithm for Part A – 4-Week, RLY5016 for Oral Suspension Treatment Phase

Serum K^+ (mEq/L) :	< 3.8	3.8 to < 5.1	5.1 to < 5.5	5.5 to < 6.5	≥ 6.5
Patiromer dose	Decrease by 8.4 g/day or more or to 0 g/day (if already on 0 g/day, early withdraw)	No change	Increase by 8.4 g/day[a,b]	Increase by 8.4 g/day [a]	Increase to 50.4 g/day (if already on 50.4 g/day, early withdraw)
RAASi dose	No change (if already on patiromer 0 g/day, early withdraw)	No change	No change	No change	Discontinue
Study Participation	Continue (if already on patiromer 0 g/day, early withdraw)	Continue	Continue	Continue	Continue (Early withdraw if already on 50.4 g/day)
Next visit	Next weekly visit (Follow-up visit if early withdrawn)	Next weekly visit	Next weekly visit	Next weekly visit	MSV, within 24 hours (Follow-up visit if early withdrawn)
2 x consecutive values:					
Patiromer dose	Decrease to 0 g/day (if already on 0 g/day, early withdraw)	-	-	Increase by 8.4 g/day or increase to 50.4 g/day [a]	Discontinue
RAASi dose	No change (if already on patiromer 0 g/day, early withdraw)	-	-	No change	Discontinue
Study Participation	Continue (if already on patiromer 0 g/day, early withdraw)	-	-	Continue	Early withdraw
Next visit	MSV, within 72 hours	-	-	MSV, within 72 hours	Part A Follow-up Visits
3 x consecutive values:					
Patiromer dose	Discontinue	-	-	Discontinue	-
RAASi dose	Early withdraw	-	-	Discontinue	-
Study Participation	Early withdraw	-	-	Early withdraw	-
Next visit	Part A Follow-up Visits	-	-	Part A Follow-up Visits	-

K^+ = potassium; MSV = Mandatory Safety Visit; RAASi = renin angiotensin aldosterone system inhibitor

[a] No titration required if the serum potassium decreased from the previous visit was ≥ 0.4 mEq/L

[b] If subject is on 50.4 g/day, discontinue RAASi. Return for next specified visit in the table. 2 x consecutive values on 50.4 g/day, early withdraw

Any subject on 50.4 g/day and who discontinued RAASi and whose serum potassium was still ≥ 5.1 mEq/L was to be early withdrawn.

Any subject who had a serum K^+ of < 3.8 mEq/L and was on 0 g/day of patiromer was to be early withdrawn.

In Part B, the randomised withdrawal phase, subjects receiving patiromer could have dose adjustments based on the local laboratory serum potassium values and according to titration algorithms (Table 2). The maximum was 50.4 g/day of patiromer. Placebo was administered at a fixed dose of 8 g/day (4 g BID) and was not titrated (the titration algorithms did include the criteria for discontinuing placebo and withdrawing a placebo-treated subject from Part B). On the first occurrence of hyperkalemia (serum potassium ≥ 5.5 mmol/L in the first 4 weeks of Part B or serum potassium ≥ 5.1 mmol/L in the second 4 weeks of Part B) one dose titration was allowed at an increment of 8.4g/day. On the second occurrence of hyperkalemia, as evidenced by a serum potassium ≥ 5.1 mmol/L or on the first occurrence of hyperkalemia (serum potassium ≥ 5.5 mmol/L in the first 4 weeks of Part B or serum potassium ≥ 5.1 mmol/L in the second 4 weeks of Part B) for those subjects on the maximum dose of 50.4 g/day patiromer, all RAASi medication was discontinued. In a placebo-treated subject, at the first occurrence of hyperkalemia (serum potassium ≥ 5.5 mmol/L in the first 4 weeks of Part B or serum potassium ≥ 5.1 mmol/L in the

second 4 weeks of Part B) doses of all RAASi medications were decreased by 50% or to the next dosage below. On the second occurrence of hyperkalemia, as evidenced by a serum potassium ≥ 5.1 mmol/L, all of the subject's RAASi medication was discontinued. Subject's whose serum potassium was < 3.8 mmol/L were withdrawn early and entered the Part B follow-up period. In either treatment group, active or placebo, if the subject had a serum potassium ≥ 6.0 mmol/L, all RAASi medications were discontinued.

In either treatment group, active or placebo, on the third occurrence of hyperkalemia (given that the first two occurrences had both corresponded to a serum potassium value < 6.0 mmol/L), patiromer or placebo was discontinued; the subject was withdrawn and entered the Part B follow-up period. In either group, if a subject had a confirmed occurrence of serum potassium ≥ 6.5 mmol/L, patiromer or placebo was discontinued and RAASi medications were discontinued the subject was withdrawn and entered the Part B follow-up period.

Table 2. Titration algorithm for first 4 weeks of Part B

Table 5 Titration Algorithm for First 4 Weeks of Part B – RLY5016 for Oral Suspension Randomized Withdrawal Phase (Part B Day 3 to Part B Week 3 Visits)

Serum K^+ Threshold		Treatment Group	Intervention	Study Participation	Next Visit
< 3.8	Any event	Active:	Discontinue patiromer/placebo No changes to RAAS inhibitor medications	Early Withdraw	Part B Follow-up Visits
		Placebo:			
3.8 - < 5.1	Any event	Active:	No changes	Continue	Next weekly visit
		Placebo:			
5.1 – < 5.5	1st event (5.1 – 5.4)	Active:	No change to patiromer, placebo or RAAS inhibitor medication(s)	Continue	Next weekly visit
		Placebo:			
	Any subsequent event in 1st 4 weeks (5.1 – 5.4)	Active:	No change to patiromer, placebo or RAAS inhibitor medication(s)	Continue	Next weekly visit
		Placebo:			
≥ 5.5 – < 6.0	1st event (≥ 5.5 - < 6.0)	Active:	Increase patiromer by 8.4 g/day[a] No changes to RAAS inhibitor medications.	Continue	Next weekly visit
		Placebo:	No change to placebo. Decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%	Continue	Next weekly visit
	2nd event (≥ 5.1 - < 6.0)	Active:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
		Placebo:	No change to placebo. Discontinue RAAS inhibitor medication(s).	Continue	Next weekly visit
	3rd event (≥ 5.1 - < 6.0)	Active:	Discontinue patiromer.	Early withdraw	Part B Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Part B Follow-up Visits
≥ 6.0 - < 6.5[b]	1st event	Active:	No change to patiromer dose. Discontinue RAAS inhibitor medication(s).	Continue	MSV within 72 hrs (At MSV, discontinue if $K^+ \geq 6.0$)
		Placebo:	No change to placebo. Discontinue RAAS inhibitor medication(s).	Continue	MSV within 72 hrs (At MSV, discontinue if $K^+ \geq 6.0$)
	2nd event (≥ 5.1)	Active:	Discontinue patiromer.	Early withdraw	Part B Follow-up Visits
		Placebo:	Discontinue placebo.	Early withdraw	Part B Follow-up Visits

K^+ = potassium; MSV = mandatory safety visit; RAAS = renin angiotensin aldosterone system

[a] If subject is on 50.4 g/day, decrease each RAAS inhibitor medication by 50% or to next available dose strength below 50%.

[b] Any subject with a serum $K^+ \geq 6.5$ must discontinue patiromer/placebo and all RAAS inhibitor medications and must return for a MSV within 24 hours. These subjects will be early withdrawn and will enter the Part B Follow-up Phase.

A3. **Document B: Table 1, pg. 10 and pg. 86: the company argues that certain comparators (active) were not included in the OPAL-HK trial because of *"ethical and clinical practice reasons".* Please clarify why these issues do not apply to the placebo arm of the OPAL-HK trial.**

Because of the inherent risks of hyperkalemia, patients were closely followed with repeated clinic visits during the 4-week treatment period (Part A); assessments included measurement of serum potassium and other electrolytes, ECGs and renal function. Potassium levels were monitored and patiromer dose adjusted, accordingly, on Day 3 visit and weekly visits (Part A Week 1, 2 and 3) to the end of 4 weeks of treatment. If a subject's serum potassium level was outside of the normal range, patiromer dose titration was performed according to a protocol specified Part A titration algorithm. The titration algorithm also specified discontinuation of the RAASi dose (1) if the serum potassium level was ≥ 6.5 mmol/L or (2) if the serum potassium level was ≥ 5.1 mmol/L and the subject was receiving the maximum dose of Patiromer (50.4 g/day). Depending on the serum potassium level, the titration algorithm specified mandatory safety visits (MSV) within 24 or 72 hours. Please refer to question A2 for the detail of the algorithm. Given that all subjects entering Part A of the study would be hyperkalaemia, a placebo control arm was considered unethical and unsafe. Only those Part A subjects whose serum potassium was controlled at the end of Part A were eligible for randomisation into Part B and hence might be randomised to placebo. This randomised withdrawal provided a safe and ethical way to incorporate the use of a placebo control in a randomised trial. Criteria for early withdrawal from Part B for hypo- or hyperkalaemia were defined in the Part B dose titration tables so that placebo exposure for 8 weeks could be undertaken without putting subjects at unacceptable risk. Furthermore, the use of sodium polystyrene sulfonate as an active control was not considered a clinically appropriate option because of its gastrointestinal (GI) side effects and lack of systematic study of chronic use (4, 5). Please note in UK calcium polystyrene sulfonate may be used and it has a similar side effect profile to sodium polystyrene sulfonate.

A4. Document B, pg. 36 of the company submission states: "*Serum potassium levels were assessed at beginning of the initial treatment phase in a central laboratory, thereafter at a local laboratory*". How well did local and central measures correlate? Was the central lab also one of the local labs?

Assessment of serum potassium and other chemistry measures during both Part A and B of the trial was done in both local and central laboratory. The central and local laboratories were independent of each other. The correlation analysis below demonstrates the relationship between local and central laboratories.

Table 3. Concordance between local and central laboratory serum potassium values at Part A baseline

Table 4. Concordance between local and central laboratory serum potassium results from post-Part A baseline

Table 5. Regression model used to impute central laboratory serum potassium values in Part A

Table 6. Regression model used to impute central laboratory serum potassium values in Part B

Table 7. Concordance between local and central laboratory serum potassium values at Part A baseline

Table 8. Concordance between local and central laboratory serum potassium values at Part B baseline

A5. There were no UK centres in the OPAL-HK study. Please supply any supporting evidence that demonstrates that the randomised population is generalisable to UK patients.

Table 27 (page 91) of Document B provides a comparison of patient characteristics in OPAL-HK with real world data from the Clinical Practice Research Datalink (CPRD) database, where patients in England were evaluated. The CPRD is an electronic medical records database representative of the primary care patient population in the UK. The CPRD collects data from 714 contributing practices across the UK, covering approximately 8% of the total UK population. Patient data is maintained by GPs who record demographic, medical and prescription details at every encounter. The CPRD was used to identify CKD stage 3-4 adult patients with hyperkalaemia.

A comparison of base line patient characteristics between cohorts showed that the populations were broadly comparable. Kidney function and serum K+ were shown to be similar, as was the use of various RAASi medication. A greater proportion of patients in OPAL-HK suffered with co-morbidities and while the mean age was different, the impact of this was explored as a scenario analysis where patiromer remained a dominant strategy. A summary of patient characteristics is provided below.

Table 9. Patient characteristics in CPRD and OPAL-HK Part B

	OPAL-HK Part B Placebo (N=55)	**CPRD (N=[redacted])**
Male	58% (30)	[redacted]
Mean age	65.0 (55)	[redacted]
Mean eGFR	39.0 (55)	[redacted]
RAASi (ACE)	73% (38)	[redacted]
RAASi (ARB)	31% (16)	[redacted]
RAASi (aldosterone)	8% (4)	[redacted]
Mean serum K+ (end)	5.17 mmol/L	[redacted]
Myocardial infarction	27% (14)	[redacted]
Hypertension	96% (50)	[redacted]
Diabetes mellitus	63% (33)	[redacted]
Heart Failure	42% (22)	[redacted]

A6. Document B, p41 Table 9: please provide further columns for:

- **A6.1. the overall baseline characteristics of the patients not randomised into the withdrawal phase in OPAL-HK**

The overall baseline characteristics for part A non-responders is not available. Subjects with a baseline serum potassium ≥ 5.5 mmol/L (central laboratory) at the beginning of Part A were entered into Part B of the study if they had responded to the 4 weeks of treatment with patiromer during Part A, and satisfying all of the following at the Part A Week 4 visit; Serum potassium (local laboratory) in the target range for Part A (3.8 to < 5.1 mmol/L), receiving a RAASi, receiving patiromer at a dose of 8.4 to 50.4 g/day.

- **A6.2. the baseline characteristics data for the AMETHYST DN trial**

Please see Table 10 below.

Table 10: Demographic characteristics of patients enrolled in OPAL-HK and AMETHYST-DN

	OPAL-HK							AMETHYST
	Initial treatment phase	Randomised withdrawal phase						Overall
	Overall (N=243)	Placebo (n=52)	Patiromer (n=55)	Placebo (EU and US)	Patiromer (EU and US)	Placebo (Eastern Europe)	Patiromer (Eastern Europe)	Patiromer (n=304)
Male sex, n (%)	140 (58)	30 (58)	28 (51)	[redacted]	[redacted]	[redacted]	[redacted]	192 (63.2)
Age, years*	64.2 ± 10.5	65.0 ± 9.1	65.5 ± 9.4	[redacted]	[redacted]	[redacted]	[redacted]	66.3 ± 8.6
White race, n (%)	239 (98)	52 (100)	55 (100)					304 (100)
Type 2 diabetes, n (%)	139 (57)	33 (63)	34 (62)	[redacted]	[redacted]	[redacted]	[redacted]	304 (100)
Heart failure, n (%)	102 (42)	22 (42)	27 (49)	[redacted]	[redacted]	[redacted]	[redacted]	105 (34.6%)
Myocardial infarction, n (%)	60 (25)	14 (27)	18 (33)	Not reported	Not reported	Not reported	Not reported	Not reported
Hypertension, n (%)	236 (97)	50 (96)	54 (98)	Not reported	Not reported	Not reported	Not reported	100%
Serum potassium (mmol/L)*	5.6 ± 0.5	5.9 ± 0.4	5.9 ± 0.6	[redacted]	[redacted]	[redacted]	[redacted]	5.3 ± 0.4
Estimated GFR (mL/min/1.73 m^2)*	35.4 ± 16.2	39.0 ± 20.4	38.6 ± 20.7	[redacted]	[redacted]	[redacted]	[redacted]	40.6 5.9 ± 50.7
RAAS inhibitor use, n (%):	243 (100)	52 (100)	55 (100)	Not reported	Not reported	Not reported	Not reported	215 (70.7)
ACE inhibitors, n (%)	170 (70)	38 (73)	37 (67)	Not reported	Not reported	Not reported	Not reported	150 (49)
angiotensin II receptor blockers, n (%)	92 (38)	16 (31)	24 (44)	Not reported	Not reported	Not reported	Not reported	75 (25)
aldosterone antagonists, n (%)	22 (9)	4 (8)	4 (7)	Not reported	Not reported	Not reported	Not reported	1 (0.3)
renin inhibitors, n (%)	2 (1)	0	0	Not reported	Not reported	Not reported	Not reported	Not reported
dual RAAS blockade, n (%)	41 (17)	6 (12)	10 (18)	Not reported	Not reported	Not reported	Not reported	Not reported
receiving maximal doses, n (%)	106 (44)	21 (40)	21 (38)	[redacted]	[redacted]	[redacted]	[redacted]	Not reported
Non-RAAS inhibitor diuretic use, n (%):	132 (54)	27 (52)	28 (51)	Not reported	Not reported	Not reported	Not reported	130 (42.8)
thiazides, n (%)	70 (29)	11 (21)	16 (29)	Not reported	Not reported	Not reported	Not reported	[redacted]
loop diuretics, n (%)	77 (32)	20 (38)	16 (29)	Not reported	Not reported	Not reported	Not reported	Not reported
Calcium channel clockers n (%)	112(46)	22 (42)	23 (42)	Not reported	Not reported	Not reported	Not reported	[redacted]
Beta blockers	128(53)	32 (62)	33(60)	Not reported	Not reported	Not reported	Not reported	[redacted]

*Mean ± standard deviation.

Other combined drugs used in AMETHYST:

ACE+diuretic n = [redacted] ([redacted]%)
Angiotensin antagonist +diuretics n = [redacted] ([redacted]%)
ACE+calcium channel blockers n = [redacted] ([redacted]%)
Angiotensin antagonist +calcium channel blockers n = [redacted] ([redacted]%)

- **A6.3. withdrawal phase subgroups K^+<5.5 at and K^+≥5.5 and by region (Eastern Europe vs. EU/US group).**

Subjects with normal potassium levels (3.8 to < 5.1 mmol/L) at the end of Part A, were eligible for randomisation into Part B. The recurrence of hyperkalaemia was defined as either ≥5.1mmol/l or ≥5.5mmol/l. The eligible subjects that were randomised into part B of the study had the same baseline characteristics at the beginning of the study and there is no data on baseline characteristics of non-responders. OPAL-HK was not designed to collect data based on K+<5.5 and K+≥5.5 in part B, thus the requested data is not available.

- **A6.4. Please also include additional rows in the revised Table 9 for the number (%) of patients receiving: (1) calcium channel blockers and (2) beta blockers.**

Please see Table 10.

A7. Document B: p63 states that: "almost half of the participating centres (n=24) were in Eastern Europe, while 21 were in the EU and 14 were in the USA.". Please provide a histogram displaying Number of Patients (y) by Number of sites (x), i.e. number of sites with 1, 2, 3 etc participants in the withdrawal phase.

The number of subjects recruited by individual sites at the start of Part B is not available. The number of sites who recruited each number of patients at the start of Part A (ITT population) is provided in Figure 1 below.

Figure 1. Number of patients recruited by site: OPAL Part A ITT

A8. Please present the numbers of patients receiving RAASi at Part A (Treatment phase) baseline and the numbers continuing and discontinuing RAASi at the end of Part A split as below.

	On RAASi at baseline	**On RAASi at 4 weeks**	**No RAASi at 4 weeks**
Non-EU patients			
Baseline K^+<5.5	**N=?**	**N=?**	**N=?**
Baseline K^+≥5.5	**N=?**	**N=?**	**N=?**
W.EU&US patients			
Baseline K^+<5.5	**N=?**	**N=?**	**N=?**
Baseline K^+≥5.5	**N=?**	**N=?**	**N=?**

Subjects with any stable dose of at least one RAASi medication (an ACEI, ARB or AA) for at least 28 days prior to screening were allowed to enter the study. Thus 100% of patients were on RAASi at baseline.

Table 11. RAASi continuation patient numbers (OPAL-HK Part A)

	On RAASi at baseline	On RAASi at 4 weeks	No RAASi at 4 weeks
Non-EU patients Baseline K+<5.5	N=[redacted](maximum RAASi dose)	N=[redacted]	N=[redacted]

Baseline K+≥5.5		N=[redacted]	N=[redacted]
W.EU&US patients Baseline K+<5.5 Baseline K+≥5.5	N=[redacted](maximum RAASi dose n=[redacted])	N=[redacted] N=[redacted]	N=[redacted] N=[redacted]

A9. Did OPAL-HK measure proteinuria? If yes, then please provide details at the withdrawal phase and treatment phase by intervention.

Urine albumin, urine creatinine and urine albumin to creatinine ratio (ACR) was collected during both part A and part B of the study;

Part A

Mean urine albumin and urine creatinine over time and mean changes from Part A baseline are provided in Table 12. Additional descriptive statistics, including medians, are provided in *

Table 13 (urine albumin) and Table 14 (urine creatinine). The overall geometric mean of the ratio of the ACR (Week 4 / baseline) was [redacted] (95% CI: [redacted]), with similar findings by starting dose group (

Table 15)

Table 12. Univariate summary of urinalysis parameters over time from Part A

[redacted]

Table 13. Urine albumin over time from Part A

[redacted]

Table 14. Urine creatinine over time from Part A

Table 15. ACR over time from Part A, by Part A baseline albuminuria

Part B

Mean urine albumin and urine creatinine over time and mean changes from Part B baseline are provided in Table 16. Additional descriptive statistics, including medians, are provided in Table 17 (urine albumin) and Table 18 (urine creatinine).

At Week 4 of Part B, the geometric mean of the ratio of the ACR (Week 4 / baseline) was [redacted] (95% CI: [redacted]) in the placebo group and [redacted] (95% CI: [redacted]) in the patiromer group (Table 19). At Week 8, the geometric mean of the ratio of the ACR (Week 8 / baseline) was [redacted] (95% CI: ([redacted]) in the placebo group and [redacted] (95% CI: [redacted]) in the patiromer group (Table 19).

Table 16. Univariate summary of urinalysis over time

Table 17. Urine albumin over time

Table 18. Urine creatinine over time

Table 19. ACR over time

A10. PRIORITY: Guidelines on chronic kidney disease (CKD) (e.g. NICE CKD guideline 2014) require eGFR<60 on two separate occasions. Please clarify whether this was a requirement in the OPAL-HK or AMETHYST-DN trials.

Due to the short duration of these trials it would have been unrealistic to measure eGFR on two separate occasions 6 months apart in a screening or run-in period as per NICE CKD CG182 guideline. In OPAL, subjects had a significant burden of comorbidities such as hypertension, diabetes, HF and CAD, with equal proportions having stage 3 and stage 4 CKD. Patients in Part A at baseline had an average of [redacted] (SD [redacted]) years since diagnosis of CKD and these patients would have been carried over to Part B if they met the Part B criteria. To ensure recruited patients are diagnosed correctly, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or the Modification of Diet in Renal Disease (MDRD) equation Chronic Kidney disease.

The overall median time since CKD diagnosis was [redacted] years in OPAL-HK and subjects in dose group 1 had been diagnosed for longer (median of [redacted] years) than subjects in dose group 2 (median of [redacted] years).

Table 20. Part A baseline medical history (Part A)

[redacted]

Patients included in AMETHYST were diabetic, and the mean time since CKD diagnosis was [redacted] years (SD [redacted]), furthermore, at screening urine albumin to creatinine ratio (ACR) ≥ 100 mg/g or ≥ 30 mg/g AND average urine ACR ≥ 100 mg/g or ≥ 30

mg/g at the beginning of the running-in phase based on up to three ACR values starting at screening visit and ending at first running period visit were collected. Similar to OPAL the eGFR was calculated using the CKD-EPI equation at screening and baseline time point and for cohort 3, screening local eGFR, was calculated by the local laboratory using the CKD-EPI or the MDRD equation.

Table 21. Local serum K+ by stratum

In both OPAL and AMETHYST, CKD was defined as eGFR ≥ 15 mL/min/1.73 m2 and < 60 mL/min/1.73m2. The CKD stages of these two trials reflect the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, definition of CKD stages (6).

Table 22. eGFR categories in CKD (KDIGO 2012 guidelines)

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

A11. PRIORITY: OPAL-HK includes 11% of patients who don't have CKD (i.e. eGFR 60+) at trial baseline (Table S5 Weir supplement). Why are these patients classified in the company submission as having CKD?

In Part A 22/243 (9%) patients had CKD stage 2 defined as 60 mL/min/1.73m^2 ≤eGFR<90 mL/min/1.73m2, this cohort of patients are still categorised as CKD, defined in KDIGO 2012 guideline, and are relatively small number of patients relative

to CKD stage 3-4. Please refer to question A10 for Time to CKD Diagnosis and A13 for the equations used to calculate eGFR.

A12. PRIORITY: Please provide analysis of patiromer effectiveness (change in serum potassium) and RAASi discontinuation by eGFR categories shown in Table S5 (Weir Supplement), 60 to ≤90; 45 to <60; 30 to <45; <30 ml/min/1.73 m^2; as well as by region (Eastern Europe vs. EU/US)

There is no analysis available for RAASi discontinuation by geographic region.

Part A primary and secondary endpoints by region (non-EU, EU combined with US [EU+US]): In the analyses by region, interaction p-values indicated a differential response for both the Part A primary and secondary endpoint. In the analysis of the Part A primary endpoint, the mean change in serum potassium was [redacted] mmol/L (95% CI [redacted]) for non-EU and [redacted] mmol/L (95% CI [redacted]) for EU+US, a difference in magnitude of [redacted] mmol/L. A difference of similar magnitude was observed at baseline: Mean serum potassium at the Part A baseline was [redacted]mmol/L higher in non-EU ([redacted] mmol/L) as compared to EU+US ([redacted] mmol/L). This baseline difference in mean serum potassium may account for the difference between the regions in the magnitude of the observed mean treatment effect for the primary endpoint in Part A. Consistent with the findings for the Part A primary endpoint, in the analysis of the Part A secondary endpoint, this finding may also have resulted from the difference in mean serum potassium at baseline.

In Part A, the primary efficacy endpoint was analysed by eGFR subgroups CKD Stage 2 or 3 and CKD Stage 4 or 5 is presented Table 23. Mean change in serum potassium from baseline was similar in both subgroups (Mean (SD) CKD Stage 2 or 3: [redacted] ± [redacted]; CKD Stage 4 or 5: [redacted] ± [redacted]; p-value for both < [redacted]). The Part A secondary endpoint is in Table 24. The estimated percentage of subjects having serum potassium values within the target range of 3.8 to < 5.1 mmol/L at Part A week 4 was [redacted] in CKD stage 2 or 3 and [redacted] in CKD stage 4 or 5.

Table 23. Part A primary efficacy outcome by subgroups: estimated change in serum potassium (mmol/L) from Part A baseline to Part A week 4

Table 24. Part A secondary efficacy outcome by subgroups: estimated percentage of subjects having serum potassium values within the target range at Part A week 4

The Part B primary endpoint is described in Table 25. The difference in change in serum potassium from Part B baseline to Part B week 4 or the first local laboratory serum potassium value of < 3.8 mmol/L or ≥5.5 mmol/L between the patiromer and placebo groups was statistically significant for both CKD subgroups. The difference in median change for CKD stage 2 or 3 was 0.70 mmol/L and was 0.71 mmol/L in CKD Stage 4 or 5. The Part B secondary endpoint of ≥5.5 mmol/L at any time through Part B week 8 is described in Table 26.The difference between the patiromer and placebo groups was similar and statistically significant in both CKD subgroups. The Part B secondary endpoint of ≥5.1 mmol/L at any time through Part B week 8 is described in Table 27. The difference between the patiromer and placebo groups was statistically significant in both CKD subgroups, but the difference was smaller in the CKD Stage 4 or 5.

Table 25. Part B primary efficacy outcome by subgroups

Table 26. Part B secondary efficacy outcome by subgroups

Table 27. Part B secondary efficacy outcome by subgroups

RAASi exposure by CKD subgroups is described in Table 28, and discontinuation of RAASi due to management of recurrent hyperkalaemia during Part B is described in Table 29.

Table 28. RAASi exposure (Part B)

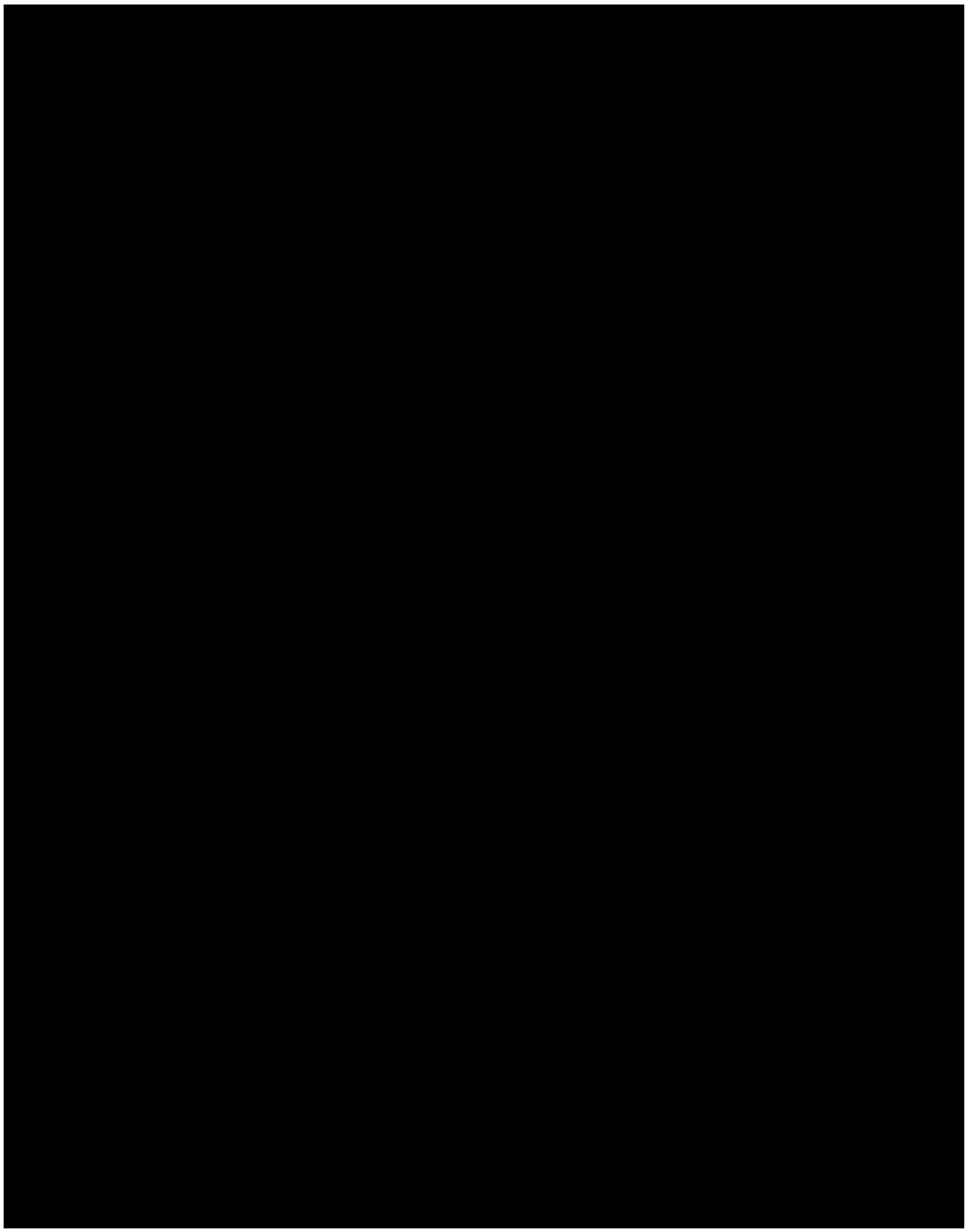

Table 29. Management of recurrent hyperkalaemia during Part B

A13. Kidney function is known to decline with age, and clinical experts note age-unadjusted eGFR overdiagnoses of CKD (e.g. see Wetzels, Kidney International 2007;72:632–637; doi:10.1038/sj.ki.5002374). Would the company like to comment on how this may affect their model?

In both OPAL-HK and AMETHYST-DN Modification of Diet in Renal Disease (MDRD) Study equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation were used to estimate GFR. Numerous equations have been developed to estimate GFR or CrCl in adults. In general, GFR estimating equations using creatinine include age, sex, race, and body size as surrogates for creatinine generation by muscle. Based on published data, MDRD equation and KD-EPI equation and modifications of these equations were developed using creatinine assays traceable to the international reference material for creatinine. The MDRD Study equation is

currently recommended for eGFR reporting in adults by the National Kidney Disease Education Program (NKDEP) and by the Department of Health in the UK. It uses standardized SCr, age, sex, and race (black versus white and other) to estimate GFR adjusted for BSA (ml/min/1.73m2). The CKD-EPI equation uses the same four variables as the MDRD Study equation. The CKD-EPI equation has less bias than the MDRD Study equation, especially at GFR≥60 ml/min/1.73m2, a small improvement in precision, and greater accuracy. Most but not all studies from North America, Europe and Australia show that the CKD-EPI equation is more accurate than the MDRD Study equation, especially at higher GFR which enables reporting of numeric values across the range of GFR. At this time, large commercial clinical laboratories in the US have changed from using the MDRD Study equation to the CKD-EPI equation for eGFR reporting. Lesser bias of the CKD-EPI equation compared to the MDRD Study equation reflects higher eGFR throughout most of the range for age and creatinine, especially in younger individuals, women and whites. Higher eGFR results in lower prevalence estimates for CKD in these groups, with more accurate risk relationships of lower eGFR and adverse outcomes [KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease]. Wetzel publication "provides age- and sex-specific values of estimated GFR using the MDRD formula with proper calibration of creatinine." In this publication, the Mean ± SD eGFR levels for patients in the group age 60-64 with comorbidities is 71±14 mL/min/1.73m2 for males and 67±12 mL/min/1.73m2 for females. In OPAL-HK, average age is 64 years and mean eGFR is 35.98 mL/min/1.73m2 for males and 37.84 mL/min/1.73m2 for females, with comorbidities such as T2D, Heart failure, HTN. The eGFR from OPAL-HK is below the reference value considered by Wetzel publication, in this publication, the mentioned age is similar to OPAL-HK with same equation for eGFR calculation.

A14. PRIORITY Changes in level of use of diuretics and RAASi dual blockade are potential confounders for serum potassium levels. Please provide blood pressure control and use of each class of hypertension drugs at the beginning and end of the withdrawal phase by intervention group.

The protocol specified that in order to control blood pressure (BP) at any time during the study, only non-RAASi and antihypertensive drugs that did not affect serum potassium levels (e.g. calcium channel blocker, alpha blocker or alpha-2 agonist) were allowed to be added or modified per the investigator's discretion. From the start of Part

B to week 8, subjects continuing on Patiromer and who completed part B demonstrated statistically significant reductions in mean ± SE SBP (-6.70 ± 1.59 mm Hg, P <0.0001) and DBP (-2.15 ± 1.06 mmHg, P ≤ 0.05). Those who switched to placebo and completed the initial treatment and withdrawal phases did not demonstrate statistically significant changes in SBP (-1.21 ± 1.89 mm Hg, P = NS) or DBP (+1.72 ± 1.26 mm Hg, P = NS) (

Table *31*) (Table 7 in Weir et al, Kidney International 2016 90, 696–704; http://dx.doi.org/10.1016/ j.kint.2016.04.019). A post-hoc analysis of OPAL, the effectiveness of patiromer in reducing K levels in CKD patients on RAASI was examined, with hypertension receiving diuretic therapy vs those not on diuretic. At baseline, 132 patients used diuretics and 111 were not on diuretics. Similar reductions in serum K were seen over 4 weeks in both subgroups. At week 4, serum K fell by -0.95 ±0.04 mmol/L with any diuretic and -1.04 ±0.05 mmol/L with no diuretic. The serum K lowering efficacy profile of patiromer in hyperkalemia patients with CKD was not compromised by diuretic therapy. [Weir et al Journal of Hypertension 2017, 35 (Suppl 1): S57–S63]. Please find below serum potassium in part A categorised by high and low ceiling diuretics and no diuretics. Also, below are blood pressure levels and baseline concomitant medications.

Table 32 demononstrates the baseline medication in Part B in OPAL. There is no data available with respect to antihypertensive medications at the end of Part B.

Table 30. Central serum potassium over time in Part A: summary statistics

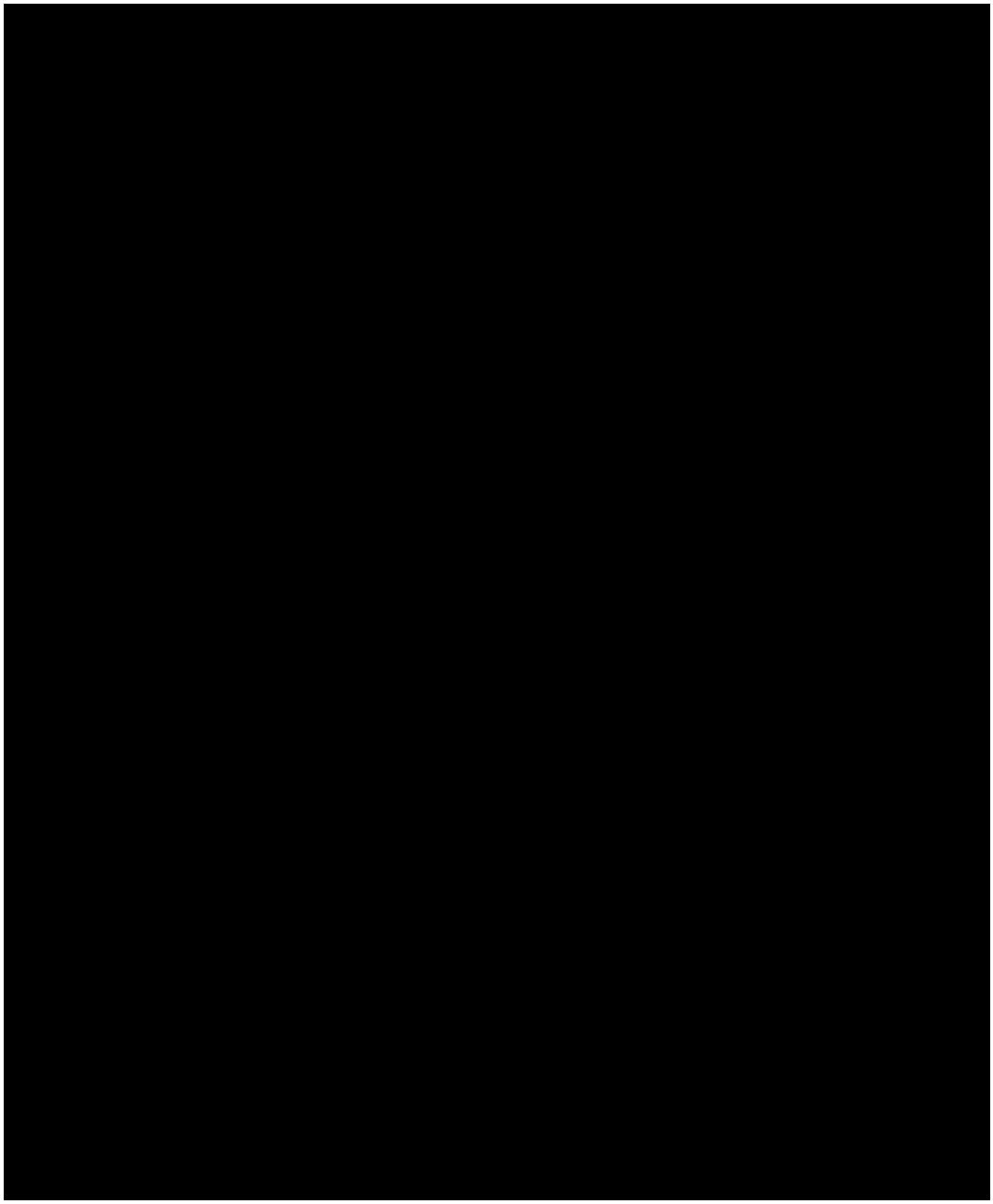

Table 31. Mean ± SE change in clinical and laboratory parameters from start of the randomised withdrawal phase to weeks 4 and 8 of the randomised withdrawal phase

Table 7| Mean ± SE change in clinical and laboratory parameters from start of the randomized withdrawal phase to weeks 4 and 8 of the randomized withdrawal phase

	Patiromer, $N = 55$				Placebo, $N = 52$			
Measure	*n*	Mean ± SE	LS mean change from start ± SE	*P* value	*n*	Mean ± SE	LS mean change from start ± SE	*P* value
Start								
Serum aldosterone (ng/dl)	55	10.52 ± 1.25	—	—	52	8.61 ± 1.38	—	—
Potassium (mEq/l)	55	4.50 ± 0.06	—	—	52	4.45 ± 0.05	—	—
Systolic blood pressure (mm Hg)	55	134.80 ± 2.19	—	—	52	135 ± 2.51	—	—
Diastolic blood pressure (mm Hg)	55	76.48 ± 1.60	—	—	52	73.65 ± 1.54	—	—
Plasma renin activity (µg/l/hr)	55	8.71 ± 1.59	—	—	52	7.90 ± 1.53	—	—
ACR[a] (mg/g)	55	441.70 ± 105.50	—	—	50	509.40 ± 124.20	—	—
Week 4								
Serum aldosterone (ng/dl)	50	11.17 ± 1.62	0.94 ± 1.18	0.4262	45	12.28 ± 2.02	3.37 ± 1.24	0.0078
Potassium (mEq/l)	50	4.55 (0.06)	0.07 (0.06)	0.2621	45	4.95 (0.07)	0.51 (0.07)	<0.0001
Systolic blood pressure (mm Hg)	50	131.30 ± 2.25	−3.91 ± 2.04	0.0582	45	135.90 ± 2.53	0.76 ± 2.14	0.7216
Diastolic blood pressure (mm Hg)	50	73.88 ± 1.38	−2.59 ± 1.20	0.0335	45	76.47 ± 1.62	0.78 ± 1.26	0.5359
Plasma renin activity (µg/l/hr)	50	7.37 ± 1.41	−0.61 ± 1.15	0.5956	44	6.34 ± 1.45	−1.66 ± 1.21	0.1718
ACR[a] (mg/g)	49	401.80 ± 115.50	50.38 ± 64.17	0.4345	42	613.50 ± 214.70	70.93 ± 69.33	0.3091
Week 8								
Serum aldosterone (ng/dl)	45	10.63 ± 1.14	0.23 ± 1.07	0.8296	29	13.08 ± 2.93	2.78 ± 1.25	0.0278
Potassium (mEq/l)	45	4.52 ± 0.06	0.04 ± 0.07	0.5050	29	4.85 ± 0.08	0.55 ± 0.08	<0.0001
Systolic blood pressure (mm Hg)	45	128.50 ± 1.88	−6.70 ± 1.59	<0.0001	29	133.50 ± 2.23	−1.21 ± 1.89	0.5234
Diastolic blood pressure (mm Hg)	45	74.98 ± 1.13	−2.15 ± 1.06	0.0458	29	77.63 ± 1.98	1.72 ± 1.26	0.1734
Plasma renin activity (µg/l/hr)	44	9.64 ± 1.71	1.71 ± 1.21	0.1624	29	4.99 ± 1.37	−3.90 ± 1.41	0.0067
ACR[a] (mg/g)	45	417.10 ± 115.80	18.85 ± 46.59	0.6870	29	339.80 ± 134.90	−88.49 ± 58.04	0.1318

ACR, albumin-to-creatinine ratio; LS, least squares.
The mean changes from the start were estimated using a mixed-effects, repeated-measures model, which included the fixed continuous covariate of start values as well as fixed categorical covariates of the analysis visit and treatment group and used an unstructured covariance structure.
P value for mean change compared with start of randomized withdrawal phase.
[a]ACR was only collected at monthly visits; the mean change from start was based on an analysis of covariance by adjusting for the start value.

Table 32. Part B baseline concomitant medication use

A15. PRIORITY A meta-analysis published at the beginning of 2013 showed dual RAASi blockade was harmful (raising HK and worsening CKD) and should be avoided. Why are these patients on dual RASSi blockade included in OPAL-HK? Please provide change in serum potassium and RAASi discontinuation by sub-group dual/no dual blockade. (see Makani H et al BMJ. 2013; 346: f360. https://doi.org/10.1136/bmj.f360.)

OPAL-HK was conducted under a Special Protocol Assessment (SPA) which is a special FDA review of a protocol which results in FDA approving the protocol. Once approved, a protocol that has SAP approval cannot be changed without review and approval by FDA. Relypsa received the FDA SPA approval letter for this study on 22 January 2013. The referenced article was published after FDA approval of the SPA; the article was published on 28 January 2013. Thus, the concern with dual RAASi blockade was not widely known at the time the protocol was developed.

In total, [redacted]% of subjects were on dual blockade (N=[redacted] dose group 1, [redacted] dose group 2) in Part A and [redacted]% in Part B (N=[redacted] placebo, [redacted] patiromer group). This a relatively small number of subjects and the N number is uninformative.

There is no data available with respect to serum potassium and RAASi discontinuation by sub-group dual/no dual blockade.

A16. Document B: Figure 6, pg.57: please supply figures with 95% CI for each arm.

Table 33. Estimated proportion with exploratory outcomes by study period (Part B)

A17. Page 63. Please define maximal and submaximal doses of RAASi.

The maximum dose was determined according to the judgment of the investors in accordance with the local standard of care.

A18. Please present the mean (95% CI) drop in K^+ from Part A baseline to Part B week 4 among those enrolled in Part B by arm, and also the equivalent means (95% CIs) for the Eastern Europe group (n=85) and the EU+US group (n=22) (6 mean values).

Patients in part B were randomised into either placebo or patiromer group therefore continues potassium levels is not available from Part A to Part B week 4 of the trial. The primary efficacy potassium levels in Part A of the study are reported as “mean

change in potassium” and in Part B as “the estimated difference in median change”. Part B primary efficacy endpoint by region is included below.

Table 34. Part B primary efficacy outcome by subgroups

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A19. B.5 In the appendices a list of excluded studies is provided (embedded word document). Please provide the list of the 16 studies excluded at the stage of full-text assessment.

Table 35. List of studies excluded following full text screening (Clinical SLR)

Author	Year	Journal	Title	DOI	Reason for exclusion
Dhaybi, O. A. and Bakris, G.	2017	Current Opinion in Nephrology & Hypertension	Mineralocorticoid antagonists in chronic kidney disease		Study design
Garimella, P. S. and Jaber, B. L.	2016	American Journal of Kidney Diseases	Patiromer for Hyperkalemia in Diabetic CKD: A New Kid on the Block	https://dx.doi.org/10.1053/j.ajkd.2016.01.001	Study design
Georgianos, P. I. and Agarwal, R.	2018	Kidney International	Revisiting RAAS blockade in CKD with newer potassium-binding drugs	https://dx.doi.org/10.1016/j.kint.2017.08.038	Study design
Henneman, A., Guirguis, E., Grace, Y., Patel, D. and Shah, B.	2016	American Journal of Health-System Pharmacy	Emerging therapies for the management of chronic hyperkalemia in the ambulatory care setting	https://dx.doi.org/10.2146/ajhp150457	Study design
Lepage, L., Desforges, K. and Lafrance, J. P.	2016	Current Opinion in Nephrology & Hypertension	New drugs to prevent and treat hyperkalemia		Study design
Li, L., Harrison, S. D., Cope, M. J., Park, C., Lee, L., Salaymeh, F., Madsen, D., Benton, W. W., Berman, L. and Buysse, J.	2016	Journal of Cardiovascular Pharmacology & Therapeutics	Mechanism of Action and Pharmacology of Patiromer, a Nonabsorbed Cross-Linked Polymer That Lowers Serum Potassium Concentration in Patients with Hyperkalemia	https://dx.doi.org/10.1177/1074248416629549	Population
Linder, K. E., Krawczynski, M. A. and Laskey, D.	2016	Pharmacotherapy	Sodium Zirconium Cyclosilicate (ZS-9): A Novel Agent for the Treatment of Hyperkalemia	http://dx.doi.org/10.1002/phar.1797	Intervention / Comparator
Montaperto, A. G., Gandhi, M. A., Gashlin, L. Z. and Symoniak, M. R.	2016	Current Medical Research & Opinion	Patiromer: a clinical review	https://dx.doi.org/10.1185/03007995.2015.1106935	Study design

Packham, D. K. and Kosiborod, M.	2016	American Journal of Cardiovascular Drugs	Potential New Agents for the Management of Hyperkalemia	https://dx.doi.org/10.1007/s40256-015-0130-7	Population
Paton, D. M.	2015	Drugs of Today	Patiromer: a significant advance in the management of hyperkalemia	https://dx.doi.org/10.1358/dot.2015.51.12.2420391	Study design
Rafique, Z., Weir, M. R., Onuigbo, M., Pitt, B., Lafayette, R., Butler, J., Lopes, M., Farnum, C. and Peacock, W. F.	2017	Journal of Managed Care & Specialty Pharmacy	Expert Panel Recommendations for the Identification and Management of Hyperkalemia and Role of Patiromer in Patients with Chronic Kidney Disease and Heart Failure	https://dx.doi.org/10.18553/jmcp.2017.23.4-a.s10	Outcomes
Sarafidis, P. A., Georgianos, P. I. and Bakris, G. L.	2015	Expert Opinion on Pharmacotherapy	Advances in treatment of hyperkalemia in chronic kidney disease	https://dx.doi.org/10.1517/14656566.2015.1083977	Study design
Sharka, I., Quka, A., Mumajesi, S., Teferici, D., Xhafaj, M., Gjyli, L., Doko, A., Cafka, M. and Myftiu, S.	2014	European Journal of Heart Failure	Renin-angiotensin system blockade and the risk of hyperkalaemia in chronic dialysis patients with heart failure with preserved ejection fraction	http://dx.doi.org/10.1002/ejhf.93_4	Intervention / Comparator
Tamargo, J., Caballero, R. and Delpon, E.	2014	Discovery Medicine	New drugs for the treatment of hyperkalemia in patients treated with renin-angiotensin-aldosterone system inhibitors -- hype or hope?		Study design
Vu, B. N., De Castro, A. M., Shottland, D., Frishman, W. H. and Cheng-Lai, A.	2016	Cardiology in Review	Patiromer: The First Potassium Binder Approved in Over 50 Years		Study design
Zannad, F., Rossignol, P., Stough, W. G., Epstein, M., Alonso Garcia Mde, L., Bakris, G. L., Butler, J., Kosiborod, M., Berman, L., Mebazaa, A., Rasmussen, H. S., Ruilope, L. M., Stockbridge, N., Thompson, A., Wittes, J. and Pitt, B.	2016	International Journal of Cardiology	New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: Considerations for trial design and regulatory approval	https://dx.doi.org/10.1016/j.ijcard.2016.04.127	Study design

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A20. Please provide justification for excluding data from PEARL-HF from the submission, particularly for informing subgroup analyses for 'people with heart failure'.

PEARL-HF was not considered relevant to the current decision problem given it included only patients with previously documented hyperkalaemia or CKD and a diagnosis of heart failure. This is different to the initial OPAL-HK population where only 42% of participants had heart failure at baseline. The PEARL-HF trial population is therefore more restricted than overall stage 3–4 CKD and was therefore not considered to be representative of the population for which reimbursement is being sought. Cost-effectiveness analyses for the heart failure sub-group were not performed since a wider population is sought for reimbursement.

A21. PRIORITY Please provide the PDFs of:

- **AMETHYST DN Clinical Study Report**
- **TOURMALINE Clinical Study Report**
- **PEARL-HF Clinical Study Report**
- **B.5 Appendices: Please provide the full reference and PDFs of the three studies identified from the hand search as stated in Figure 1, p39.**

The clinical study report PDFs have been provided. Epstein et al (2016) (7), Pitt et al (2015) (8) and Pina et al (2017) (9) were the three records found by hand searching. Please see the reference list for the full reference details.

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Section B: Clarification on cost-effectiveness data

B1. PRIORITY: The prognosis of patients with CKD is heavily dependent upon the stage of CKD (e.g. 3a, 3b or 4). Please explain the rationale for modelling these as one group (Document B, Figure 10, p83) and the impact of this assumption on the model results.

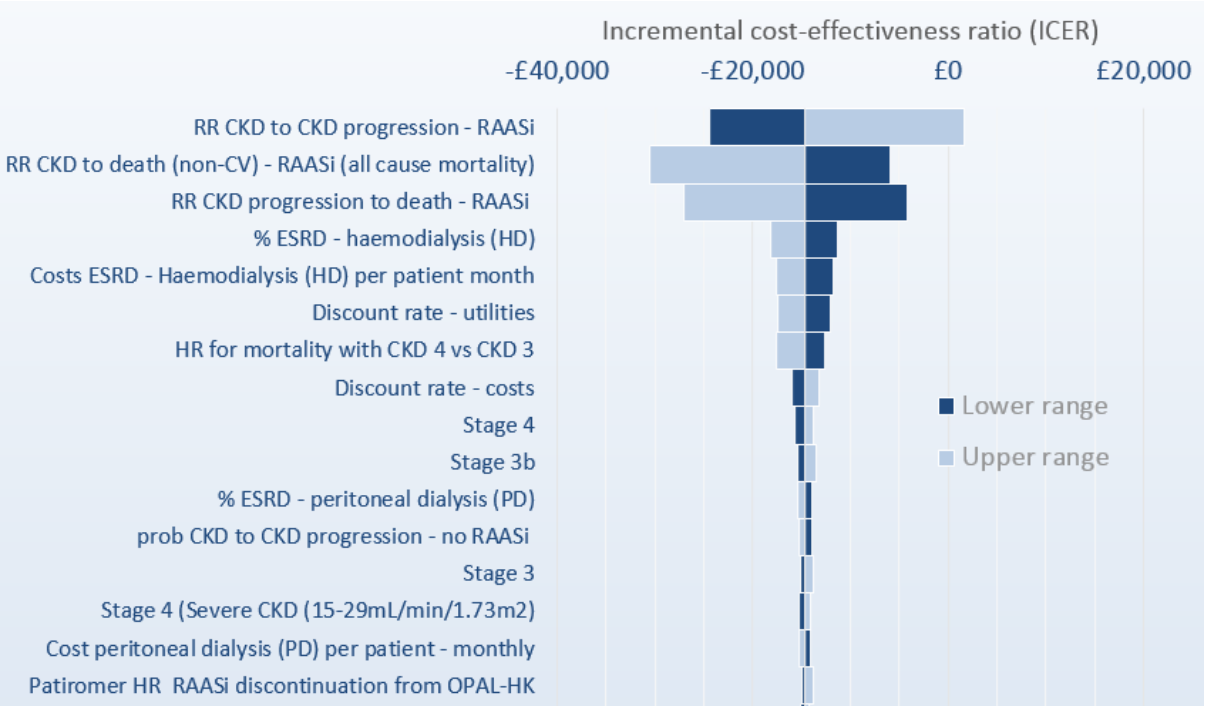
Extensive subgrouping of clinical trials is generally regarded quite critically by experts in clinical epidemiology and trial statistics. This is particularly true in the case of small trials such as OPAL-HK (Part A n=243; Part B n=107) as spurious results may be generated. The patient mix of stage 3 and 4 CKD in OPAL-HK were well balanced, 46% and 45% respectively and, given the short trial duration, this would not be expected to change over the study period. The results produced by the economic model are valid for the patient mix enrolled in OPAL-HK given trial data imputed into the model are reflective of this. Further, preference was given to selecting literature sourced model input parameters which reflected a mix CKD disease stages. Sub-group analyses for specific stages of CKD could therefore be misleading given the above.

The primary objective of the economic analysis is to evaluate the impact of patiromer on time to hyperkalaemia and RAASi discontinuation rather than progression of CKD. It was therefore considered appropriate to not extensively model CKD by multiple disease stage health states. The transition probability for CKD to end-stage renal disease (0.0139) is calculated using data from a study which included patients with stage 3–5 disease (Landray 2010) and hence it is appropriate to not model kidney disease by discrete health states.

The probability of transitions from CKD states to other health states (Post-CV, CV event, hyperkalaemia and ESRD) are based on data sources which included a mix of patients in various stages of kidney disease. Similarly, the relative risks applied in the model (for example from Xie 2016) also include patients from different stages of chronic kidney disease (CKD). While the company cannot comment on the impact of

sourcing individual probabilities and risks by CKD stage, one-way sensitivity analyses showed that none of these, when varied to extreme values, resulted in the incremental cost-effectiveness ratio (ICER) exceeding the £20,000/QALY threshold. Since probabilities and risks used in the economic model are for a mix of CKD stages it would be reasonable to expect those for individual stages would lie within the range. The one-way sensitivity analysis at the PAS price is provided in Figure 26 of Document B and reproduced below.

Figure 2. One-way sensitivity analysis (PAS)



B2. Please explain why the numbers at risk in graphs of Document B Figure 9 and 13 are different.

Figure 3 below provides the Kaplan-Meier (KM) analysis for RAASi discontinuation in OPAL-HK as published by Weir et al. 2015 (equivalent to Figure 9 in Document B) while Figure 4 provides the same analysis as generated for this submission (equivalent to Figure 13 in Document B) using individual patient level data from OPAL-HK. Figure 4 below (compared with Figure 13 in Document B) has been updated to the format used by Weir et al, including conversion of time to weeks.

Figure 3: Time to RAAS inhibitor discontinuation during the randomised withdrawal phase (Weir 2015).

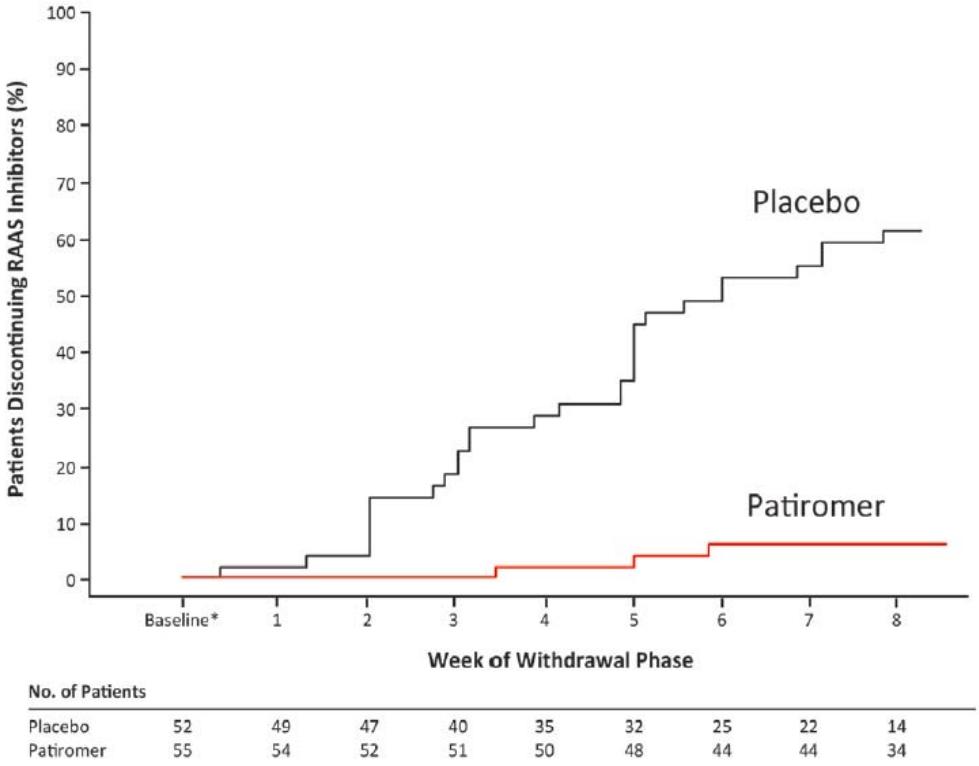
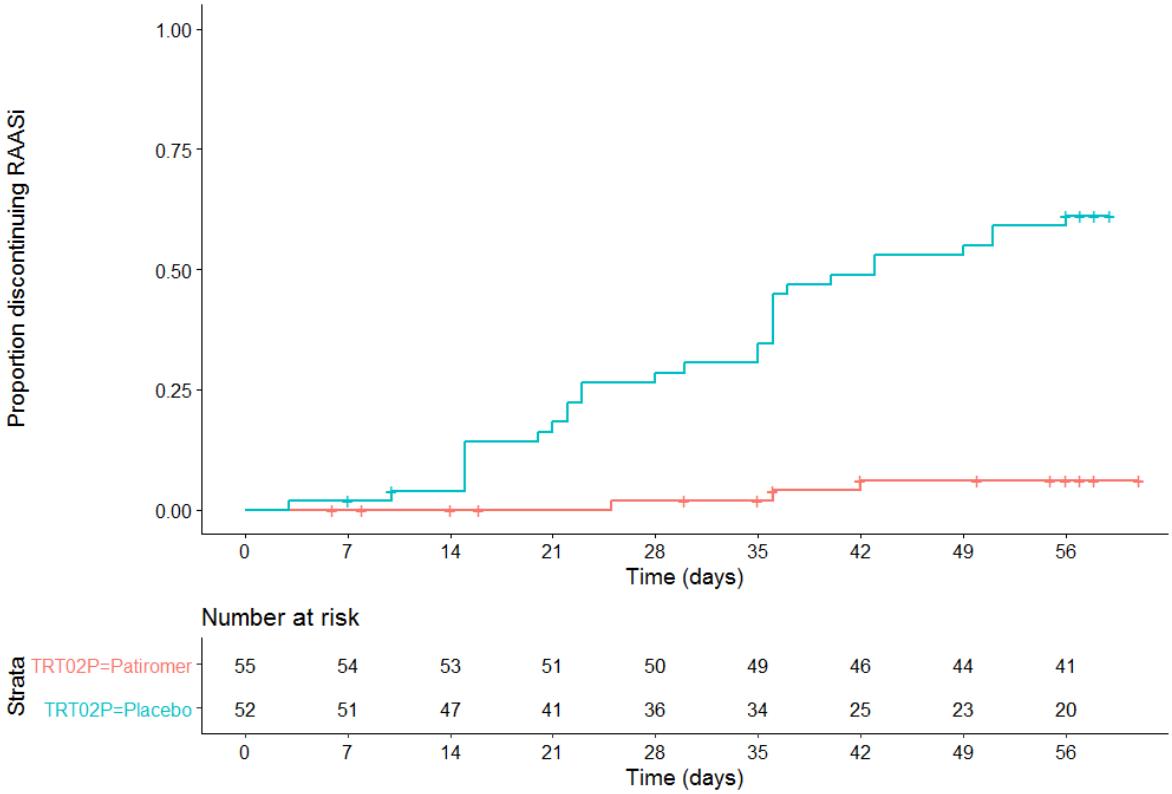


Figure 4. Kaplan-Meier time to RAASi discontinuation estimates from OPAL-HK based on Individual Patient-level Data (IPD); used in the current economic model



A comparison of the two KM curves shows that the event rates are the same across the two analyses. The company believe that the difference in the numbers at risk may stem from a difference in how censoring was handled in the two analyses. The Kaplan-Meier (KM) data from both sets of analyses were compared in order to identify the source of the discrepancy between the numbers at risk summaries from the two figures. The numbers at risk and survival proportions produced for this analysis are the same as reported by Weir (Excel supplement, sheet B2). This indicates that the underlaying data are the same and that the discrepancy between numbers at risk may lie in how different statistical packages summarise daily events and censoring into weekly numbers at risk. As noted at the bottom of the Weir data table, their results were generated using SAS while the results for this submission were generated using R and Stata.

For this submission, individual patient level data was used to perform the survival analysis. Within the dataset, the censoring flag was used to determine a censoring or

time to RAASi discontinuation event, and the time to event variable utilised to determine the time from randomisation to event or censoring

B3. PRIORITY: Please provide Document B Figures 12 and 15 showing the "observed" data (and 95% CI) that is being fitted as well as the modelled curves. Please provide the CPRD individual patient data that underlie Figure 12 and 15, or the CPRD Kaplan–Meier RAASi discontinuation data), in the following format.

T (Day)	N Risk	Event	Censored	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…

The observed data from the CPRD analysis for time to RAASi discontinuation is provided in Table 36 below. The Kaplan-Meier curves using this data and the associated parametric functions are provided in Figure 5. This data is used to inform the 'no patiromer' arm of the economic model. Equivalent data for the patiromer arm is not available as parametric functions for this arm are generated by applying the hazard ratio ([redacted]) for time to RAASi discontinuation in OPAL-HK to the CPRD curves. This hazard ratio was calculated based on the observed difference in RAASi discontinuation during the 8-week withdrawal phase (Part B) of OPAL-HK.

Figure 5. Kaplan-Meir and parametric functions for time to RAASi discontinuation, no patiromer (CPRD)

Table 36. CPRD: observed data for time to RAASi discontinuation

T (Day)	N Risk	Event	Censored	S(t)
[redacted]				

B4. PRIORITY: Please provide Document B Figures 19 and 20 showing the "observed" data (and 95% CI) that is being fitted as well as the modelled curves, with the time scale reduced to show the first 120 days.

Figure 6. Kaplan-Meir and parametric functions for time to hyperkaliemia (≥5.5mmol/L), no patiromer (Part B); based on Individual Patient-level Data (IPD);

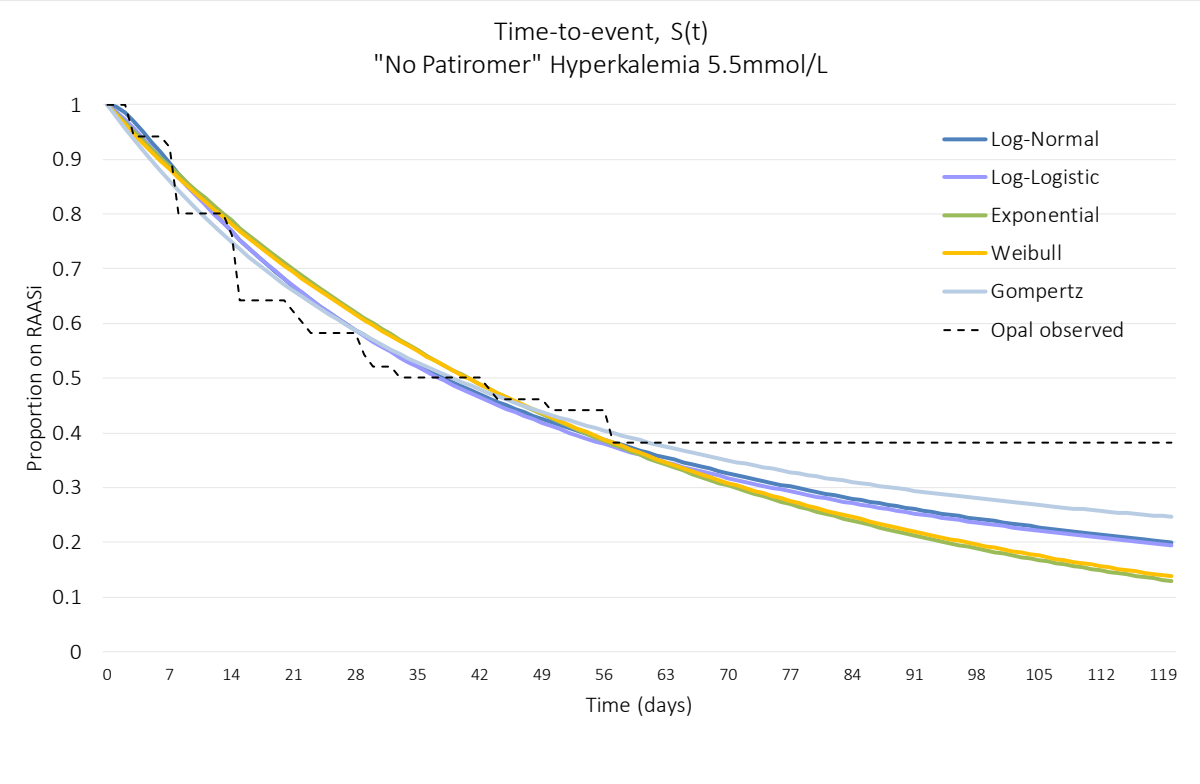
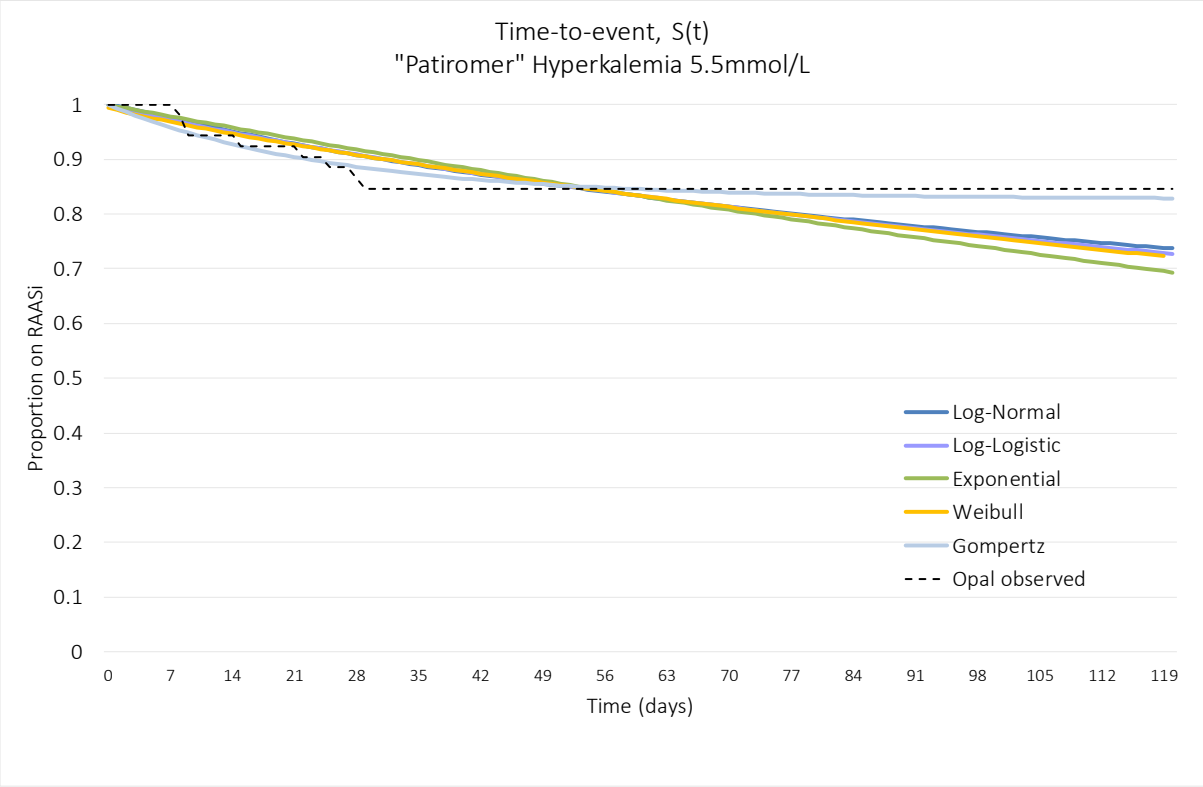


Figure 7. Kaplan-Meir and parametric functions for time to hyperkaliemia (≥5.5mmol/L), patiromer (Part B); based on Individual Patient-level Data (IPD);



B5. Within the CPRD data how was the expected termination date of the RAASi prescription calculated? Why was the period defining RAASi discontinuation limited to 90 days after the anticipated end of the RAASi prescription? Was there any analysis of the CRPD RAASi discontinuation data that examined whether patients ever (a) resumed RAASi after "discontinuing", as defined on page 89 of Document B or (b) switched to an alternative blood pressure treatment regime following RAASi discontinuation. If there was what were its conclusions?

The period defining RAASi discontinuation was not limited to 90 days after the anticipated end date, rather it was 30 days (there is a transcription error in page 90 of Document B where 90 days is specified).

Patients were considered to be prescribed 106 days of medication for each prescription. This was determined based on analysing the data showing that 99% of patients had a prescription duration of 106 days or less. The data analysis further revealed that sometimes there were gaps between consecutive prescriptions, i.e. between a prescription end date and start date of the subsequent prescription. The average number of days of delay when this occurred was 30 days. Hence an additional grace period of 30 days was then allowed in case there were delays in a patient obtaining a new prescription. Therefore, 136 days must pass without a prescription refill to constitute as RAASi discontinuation event.

Specific rules which were applied are:

- Index date was defined as the date of RAASi initiation, pre-hyperkalaemia
- Discontinuation was defined as no subsequent record of the prescription at the end of supply
- The end of supply was estimated as starting from the index date + prescription duration + a grace period to allow for any delays in re-supply of prescription
- The distribution of average prescription lengths was investigated, and found that [redacted] of patients had a prescription duration of [redacted] days or less
- Thus, it was assumed that each patient had RAASi prescription duration of [redacted] days; an additional 30-day grace period was then allowed
- The minimum length of RAASi prescription was therefore [redacted] days, and if there was no subsequent prescription after that, they were flagged as discontinued
- [redacted] days is approximately [redacted] months, explaining why there was no discontinuation in first [redacted] months

To answer (a) and (b), whether patients resumed RAASi after discontinuation was not examined; once a patient was flagged as discontinued, their follow-up ended and did not contribute to the analysis any further. Furthermore, switches to alternative blood pressure treatments were also not considered as this was not relevant to the decision problem. RAASi are proven to reduce mortality and morbidity in HF and to slow down kidney function decline in CKD. This is the reason why CKD and Heart Failure (HF)

guidelines[1] recommend RAASi at highest tolerated doses in HF and in moderate to high doses in CKD. However, the RAASi treatment is often compromised due to hyperkalaemia which is the reason why the company have focused on the RAASi treatment in the clinical trial programme.

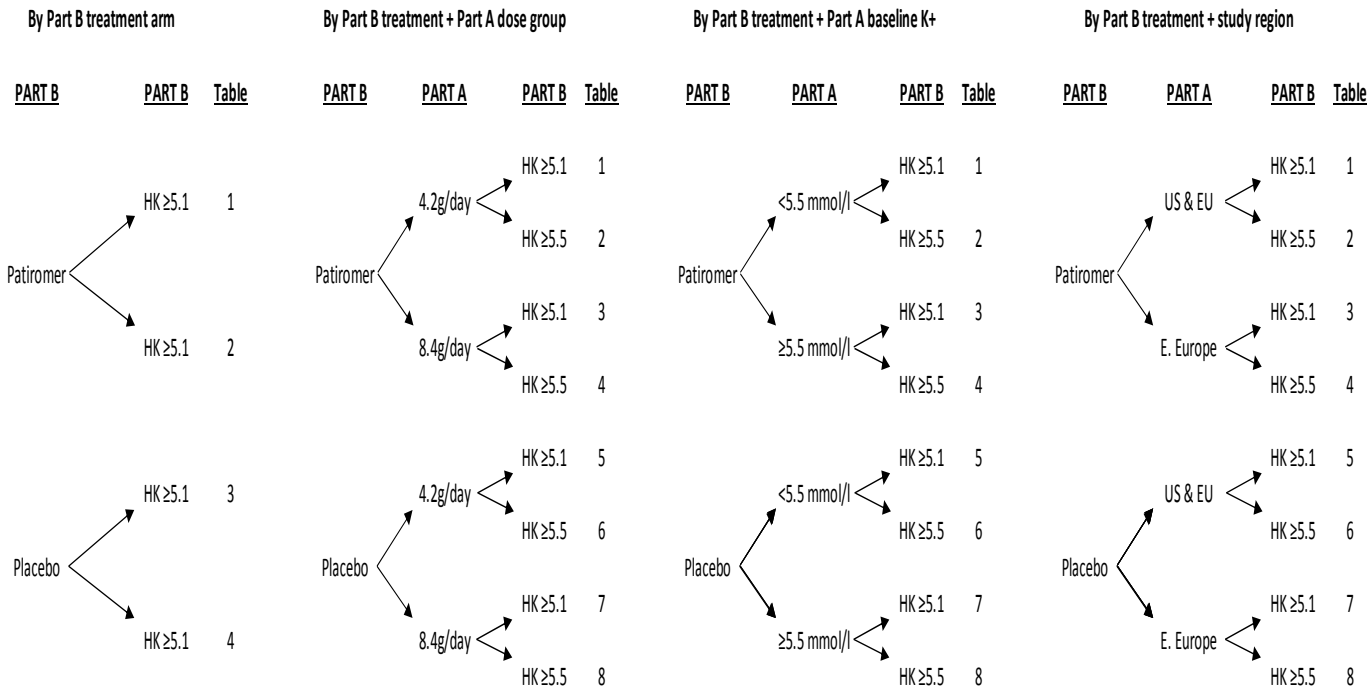
However, switches to either calcium polystyrene sulfonate or sodium polystyrene sulfonate (hyperkalaemia treatments) were examined, but evidence of these switches occurring were not found.

B6. PRIORITY: Please provide the Kaplan–Meier data by: (1) intervention arm that underlies Figure 6 of Document B (4 tables); (2) split by Part A Dose groups (8 tables); (3) split by K^+<5.5 or K^+≥5.5 at Part A baseline, (8 tables) and (4) for the region subgroups (Eastern Europe vs EU/US) (8 tables) in the following format. If the Kaplan–Meier data underlying Figure 18 of Document B differs from this, please outline how and provide the parallel data for Figure 18.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…
EoT: End of trial, LTFU: Lost to Follow-Up						

The company understood the requested tables in the following manner:

[1] **HF guidelines:** 1. European Society of Cardiology (ESC) 2016 Heart Failure guidelines: Ponikowski P, et al. *Eur Heart J.* 2016;37:2129–200; 2. AHA, American Heart Association: Yancy CW, et al. *Circulation*. 2013;128:1810–52.
CKD guidelines: 1. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1); 2. National Institute for Health and Care Excellence. Chronic kidney disease (CG73): Early identification and management of chronic kidney disease in adults in primary and secondary care. 2008. Available at: http://www.nice.org.uk/CG73. Accessed March 2017; 3. National Kidney Foundation. KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. 2004. Available at: http://www2.kidney.org/professionals/KDOQI/guidelines_bp/.



These results are presented below, in the order shown in the figure above. The requested survival table data can be found in the accompanying Excel supplement. We were unable to separate censoring from lost to follow-up in the KM data tables, but the summary of censoring events below indicates that only one patient was lost to follow-up over the course of Opal Part B (N=107):

Table 37. Observed events in OPAL-HK

Event	Number
Adverse event	[redacted]
Completed	[redacted]
Death	[redacted]
Lost to follow-up	[redacted]
Met protocol specified withdrawal criteria (eGFR decrease to <10 mL/min/1.73m^2 or need for dialysis	[redacted]
Met protocol specified withdrawal criteria (high serum potassium results)	[redacted]
Met protocol specified withdrawal criteria (low serum potassium results)	[redacted]
Met protocol specified withdrawal criteria (serum potassium results)	[redacted]
Non-compliance with study drug	[redacted]

Physician decision	[redacted]
Protocol violation	[redacted]
Withdrawal by subject	[redacted]
Adverse event	[redacted]
Completed	[redacted]
Death	[redacted]
Lost to follow-up	[redacted]

All analyses for this question are based on Individual Patient-level Data (IPD);

B6.1 TIME TO HK EVENT BY TREATMENT ARM

B6.1.1 Time to HK ≥5.1 by treatment arm (Par B: Patiromer vs Placebo)

The following data are provided in this section:

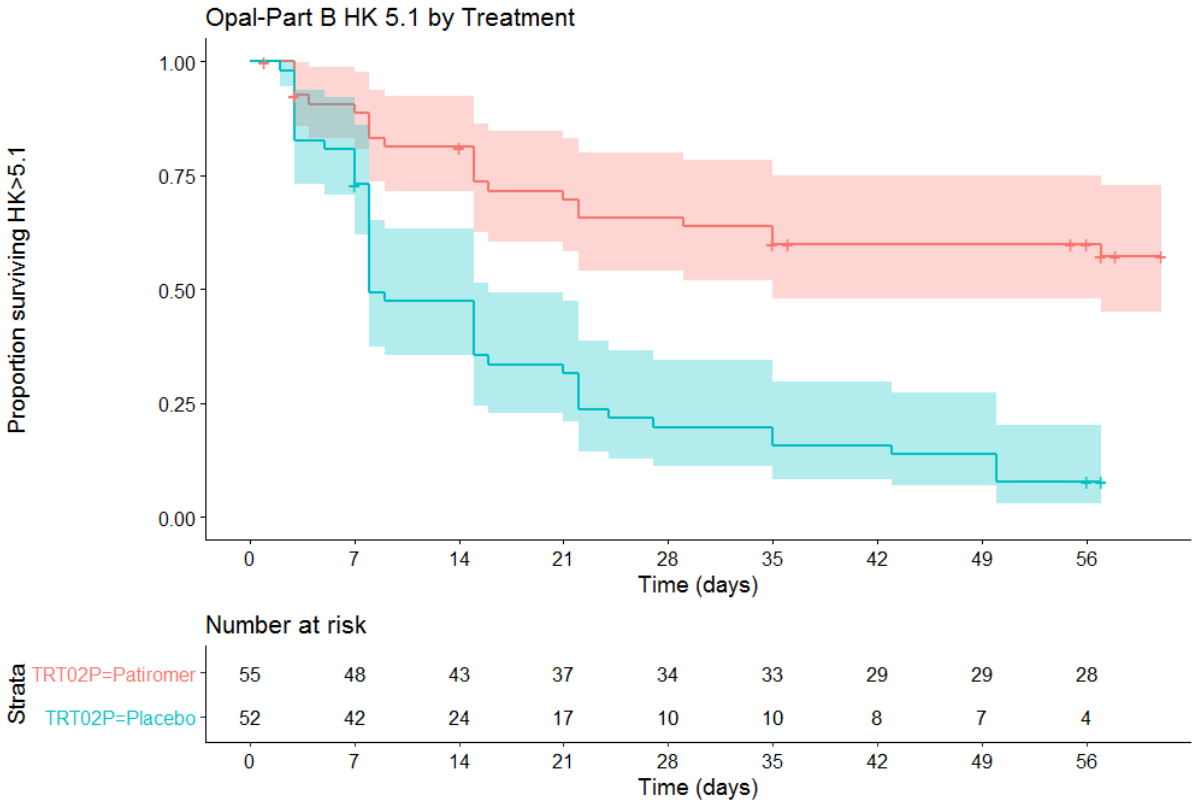
1. Part B: Time to HK 5.1, patiromer (Excel supplement, Table A)
2. Part B: Time to HK 5.1 no patiromer (Excel supplement, Table B)

The hazard ratio associated with patiromer (HR=[redacted], 95% confidence interval: [redacted]) in a Cox proportional hazards model was statistically significant (p<[redacted]), suggesting that patients on patiromer had a [redacted] ([redacted]) lower risk of an HK ≥5.1 event compared to patients receiving placebo.

Table 38. Cox proportional hazard model of HK ≥5.1 - <5.5 by treatment

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 8. Time to hyperkalaemia 5.1mmol/L, Part B by treatment



B6.1.2 Part B, time to HK ≥5.5 by treatment arm (Part B Patiromer vs Placebo)

The following data are provided in this section:

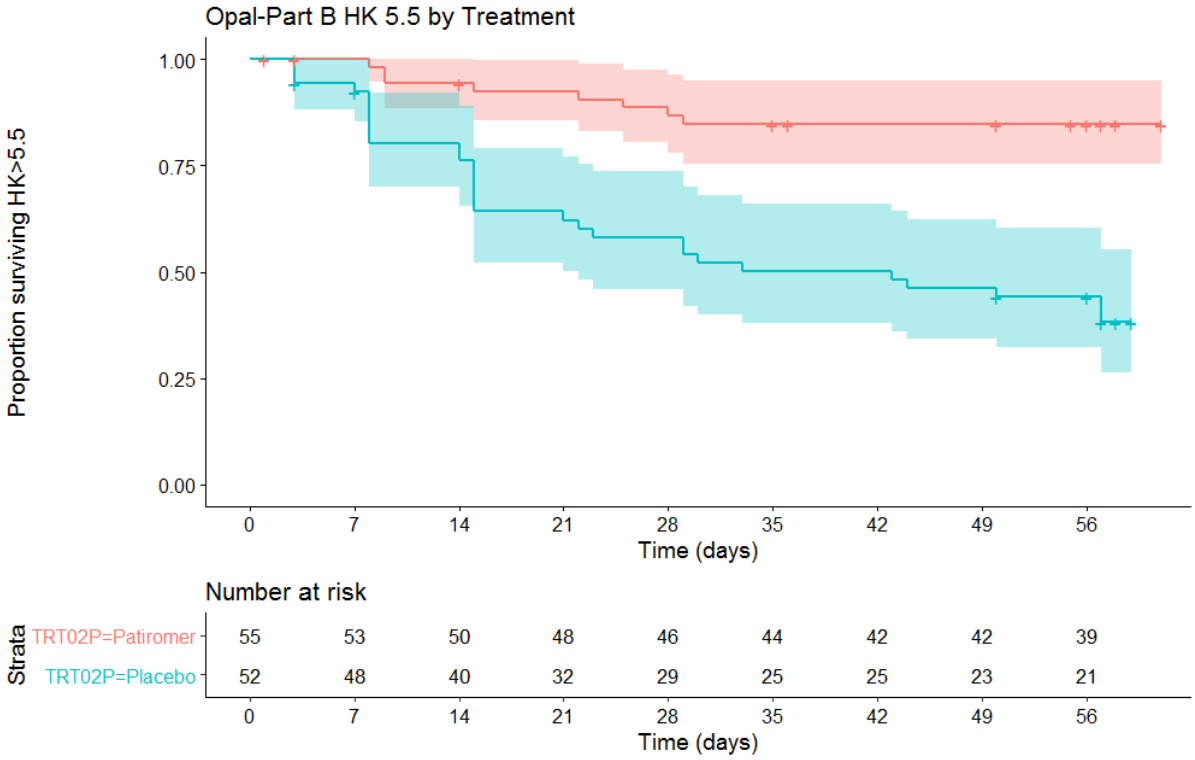
1. Part B: Time to HK 5.5, patiromer (Excel supplement, Table C)
2. Part B: Time to HK 5.5 no patiromer (Excel supplement, Table D)

The hazard ratio associated with patiromer (HR=[redacted]) in a Cox proportional hazards model was statistically significant (p<[redacted]), suggesting that patients on patiromer had an [redacted]% ([redacted]) lower risk of an HK ≥5.5 event compared to patients receiving placebo.

Table 39. Cox proportional hazard model of HK ≥5.5 by treatment

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 9. Time to hyperkaliemia 5.5mmol/L, Part B by treatment



B6.2 TIME TO HK EVENT BY TREATMENT ARM + PART A DOSE

The following data are provided in this section:

1. Part B: Time to HK 5.1, patiromer (Part A 4.2g patiromer) – Excel supplement, Table E)
2. Part B: Time to HK 5.1 no patiromer (Part A 4.2g patiromer) – Excel supplement, Table F)
3. Part B: Time to HK 5.1, patiromer (Part A 8.4g patiromer) – Excel supplement, Table G)
4. Part B: Time to HK 5.1 no patiromer (Part A 8.4g patiromer) – Excel supplement, Table H)
5. Part B: Time to HK 5.5, patiromer (Part A 4.2g patiromer) – Excel supplement, Table I)
6. Part B: Time to HK 5.5 no patiromer (Part A 4.2g patiromer) – Excel supplement, Table J)
7. Part B: Time to HK 5.5, patiromer (Part A 8.4g patiromer) – Excel supplement, Table K)

8. Part B: Time to HK 5.5 no patiromer (Part A 8.4g patiromer) – Excel supplement, Table L)

B6.2.1 Time to HK ≥5.1–<5.5 by treatment arm + Part A dose (4.2g vs 8.4g per dose)

Patients in Part A were assigned to a dose of 4.2g or 8.4g twice per day on the basis of their baseline K^{+}. Patients with a baseline K^{+} < 5.5mmol/L were assigned 4.2g per dose (dose group 1) and patients with a baseline K+ ≥ 5.5mmol/L were assigned 8.4g per dose (dose group 2).

Compared with placebo, patiromer is associated with a statistically significant reduction in time to hyperkalaemia (5.5mmol/L) in the combined dose group as well as the 4.2g and 8.4g subgroups. Between the subgroups, the 95% confidence intervals overlap, suggesting no significant difference between dose groups with regards to time to hyperkalaemia (5.1mmol/L). The subgroup analysis must be interpreted with caution given the small number of patients in dose group 1, 4.2g (N=15).

Table 40. Cox proportional hazard model of HK >5.1–<5.5 by treatment arm (Part B) + Part A dose (reference=4.2g/dose)

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Overall [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Dose group 1 (4.2g bd) [N=15]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Dose group 2 (8.4g bd) [N=92]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

bd, twice daily

Figure 10. Time to hyperkalemia 5.1mmol/L, by Part A dose and treatment

Dose group 1 = 4.2g/dose; dose group 2 = 8.4g/dose

B6.2.2 Time to HK ≥5.5 by treatment arm (Part B) + Part A dose (4.2g vs 8.4g per dose)

Patients in Part A were assigned to a dose of 4.2g or 8.4g twice per day on the basis of their baseline K+. Patients with a baseline K+ < 5.5mmol/L were assigned 4.2g per dose (dose group 1) and patients with a baseline K+ ≥ 5.5mmol/L were assigned 8.4g per dose (dose group 2).

Compared with placebo, patiromer is associated with a statistically significant reduction in time to hyperkalaemia (5.5mmol/L) in the combined and 8.4g dose groups. The result is not statistically significant at the 4.2g dose although patient numbers are very small (n=15).

Comparison between the sub-groups by dose level shows that the confidence intervals between the two dose subgroups overlap, suggesting no difference in the effect of patiromer by dose level. The confidence interval for dose group 1 (4.2g) includes 1.0 suggesting the possibility of no statistically significant effect, but note that this subgroup is very small and the results must be interpreted with caution.

Table 41. Cox proportional hazard model of HK ≥5.1 by treatment + Part A dose (reference=4.2g/dose)

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Overall [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Dose group 1 (4.2g bd) [N=15]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Dose group 2 (8.4g bd) [N=92]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

bd, twice daily

Figure 11. Time to hyperkalemia 5.5mmol/L, by Part A dose and treatment

** Dose group 1 = 4.2g/dose; dose group 2 = 8.4g/dose*

B6.3 TIME TO HK EVENT BY TREATMENT ARM + PART A K^+

In Part A patients who met all the entry criteria were assigned to one of two patiromer starting doses according to the severity of the hyperkalaemia: patients with a potassium level of 5.1 to <5.5 mmol/L (mild hyperkalaemia) received 4.2g of patiromer twice daily, and those with a potassium level of 5.5 to <6.5 mmol/L (moderate-to-severe hyperkalaemia) received 8.4 g of patiromer twice daily. Therefore, stratification by Part A patiromer dose level is equivalent to stratification by K^+ level as provided above.

B6.4 TIME TO HK EVENT BY TREATMENT ARM + STUDY REGION

The following data are provided in this section:

1. Part B: Time to HK 5.1, patiromer (Eastern Europe) – Excel supplement, Table M
2. Part B: Time to HK 5.1 no patiromer (Eastern Europe) – Excel supplement, Table N

3. Part B: Time to HK 5.1, patiromer (US/EU) – Excel supplement, Table O
4. Part B: Time to HK 5.1 no patiromer (US/EU) – Excel supplement, Table P
5. Part B: Time to HK 5.5, patiromer (Eastern Europe) – Excel supplement, Table Q
6. Part B: Time to HK 5.5 no patiromer (Eastern Europe) – Excel supplement, Table R
7. Part B: Time to HK 5.5, patiromer (US/EU) – Excel supplement, Table S
8. Part B: Time to HK 5.5 no patiromer (US/EU) – Excel supplement, Table T

B6.4.1 Time to HK ≥5.1 by treatment arm + region (EU & US vs Eastern Europe [non-EU])

For all patients, the hazard ratio associated with patiromer (HR [redacted], 95% confidence interval: [redacted]) was statistically significant, suggesting that the time to a hyperkalaemia event ≥5.1 amongst patients receiving patiromer was greater than amongst patients receiving placebo.

Sub-group analysis by region indicate that there is a statistically significant difference in the time to event between patiromer and placebo for patients enrolled to Eastern European sites but not for US/EU.

The company would like to highlight that while there is an observed difference in time to hyperkalaemia between the two regions (as measured by K^+≥5.1mmol/L), this analysis is not used in the economic model as patients are not actively treated at this K^+ level in UK clinical practice. Rather, the economic model uses time to hyperkalaemia measured as K^+≥5.5mmol/L which is more reflective of UK clinical practice. Further, the US/EU sub-group is small (n=22) and therefore any results should be viewed with a degree of caution.

To compare impact of patiromer on time to hyperkalaemia across the regions, the confidence interval around the estimated hazard ratio for each region was calculated. As the confidence interval around the hazard ratio in US/EU region is overlapping the confidence interval around the hazard ratio in Eastern Europe (Table 42), this suggests that there is no statistical difference between regions.

Table 42. Cox proportional hazard model of HK ≥5.1 by treatment and region

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Overall [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
European Union and US [N=22]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Eastern Europe (Non-EU) [N=85]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 12. Time to hyperkalemia 5.1mmol/L, by Part B treatment and region

B6.4.2 Time to HK ≥5.5 by treatment arm + region (EU & US vs Eastern Europe [non-EU])

The hazard ratio associated with patiromer (HR [redacted], 95% confidence interval: [redacted]) was statistically significant in the overall results, suggesting that the time to a hyperkalaemia event ≥5.5mmol/L amongst patients receiving patiromer was greater than those receiving placebo. Analysis by region show a statistically significant result in both regions.

To compare impact of patiromer on time to hyperkalaemia (≥5.5mmol/L) across the regions, the confidence interval around the estimated hazard ratio for each region was calculated. As the confidence interval around the hazard ratio in US/EU region is overlapping the confidence interval around the hazard ratio in Eastern Europe (Table 43), this suggests that there is no statistical difference between regions in relation to time to hyperkalaemia ≥5.5mmol/L.

Given the small patient numbers in the US/EU region, the economic model uses the time to hyperkalaemia (≥5.5mmol/L) for the entire OPAL-HK population. This potassium level is more reflective of when active treatment may be initiated in clinical practice.

Table 43. Cox proportional hazard model of HK ≥5.5 by treatment and region

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Overall [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
European Union and US [N=22]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Eastern Europe (Non-EU) [N=85]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 13. Time to hyperkalemia 5.5mmol/L, by Part B treatment and region

B7. ***(No question provided; confirmed during teleconference with NICE 26th July 2018).***

B8. PRIORITY: Please provide the OPAL-HK Kaplan–Meier patiromer/placebo discontinuation data for the withdrawal phase for all patients and separately for the region subgroups (Eastern Europe vs EU/US) (6 tables) in the following format. If it is felt more appropriate to include LTFU (lost to follow-up) as an event than as censoring, please outline the rationale for this and split Events into two columns of (a) observed discontinuations and (b) LTFU

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…

The responses to this question are presented below. The requested survival table data can be found in the accompanying Excel supplement. We were unable to separate censoring from lost to follow-up in the KM data tables, but the summary of censoring events below indicates that only one patient was lost to follow-up over the course of Opal Part B (N=107).

Table 44. Observed events in OPAL-HK

Event	Number
Adverse event	[redacted]
Completed	[redacted]
Death	[redacted]
Lost to follow-up	[redacted]
Met protocol specified withdrawal criteria (eGFR decrease to <10 mL/min/1.73m^2 or need for dialysis	[redacted]
Met protocol specified withdrawal criteria (high serum potassium results)	[redacted]
Met protocol specified withdrawal criteria (low serum potassium results)	[redacted]
Met protocol specified withdrawal criteria (serum potassium results)	[redacted]
Non-compliance with study drug	[redacted]
Physician decision	[redacted]
Protocol violation	[redacted]
Withdrawal by subject	[redacted]

Please note that the time to treatment discontinuation from OPAL-HK was not applied in the economic model due to the short trial duration. Instead an analysis of AMETHYST-DN was performed and used in the model given the longer-term data from this study (see question B11).

All analyses for this question are based on Individual Patient-level Data (IPD);

B8.1 Time to treatment discontinuation by treatment arm (Patiromer vs Placebo) – Excel supplement, Table U and V

The hazard ratio associated with Patiromer (HR=[redacted]) in a Cox proportional hazards model was statistically significant (p=[redacted]), suggesting that patients on patiromer were less likely to discontinue their Part B treatment compared to patients on placebo.

Table 45. Cox proportional hazard model of treatment discontinuation by treatment

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 14. Time to treatment discontinuation by treatment arm (Part B)

[redacted]

B8.2 Time to treatment discontinuation by treatment arm + region (EU & US vs Eastern Europe [non-EU]) – Excel supplement, Table W, X, Y and Z

When time to patiromer discontinuation is stratified by region, sub-group analyses show that the difference in continuation rates versus placebo is not significant in either region. This statistical insignificance is likely driven by relatively small differences in completion rates and small numbers in the regional subgroups. Based on interpretation of the confidence intervals for the hazard ratios across regions (overlapping), there is no difference in patiromer discontinuation across regions.

Table 46. Cox proportional hazard model of treatment discontinuation by treatment + region

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Combined [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
European Union and US [N=22]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Eastern Europe (Non-EU) [N=85]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 15. Time to treatment discontinuation by treatment arm and region (Part B)

B9. Please provide scenario analyses exploring the primary outcome stratified by Eastern Europe compared to US/EU.

This requires a new survival analysis which is not feasible in time given to respond. This analysis can be performed and cost-effectiveness results produced if an extension of time is permitted. However, it should be noted that the US/EU cohort is very small (n=22) and so results from any survival analysis would be subject to uncertainty and not be robust.

The company also request that the parametric survival curves for RAASi discontinuation and time to hyperkalaemia in Document B (Figure 12, Figure 15, Figure 19 and Figure 20) are examined, where it can be seen that there is variation in the shape and survival estimates of alternative parametric curves. The impact of each is examined in scenario analyses (Document B, Table 47) where patiromer remains a dominant strategy. Given these time to event analyses comprise of both US/EU and

Eastern European cohorts and the variation in survival between parametric curves is large, the company expect that the true time to RAASi discontinuation and hyperkalaemia for individual regions lies somewhere between the current (all patients) curves and would therefore result in similar ICERs to those provided in Table 47 of document B.

B10. PRIORITY: Please provide the OPAL-HK Kaplan–Meier RAASi discontinuation data for the withdrawal phase that underlies Document B Figure 13 for all patients and also separately for the EU/US subgroup in the following format. (4 Tables). If LTFU was treated as a RAASi discontinuation rather than as censoring, please split events into two columns of (a) observed RAASi discontinuations and (b) LTFU. If the data underlying Document B Figure 9 differs from Figure 13, please provide the rationale and the parallel Kaplan–Meier data underlying Document B Figure 9 in the same format.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…
EoT: End of trial, LTFU: Lost to Follow-Up						

The requested analyses are provided below. The survival table data can be found in the accompanying Excel supplement.

All analyses for this question are based on Individual Patient-level Data (IPD);

B10.1. RAASi discontinuation by treatment arm (all patients) – Excel supplement, Table AA and BB.

The hazard ratio associated with patiromer (HR=[redacted]) in a Cox proportional hazards model of RAASi discontinuation was statistically significant (p<[redacted]), suggesting that patients receiving patiromer were less likely to discontinue RAASi than patients receiving placebo. This is illustrated by the Kaplan-Meier survival curves below.

Table 47. Cox proportional hazard model of RAASi discontinuation by treatment

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 16. Time to RAASi discontinuation by treatment arm (Part B)

[redacted]

B10.2. RAASi discontinuation by treatment and region – Excel supplement, Table CC, DD, EE, FF

Analysis of RAASi discontinuation show the time to event is statistically significant in the overall population and at the regional level for patiromer vs. placebo. The confidence intervals for the regional hazard ratios overlap indicating that there isn't a statistically significant difference in time to RAASi discontinuation across the two

regions. As mentioned previously, regional comparisons should be interpreted with caution given the low patient numbers enrolled to US/EU study site(n=22).

Table 48. Cox proportional hazard model of RAASi discontinuation by treatment

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Overall [N=107]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
European Union and US [N=22]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Eastern Europe (Non-EU) [N=85]				
Patiromer (vs Placebo)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 17. Time to RAASi discontinuation by treatment arm and region (Part B)

[redacted]

Figure 9 and Figure 13 show equivalent data. Figure 9 is reproduced from the Weir 2015 whereas Figure 9 is generated from individual patient level data for the purposes of informing the economic analysis in this submission.

B11. PRIORITY: Please provide the AMETHYST-DN Kaplan–Meier discontinuation data that underlies Figure 16 of Document B in the following format, preferably split by dose (3 doses in two strata) but if this is not possible then split by strata. If Figure 16 is derived from a subset of AMETHYST-DN please define this subset. Please confirm if this data relates to the latest data cut of AMETHYST-DN.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…

The responses to this question are presented below. The requested survival table data can be found in the accompanying Excel supplement. The company can confirm that the data used to generate Figure 16 in document B used individual patient level data for the entire AMETHYST-DN population and is the final data cut.

B11.1 Overall Patiromer discontinuation – Excel supplement, Table GG

Amethyst was a dosing study with no placebo arm, so there is no comparator and no hazard ratio. The overall discontinuation rate is presented below.

Figure 18. Time to patiromer discontinuation (AMETHYST-DN)

B11.2 Patiromer discontinuation by dose (8.4g/16.8g/25.2g per day) – Excel supplement, HH, II and JJ.

Patiromer discontinuation rates in the Amethyst trial were not statistically significantly different for the 16.8g dose (p=0.60) or the 25.2g daily dose (p=0.68) relative to the reference dose of 8.4g per day. This is illustrated in the overlapping confidence intervals and the survival curves below.

Table 49. Cox proportional hazard model of time to patiromer discontinuation by dose (AMETHYST-DN), (reference level = 8.4g)

Parameter	Coefficient	Hazard ratio	SE of coefficient	p-value
Dose 25.2g (vs 8.4g dose)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		
Dose 16.8g (vs 8.4g dose)	[redacted]	[redacted]	[redacted]	[redacted]
HR 95% confidence interval		[redacted]		

Figure 19. Time to patiromer discontinuation by dose (AMETHYST-DN)

B12. PRIORITY: Did AMETHYST-DN collect RAASi discontinuation data? If it did, please provide the Kaplan–Meier RAASi discontinuation data in the following format, preferably split by dose but if this is not possible split by stratum. Please confirm if this discontinuation data is restricted to patients who discontinued RAASi and did not resume RAASi during AMETHYST-DN. Was switching to an alternative blood pressure medication after discontinuing RAASi permitted during AMETHYST-DN? Please confirm if this data relates to the latest data cut of AMETHYST-DN.

			Censored			
T (Day)	N Risk	Event	EoT	LTFU	Other	S(t)
T=0 T=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…	N=? N=? etc…

AMETHYST-DN did collect data relating to discontinuation of anti-hypertensive medication, however this was not limited to only RAAS inhibitor drugs. Only the time to any hypertensive discontinuation was recorded at the individual patient level and therefore an analysis of this is not informative for the purposes of this question given the interest is in analysing the time to RAASi discontinuation due to hyperkalaemia. Please see Table 14.3.7.10 of the AMETHYST Clinical Study Report (provided separately, document rly5016-205_end-of-text-tables-and-figures AMETHYST-DN) for a list of anti-hypertensive medication used during the study. It should also be noted that AMETHYST-DN is only used in the economic model to inform patiromer discontinuation given the data is longer term than that available from OPAL-HK. Therefore, the company have not performed the requested analysis.

B13. Section 3.3.5 notes the use of Landray et al, Ariyaratne et al, Parving et al, Thomsen et al and Eriksen et al for various inputs to the economic model. How were these studies identified and why were they chosen over the alternatives?

Ariyaratne et al 2013, Eriksen et al 2006 and Landray et al 2010 were identified by targeted literature searches, which were necessary as the scope of the mandatory systematic literature reviews (clinical, HRQL, economics and resource use) were not

broad enough to cover all inputs needed for the economic model. The nature of these targeted searches was to identify literature which could provide data for populating the economic model rather than to identify all possible data sources. While there may be alternative sources available, the above sources were considered appropriate for the inputs for which they were used.

As well as targeted searches, an additional SLR was performed to identify the relationship between hyperkalaemia and major adverse cardiac events or mortality in a CKD population (Appendix L in Document B5). Parving et al 2012 and Thomsen et al 2017 were identified via this SLR and were considered the most appropriate sources, due to being conducted in a European cohort and having the largest sample sizes compared with the alternatives.

B14. It is not obvious why the probabilities calculated from Landray et al for CKD patients should be viewed as being 'No RAASi'. Has this been assumed and if so why? Similarly, please outline separately for each of the probabilities calculated from Thomsen 2017, Parving 2012, Ariyaratne 2013 and Luo 2016 if these are viewed as relating as being 'No RAASi', and if so why?

It has been assumed that the probabilities resulting from the above-mentioned studies are 'No RAASi'. During the literature searching process, parameter values could not be informed by excluding patients on RAASi because studies included a mix of patients who were both on and not on RAASi therapy in varying proportions, and did not report probabilities for each subset of patients. For modelling purposes, the relative risk associated with RAASi use was applied to these probability estimates such that there is a higher or lower risk of an event occurring (depending on the event) in patients in the RAASi arms of the model.

B15. Please provide the RAASi proportions data on file from Reference 73 and outline how it has been derived from the CPRD. Are the RAASi costs within the model aligned with these proportions?

The average cost of RAAS inhibitors was based on the mean doses from a selection of 141 patients who were on Angiotensin Converting Enzyme (ACE) inhibitors in the OPAL-HK trial, part A. ACE inhibitors were selected for costing as these were the most commonly used agents in OPAL-HK. The ACE inhibitors considered were enalapril, ramipril, perindopril and lisinopril. Based on the BNF and MIMS, the average monthly cost was determined to be £3.60 assuming 100% compliance. The RAASi costs are therefore not aligned with the CPRD, however this has been explored in a sensitivity analysis presented below.

To derive the proportion of patients on RAASi from the CPRD, the RAASi drug(s) which patients were on at the patients' index date (i.e. date of RAASi initiation) were recorded. Table 50 provides a count and relative percentage of patients with each prescription on the index date. This data is within the following dof (data on file) shared in the initial submission, file name 'Critical and Important Analysis_QCd DOF - VPUK_DOF_108.xlsx'.

Table 50. Proportion of CKD patients on RAASi therapies receiving ACE inhibitors, angiotensin receptor blockers (ARB) and aldosterone antagonists (AA)

Type of RAASi	**Count of Rx**	**Percent**
ACE Inhibitors	[redacted]	[redacted]
Angiotensin Receptor Blockers	[redacted]	[redacted]
Aldosterone antagonists	[redacted]	[redacted]
Total	[redacted]	[redacted]

*Note: One patient can have more than 1 prescription at index date (RAASi index). Unique patient count is [redacted]

The CPRD provides the proportional use at a class level only (there is no data for individual molecules), therefore this sensitivity analysis uses the weighted average cost of a range of RAAS inhibitors at a class level. From the ACE inhibitors, an average was taken across enalapril, ramipril, perindopril and lisinopril. From the ARBs, an average was taken across losartan, candesartan, telmisartan, valsartan, irbesartan, eprosartan and olmesartan. From the aldosterone antagonists, an average was taken between spironolactone and eplerenone. The weighted average cost of RAASi per month was £3.95. This results in an £84.44 increase of the ICER from -£14,650.83 to -£14,566.50. See Table 51 for a full breakdown of costs and QALYs.

Table 51. Impact of weighting the use of ACEIs, ARBs and AAs according to a CPRD analysis of the proportionate use of these drug classes.

	Unweighted	Weighted according to CPRD	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	18.0924831
No Patiromer	[redacted]	[redacted]	9.42939047
Incremental	-1,505.02	-1,496.36	8.66309264
	QALYs		
Patiromer	[redacted]	[redacted]	0
No Patiromer	[redacted]	[redacted]	0
Incremental	0.103	0.10272612	0
	With PAS ICER (£/QALY)		
	-£14,650.83 (Dominant)	-£14,566.50 (Dominant)	£84.33

B16. Please outline the reasons for exclusion of studies in Table 57 of the appendices. Why was Xie used in preference to Palmer in the economic model?

Xie was used in preference to Palmer as it investigates the efficacy of RAAS inhibitors in CKD patients (including diabetic CKD patients), however Palmer is restricted to diabetic CKD patients, therefore, the population in the Xie NMA is a closer match to that of the OPAL-HK trial than Palmer. In addition, Xie was published more recently (i.e. systematic searches of the literature were performed at a later date) and uses a Bayesian as opposed to frequentist approach.

B17. PRIORITY: Please clarify some of the calculations in the model:

- **B17.1. Provide an excel spreadsheet that separately calculates the RAASi odds ratios of *Calculations* Y40:Y44 from the data of Xie et al 2016, with full table/text/figure referencing of the values taken from Xie et al 2016.**

The RAASi odds ratios stated are taken directly from the Xie paper (i.e. they are not calculated values). Page number, table/text/figure referencing is provided in Table 52.

Table 52. Odds Ratios (ORs) from Xie et al 2016.

ORs from Xie et al, CKD NMA converted to RR in model				
	OR	Xie 2016 location		
CKD to ESRD	0.61	Page 733	Figure 2A.	Placebo -> ACEI
CV event	0.82	Page 733	Figure 2B.	Placebo -> ACEI
CKD mortality (all cause)	0.87	Page 733	Figure 2D.	Placebo -> ACEI
CV event mortality	0.88	Page 733	Figure 2C.	Placebo -> ACEI
Hyperkalaemia (with RAASi)	2.16	Page 733	Under "Adverse events" heading	

- **B17.2. clarify why the relative risk for CKD to ESRD of 0.61 calculated from Xie, *Calculations* AB40 is not used and why the value of 0.64, *Inputs* K23, is used.**

The value of 0.64 for the risk for CKD to ESRD was calculated by taking a weighted average of the risks for patients on ACE inhibitors and angiotensin receptor blockers (ARBs), based on the relative use of these medications in CKD patients on RAASi according to the CPRD (Table 50). The company consider this more reflective of real world risk associated with CKD progression and use of RAASi.

- **B17.3. provide the full arithmetic of the calculation of the 0.64 value, together with full table referencing of the RR source data.**

Step 1: RAASi proportions data from the CPRD (Table 50) were used to calculate the relative weight of ACE and ARBs as a proportion of all reported RAASi drugs (ACEI, ARB, aldosterone antagonists [AA]).

Proportional use ACEIs:

=Proportion patients using ACEI / proportion using ACEI + ARBs

=[redacted]

=0.71

Proportional use ARBs:

=[redacted]

=0.29

Step 2: Weight average risks for ACEIs and ARBs from Xie et al (Table 53*Table 53. ORs from Xie et al*)

= (0.61*0.71) + (0.70*0.29)

= 0.64

Table 53. ORs from Xie et al

	Risk	**Xie 2016 location**		
CKD to ESRD (ACEI)	0.61	Page 733	Figure 2A.	Placebo -> ACEI
CKD to ESRD (ARB)	0.70	Page 733	Figure 2A.	Placebo -> ARB

- **B17.4. provide an excel spreadsheet that calculates the No RAASi annual rate of 3.6% for post-MACE to Dead from the data of Xie et al 2016, with full table/text/figure referencing of the values taken from Xie et al 2016.**

A supporting document and Excel supplement has been provided (sheet B17.4).

B18. Please present the equivalent of Calculations W72:AC77 for Part A of OPAL-HK.

Please see Table 54 for the most common adverse events (individual events occurring in ≥ 2% of patients) in either dose group for Part A, and Table 55 for serious adverse events in either dose group for Part A, adapted from the Weir et al (2015) (10) supplementary appendix (provided with this response).

Table 54. Adverse events – OPAL-HK Part A.

	All patients	Dose group 1 (mild HK)	Dose group 2 (moderate to severe HK

	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Adverse events						
At least one adverse event	114	47	42	46	72	48
Gastrointestinal Disorders		0				
Constipation	26	11	9	10	17	11
Diarrhoea	8	3	2	2	6	4
Nausea	8	3	4	4	4	3
Flatulence	4	2	1	1	3	2
Metabolism and Nutrition Disorders						
Hypomagnesaemia	8	3	3	3	5	3
Hyperkalaemia	6	2	4	4	2	1
Dyslipidaemia	4	2	1	1	3	2
Hyperglycaemia	4	2	1	1	3	2
Investigations						
Glomerular filtration rate decreased	4	2	2	2	2	1
Cardiac disorders						
Left ventricular hypertrophy	6	2	0	0	6	4
Atrioventricular block first degree	4	2	0	0	4	3
Blood and Lymphatic System Disorders						
Anaemia	7	3	4	4	3	2
Renal and urinary disorders						
Renal failure chronic	7	3	2	2	5	3
Vascular disorders						
Hypertension	4	2	1	1	3	2
General Disorders and Administration Site Conditions						
Fatigue	4	2	2	2	2	1
Skin and subcutaneous tissue disorders						
Pruritus	3	1	2	2	1	1

Table 55. Serious adverse events in OPAL-HK Part A

	All patients		Dose group 1 (mild HK)		Dose group 2 (moderate to severe HK	
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Serious adverse events						
At least one	3	1	2	1	1	1
Cardiac Disorders						

Atrial fibrillation	1	0	0	0	1	1
Infections and infestations						
Endocarditis enterococcal	1	0	0	0	1	1
Escherichia bacteraemia	1	0	0	0	1	1
Urinary tract infection	1	0	0	0	1	1
Investigations						
Sub-therapeutic anticoagulant blood levels	0	0	1	1	0	0
Renal and urinary disorders						
Chronic renal failure	1	0	1	1	0	0

None of the serious adverse events were considered treatment related (10).

B19. PRIORITY: The probabilities of HK to Death and HK to MACE from Luo et al have two values for CKD 3b. Why is this? Please provide fuller referencing for the values of Luo et al that underlie each of Calculations cells X98, X100:Y103 and X108:Y111 together with the details of any additional calculations that are required to derive the values in Calculations cells X98, X100:Y103 and X108:Y111.

The values used in sheet Calculations, cells X100:Y103, were taken from Luo et al. (2016), Table 3 (entitled 'Rate of death according to serum potassium by eGFR stratum'). The values in column X refer to patients with a serum potassium level of 5.0-5.4 mmol/L and those in column Y to patients with a serum potassium level of 5.5-5.9 mmol/L.

Equivalently, the values in X108:Y11 were taken from Luo, Table 4 (entitled 'Rate of major adverse cardiovascular events according to serum potassium by eGFR stratum').

The reason for the double occurrence of stage 3b is that Luo did not group patients by stage but by eGFR category. The values assigned stage 3b in the model are those for the eGFR 40–49 ml/min and eGFR 30–39 ml/min categories in Luo.

B20. The electronic model appears to include CHF, MI and stroke in the probability of secondary MACE events derived from Ariyaratne 2013.

Please give a rationale for including CHF as a MACE event. Please clarify how the probabilities and relative risks are aligned with this. It can also be noted that Ariyaratne 2013 was for the 12-month period following PCI. Is there evidence that these probabilities apply beyond the 12-month period following PCI or is this a company assumption?

There is no standard definition of MACE, and inclusion of individual events is dependent of the study design and investigators assessment. In some recent studies such as EMPA trial (11), worsening of HF, HF hospitalisation and HF death was used as composite measure of MACE. Therefore, this was included to ensure all the data has been captured in the review process.

A sensitivity analysis removing CHF as a MACE event from Ariyaratne is explored below. This change results in a decrease in the ICER (i.e. a more dominant result) of £105.94 from £14,650.83 to -£14,756.77. Please see Table 56 for a full breakdown of the results.

Table 56. Breakdown of cost-effectiveness results after removing CHF as a MACE event.

	With CHF	Without CHF	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	-399.69
No Patiromer	[redacted]	[redacted]	-388.80
Incremental	-1,505.02	-1,515.91	-10.89
	QALYs		
Patiromer	[redacted]	[redacted]	-0.0004
No Patiromer	[redacted]	[redacted]	-0.0004
Incremental	0.103	0.103	0.0000005
	With PAS ICER (£/QALY)		
	-£14,650.83 (Dominant)	-£14,756.77 (Dominant)	-£105.94

It assumed that the probability of having a secondary MACE event in the 12-month period following PCI applies beyond a 12-month period.

B21. PRIORITY: Table 3 of Landray et al outlines all patient incidences of 12.1%/y ESRD and 6.5%/y Death. These are not obviously aligned with the values in the electronic model. Please provide an excel spreadsheet outlining how the values in the electronic model have been calculated and why they differ from those of table 3 of Landray et al.

Landray et al. 2010 was only used to model transition to ESRD, not transition to death. The sources underlying the modelling of mortality are described in Document B, sections 3.3.4 and 3.3.5.

Regarding the transition to ESRD, an Excel supplement (sheet B21) has been provided. The annual rate assumed in the model was calculated using the standard probability-to-rate conversion formula as provided by Briggs:

$$Rate=-Ln(1-p)/t$$

Where p = probability, t=time in years

Parameter values represent the number of ESRD events (190) (patient incidence 12.1%/y), the number of patients in the study (382) and the mean observation time (4.1 years), from Landray et al, resulting in a calculation of:

$$-Ln(1-(190/382))/4.1 = 0.168$$

The annual event rate was converted to a monthly transition probability as per Briggs:

$$probability = 1- Exp (-rate*t)$$

Resulting in a monthly probability of:

$$1-Exp(-0.168*(1/12)) = 0.0139$$

B22. PRIORITY: Please provide fuller referencing for the source of the Thomson et al data within the ((0.338*1.72)-0.338)/0.5 formula that underlies the calculated No RAASi 48.7% annual rate of CKD to HK hospitalisations. Explain the rationale underlying the formula.

Thomsen et al. observed elevated potassium levels and associated clinical events in a Danish population-based cohort study observing 157,766 patients with CKD stage 3A, 3B, 4 or 5. Patients with an event of hyperkalaemia, defined as elevated serum potassium > 5.0 mmol/L, had a probability of acute hospitalisation of 33.8% in the half-

year before the event and of 57.1 % in the half-year after the event (Thomsen et al., Table 3). The after versus before relative risk, adjusted for the competing risk of death, was calculated by the authors to be 1.72. We estimated the excess probability (risk difference) of acute hospitalisation after an event of hyperkalaemia to be 0.338*1.72 – 0.338. As this value applies to a half-year, it was divided by 0.5 to achieve an estimate for the one-year period after the event, resulting in the calculated value of 0.487.

B23. Please provide more explicit referencing for the source of the QoL values for MI and stroke from Sullivan et al 2011 and the details of any calculations to derive the values in Table 34. Please provide the link to the calculations if used, and outline what inputs were specified in it to arrive at the values of Table 34.

The company have not responded to this question, as it is no longer applies considering the response to the following question (B24).

B24. Table 3 of Pocket et al 2018 gives quality of life values for a number of time points. At 6 months, the values are reported as all patients 0.672, MI 0.702, UA 0.637 and Stroke 0.525. Are the 6-month values those applied in the model? If they are why was this time point used and has the MI value been incorrectly transcribed? If not, please provide fuller referencing to which values from Pocket et al 2018 have been used and why. Given the NICE/DSU preference for sourcing quality of life values from a single coherent source, why have the 0 months QoL values of Pocket et al 2018 been ignored in preference to values from Sullivan et al 2011?

Pockett et al (2018) was used as it was considered the best source for post-MACE utility values from the HRQL SLR, being the most recent source reporting both post-MI and post-stroke EQ-5D values for the largest sample of UK patients.

The 6-month values from Pockett et al (2018) were applied in the model for the “post-MACE MI” and “post-MACE stroke” utility inputs. The 6-month values were chosen as this time point was considered to reflect the post-MACE event state, in that the disutility

is not as severe in the immediate aftermath of the MACE event (i.e. at baseline), however acknowledges that patients still suffer from an impairment in quality of life. The other time points available in Pockett were considered too far post-event to be appropriate for the post-MACE health state utilities.

The 6-month value for "post-MACE MI" was transcribed incorrectly; the utility value for 'all' patients (0.6720) was used rather than the utility value for MI patients (0.702). Changing this in the model leads to a change in the with PAS ICER from -£14,650.83 to -£14,544.28 (an increase of £106.55). See Table 57 for a full breakdown of these results.

Table 57. Breakdown of results after correcting the Post-MI utility value

	Original	Corrected	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	0.00
No Patiromer	[redacted]	[redacted]	0.00
Incremental	-1,505.02	-1,505.0231	0.00
	QALYs		
Patiromer	[redacted]	[redacted]	0.0138
No Patiromer	[redacted]	[redacted]	0.0131
Incremental	0.103	0.10347868	0.0008
	With PAS ICER (£/QALY)		
	-£14,650.83 (Dominant)	-£14,544.28 (Dominant)	£106.55

The company used the values from Sullivan et al (2011) for the baseline MI and stroke values (0.6046 and 0.5189, respectively), as this is a commonly used source for utility values in HTA submissions, however the company accepts that given the NICE/DSU preference, Pockett et al (2018) is the more appropriate source for the baseline utility values for MI and stroke (0.690 and 0.495, respectively). Changing this in the model (original model submitted to NICE, not accounting for the above correction in the post-MI utility) results in a £2.60 increase in the ICER from -£14,650.83 to -£14,648.23. Please see Table 58 for the full breakdown of cost and QALYs.

Table 58. Impact of changing the source for MI and stoke utility values from Sullivan et al (2011) to Pockett et al (2018) in base case model

	Sullivan (2011)	Pockett (2018)	Change

	Costs (£)		
Patiromer	[redacted]	[redacted]	0.00
No Patiromer	[redacted]	[redacted]	0.00
Incremental	-1,505.02	-1,505.02	0.00
	QALYs		
Patiromer	[redacted]	[redacted]	0.00118
No Patiromer	[redacted]	[redacted]	0.00116
Incremental	0.103	0.103	0.00002
	With PAS ICER (£/QALY)		
	-£14,650.83 (Dominant)	-£14,648.23 (Dominant)	£2.60

Changing the source from Sullivan to Pockett in the model which accounts for the correction of the 6-month post-MI value results in a £2.56 increase in the ICER from -£14,544.28 to -£14,541.72. Please see Table 59 for a full breakdown of costs and QALYs.

Table 59. Impact of changing the source for MI and stoke utility values from Sullivan et al. (2011) to Pockett et al (2018) following the correction to the post-MI utility value.

	Sullivan (2011)	**Pockett (2018)**	**Change**
	Costs (£)		
Patiromer	[redacted]	[redacted]	0.00
No Patiromer	[redacted]	[redacted]	0.00
Incremental	-1,505.02	-1,505.02	0.00
	QALYs		
Patiromer	[redacted]	[redacted]	0.00118
No Patiromer	[redacted]	[redacted]	0.00116
Incremental	0.103	0.103	0.00002
	With PAS ICER (£/QALY)		
	-£14,544.28 (Dominant)	-£14,541.72 (Dominant)	£2.56

B25. Please provide a more explicit table/text/figure reference for the source the - 0.0616 value of Document B table 34 for CKD progression from Lee et al 2005 and if necessary outline how this value has been calculated from values within Lee et al 2005.

There is an error in the Table 34 of Document B (page 109) which gives a disutility for ESRD (CKD progression). The disutility value of -0.0616 in the calculations page of

the model (O289) does not feed into the model engine as disutilities have been replaced with utilities relative to the general population (see Question C2 in this document and section 3.4.5. of Document B). The utility applied to ESRD (CKD progression) is 0.5852. This is a weighted average of haemodialysis (HD), peritoneal dialysis (PD) and transplant (see Table 60 below) to provide an overall relative utility.

Table 60. Calculation of ESRD utility.

Health state	**Utility (Lee et al)**	**Utility weighted to general CKD population utility (0.8210 - derived form Ara & Brazier [Q. C2])**	**Proportion of patients (UK Renal Registry Report)**
HD	0.443	0.5396	0.730
PD	0.530	0.6456	0.192
Transplant	0.712	0.8673	0.077

B26. Please provide the full calculation of the monthly costs of CKD of £162, full table/text/figure referencing to all values used and also the rationale underlying this cost. Does it include all annual costs likely to be incurred by CKD patients, given the differential overall survival estimates of the model? For the other costs within the model neither Thokla 2013 nor Seaton (year unspecified) appear to be within the reference pack. Please provide these. What is the source for the post-transplant average life expectancy of 5 years?

There was an error in the submission in the imputed monthly cost of CKD. Below is a breakdown of the calculation of the monthly cost of CKD which considers primary care, outpatient visits and inpatient visits. The costs of other elements such as medication, renal replacement therapy and complications are modelled separately.

Table 61. Breakdown of costs of CKD management

Primary care	**Cost**	**Frequency**	**Total cost**
GP consultation	£32	2	£64.00
Nurse visit	£10.00	2	£20.00
ACR or PCR test*	£3.46	2	£6.92

		£90.92
Outpatient cost		
Total cost per year	£679,538.00	
Total cost	£106,000,000.00	
Proportion of CK stages 3-5	£0.50	
Cost per patient per year	**£77.99**	
Inpatient costs		
Average length of stay without CKD	6.78	
Additional average length of stay with CKD	Without CKD *1.35 =9.15	
Cost per inpatient visit	£225.00	
Cost per patient per year	**£2,059.43**	
Total annual cost	£2,228.34	(Primary care + outpatient cost + inpatient cost)
Total monthly cost (2009/2010)	£185.69	(Primary care + outpatient cost + inpatient cost)

**ACR= urine albumin to creatinine ratio; PCR= protein to creatinine ratio*

These costs were then inflated to May 2018, to provide an annual cost of £2,846 and a monthly cost of £237.20.

The impact of correcting this within the model results in an £1,994.97 increase in the ICER from -£14,650.83 to -£12,655.86. See Table 62 for a breakdown of costs and QALYs.

Table 62. Impact on cost-effectiveness of correction to the cost of CKD

	Original cost of CKD	**Corrected cost of CKD**	**Change**
	Costs (£)		
Patiromer	[redacted]	[redacted]	3,909.56
No Patiromer	[redacted]	[redacted]	3,704.62
Incremental	-1,505.02	-1,300.09	204.93
	QALYs		
Patiromer	[redacted]	[redacted]	0.000
No Patiromer	[redacted]	[redacted]	0.000
Incremental	0.103	0.103	0.000
	With PAS ICER (£/QALY)		
	-£14,650.83	-£12,655.86	£1,994.97

In the model, the monthly cost of CKD is applied for every month a patient is alive, therefore the differential overall survival of CKD patients is accounted for.

Values taken from Seaton et al (2014) and Thokla (2013) are no longer applied in the economic model. Although the calculations (and references to Seaton and Thokla) were not removed from the model, they do not inform the model outputs, and therefore the references are not provided in the reference pack.

The post-transplant average life expectancy of 5 years was a transcriptional error and was intended to be 3.5 years, sourced from the 19th Annual Report of the Renal Association (12), page 122. Accounting for this correction in the model results in a £367.39 reduction in the ICER from -£14,650.83 to -£15,018.22.

Table 63. Impact on cost-effectiveness results of correction to life expectancy following transplant.

	5 years (Original)	3.5 years (Corrected)	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	956.13
No Patiromer	[redacted]	[redacted]	993.87
Incremental	-1,505.02	-1,542.76	-37.74
	QALYs		
Patiromer	[redacted]	[redacted]	0.000
No Patiromer	[redacted]	[redacted]	0.000
Incremental	0.103	0.103	0.000
	With PAS ICER (£/QALY)		
	-£14,650.83	-£15,018.22	-£367.39

B27. Please provide more explicit table/text/figure referencing to the UK Renal Registry for the following data on ESRD: 19.2% on PD, 73.1% on HD and 7.7% receiving transplant.

This data can be found on page 28 of the 19th UK Renal Registry report in paragraph 4. Incident patients were used to reflect current clinical practice, however a sensitivity analysis using prevalent patients (19.6% on PD, 71.3% on HD and 9.1% transplant patients; UK Renal Registry Report, pg. 31, Fig 1.8), has been presented below. This results in a £221.57 increase in the ICER from -£14,650.83 to -£14,429.26.

Table 64. Impact on cost-effectiveness of using estimates from prevalent patients compared with incident patients.

	Incident patients	Prevalent patients	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	-741.10
No Patiromer	[redacted]	[redacted]	-770.35
Incremental	-1,505.02	-1,475.77	29.25
	QALYs		
Patiromer	[redacted]	[redacted]	0.011
No Patiromer	[redacted]	[redacted]	0.012
Incremental	0.103	0.102	0.000
	With PAS ICER (£/QALY)		
	-£14,650.83	-£14,429.26	£221.57

B28. In document B p116 table 39 upper and lower limits are not given for the parameter '% of non-responders to patiromer', however the 95% CI is 42% to 71% (document B p60). Please provide the sensitivity analysis for this parameter or if not please provide justification.

The point estimate in Document B p60 provides the proportion of patients who discontinued RAAS inhibitor therapy due to hyperkalaemia during the randomised withdrawal phase (Part B). The proportion of non-responders for which the sensitivity analysis is requested refers to the proportion of non-responders from Part A of OPAL-HK. This was calculated as the number of patients who entered Part B as a proportion of all patients entering Part A (1-(107/243) = 0.56). The calculated 95% confidence interval of the 0.56 value is 0.50–0.62. Using the lower and upper 95% confidence interval values results in an ICER of -£13,096 and -£16,121 respectively. See Table 65 and Table 66 for a breakdown of costs and QALYs.

Table 65. Cost-effectiveness results when using the lower confidence interval for the 'proportion of non-responders' from Part A input.

	Proportion of non-responders = 0.56	Proportion of non-responders = 0.50	Change
	Costs (£)		
Patiromer	[redacted]	[redacted]	-23.73
No Patiromer	[redacted]	[redacted]	0.00
Incremental	-1,505.02	-1,528.75	-23.73
	QALYs		

Patiromer	[redacted]	[redacted]	0.014
No Patiromer	[redacted]	[redacted]	0.000
Incremental	0.103	0.117	0.014
	With PAS ICER (£/QALY)		
	-£14,650.83	-£13,096.00	£1,554.83

Table 66. Cost-effectiveness results when using the higher confidence interval for the 'proportion of non-responders' from Part A input.

	Proportion of non-responders = 0.56	**Proportion of non-responders = 0.62**	**Change**
	Costs (£)		
Patiromer	[redacted]	[redacted]	74.76
No Patiromer	[redacted]	[redacted]	0.00
Incremental	-1,505.02	-1,430.26	74.76
	QALYs		
Patiromer	[redacted]	[redacted]	-0.014
No Patiromer	[redacted]	[redacted]	0.000
Incremental	0.103	0.089	-0.014
	With PAS ICER (£/QALY)		
	-£14,650.83	-£16,121.45	-£1,470.62

Section C: Textual clarifications and additional points

C1. Please confirm the value for the post-CV event proportionate utility of Document B Table 35. It does not seem aligned with the values given in table 34.

NB: Please see response to question C2 below prior to the below response to C1.

The proportionate utility value for post-CV event is an average of the utilities of post-MI (0.6720) and post-stroke (0.5250), weighted by the proportion of CKD patients experiencing an MI (0.6468) and stroke (0.3532) according to Kerr et al 2012 (13).

C2. PRIORITY: Please provide the arithmetic explaining how the health state utility values in Document B Table 35 have been calculated from specified and identified values within the relevant source papers.

Utility in the model is calculated based on the individuals' age and derived from a general population utility equation developed by Ara & Brazier. This equation was derived from the UK National Health Survey 2012 cited in a previous NICE submission appraisal by Jones-Hughes et al. as follows:

Utility = C-coeffage*age-coeffage2*age2 +coeffsex *male

The general population equation calculates the utility for a healthy person of 65 years of age as 0.8210. Thereafter utilities for CKD, model health states and cardiovascular and hyperkalaemia events are taken and the relative utility compared with the general population utility is calculated. Thereafter, this relative utility is applied to the declining general population utility (as the cohort ages) as model events are experienced. This ensures the utility of events is always linked to the utility of a healthy person of any age in the model.

For example, the baseline population utility at 65 years is 0.8210 and the utility of Stage 3 CKD is 0.8000. Therefore, the relative utility of CKD is calculated as:

Relative utility = (0.8000/0.8210) = 0.9745

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Patiromer for treating hyperkalaemia [ID877]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Prof Sunil Bhandari**
2. Name of organisation	**Representing "The Renal Association" and "Royal College of Physicians"**

3. Job title or position	**Consultant Nephrologist/Honorary Professor and Vice Chair of Education and Training Committee of The Renal Association**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Renal Association is the leading professional body for the UK Renal Community, dedicated to improving services and outcomes for patients and families through education, research and training for prevention and effective treatment of kidney disease. It is funded through the subscription of its members.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NONE**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, stop progression, improve mobility, cure the condition, or prevent progression or disability.)	Patiromer is indicated for the treatment of hyperkalaemia in adults. For renal services it would allow clinicians to maintain medications for patients with chronic kidney disease and hypertension and heart failure and thus prevent unnecessary admissions to hospital for acute hyperkalaemia. It would also potentially reduce the frequency of follow-up. This use may lead to improvements in quality of life for patients via a more relaxed diet (unknown). In addition Angiotensin converting enzyme inhibitors (ACE-I), a low cost therapy, is recommended by NICE

	for people with proteinurica chronic kidney disease, hypertension and an ACR of 30mg/mmol and diabetics with an ACR of 3mg/mmol or more.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	I would expect a reduction in measured serum potassium levels of the order of 1 mmol/L and this to be maintained throughout the duration of therapy. I would apply this for all treatment groups. The rate of reduction is less important in the management of chronic hyperkalaemia but it should occur within a week of therapy. In addition I would expect that if there was a future plan to manage acute hyperkalaemia – I would want data to confirm a 0.5 mmol/l fall in serum potassium within the first 2 hours of therapy. Again this should persist with therapy.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is a new field of therapy which is niche to certain medical fields including nephrology, diabetes, cardiology and medicine for the elderly. Therapies directed at augmenting gastrointestinal potassium excretion In the form of resonium has been in use for many years, it has been unreliable in the acute setting and generally poorly tolerated. Despite this there is an unmet need in this field of hyperkalaemia to assist in optimal patient care. A recent "real world" study of use of ACE-I and ARB, suggests an overall low rate (<2%) of hyperkalaemia (e.g., >5 mmol/L), but this is increasing with increased optimisation of these therapies and the aging population with chronic kidney disease.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Calcium Polystyrene Sulfonate – (Resonium) is the current treatment. This is ineffective and poorly tolerated. In addition there are significant complications such as constipation and major issue in chronic kidney disease. Finally in the majority of cases the treatment is to discontinue important medications such as those that block the Renin Aldosterone Angiotensin System (RAAS) such as Angiotensin converting

	enzyme inhibitors (ACEi) which have a wealth of data in proteinuric chronic kidney disease and diabetes mellitus. In addition reduction or discontinuation of medications known to increase the risk of hyperkalaemia. Finally dietary restriction of foods rich in potassium is used in renal services mainly.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are recognised guidelines for the treatment of acute hyperkalaemia – see The Renal Association web pages. This does not include Patiromer and is unlikely to in the near or medium term future. Currently there are no guidelines for the treatment of chronic hyperkalaemia except current best practice which includes reduction or discontinuation of those drugs which may exacerbate hyperkalaemia and introduction of potassium restricted diets. There are however recommendations about the level of potassium (5.0mmol/L) at which one should consider use of drugs such as ACE-I with caution and close monitoring.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	International guidelines are clear on the optimal therapy for those patients with chronic kidney disease (CKD), hypertension and heart failure with reduced ejection fraction (HF) and the benefits of blocking the RAAS. Therefore there is a well-defined universal pathway of care which is evidence based. NICE heart failure guidelines also recommend ACE-I as the mainstay therapy for heart failure in addition to beta-blockers, both of which may cause hyperkalaemia. The KDIGO guidelines endorse these views for CKD. However there is tittle well defined evidence on the optimal method of potassium control in these populations and is based on the recent trial data from a number of studies in this field. As this is a relatively new area there are few opinions and most of the current experience emanates from the USA where the drug has been in use for much longer. It is clear from these views that the ability to reduce the need to down titrate or discontinue RAAS inhibitors is of value in view of the associated worsening clinical outcomes in chronic kidney disease patients (at least in the early stages G1-4).
• What impact would the technology have on the current pathway of care?	Patiromer is indicated for the control of hyperkalaemia. This may enable optimisation of RAAS inhibitors in patients who develop elevated K^+, after the use of the normal potassium reducing measures such a diet restriction. In addition it will reduce unnecessary hospital admission with acute high potassium levels.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I would suggest that patiromer should be used selectively for those challenging patients who require numerous samples and repeat admissions with hyperkalaemia in the first instance with the aim to achieve long-term control of serum K^+; prevent recurrence of elevated K^+ and allow optimal dosing for RAAS inhibitors. This is a change in clinical practice from that in current practice.
• How does healthcare resource use differ between the technology and current care?	This is an additional therapy not previously available and adds to the armoury for the clinician in the effective management of a group of patients with relative high co-morbidity and mortality
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is my opinion that this technology should be initially restricted to secondary care in view of the monitoring required and treatment optimisation for maximum benefit. However in the longer term once there is a wealth of real world clinical experience I see no reason why it could not be extended to primary care. My one reservation for the latter is the current, evidence of the poor adherence to guidelines and detailed recommendations for the monitoring of patients on RAAS inhibitors in primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The main investment will be education of clinicians and prescribers of medications and implementation of a strategy of use in targeted patients who are likely to have the most benefit. Although it may lead to an increase in measures of potassium in the early stages of introduction, in the longer term it is likely to lead to a reduction in the frequency of tests, and monitoring.
11. Do you expect the technology to provide clinically meaningful benefits compared	Yes: - Real world data suggest that there is an odds ratio of discontinuation of RAAS medication in the order of 1.19, 1.66 and 2.69 for potassium levels of >5; >5.5;>6.0 respectively while the odds ratio of dose reductions were 1.76; 2.81 and 3.81 respectively. Therefore potential use of a potassium binder may reduce this effect and lead to positive outcomes for patients. There is no long term data to conclusively

with current care?	prove this outcome.
• Do you expect the technology to increase length of life more than current care?	This is unknown and no data currently exists. What is known is that patients with a higher that average potassium concentration have a reduced length of life from epidemiological data. Recent published retrospective observational trials in haemodialysis patients has showed that potassium levels 5.5–6.0 mmol/L were associated with higher risk for subsequent hospitalization, emergency department visits, and mortality. This is also seen in non-dialysis patients from observational data.
• Do you expect the technology to increase health-related quality of life more than current care?	The potential for this drug to impact HRQOL are significant but may not be easily measureable. The ability to relax diet from a patient perspective is a potential gain, leading to a healthier diet and less malnutrition in patients with CKD, dialysis and diabetes. This has an impact in the home in relation to the simply ability of cooking meals for the whole family. In addition the ability to maintain a maximal dose regime of cardiac drugs and use of spironolactone will be of great benefit to selected patients and their outcomes.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The use of patiromer may be most appropriate in patients with advancing CKD (stages 3b or worse) and comorbidities such as heart failure/severe hypertension/diabetes, who have had repeated hospital re-admissions due to episodes of hyperkalaemia or exacerbation of their blood pressure or heart failure HF from sub optimal dosing of medications due to high potassium levels. As with all studies the data on subgroups analysis is difficult to interpret with any reliability and should be viewed with caution.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Implementation, including the resource availability to support implementation should not be an issue and I would expect that clinical practice would not be impacted, indeed it may possibly allow reduced monitoring, and assuming there is no significant increase in adverse effects, a better outcome. There is the possible risk of reduced absorption of other medications due to binding so it is advisable to allow 3 hours between taking this drug and others. This is one important aspect of education and training. Drugs known to be affected include ciprofloxacin; thyroxine and metformin. Also some drug peak concentrations are affected such as amlodipine, furosemide; clopidogrel and metoprolol. Currently KDIGO guidelines and NICE recommend monitoring of patients between one - two weeks after initiation of ACEI therapy and at each dose increment. This will not change as the impact on renal function needs to be assessed.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There will need to be a clear guidance on the measurement and duration of medication used to ensure that effectiveness is obtained. I expect a reduction of at least 0.5 mmol/L of potassium within a two week period, should be used as a bench mark. Additional testing will be needed within the first 2 weeks and after any dose escalation but based on the literature the potassium levels are stable. In addition testing of magnesium levels may be necessary within the first month of therapy as these may fall.
15. Do you consider that the use of the technology will	Patiromer may enable optimal RAAS inhibitor therapy in patients with HF and/or CKD who would otherwise be at risk of elevated K+. This should lead to an increase in cost from more effective use of these

result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	therapies. Currently, patients with HF and/or CKD receive RAAS inhibitor therapy as the mainstay of their treatment; however, RAAS inhibitor therapy may be suboptimal owing to the risk of elevated K+, leading to compromised outcomes for patients. NICE recommends discontinuation of RAAS inhibitors if the serum potassium is >6mmol/l and this additional treatment could reduce this need and allow maintenance of therapy.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is a new area on management of patients with electrolyte disorders mainly as a consequence of medications and in part diet. This addition may transform our ability to effectively manage patients with chronic hyperkalaemia. Normalising the diet of patients and maximising treatments (ACE-I and ARB) may have long term benefits but these are yet to be confirmed in randomised controlled trials.
• Is the technology a 'step-change' in the management of the condition?	Calcium Polystyrene Sulfonate is licensed for the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis. There is no licensed drug therapy currently indicated for the treatment of elevated K+ in adult patients, including patients treated with RAAS inhibitor therapy who develop elevated K+. However I would expect over time that Resonium, which is used occasionally, becomes obsolete as this technology is added and replaces it.

• Does the use of the technology address any particular unmet need of the patient population?	Yes: an unmet need in several groups of patients including those on medications which tend to increase potassium (beta blockers; ACE-I; ARB; mineralocorticoid antagonists) but are essential to reduce risk of cardiovascular; cerebrovascular events and renal progression: 1. Elderly 2. Patients with Acute Kidney Injury (AKI) 3. Dialysis patients 4. Kidney transplants and those with CKD patients 5. Patients post myocardial infarction
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is limited data on this but overall there appears to be great tolerability. The main symptoms or adverse effects which have been described include: Gastrointestinal side effects - flatulence; abdominal pain; diarrhoea and constipation. In addition headache occurs
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Current UK practice is still in evolution and the introduction and use of this new medication is low and not universal in the UK. Sometime will be required before this data is available for analysis and interpretation. The international data would potentially translate to a UK population who have similar co-morbidities.
• If not, how could the results be extrapolated to the UK setting?	The data are encouraging on use in the USA patient population and elsewhere and equally applicable to a UK population.
• What, in your view, are	The outcome measures which are important to examine should include, hard end points and qualitative

the most important outcomes, and were they measured in the trials?	measures: These would consist of: - Potassium levels which have been measured in trials - Effect on ability to use RAAS inhibitors which appear in real world data - Adverse events which have been measured in trials. Other measures are important but have not been studied to in detail in trials: - Hospitalisations - Survival - Health related quality of life In addition I would record episodes of moderate hyperkalaemia (6.0-6.4) as these levels precipitate a visit to the emergency department for a further blood test and possible intervention and reduction of these would have a significant health gain for the patient and economic gain for the NHS. Some data on the ability to relax dietary restrictions and thus allow consumption of “healthier foods may be useful but I am not sure easily measurable (it might be captured in the health related quality of life assessment). I would record cardiovascular death separately
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcome measures are open to extreme bias and should be avoided. They are of interest only scientifically in hypothesis generation.
• Are there any adverse effects that were not	None that I am aware of when speaking to colleagues who use the drug in the USA as there is limited use in the UK currently but more extensive use in the USA.

apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None again and on speaking with colleagues from other countries.
20. How do data on real-world experience compare with the trial data?	Similar data on real world experience with no new findings. The main findings are the large percentage of patients discontinuing or reducing the dose of important therapies to reduced comorbidity risk.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Need to ensure access for elderly patients
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Ability of optimise use of RAAS inhibitors in patients with chronic kidney disease; hypertension; diabetes and heart failure • Reduction of potential episodes of acute hyperkalaemia requiring hospitalisations • Relative safety but need to measure magnesium levels • Sustained effect of the drug on potassium concentrations •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Patiromer for treating hyperkalaemia [ID877]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Chair of Clinical Biochemistry Specialty Advisory Committee (RCPath)** **Consultant Chemical Pathologist**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The College is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates and trainees, supported by the staff who are based at the College's London offices. As such it is funded by subscription from its members. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 19 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology. (adapted from RCPath website https://www.rcpath.org/about-the-college.html)
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment is to reduce potassium levels in patients with hyperkalaemia. This is often due to chronic kidney disease (CKD) and the hyperkalaemia is exacerbated by drugs such as ACEi. ACEi, ARBs, and spironolactone have been shown to improve cardiovascular outcomes and ideally these would be continued in patients with CKD, as adverse cardiovascular events are the major cause of mortality in this patient group. Reducing potassium levels with this treatment may lead continued use of ACEi, ARBs and spironolactone could prolong survival in these patients.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant response would be reduced hospitalisation for hyperkalaemia treatment, reduced cardiovascular events and increased time to renal replacement therapy.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	The condition is currently treated by adjusting doses of potassium raising drugs, and administering calcium resonium and treating acute hyperkalaemia with insulin and glucose infusions, inhaled salbutamol and IV calcium gluconate.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are Clinical Practice Guidelines for Management of Acute Hyperkalaemia published in 2014 by the UK Renal Association. Patiromer is recommended for use in chronic but not acute hyperkalaemia.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not clearly defined and often in involves a number of the steps outlined in the first part of question 9.
• What impact would the technology have on the current pathway of care?	The technology might reduce the frequency of admission for treatment of acute hyperkalaemia and enable doses of potassium raising drugs to be maintained at optimum levels.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	no

• How does healthcare resource use differ between the technology and current care?	There is no equivalent medication (calcium resonium is poorly tolerated and so infrequently used in clinical practice).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be used in primary care, outpatient secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is needed. Blood tests would be checked frequently in any case in the patient group in whom this would be used.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to provide meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to increase length of life.

• Do you expect the technology to increase health-related quality of life more than current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to increase health-related quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with CKD.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It will add an extra step to the treatment pathway for patients with CKD and recurrent or chronic hyperkalaemia but should not be more difficult than current care.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules which may be required around this technology would be assessing if it reduces potassium levels in individuals and stopping treatment if it is ineffective. I do not think this will result in additional testing as the patients underlying condition requires frequent blood tests.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	It has potential to be innovative

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Prevention of hyperkalaemia Reduction in adverse cardiovascular outcomes including death (if able to remain on ACEi and other medication)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be	

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This is a potentially useful treatment which would enable drugs known to improve cardiovascular outcomes to be continued longer or at a more effective dose.
- It could potentially reduce hospitalisation for management of acute hyperkalaemia.
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

xProfessional organisation submission

Patiromer for treating hyperkalaemia [ID877]

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	UK Renal Pharmacy Group

3. Job title or position	Renal Pharmacist
4. Are you (please tick all that apply):	☐ * an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK Renal Pharmacy Group (RPG) aims to promote excellence in the provision of pharmaceutical services to renal patients and associated healthcare professionals. It is a non-profit making organisation.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To control the level of potassium within the body, preventing hyperkalaemia, to enable the up titration of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) to treat diabetes or proteinuria in renal diseases or heart failure, and also spironolactone in heart failure. Often hyperkalaemia prevents these medications from being used in doses high enough to enable prevention of disease progression and control of symptoms. It may also be used to reduce hyperkalaemia in haemodialysis patients over the weekend in patients where this is problematic.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	To keep the potassium levels within the normal range.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Renin-angiotensin-aldosterone system (RAAS) inhibitor therapy spans several drug classes, including angiotensin-converting-enzyme inhibitors (ACE-Is), such as enalapril; angiotensin II receptor blockers (ARBs), such as valsartan; beta blockers (BBs), such as metoprolol; direct renin inhibitors, such as aliskiren; and mineralocorticoid receptor antagonists (MRAs), such as spironolactone; these are taken to treat, among other conditions, heart failure (HF) diabetes and chronic kidney disease (CKD). Patients with cardiorenal syndrome will have multiple comorbidities, such as CKD, HF, hypertension and diabetes. RAAS inhibitors have been proven in landmark clinical studies to reduce mortality and hospitalisation in patients with cardiorenal syndrome and may slow disease progression in the case of CKD. However, RAAS inhibitor

	therapy (especially MRAs) increases the risk of elevated K+. In clinical practice, this can lead to inadequate RAAS inhibitor dosing in patients with HF or CKD. Patiromer is indicated for the control of hyperkalaemia. This may enable optimisation of RAAS inhibitors in patients who develop elevated K+, with the threshold set at serum K+ > 5 mmol/L or > 5.5 mmol/L depending on the guideline, through the following means: □ Long-term control of serum K+ □ Maintenance of K+ within the normokalaemic range □ Prevention of recurrence of elevated K+ □ Optimal addition of spironolactone as combination therapy in patients with HF □ Prevention of RAAS inhibitor discontinuation □ Facilitation of single or combination RAAS inhibitor treatment in multimorbid patients □ Facilitation of RAAS inhibitor treatment at clinically optimised doses. Patients receiving RAAS inhibitor therapy can be stratified into two groups: patients primarily with HF (specifically New York Heart Association [NHYA] class II–IV) and comorbid CKD (stage 3–4), and patients with CKD (stage 3–4) and comorbidities. Patients are taken off their ACEi or ARB if hyperkalaemia occurs and therefore do not gain the benefit from these medications from a heart failure or proteinuria point of view.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National Institute for Health and Care Excellence. Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care [CG182]. July 2014. https://www.nice.org.uk/guidance/CG182 KDIGO. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Dec 2012. http://kdigo.org/guidelines/blood-pressure-in-ckd-2/. National Institute for Health and Care Excellence. Chronic heart failure in adults: management [CG108]. August 2010. https://www.nice.org.uk/guidance/CG108
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes it is well defined

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would enable patients to remain on RAAS therapy, and prevents admissions for hyperkalaemia.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes if funding is identified.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary and secondary care so should be funded for use within secondary and primary care with or without shared care guidelines
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Funding for the drug

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as it will enable patients to remain on RAAS therapy and improve control of heart failure and proteinuria
• Do you expect the technology to increase length of life more than current care?	Possibly if heart failure is treated more effectively. Time to renal replacement therapy may be extended in diabetic patients and those with proteinuria and CKD.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes for the reasons above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Could be beneficial in dialysis patients to reduce hyperkalaemia and hospitalisation over the weekend i.e. the long dialysis break.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Patients will need their potassium levels monitored as clinically indicated. Magnesium levels should also be checked one month after starting.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start when hyperkalaemia occurs.
15. Do you consider that the use of the technology will result in any substantial health-	I have not calculated

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	At the moment it is the only licensed potassium binder although another is due to come to market soon. There is no other medication licensed for the prevention of hyperkalaemia. Calcium polystyrene sulfate is licensed for the treatment of hyperkalaemia but not the prevention.
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Prevention of hyperkalaemia

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The majority of the adverse reactions (ARs) reported from trials were gastrointestinal disorders, with the most frequently reported ARs being constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%). Gastrointestinal disorder reactions were generally mild to moderate in nature, did not appear to be dose related, generally resolved spontaneously or with treatment, and none were reported as serious. Hypomagnesaemia was mild to moderate, with no patient developing a serum magnesium level <1 mg/dL (0.4 mmol/L)
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	As yet this is not being used in many centres
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	That patients were able to attain maximal doses of RAAS therapy to aim to improve heart failure and proteinuria.
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No

21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	This should be available via all CCGs and NHS trusts.
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- A potassium binder will have an important place in therapy to enable dose titration of RAAS therapy with the minimisation of hyperkalaemia
- A potassium binder will have an important place in a few patients who suffer life threatening hyperkalaemia on their long gap between dialysis over the weekend.
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient expert statement

Patiromer for treating hyperkalaemia [ID877]

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To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Fiona Loud**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☒ other (please specify): Someone who has had the condition
3. Name of your nominating organisation	Kidney Care UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: through working with other patients over the past 15 years, through our Facebook support group and from being on dialysis with other patients for 5 years
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hyperkalaemia can come in bouts, if dialysis has not been enough to reduce potassium levels, especially in between dialysis sessions. This can be particularly bad for people on 3 days a week dialysis in hospitals/satellite units during the 2 day gap at weekends when eating or drinking something with a high potassium level which the body is not able to process. In my personal experience it makes a person feel sick, shake, have a racing heart and feel disoriented. Living with someone who develops hyperkalaemia is difficult for partners/carers especially if they are struggling to work out what food to buy and cook.
Current treatment of the condition in the NHS	
9. What do patients or carers	Patients say that current treatments are extremely unpalatable. Sometimes they struggle to get enough dialysis, or to eat. For people not on dialysis they may not recognise the symptoms and be in great need

think of current treatments and care available on the NHS?	of dietary advice, although amending diet is not always effective. A low potassium diet is very demanding, especially as it restricts common items like bananas, coffee and chocolate and if alongside other restrictions on dairy food if phosphate levels are also too high and accompanied by the very common liquid restriction of 500ml/day.
10. Is there an unmet need for patients with this condition?	There is an unmet need for effective strategies to reduce or ideally avoid hyperkalaemia.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients are looking forward to new developments in this area.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Not being able to benefit from it if it is restricted in some parts of the country, or only made available or effective for pre-dialysis patients.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Those on dialysis, with CKD 5 but not on dialysis, such as those on conservative care, people with failing transplants would all be likely to benefit but special care should be taken with the latter 2 groups. For those on conservative care they may be looked after in the community and there is (unsurprisingly) often a reluctance to prescribe specialist drugs by non-specialists, so patients can lose out.

please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Please consider how the medication could be taken and those who would need to receive it in liquid form rather than by tablets.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • Hyperkalaemia is dangerous and distressing	

- Current treatments are not adequate
- Dietary intervention is not always effective
- Dietary restrictions are very difficult
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Patient expert statement

Patiromer for treating hyperkalaemia [ID877]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nick Hartshorne-Evans**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	The Pumping Marvellous Foundation
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: **I am the CEO of the UK's Heart Failure Charity**
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •

Thank you for your time.

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Patiromer for treating hyperkalaemia [ID877]

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Contributions of authors: Lena Alkhudairy (Senior Researcher) co-ordinated and conducted the critique of clinical effectiveness evidence. Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence. Martin Connock (Senior Researcher) supported the critique of clinical and cost effectiveness evidence. Rachel Court (Information Specialist) conducted the critique of the company searches and conducted ERG searches. James Mason (Professor of Health Economics) provided oversight and coordination.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF AÌBBREVIATIONS

AC	Active control
ACE	Angiotensin-converting enzyme
ACR	Albumin:creatinine ratio
AE	Adverse event
AIC	Akaike information criterion
ARB	Angiotensin II receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
AUC	Area under the curve
BIC	Bayesian information criterion
CABG	Coronary artery bypass graft
CCB	Calcium Channel Blocker
CEAC	Cost-effectiveness acceptability curve
CH	Cumulative hazard
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
CRIB	Chronic Renal Impairment in Birmingham
CS	Company submission
CSR	Complete study report
CV	Cardiovascular
CVD	Cardiovascular disease
df	Degrees of freedom
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESA	Erythropoietin /Erythropoiesis-stimulating agent
ERG	Evidence Review Group
ESC	European Society of Cardiology
ESRD	End stage renal disease
EQ-5D	EuroQol Five Dimensions
FDA	Food and Drug Administration
GP	General practitioner
HR	Hazard ratio
HK	Hyperkalaemia
HTA	Health Technology Assessment
IC	Information Criteria

ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRR	Incidence risk ratio
ITT	Intention to treat
IWRS	Interactive Web Response System
K^+	Potassium
KF	Kidney Failure
KM	Kaplan-Meier
LCI	Lower confidence interval
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
obs	Observations
OR	Odds ratio
OP	Outpatient
PATR	Patiromer
PAS	Patient access scheme
PBO	Placebo
PCI	Percutaneous Coronary Intervention
PD	Patiromer discontinuation
PH	Proportional Hazard
Phase A	The (uncontrolled) treatment phase of the OPAL-HK trial
Phase B	The (randomised) withdrawal phase of the OPAL-HK trial
PLAC	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
prob	Probability
prog	Progression
PSA	Probabilistic Sensitivity Analysis
PSP-CKD	Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease
QALY	Quality Adjusted Life Year
QoL	Quality of life
RAAS	Renin–angiotensin–aldosterone system
RAASi	RAAS inhibitor/inhibition
RCT	Randomised controlled trial

RD	RAASi discontinuation
refs	References
RRs	Relative Risks
SD	Standard deviation
s.e.	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SMR	Standardised mortality ratio
SPS	Sodium polystyrene sulphate
SR	Systematic Review
STA	Single technology assessment
TP	Transition probability
T2DM	Type 2 diabetes mellitus
UCI	Upper confidence interval
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
US	United States

1 SUMMARY

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

The company submission (CS) decision problem matches the intervention and outcomes described in the final NICE scope, as seen in Box 1.

Box 1: NICE Final Scope

Population	Adults with hyperkalaemia
Intervention	Patiromer
Comparator	Standard care. This includes a low-potassium diet with or without agents that reduce levels of potassium in the body
Outcomes	• serum potassium level • use of renin–angiotensin–aldosterone system inhibitor therapy • mortality • time to normalisation • adverse effects of treatment • health-related quality of life.

The CS decision problem differs from the NICE scope on the population. The scope addresses people with hyperkalaemia (HK), consistent with the licence. The CS is restricted to people with hyperkalaemia and stage 3-4 chronic kidney disease (which may include other co-morbidities such as heart failure and diabetes) treated with RAAS inhibitors. The CS provides no evidence of the effectiveness or cost-effectiveness of Patiromer to the broader hyperkalaemic population.

The comparator in the decision problem is 'standard care', with RAAS inhibition discontinued or reduced in patients where hyperkalaemia is uncontrolled. In accordance with guidelines, standard care preceding use of Patiromer might include introducing support for a low-potassium diet and optimised hypertension management (as various drugs are potassium sparing or depleting). However, the company's position is that these elements are part of the routine context of care and thus neither comparators nor pre-treatments. While the company assert limited evidence for efficacy and adherence to a low potassium diet, this is a first step in national guidance for managing chronic hyperkalaemia[1]. Recent evidence highlights the benefits of dietary modification on renal parameters in patients with CKD [2, 3].

1.2 *Summary of clinical effectiveness evidence submitted by the company*

The clinical effectiveness evidence in the CS comes from a single randomized controlled trial (RCT), the OPAL-HK trial of Patiromer in people with hyperkalaemia, stage 3-4 CKD and receiving a RAAS inhibitor therapy. The trial was a phase III, single-blind, multi-national study that included 10 countries from Europe, Eastern Europe and the US. The OPAL-HK [4] trial provides evidence that Patiromer reduces serum potassium (K) and RAASi discontinuation in patients with CKD. 243 patients entered the two-phase trial:

- A single arm treatment phase (A) for 4 weeks: initial oral intake of 4.2g of Patiromer (twice daily) for 92 patients with mild hyperkalaemia (serum K^+ 5.1-<5.5 mmol/l) or 8.4g initially of Patiromer (twice daily) for 151 patients with moderate to severe hyperkalaemia (K^+ 5.5-<6.5 mmol/l).
- A randomized 8-week placebo-controlled withdrawal phase (B): patients who completed phase A remaining on RAAS inhibition, with a baseline serum $K^+ \geq 5.5$ mmol/l in phase A, and responding to Patiromer (K^+ 3.8 to <5.1 mmol per litre)) were randomly assigned either to intervention (same dose they were receiving at the end of phase A) or to placebo.

Pre-specified primary outcome (ITT population):

- Phase A: serum potassium levels (mean± SE) from baseline to week 4 was −1.01 ± 0.03 mmol/l (95% confidence interval [CI]: −1.07 to −0.95; p<0.001).
- Phase B: serum potassium levels (median change) from the start of phase B to week 8 was 0.00 mmol/l (95% CI: −0.30 to 0.30) in the Patiromer group and 0.72 mmol/l (95% CI: 0.22 to 1.22) in the placbo group. The between-group difference of 0.72 mmol/l was statistically significant ($p < 0.001$).

Secondary outcomes (ITT population), Phase B:

- The proportion of patients at 8 weeks having serum $K^+ \geq 5.5$ mmol/l was 60% (95% CI: 47% to 74%) in the placebo group and 15% (95% CI: 6% to 24% in the Patiromer group ($p < 0.001$ for the between group difference). The proportion of patients with serum $K^+ \geq 5.1$ mmol/l was 91% (95% CI: 83% to 99%) in the placebo group and 43% (95% CI: 30% to 56%) in the Patiromer group ($p < 0.001$ for the between group difference).
- Time to first occurrence of hyperkalaemia for serum $K^+ \geq 5.5$ mmol/l and ≥ 5.1 mmol/l over the eight weeks. At 8 weeks, HK recurrence (≥5.5 mmol/l) occurred in 60% of the placebo patients and 15% of Patiromer patients.

- Continuation of RAAS inhibitor therapy was higher in the Patiromer group (94%) compared to the placebo group (44%) at the end of phase B ($p < 0.001$).
- RAASi discontinuation occurred in 56% of placebo and 6% of Patiromer patients.

The company submission also draws upon the AMETHYST-DN trial. This was a one-year uncontrolled, dose-ranging study of Patiromer including 306 patients with diabetic kidney disease and hyperkalaemia who were receiving RAAS inhibitors. AMETHYST-DN was not judged by the company relevant to inform effectiveness but is used to provide longer-term safety data and model Patiromer discontinuation in the company model.

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

The ERG has the following concerns about OPAL-HK, the sole source of randomised comparative evidence for the value of Patiromer:

- There was no initial sequential testing to establish CKD diagnosis in accordance with guidelines (about [redacted]% of screened eligible patients had stage 2 disease [eGFR 60+ ml/min/ per minute/1.73m^2] at baseline, contravening trial inclusion criteria).
- There was no formal test of a potassium reducing diet before recruitment, as recommended in guidelines and the ERG's clinical experts.
- There was no formal review of hypertension management before recruitment (e.g. optimising the use of diuretics as potassium-depleting drugs). Also [redacted]% of patients were on dual blockade with ACEi and ARB, now contraindicated.
- The specified OPAL-HK population was limited to patients with stage 3-4 CKD on RAAS inhibitor therapy with hyperkalaemia: the value in the broader hyperkalaemia population is not addressed.
- Longer term effectiveness and safety outcomes are uncertain because of the short duration of the trial. The CS includes evidence from AMETHYST-DN to augment safety evidence: an uncontrolled dose-ranging study of Patiromer with 1-year follow-up in patients with diabetes and mild to moderate hyperkalaemia.
- OPAL-HK includes 100% white patients in the withdrawal phase, thus the trial provides no evidence of efficacy or safety for other ethnic groups. AMETHYST-DN similarly recruited 100% white patients.
- OPAL-HK was conducted in the US, EU and Eastern Europe (not the UK) with the majority of patients from Eastern Europe (65%). It is unclear if these populations, or the care they receive, are representative of the UK.

- During the withdrawal phase the management protocol for dose reduction or discontinuation of RAAS inhibitor therapy was more aggressive in the placebo than Patiromer arm, which may have contributed to the difference in RAAS inhibitor discontinuation rates.
- Patients responding in the treatment phase and included in the withdrawal phase had initial serum K^+ 5.5 to <6.5 mmol/l and achieved the target range 3.8 to <5.1 mmol/l while receiving Patiromer and RAAS inhibitors over 4 weeks. Thus, no randomised evidence is offered for the patients included in the treatment phase with mild hyperkalaemia at baseline (5.1 to <5.5 mmol/l) or non-responders. These two groups constitute 56% of recruitment. The value of Patiromer in mild hyperkalaemia is not established by the CS (the company model includes them as non-responders).

With respect to the first three concerns, effective management of patients in accordance with guidelines might have altered the population eligible for and recruited to OPAL-HK. It is unclear how a more difficult-to-treat population would have responded to Patiromer.

1.4 *Summary of cost effectiveness submitted evidence by the company*

The company developed a Markov model with a monthly cycle. The direct trial treatment effects in the model include the number of hyperkalaemia events by arm and RAASi discontinuations by arm. Hyperkalaemia events have an immediate impact upon cost and quality of life. RAASi discontinuation is assumed to cause an increased risk end of stage renal disease (ESRD), cardio-vascular events and death (from CVD, ESRD and other causes). The model assumes no replacement antihypertensive is given for discontinued RAASi treatment.

The model takes as its starting point the end of the OPAL-HK trial. Patients in the Patiromer arm are first partitioned according to the treatment phase into those eligible to enter the withdrawal phase (44%) or are assumed to discontinue Patiromer (56%). Patiromer patients are then further partitioned to remain on RAASi (95%) or discontinue (5%) reflecting the withdrawal phase. For those receiving placebo, patients are partitioned as those remaining on RAASi (48%) or have discontinued (52%) at the end of the withdrawal phase. This latter partition applies to both those in the placebo arm, and those in the Patiromer arm that discontinue Patiromer (56%). Thus 69% of Patiromer and 48% of placebo patients start the model on RAAS inhibition.

Subsequently a Patiromer discontinuation curve is applied those on Patiromer, estimated from AMETHYST-DN rather than OPAL-HK due the longer follow-up of AMETHYST-DN.

The model then applies:

- A placebo hyperkalaemia event curve (estimated from the 8-week withdrawal phase of OPAL-HK) to those modelled as not having received Patiromer or as having discontinued Patiromer.
- A Patiromer hyperkalaemia event curve (estimated from the 8-week withdrawal phase of OPAL-HK) to those modelled as remaining on Patiromer.
- A placebo RAASi discontinuation curve (estimated from UK CPRD data).
- A Patiromer hazard ratio of RAASi discontinuation of [redacted] (estimated from the 8-week withdrawal phase of OPAL-HK).

These features determine the proportions of patients in each cycle on Patiromer having hyperkalaemia events and remaining on RAASi. The proportion remaining on RAASi in the Patiromer arm is modelled as being considerably superior to placebo.

The baseline risks for no RAASi treatment of ESRD, CV events and death (from CVD, ESRD and other causes) are calculated from sources in the literature. The risks of these events for placebo, (i.e. no RAASi treatment and no replacement), are applied to those who have discontinued RAASi. The risks for those who remain on RAASi are calculated by applying NMA relative risks of a systematic review of the effects of RAASi among CKD patients.

A baseline quality of life value for CKD is taken from the literature, and reduced over time in proportion to usual UK age-related norms. Events such as developing ESRD have a proportionate effect upon the CKD quality of life. The proportion is calculated as the quality of life value for the event taken from the literature relative to the baseline UK population norm.

Patiromer is available as a 30-day pack costing £300, providing an annual cost of £3,652 per patient. A simple PAS discount of [redacted] applies, which reduces the pack cost to [redacted], or an annual cost of [redacted] per patient. In the model, in addition to the PAS the company incorrectly applies a further 56% discount to the Patiromer costs, the 56% being the Patiromer non-responder percentage (see section 5.2.11). This effectively reduces the annual cost of Patiromer from [redacted] to [redacted] per patient. Ongoing CKD management and the events are also associated with costs, the latter being taken from the literature.

The company deterministic base case estimates a net saving of £1,505 and a net gain of 0.103 QALYs, resulting in Patiromer being estimated to dominate placebo. Sensitivity analyses provided by the company find these estimates show some sensitivity to:

- The RAASi (vs. placebo) relative risk of ESRD

- The RAASi (vs. placebo) relative risk of all-cause mortality
- The RAASi (vs. placebo) relative risk ESRD to death
- The costs of ESRD
- The increased mortality risk for CKD stage 4 patients relative to CKD stage 3 patients.

All analyses still estimate that Patiromer dominates placebo.

Despite the probabilistic model also estimating that Patiromer dominates placebo, the CEAC is surprising flat with only a 53% likelihood of Patiromer being cost saving and a 61% likelihood of patients benefitting from Patiromer.

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

In addition to applying a further 56% discount to the Patiromer costs the company model applies daily probabilities of hyperkalaemia in the context of a monthly cycle length. Correcting these two errors revises the net gains to 0.100 QALYs the net savings to £572, but dominance of Patiromer still results.

The company bases its Patiromer response percentage on those going forward to the OPAL-HK withdrawal phase from the treatment phase as a proportion of those recruited the trial. However, the withdrawal phase only allowed those who were moderately hyperkalaemic at recruitment to be randomised. Alternatively, Patiromer response could be based on moderately hyperkalaemic patients recruited to the trial, increasing the response percentage. However, this increased response could be further conditioned by the revised 18% withdrawal phase discontinuation percentage. Together these have a balancing affect upon net QALYs and net costs, and the ICER remains much the same.

The key assumption that Committee will need to address is whether RAASi discontinuation rates for current UK practice are best reflected in the UK CRPD data submitted by the company or are best reflected by those remaining on RAASi in the placebo arm of the OPAL-HK trial. There is the possibility of the latter being artificially protocol driven. The CS model base case placebo RAASi discontinuation curve bears little relation to the UK CRPD Kaplan Meier data or to the company parameterised Weibull placebo RAASi discontinuation curve.

It is also possible that the difference in RAASi discontinuation between the arms OPAL-HK may have been driven in part by the trial protocol. If so, this would affect the reliability of any Patiromer hazard ratio of RAASi discontinuation estimated from OPAL-HK. The Kaplan Meier RAASi discontinuation data supplied at clarification coupled with values in the

submission may also suggest that the company has assumed informative censoring in the placebo arm but non-informative censoring in the Patiromer arm. If so, the company estimate of the Patiromer hazard ratio of RAASi discontinuation is biased.

Those on placebo have a very high initial probability of hyperkalaemia but this then drops away. Those discontinuing Patiromer have the contemporaneous placebo probability of hyperkalaemia applied. As a consequence, they never experience the initial high placebo probability of hyperkalaemia. Whether this is reasonable or whether Patiromer patients should be assumed to experience the start of the placebo hyperkalaemia curve when discontinuing Patiromer is an open question. If they should, the model structure is biased in favour of Patiromer in this regard.

The company assumes that those discontinuing RAASi would not receive another active treatment for hypertension. The ERG disagrees with this (97% of patients in OPAL-HK were being managed for hypertension) and thinks that patients would trial an alternative such as a calcium channel blocker. As a consequence, the RAASi relative risks of events should be based upon an active comparator. The ERG also does not find the RAASi relative risk of all-cause mortality credible as a measure of 'other mortality' in the model, and is further concerned that to apply this within the model will double count the RAASi effects of avoiding ESRD and cardiovascular events. As a consequence, the ERG sets this relative risk to unity.

The company estimates of baseline risks may be biased. This applies particularly to the most important risk taken from the literature, that of developing ESRD. The company includes CKD stage 5 patients, which heavily skews the estimate. In the opinion of the ERG it is more appropriate to only include CKD stage 3 and CKD stage 4 patients in the estimate.

The company estimation of baseline risks of events among those with hyperkalaemia incorrectly treats relative risks as risks. The ERG applies these relative risks to the baseline risks for CKD patients without hyperkalaemia.

For its revised base case the ERG prefers to calculate the baseline risks of events as those underlying the relative risks of the NMA [5] of the effects of RAASi.

There is some misalignment between the baseline risks of cardiovascular events and the costs and quality of life values applied to these events. Costs and quality of life values are based upon stroke and MI throughout, so the ERG have revised baseline risks taken from the literature to be similarly restricted to stroke and MI.

Hyperkalaemia costs have been overestimated. The company estimates a probability of hyperkalaemia resulting in hospitalisation from a study of the relative risk of hospitalisation

in the six months before and six months after hyperkalaemia. It then simply doubles this probability. The ERG views the doubling of the probability as invalid. But in any case, the company does not apply this and assumes that all hyperkalaemia results in hospitalisation. The ERG corrects this, and based upon expert opinion assumes that those not hospitalised require two outpatient clinic appointments in addition to their routine CKD monitoring.

The company agreed at clarification that the quality of life values for cardio-vascular events were inappropriate and should be revised.

The selection of the quality of life values for ESRD may be biased, being lower than the UKPDS which have been used in many previous NICE assessments. The values selected are also considerably worse than those of a systematic review identified but not used by the company for ESRD, despite the company using the review for the quality of life for hyperkalaemia.

Given the high proportion of diabetics in OPAL-HK there may be an argument for using UKPDS costs. A sensitivity analysis that applies these has relatively limited effect.

It does not seem reasonable to assume that treatment effects upon RAASi discontinuation and upon hyperkalaemia estimated from an 8-week trial will last a life time. In line with NICE guidelines, scenario analyses which wane the duration of effect have been applied.

The direct drug costs of Patiromer do not allow for Patiromer use during Phase B of OPAL-HK. They are also based upon half cycle corrected patient numbers rather than start of cycle patient numbers, so underestimate wastage: this is corrected by the ERG. The CS model makes no allowance for prescribing costs from a hospital pharmacy, for which the ERG has made an adjustment.

Adverse events are not considered.

There are concerns around the probabilistic modelling, although time constraints have limited the ERG exploration of these concerns. The CEACs are extremely flat and do not vary significantly from a 50% likelihood of Patiromer being cost effective at any threshold, suggesting an unusually high degree of model uncertainty.

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

1.6.1 Strengths

In the opinion of the ERG there are relatively few strengths to the economics of the company submission. The additional 56% discount to the cost of Patiromer undermines confidence that the submission presents an accurate estimate of cost effectiveness.

1.6.2 Weaknesses and areas of uncertainty

The main weaknesses and areas of uncertainty are reviewed in section 1.5 above. In summary there appear to be a number of biases within the company submission. Additionally, the CS fails to explore some basic scenarios, such as OPAL-HK estimates of Patiromer discontinuation and waning the treatment effect upon hyperkalaemia and RAASi discontinuation, the latter being required by NICE guidelines.

The company presents CPRD data for patients with CKD in UK primary care to estimate RAASi discontinuation rates due to hyperkalaemia. These data show that the OPAL-HK population differ significantly from the CPRD population being older and more co-morbid as well as far lower RAASi discontinuation rates. These differences may limit the representativeness of the OPAL-HK trial findings.

1.7 *Summary of exploratory and sensitivity analyses undertaken by the ERG*

Firstly, the ERG provides analyses that retain the main modelling assumption of the company: that the proportion on RAASi in the placebo arm at the end of the OPAL-HK withdrawal phase is a reasonable estimate for current UK clinical practice and that the RAASi discontinuation risks of the UK CPRD data should be appended to this. Applying the company PAS, correcting the two major errors (see 1.5 first para), assuming that those discontinuing RAASi would not be left untreated but would receive another active anti-hypertensive treatment and revising the ESRD baseline risk to the correct CKD population results in a cost effectiveness estimate of £20,654 per QALY.

Secondly, retaining the company parameterised curves and the main modelling assumption of the company but applying the other ERG preferred revisions results in a cost effectiveness estimate of £38,905 per QALY.

Thirdly, the ERG revised base case also assumes that the most reasonable estimate for RAASi discontinuations for placebo, reflecting current UK practice, are those derived from the UK CPRD data (rather than the OPAL-HK placebo arm). The ERG applies its corrected Patiromer hazard ratio of RAASi discontinuation estimated from OPAL-HK to the CRPD curve to estimate the risks of RAASi discontinuation among those receiving Patiromer. The ERG applies curves for:

- Hyperkalaemia, estimated from the withdrawal phase of OPAL-HK.
- Placebo RAASi discontinuations, estimated from the CRPD data, the ERG curve being similar to that of the company.

- Patiromer discontinuation, estimated from AMTHYST-DN: again, the ERG curve is similar to that of the company.

The ERG also assumes that those discontinuing RAASi would receive an alternative antihypertensive treatment such as a calcium channel blocker. Other less important revisions are summarised in section 5.4. These changes together provide the ERG base case of an estimated net gain of 0.012 QALYs, net costs of £2,787 and an ICER of £236k per QALY. The model PSA is similar but reflects the uncertainty in the model: £209k per QALY (95%CI: placebo dominates to Patiromer dominates).

In part due to the small QALY gains that are estimated, these results are further sensitive to other assumptions (not included in the ERG base case):

- Applying the Patiromer discontinuation curve estimated by the ERG from OPAL-HK, which worsens the ICER to £681k per QALY.
- Assuming no active antihypertensive treatment after discontinuing RAASi, which improves the ICER to £184k per QALY.
- Assuming informative censoring when estimating the Patiromer hazard ratio for RAASi discontinuation, which worsens the ICER to £272k per QALY.
- Waning of the treatment effect, which worsens the ICER to more than £300k per QALY.
- Applying the company parameterised curves, which worsens the ICER to £247k per QALY.
- Assuming no quality of life effect from hyperkalaemia, which worsens the ICER to £265k per QALY.
- Applying the ESRD quality of life estimates of the company identified systematic review, which worsens the ICER to £342k per QALY.

2 BACKGROUND

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

On CS pages 17-20 the company describes the underlying health condition with emphasis on its stages, prevalence, symptoms and risk factors. Hyperkalaemia is an abnormally high level of potassium in the blood and at acute severe levels is a potentially life-threatening emergency [6]. The CS follows the European Resuscitation Council Guidelines [7] for Resuscitation to categorise hyperkalaemia:

- Mild hyperkalaemia: 5.5 to 5.9 mmol/l
- Moderate hyperkalaemia: 6.0 to 6.4 mmol/l
- Severe hyperkalaemia: ≥ 6.4 mmol/l or if ECG changes or symptoms present

Similarly the National Institute for Health and Care Excellence (NICE) 'Treatment summary for fluids and electrolytes' defines acute severe hyperkalaemia as > 6.5 mmol/l [8], (incorrectly reported as above >6.0 mmol/l in the CS).

UK hyperkalaemia guidelines focus on the management of acute elevations of serum potassium [6, 9, 10]. Consequently, management of chronic hyperkalaemia is often based on clinical judgement [11-13]. However NICE CKD guidelines do have specific management recommendations for hyperkalaemia [1], e.g.: 'Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued.'

The overall incidence of a hyperkalaemia event in patients seeking health care services in England is 2.86/100 patient years. Comorbidities are prevalent in patients with moderate to severe hyperkalaemia, with heart failure being the most common followed by chronic kidney diseases (CKD) and other cardiovascular diseases (CVD) [14]. The CS presents the prevalence of hyperkalaemia prevalence among patients with CKD stage 3-4 ([redacted]) and patients with CKD and comorbid chronic heart failure ([redacted]) [15]. The overall prevalence of hyperkalaemia was not presented in the CS.

Symptoms of hyperkalaemia vary, the majority of people are asymptomatic while a minority report muscle pain such as stiffness, weakness or fatigue [6]. The management of hyperkalaemia varies in guidelines. Treatment options for mild and moderate hyperkalaemia include a loop diuretic to increase urinary potassium excretion. Dietary potassium should be restricted and medicines that cause hyperkalaemia should be reduced or stopped[16]. Severe hyperkalaemia is a life-threatening condition and requires aggressive treatment [17]. While

Patiromer has not been trialled in severe hyperkalaemia (≥ 6.5 mmol/l)[18], management of mild to moderate hyperkalaemia is commensurate with preventing progression.

Patients with CKD are at particular risk of hyperkalaemia, especially when CKD combines with other risk factors for increased serum potassium, such as co-morbid cardio-renal conditions, including CHF and diabetes mellitus[19-22].

Dietary intake of potassium and certain drugs promote hyperkalaemia. Of particular note are renin-angiotensin system (RAAS) inhibitors, which are recommended for people with CKD to reduce the rate of disease progression and mortality [1]. Hyperkalaemia is a recognized adverse drug reaction of RAAS inhibitors, caused by sodium elimination resulting in potassium retention. While Beta-blockers may increase serum potassium levels, diuretics are potassium-depleting.

The company presents several epidemiological studies and meta-analysis showing the value of RAASi in patients with hyperkalaemia and with various comorbidities, as well as patterns of discontinuation in various cohorts with varying levels of hyperkalaemia.

2.2 *Critique of company's overview of current service provision*

NICE promotes dietary advice about potassium, phosphate, calorie and salt intake to patients with CKD [1]. Generally, guidelines recommend the use of RAAS inhibitor therapy in patients with CKD and the only recommendation for managing chronic hyperkalaemia is the discontinuation of RAAS inhibitor. However, it is not clear from the evidence submitted by the company (OPAL-HK trial [4] if included patients have chronic hyperkalaemia (i.e. persisting over time).

The company presents several guidelines (NICE [1], European Society of Cardiology [ESC] [23], Scottish Intercollegiate Guidelines Network [SIGN] [24]) that provide guidance on RAAS inhibitor management for patient with high K^+ levels and co-morbidities. It is worth noting that the serum K^+ threshold varies across guidelines.

The following summary of NICE [1] provide guidance on RAAS inhibitor management for patients with CKD and raised K^+ levels:

- When hyperkalaemia precludes use of RAAS: assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked.

- Not to routinely offer a RAAS to people with CKD if their pre-treatment $K^+ > 5.0$ mmol/l.
- Stop RAAS if K^+ concentration ≥ 6.0 mmol/l or more and other drugs known to promote hyperkalaemia have been discontinued.

The CS discusses the use of potassium binders. However, the company argues that these agents lower K^+ in acute settings, there is insufficient long-term data and they cause serious gastrointestinal adverse events that prevents their use in a chronic setting [18, 25]. Additionally, the company argues that these drugs require frequent adjustment complicating their usage in clinical practice [18].

Dietary management was disregarded by the company for the management of elevated K^+ because of claims of difficulties in changing dietary habits, poor adherence and the prevalence of K^+ in food [13, 26]. NICE clearly promotes lifestyle modification in the treatment pathway of CKD and recommend adjustment of potassium, phosphate, calorie and salt intake depending on the severity of CKD [1]. A recent Cochrane review [3] evaluated the efficacy of dietary interventions among adults with CKD including patients with end-stage kidney disease treated with dialysis or kidney transplant. The review included 17 RCTs: dietary interventions improved eGFR levels, blood pressure parameters and quality of life. The trials were not designed to examine all-cause mortality or CVD events.

A recent 24-month prospective, single-blind, RCT was undertaken 47 patients with stage 3 and 4 CKD [2]. The trial investigated the effect of a low potassium diet in comparison to usual clinical care on neuropathy score and clinical outcomes. The trial found a greater increase in the total neuropathy score in the control group in comparison to the intervention ($p < 0.01$). The intervention group had lower K^+ levels (4.6 ± 0.1 mmol/l) compared to controls (4.8 ± 0.1, $p = 0.03$) although the principle benefit was in reduced neuropathy.

The company states that there is no current treatment available for patients with CKD and hyperkalaemia who are on RAAS inhibitor therapy. Therefore, an unmet need exists for treatment of chronic hyperkalaemia in patients with CKD where continuation of RAAS inhibitor therapy would have clear prognostic benefit.

2.2.1 Positioning of Patiromer in the treatment pathway

Patiromer (Veltassa®) is a drug produced by Relypsa (a Vifor Pharma Group Company) [27]. Patiromer is a non-absorbed, cation-exchange polymer that binds potassium predominantly in

the lumen of the colon where potassium is the most abundant cation. This increases faecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in hyperkalaemic patients [18]. The drug comes in a powder form for oral suspension and each sachet can contain either 8.4 g or 16.8 g or 25.2 g of Patiromer [18]. The European Medicine Agency issued a marketing authorisation (19.07.2017) for the use of Patiromer in the treatment of adults with hyperkalaemia. The company presents a visual figure of positioning of Patiromer in the treatment pathway in Figure 1 (CS, p22).

The ERG notes that the key points related to the case for Patiromer are that:

- RAASi therapy has a special effect in reducing the progression to ESRD in people with CKD, which may have sequelae effects for cardiovascular disease or mortality [5].
- Consequently RAASi treatment is the first line indicated hypertensive treatment for patients with CKD [1, 23, 28]
- Hyperkalaemia is a prominent reason for RAASi discontinuation – one of a number of strategies for serum potassium reduction.
- Patiromer's particular value proposition is that it provides a simple strategy to enable more CKD patients to remain on RAASi therapy

3 Critique of company's definition of decision problem

3.1 *Population*

The NICE final scope reflects the licenced indication for Patiromer: adults with hyperkalaemia. However, the CS restricted the population to hyperkalaemia patients with stage 3-4 chronic kidney disease (which may include other co-morbidities such as heart failure and diabetes) treated with RAAS inhibitors. The CS did not clearly justify the rational for restricting the population to patients with chronic kidney disease. Given its therapeutic indication, the ERG questions the restricted population of the submission, since no value proposition is presented for other populations.

3.2 *Intervention*

The CS intervention matches that in the NICE final scope: Patiromer (8.4 to 16.8 g/day).

3.3 *Comparators*

Both Patiromer-treated and untreated patients are assumed to receive the same advice on potassium diet and general clinical care for related conditions. The comparator in the decision problem is 'standard care', with RAAS inhibition discontinued or reduced in patients where hyperkalaemia is uncontrolled. The ERG asked the company (clarification question A1) to provide a rational for excluding from standard care low-potassium diet with or without agents that reduce levels of potassium in the body. In response the company stated: "…a low potassium diet restricts consumption of healthy foods and that there is limited evidence on the efficacy of and adherence to a low potassium diet". The ERG disagrees with this statement: the company provided no evidence for its assertion either in its original submission or in its clarification response to the ERG's request for evidence. CS evidence includes: a website giving advice about how to maintain a low potassium diet [26]; findings from an unpublished company survey of Scottish GPs (data on file), which found that the majority of GPs would recommend diet change (numbers not provided); reference to the EPAR Report for Veltassa [18], which provides an unreferenced opinion that dietary modification is difficult due to the ubiquitous presence of potassium in foods.

The NICE guideline on CKD states:

"1.4.7 Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD.

1.4.8 Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented."

The company argues that a low potassium diet should be considered as an additional component of the treatment rather than a standalone or prior option. The latter was concluded from the systematic review performed (but not presented) by the company in preparing its submission. The significance of the company's approach to diet is that there was no evidence of an appropriate attempt to evaluate dietary control in patients before receiving Patiromer, consistent with guidelines, and which may have affected patient selection for Patiromer trials.

3.4 *Outcomes*

The NICE final scope outcomes of serum potassium level, use of RAASi therapy, mortality, health related quality of life, and adverse effects of treatment are addressed in the CS. Trial-based evidence is lacking for the longer-term consequences of hyperkalaemia and RAASi discontinuation. Instead lifetime cardiovascular and stroke events, end stage renal disease, survival and health related quality of life are modelled.

3.5 *Other relevant factors*

The European Medicine Agency issued a marketing authorisation (19.07.2017) for the use of Patiromer in the treatment of adults with hyperkalaemia. The population in the CS is narrower than the NICE scope and the Marketing Authorisation for Patiromer. The CS is based on CKD stage 3 and 4 patients because of the unique role of RAASi in reducing the progression of CKD when compared to other antihypertensive treatments. For non-CKD hyperkalaemia, if RAASi therapy is discontinued other antihypertensive medication can be substituted as there is no evidence of difference in long-term cardiovascular or stroke outcomes. Thus the cost-effectiveness of Patiromer hinges on maintaining RAASi therapy in CKD patients, no value proposition is offered for non-CKD stage 3 and 4 patients.

4 CLINICAL EFFECTIVENESS

4.1 *Critique of the methods of review(s)*

The company employed standard systematic review methods: literature search, study selection, data extraction and synthesis. The ERG's appraisal of the CS systematic review of clinical effectiveness is summarised in Table 1. The literature searches (CS Appendix D, Table 2) were conducted in May 2018 and limited to publications dated after 2008 and English language. The search yielded to 40 potentially relevant records. The population eligibility criteria was narrower than the NICE final scope (the CS included only patients with chronic kidney disease). The ERG noted some discrepancies between the comparators reported in the company's decision problem (Document B, Table 1. p10) and the comparators reported in Appendix D (table 3. p17). Non-pharmacological interventions, placebo and other pharmacological interventions to treat hyperkalaemia were listed in the company's selection criteria but were eliminated in the company's decision problem. Discontinuation or withdrawal of RAASi therapy were included as comparators while the ERG considers them as outcomes. One trial was included (OPAL-HK) [4] as relevant to the clinical effectiveness evidence and two trials were included (OPAL-HK and AMETHYST-DN) [4, 29] as relevant for safety endpoints.

Table 1: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	No, the population was limited to patients with chronic kidney disease.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Uncertain, quality assessment of multiple publications of the same trial were carried out separately, making the interpretation of risk of bias difficult.
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	No, the ERG requested further details in clarification questions that were provided by the company.

4.1.1 Searches

Searches in an appropriate set of bibliographic databases were undertaken in May 2018. Suitable terms, including those for Patiromer, were included. Searches also included terms for the comparators, resulting in a broad search suitable for retrieving non-Patiromer studies. The inclusion of an RCT filter, but not an SR filter, in Medline and Embase and the use of an RCT filter in the Cochrane Library databases may have resulted in some SRs being missed. In addition, the CS states that searches of a trials register and relevant conferences (limited to the past five years) were undertaken.

4.1.2 Inclusion criteria

Eligibility criteria for study selection are summarised in Appendix D (table 3, p17-18) of the CS and are summarised by the ERG in Table 2. The ERG noted some discrepancy for the number of included studies between document B (p24) and Appendix D (table 8, p35 -38). In the CS document B, clinical effectiveness and safety data were drawn from two studies while in the supplementary material table 8 lists a total of 27 included records [4, 29-52].

Table 2: Study selection criteria

Domain	Inclusion criteria	ERG comment
Population	Patients with CKD (CKD was defined as GFR <60 mL/min/1.73 m^2, or elevated serum creatinine level or albuminuria with albumin excretion >30 mg/d and/ or >300 mg/g, or abnormalities detected by histology or dialysis) **and** who develop hyperkalaemia **and** on RAASi therapy.	Narrower than the decision problem. The decision problem includes adults with hyperkalaemia.
Intervention	Patiromer	-
Comparator (s)	Discontinuation or withdrawal of RAASi therapy: ACEi/ARB/ARNi, other pharmacological interventions to treat hyperkalaemia (sodium or calcium polystyrene sulphonate or zirconium	Meets the decision problem however some comparators were not used in the CS (diet and other pharmacological interventions to treat hyperkalaemia were not included).

	cyclosilicate), diuretics (aldosterone antagonists, epithelial sodium channel blockers), dialysis, non-pharmacological intervention: diet, placebo.	Discontinuation or withdrawal of RAASi therapy are outcomes and not comparators.
Outcomes	Serum potassium level, episodes of severe hyperkalaemia (serum potassium level ≥6.5 mmol/l), cardiac arrhythmia, end stage renal disease, overall survival, adverse effects of treatment, health-related quality of life, death/all-cause mortality.	Time to normalisation and use of renin-angiotensin-aldosterone system inhibitor therapy were not listed in the inclusion criteria. The remaining outcomes meet the decision problem but included additional outcomes (cardiac arrhythmia, end stage renal disease and overall survival)
Study design (s)	RCTs and Systematic reviews	-

The CS PRISMA diagram (figure 1, Appendix D p39) itemises the identification of 1287 records from searches, the exclusion of 1256 for specified reasons and the final inclusion of 27 records[4, 29-52]. The ERG requested the list of excluded studies at the stage of full-text assessment (clarification question A19) and they were provided by the company. Study exclusions were assessed by the ERG to be appropriate.

4.1.3 Critique of data extraction

Study selection was undertaken by one reviewer. Two reviewers assessed studies when the decision was uncertain and disagreements were resolved by discussion or referral to a third reviewer (unclear if the two reviewers carried out the assessment independently). Data extraction was carried out in Excel: it was unclear whether this was carried out by one or more reviewer. Data extraction variables were listed by the company in Appendix D p19-20. Data of multiple publications of the same study were extracted separately. The ERG disagrees with this approach preferring that multiple publications should be combined and extracted as one and not separately, to reduce potential reporting bias. There was some discrepancy between the studies that were considered relevant to the clinical effectiveness section in document B (p24) and data extraction. The company states that OPAL-HK [4] was the only study that was relevant to capture the population of interest while both AMETHYST-DN [29]

and OPAL-HK [4] were synthesised for safety endpoints. However, the embedded data extraction Excel sheet includes data from 27 records that were excluded in the clinical effectiveness section of the CS.

4.1.4 Quality assessment

The company's assessment of study quality of the included studies (Appendix D, embedded Excel file, p35 and table 10, p44) is summarised in Table 3 together with the ERG's independent assessment. The company states that they carried out quality assessment using The Cochrane Collaboration tool, however the ERG believes they used the NICE checklist. The ERG could not locate the judgment rational for AMETHYST-DN in CS. The company assessed the quality of multiple publications of the same trial separately. For the OPAL-HK study [4], the ERG partially agrees with company's assessment, except for potential bias from randomisation methods, allocation concealment, blinding and imbalance in number of drop-outs between the study arms. For the AMETHYST-DN [29], the ERG partially agrees with the company's assessment except for potential bias from baseline characteristics imbalance in number of patients with chronic kidney disease stage (eGRF) and New York Heart Association class at screening. Overall, the ERG considers the quality assessment of trials made difficult to interpret because multiple publications of the same study were presented separately.

Table 3: Quality assessment of included studies

OPAL-HK study [4]	**Quality assessment judgment in CS and rational**	**ERG judgement – rational**
Was randomisation carried out appropriately?	Yes "*Randomisation for the randomised withdrawal phase was performed centrally by IWRS, according to the time of the randomisation request across all sites".*	Yes – "*Central Randomisation"*
Was the concealment of treatment allocation adequate?	Yes *"During both parts of the study, patients were blinded to their assigned treatment; the Informed Consent form signed by each patient stated that the patient would receive Patiromer at some point during the study, either during the initial treatment phase or the Randomised Withdrawal Phase'.*	Yes– *"Telephone Response System (IWRS) will assign all subjects to one of two Patiromer dose groups based"*
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes *"The baseline characteristics of patients in the two randomised groups were similar during the initial*	-

	treatment phase, and were balanced at the randomised withdrawal phase baseline"	
Were the care providers, participants and outcome assessors blind to treatment allocation?	"At each site, personnel involved in the collection, handling, and processing of blood specimens were blinded. To manage serum potassium appropriately, and to facilitate titration of Patiromer and decision-making about RAAS inhibitor dosing, study investigators were aware that all patients were treated with Patiromer during the initial treatment phase. They also knew which patients had been randomised to Patiromer or placebo during the randomised withdrawal phase"	No – care providers were not blinded. Patients, staff involved with collection, handling, and processing of blood specimens were blinded.
Were there any unexpected imbalances in drop-outs between groups?	No *"There appeared to be no unexplained differences in drop-out rates between the two groups during the randomised withdrawal phase of the study".*	Yes – 82% (45/55) of the intervention remained at week 8. 58% (30/52) of the placebo remained at week 8. (p=0.006)
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?	Yes *"Statistical analyses of the primary endpoint in both parts of the study were performed on an ITT basis, and appropriate imputation methods were used to replace missing data".*	ITT: Yes - Primary analyses of the primary and secondary efficacy outcomes, as well as some sensitivity and exploratory analyses, were performed using the ITT population. Missing data: unclear. Missing serum potassium values were estimated either by a regression model for local laboratory missing values or by multiple imputation if both local and central values were missing. No detail of these estimation methods is provided.
AMETHYST-DN [29]		
Was randomisation carried out appropriately?	Yes	Yes – "*validated interactive web response system was used to assign patients to cohorts and starting doses using computer generated randomization"*
Was the concealment of treatment allocation adequate?	Yes	Yes - *"assignment to cohort will be performed using an*

		Interactive Voice/Web Response System (IXRS)"
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes – "*baseline characteristics by starting-dose group were generally balanced within each stratum"*
Were the care providers, participants and outcome assessors blind to treatment allocation?	No or NR*	No – "*open-label study"*
Were there any unexpected imbalances in drop-outs between groups?	No or NR*	No
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?	NA	ITT Yes – *"The main analysis of the primary efficacy parameter and secondary efficacy parameters will include intent-to-treat population"* Missing data: No, Last observation carried forward was used for missing or incomplete data.

*No or NR: multiple publications of the same trial with different risk of bias judgment.

4.1.5 Evidence Synthesis

In the CS systematic review of clinical effectiveness, one RCT (Patiromer in Patients with Kidney Disease and Hyperkalaemia Receiving RAAS Inhibitors, NCT01810939 [OPAL-HK]) [4] is presented in tabular, graphical and narrative form. As only one trial was included, no meta-analysis was conducted and no indirect comparison was undertaken. This is consistent with the NICE final scope except for the trial population: limited to hyperkalaemia patients with stage 3-4 chronic kidney disease and including other co-morbidities such as diabetes and heart failure.

For safety endpoints, the CS pooled data from two Patiromer trials (CS document B):

- OPAL-HK [4]: Phase III placebo-controlled trial in chronic kidney disease patients with hyperkalaemia on RAAS inhibitors (main study in the CS)
- AMETHYST-DN [29]: Phase II open-label, Patiromer dose-ranging in chronic kidney disease and type 2 diabetes patients RAAS inhibitors.

Data were included from an open-label and single-blinded trials; the CS notes the potential bias of the studies. All patients who received at least one dose of Patiromer were pooled for safety endpoints.

4.2 *Critique of trials of the technology of interest*

Evidence for clinical effectiveness on Patiromer is presented from a single pivotal RCT. The OPAL-HK (NCT01810939) was a phase III, two-phase, single-blind, multi-national placebo controlled RCT sponsored by the Relypsa (a Vifor Pharma Group Company) [4]. The EMA issued a marketing authorisation (19.07.2017) for the use of Patiromer in the treatment of adults with hyperkalaemia. The results of the study were included in the EMA public assessment report [53]. Summary details of the trial were provided in the CS p31-42. The trial was reported in a number of peer reviewed records (main publication Weir et al. 2015 [4]) and a confidential study protocol which have been submitted to the ERG. The OPAL-HK trial [4] was relevant to the company's decision problem in terms of population, intervention, comparator and outcomes (see section 3 for comparison to the NICE decision problem).

4.2.1 Conduct of the trial

The trial was designed to evaluate the efficacy and safety of Patiromer in patients with chronic kidney disease who were receiving at least one RAAS inhibitor and who had hyperkalaemia. The trial was conducted over two phases:

Phase A: a single arm, 4-week initial treatment phase. Oral intake of 4.2 g of Patiromer (twice daily for patients with mild hyperkalaemia: K^+ level of 5.1-<5.5 mmol/l) or 8.4 g of Patiromer (twice daily for patients with moderate to severe hyperkalaemia: K^+ level of 5.5-<6.5 mmol/l). Dose modifications in both groups were made according to a treatment algorithm provided in Appendix M. RAAS inhibitor dose was unchanged during the initial treatment phase unless medically necessary, when discontinuation was permitted.

Phase B: a randomised, 8-week placebo controlled, single-blind withdrawal phase. Patients who completed phase A, had a baseline serum K^+ level of ≥ 5.5 mmol/l at phase A, and responded to Patiromer were randomly assigned to either intervention or placebo. Patient were randomised in a 1:1 ratio to either (1) continue receiving Patiromer at the same daily does that they were receiving in phase A at week 4 plus continue RAAS inhibitor; or (2) receive four packets of blinded placebo plus continue RAAS inhibitor. The ERG noted a difference in RAAS inhibitor management comparing treatment arms as stated in the trial protocol. For the intervention group, RAAS inhibitor was discontinued on the second occurrence of hyperkalaemia or for those patients on a maximum Patiromer dose (50.4 g/day).

For the placebo group, RAAS inhibitor was decreased by 50% or the next dosage below at the first occurrence of hyperkalaemia. RAAS inhibitor was discontinued on the second occurrence of hyperkalaemia.

Participants were enrolled from February 2013 from 10 different countries (Eastern Europe, Europe and US sites), none from the UK. The last study visit was in August 2013. There was some discrepancy in the number of sites reported in the CS and the trial publication, however the conduct of the trial was fairly presented in the CS.

4.2.2 Selection of participants

The CS reported the key inclusion criteria in table 5 p34 and Appendix D (table 9); in summary (phase A) these were patients 18 to 80 years of age, had stage 3 or 4 chronic kidney disease (estimated glomerular filtration rate [eGFR] 15 to < 60 ml per minute per 1.73m^2 of body-surface area) at screening, had serum K^+ levels of 5.1 to > 6.5 mmol/l at two screening (hyperkalaemia), and had been receiving a stable dose of one or more RAAS inhibitors for at least 28 days. For phase B: patients were eligible if they had a serum K^+ level of ≥ 5.5 mmol/l at baseline of phase A, had a serum K^+ level at the end of phase A within the target range (3.8 - < 5.1 mmol/l) while receiving Patiromer and RAAS inhibition. Thus the randomised trial evidence only relates to subjects with serum K^+ level of ≥ 5.5 mmol/l who respond to Patiromer in the target range, the company offer no value proposition for mild hyperkalaemia (serum K^+ levels of 5.1 to <5.5 mmol/l) or non-responders.

Mild hyperkalaemia was defined as K^+ levels 5.1 to < 5.5 mmol/l and moderate to severe hyperkalaemia was defined as 5.5 to < 6.5 mmol/l. The ERG notes that the definition of hyperkalaemia can vary, for example The National Institute for Health and Care Excellence (NICE) 'Treatment summary for fluids and electrolytes' defines acute severe hyperkalaemia as > 6.5 mmol/l [8].

Hyperkalaemia (K^+ level) was determined using local and central laboratory results (CS p36).

- Central laboratory: phase A baseline values
- Local laboratory: phase A post baseline values
- Both central and local laboratory: phase B withdrawal

During each phase patients could have dose adjustments based on the local laboratory serum potassium values and according to titration algorithms. The ERG asked the company how well the measures (central vs. local) correlated (clarification question A4) and the company provided correlation analysis and visual figures. The concordance between local and central laboratory serum K^+ for phase A baseline and post-phase A baseline was provided in

Clarification Table 3 and Table 4). For phase A baseline (Table 3), [redacted] of the sample [redacted]) fell within the same serum K^+ category of 5.1 to <5.5 in central and local laboratories while the remaining of the sample fell within different categories. For the K^+ range of 5.5 to < 6.5 [redacted] fell within the same category. The ERG notes that discrepancies may have affected categorisation during each phase, dose titration and RAASi discontinuation in phase B.

In its submission the company defined CKD and its study population as stage 3 or 4 chronic kidney disease (i.e. eGFR 15–<60 mL/min/1.73 m^2): this doesn't entirely match clinical guideline definitions. The NICE guideline[1] defines CKD as abnormalities of kidney function or structure present for more than 3 months. Patients with eGFR (creatinine – used in IDEA-HK) >45 ml/min/1.73 m2 and no other marker of kidney disease should not be diagnosed with CKD. Classification requires assessment of raised albumin:creatinine ratio (ACR) as well as estimated glomular filtration rate (eGFR).

The company in its clarification confirmed that it made no attempt to conduct serial measurements to confirm CKD. Central laboratory values (Table S4 and S4, Weir suppl) provide a consistent comparison of treatment phase and withdrawal phase patient values of eGFR at baseline. According to the company definition of CKD, these tables show that 9% of subjects not classed as CKD entering the treatment phase and 11% entered the withdrawal phase. In clarification (A11) the company stated:

'InPhase A 22/243 (9%) patients had CKD stage 2 defined as 60 mL/min/1.73m2 ≤eGFR<90 mL/min/1.73m2, this cohort of patients are still categorised as CKD, defined in KDIGO 2012 guideline, and are relatively small number of patients relative to CKD stage 3-4.'

This response contradicts the OPAL-HK [4] trial protocol inclusion criteria, main trial report and clarification response in A10:

'In both OPAL [4] and AMETHYST [29], CKD was defined as eGFR ≥ 15 mL/min/1.73 m2 and < 60 mL/min/1.73m2.'

It is also a misleading representation of KDIGO 2012 which states:

"CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA)."[28]

When asked, the company did not provide trial outcomes stratified by eGFR category so that the ERG could attempt model revision (Clarification A11).

The ERG has previously noted the company made no a rigorous attempt to modify hyperkalaemia using diet, as consistent with guidelines (Clarification A1). Additionally, there is no record of attempt to optimise use of antihypertensive medication before recruitment to OPAL-HK [4]. Patients entering OPAL-HK [4] were being managed for hypertension (Table S4, Weir suppl). Thiazide and loop diuretics are potassium depleting and optimisation of therapy may have rendered some patients ineligible for the trial. Table S4 reports that at baseline 29% of patients received a thiazide and 32% a loop diuretic but it is unclear whether dose was optimised. Since the trial, evidence has emerged that dual RAASi blockade (combining an ACEi and ARB is contraindicated[53], since it raises serum K^+ and worsens CKD. When asked, the company did not provide a sub-group analysis of trial effectiveness outcomes by dual/no dual blockade (Clarification A15).

4.2.3 Consort diagram

Flow charts of participants through the OPAL-HK [4] trial phases were presented in figure 3 and 4 of the CS. Phase A included 243 patients that started the treatment phase: 92 patients (K^+ 5.1 to <5.5 mmol/l) initially received 4.2 g of Patiromer twice a day and 151 (K^+ 5.5 to <6.5 mmol/day) initially received 8.4 g of Patiromer twice a day. Serum K+ level was the most prevalent reason that disqualifying patients from phase B. Phase B included 52 patients that were randomly assigned to placebo and 55 patients that were randomly assigned to Patiromer. At end of the phase B trial, 30 patients remained on placebo and 45 patients remained on Patiromer. ERG Note: there is a potential confusion in the Consort Phase A diagram that shows 15 patients randomised to Phase B who had local lab serum K^+ 5.1 to <5.5 mmol/l at baseline. These were admitted because the central lab baseline value found a higher value (5.5+ mmol/l) at baseline.

4.2.4 Follow-up

For phase A, patient assessments of efficacy and safety were performed at day 3, week 1, week 2, week 3 and week 4. Patients in phase B were followed up at day 3, and at weekly visits for the eight-week period. Early withdrawals and patients who did not qualify for phase B were followed up in a safety-follow up period for 1 to 2 weeks.

4.2.5 Withdrawals and discontinuation of follow up

In phase A 24/243 participants withdrew because of adverse events (10/24), withdrew consent (5/24), low/high K^+ levels (4/24), decreased eGFR (2/24), protocol violation (2/24) or not compliant to intervention (1/24).

In phase B 22/52 discontinued placebo and the main reason was protocol pre-specified withdrawal criteria for high/low K^+ levels (17/22). In the Patiromer group 10/55 discontinued treatment and the main reason was high/low K^+ levels (5/10). The ERG notes that low concordance between central and local laboratories may have influenced patient withdrawals and treatment discontinuation.

4.2.6 Duration of dose exposure

Table 17 (CS p65) and supporting text provide information about treatment duration and dose, statistical significance between groups was not provided. For phase A the overall mean (±SD) daily dose was 18.2±6.6 g/day and the mean treatment duration was 27±6.3 days. There was no clear difference in mean daily dose or duration of exposure by sex. However, patients aged <65 years had a slightly higher mean dose intake [redacted] and duration [redacted] in comparison to older patients [redacted] Eastern Europe patients had a higher mean daily dose [redacted] in comparison to the European Union and US [redacted]

For phase B the placebo group had a lower dose duration [redacted] compared to the intervention group (duration 51.4±13.5 days), *p* values were not provided. The placebo group had lower mean dose duration compared to the intervention across all subgroups (sex, age and region). There was no clear subgroup difference (age, sex and region) in the intervention group for both mean dose intake and duration of exposure. However, females had a slightly higher dose intake compared to males and patients aged < 65 years in comparison to older patients.

4.2.7 Baseline characteristics

Baseline characteristics were presented in the CS, table 9 p41-42. Demographic and clinical characteristics were presented for both phase A and phase B. The ERG requested the baseline characteristics of patients that did not qualify for phase B of the trial but the company did not provide this information (Clarification A6.1).

For phase A, the mean age was 64.2±10.5 years and was majority male (140/243, 58%). In Phase A 45% of patients were Stage 4 (eGFR < 30 mL/min/1.73 m2) and 44% in Phase 2. Nearly all patients in phase A were white (98%) and were all white (100%) in phase B. The ERG notes that evidence for the safety and effectiveness of Patiromer in other ethnic groups has not established been and is potentially an equity issue for NICE.

The ERG requested region stratified baseline characteristics for phase B and that was provided by the company for some items but not others (e.g. myocardial infraction, hypertension, RAAS inhibitor use or diuretic use; Clarification A6.2). Therefore the ERG is not clear that RAAS inhibitor therapy or blood pressure management more generally is consistent across regions. The majority of the sample was from Eastern Europe (total = [redacted], Patiromer = [redacted], placebo = [redacted]); fewer patients were from the US and Europe (total = [redacted], Patiromer = [redacted], placebo = [redacted]). Patients recruited to the OPAL-HK [4] trial had mild-moderate hyperkalaemia ($K^+ \geq 5.1$ to less than 6.1 mmol/l).

The ERG notes that the trial did not include any UK centres and asked the company to supply supporting evidence to demonstrate the generalisability of the OPAL-HK [4] population to the UK population (clarification question A5). The company referred to CS table 27 on page 91 where the placebo group of phase B was compared to the Clinical Practice Research Datalink (CPRD) database [54]. CPRD is governmental non-profit research service (funded by the NHS and NIHR) that provides anonymised primary care records for public health research. The company assertion that baseline characteristics between the cohorts were broadly comparable is not supported (Table 4). CPRD patients were more likely to be female, on average [redacted] years younger, not on dual blockade and considerably less likely to have diabetes, hypertension, heart failure or previous myocardial infarction. The ERG did not find the OPAL-HK [4] patients comparable to the CPRD population [54].

Table 4: Patient characteristics in OPAL-HK Part two (B) and CPRD England [4, 54]

	OPAL-HK Placebo (N=52)	OPAL-HK Patiromer (N=55)	CPRD (N=[redacted])
Male, % (*n*)	58% (30)	51% (28)	[redacted]
Mean age, mean±SD	65.0 (55)	65.5 ± 9.4	[redacted]
Mean eGFR, mean±SD	39.0± 20.4	38.6 ± 20.7	[redacted]
RAASi (ACE), % (*n*)	73% (38)	67% (37)	[redacted]
RAASi (ARB), % (*n*)	31% (16)	44% (24)	[redacted]
RAASi (aldosterone), % (*n*)	8% (4)	7% (4)	[redacted]
Mean serum K^+ mmol/l, mean±SD	5.9 ± 0.4	5.9 ± 0.6	[redacted]
Myocardial infarction, % (*n*)	27% (14)	33% (18)	[redacted]
Hypertension, % (*n*)	96% (50)	98% (54)	[redacted]
Diabetes mellitus, % (*n*)	63% (33)	62% (34)	[redacted]
Heart Failure, % (*n*)	42% (22)	49% (27)	[redacted]

4.2.8 Outcome selection

The outcomes reported in the CS partially matched the final scope. Two outcomes listed in the final scope but not measured in the OPAL-HK [4] trial were health related quality of life and time to normalisation. OPAL-HK [4] was conducted over a short period of time therefore it was not possible to capture health related quality of life due to changes cardiovascular or CKD status. Table 5 summarises the outcomes reported in the CS and the ERG's comments.

Table 5: CS reported outcomes and ERG comments

CS outcome	In line with NICE scope	ERG comments
Primary outcome:		
Phase A: Change in serum K^+ from baseline to week 4. Phase B: Change in serum K^+ form baseline (B) from the start of phase B to 4 weeks (or uncontrolled serum K+)	Yes	K^+ levels were measured in different laboratories (central or local) at different phases of the trial, the ERG notes the potential variation that this may produce. Serum levels were measured frequently throughout the trial (weekly). The ERG notes that repeated assessment (with chance variations) may have led to over-modification of RAAS inhibitor therapy. This outcome was stated in the protocol.
Secondary outcomes:		
Phase A At 4 weeks: The proportion of patients falling in the K^+ target range 3.8 to <5.1 mmol/l	Yes	This measure qualified patients for the randomised phase of the study, if they were initially ≥5.5 mmol/l. It is a short-term indication of the impact of Patiromer (or varying dose) on serum K^+ This outcome was stated in the protocol.
Phase B At 8 weeks: serum K^+ value ≥ 5.5 mmol/l At any time through the 8 weeks: serum K^+ value ≥ 5.1 mmol/l	Yes	The outcome indicates withdrawal phase failure, a return to moderate hyperkalaemia. This outcome was stated in the protocol.
Exploratory endpoints:		
Time to first recurrence of hyperkalaemia	No but relevant	Weekly monitoring of hyperkalaemia was carried out over the short duration of the trial. Given potential measurement variations in readings, recurrence may have been over-reported Not clearly stated in the protocol.
At any time through the 8 weeks: RAASi adjustment	Yes	Adjustment followed a specific algorithm. This was reported in the trial protocol. The algorithm differentially reduced RAASi does more quickly in the placebo than treatment arm, but doesn't seem to have affected time to discontinuation (used in the CS model)

At 8 weeks: proportion of patients receiving any dose of RAASi	Yes	This was stated in the protocol.
Time to RAASi dose discontinuation	Yes	Not clearly stated in the protocol.
Safety endpoints:		
Adverse events	Yes	The ERG notes that this indicates short-term adverse events (over 12 weeks). This was stated in the protocol.
Renal events	No	This is relevant to the population studied in the trial. The trial population are narrower than the final scope. This was stated in the protocol.
Clinical laboratory test results	Yes	This was stated in the protocol.
Vital signs	No but relevant	This was stated in the protocol.

4.2.9 Safety (adverse events)

Safety and tolerability data were presented in the CS (document B, pp64-73). Safety data and adverse events were not included in the economic analysis of the CS. Adverse events were pooled from OPAL-HK [4] and AMETHYST-DN [29], two trials of very different duration.

Briefly, AMETHYST-DN was phase 2, multicentre, open-label, dose-ranging RCT conducted over 52 weeks. Patients were eligible aged 30 to 80 years, with type 2 diabetes, CKD, and with or without hypertension [29]. The trial included a 4-week run-in period, 8-week treatment phase followed by a long-term maintenance phase of up to 44 weeks. Patients (n = 306) were randomly assigned, based on their hyperkalaemia status, to 1 of 3 Patiromer starting doses per stratum (mild hyperkalaemia: 4.2 g/day, 16.8 g/day or 25.2 g/day); moderate hyperkalaemia: 16.8 g/day, 25.2 g/day, 33.6 g/day). Of those recruited 222 (73%) patients had mild hyperkalaemia (>5.0 to 5.5 mmol/l) and 84 (27%) moderate hyperkalaemia (>5.5 to <6.0 mmol/l).

Pooled safety data from OPAL-HK [4] and AMETHYST-DN [29] are presented in the CS tables 17-21. The company states that inclusion of AMETHYST-DN safety data is considered relevant to as it provides long term safety profile of Patiromer. The ERG notes several issues with the company's approach. There is ambiguity around the number of patients (n =547) and the intervention arms used in the pooled analysis. The ERG believes that it is inappropriate to pool data from the two trials for the following reasons:

OPAL-HK [4] investigated the efficacy of Patiromer while the AMETHYST-DN [29] was a dose ranging study to inform dose selection. Patiromer dosage varied comparing the two trials,

with starting doses generally lower in OPAL-HK [4]. The inclusion criteria for patients differed across the two trials, the company considered AMETHYST-DN [29]not relevant for efficacy in the CS because all patient required to have a diagnosis of diabetes in addition to CKD. The trials widely varied in duration, OPAL-HK [4]was 12 weeks while AMETHYST-DN [29] was 52 weeks; the definitions and cut-offs for hyperkalaemia differed (excluding more severely hyperkalaemic patients in AMETHYST-DN [29]).

The ERG believes that methodological issues in safety data analysis, particularly small numbers of patients with moderate hyperkalaemia providing one-year data, make the safety findings inconclusive.

Although the OPAL-HK [4] was a short-term trial, patients in the initial phase (A) had a high prevalence of ≥1 adverse events (114/243, 47%), and the same was observed in second phase (Patiromer: 26/55, 47%). Diarrhoea, constipation and nausea were the most common gastrointestinal disorders reported in both phases. Serious adverse events such cardiovascular disorders were reported infrequently reflecting the short-term duration of the trial.

4.2.10 Description and critique of the company's approach to trial statistics

The use of statistics within the OPAL-HK [4] and AMETHYST-DN [29] trials is appropriate, and their use consistent in the CS. The ERG notes the limitations of the company's approach to safety data, but these don't feature in the company model.

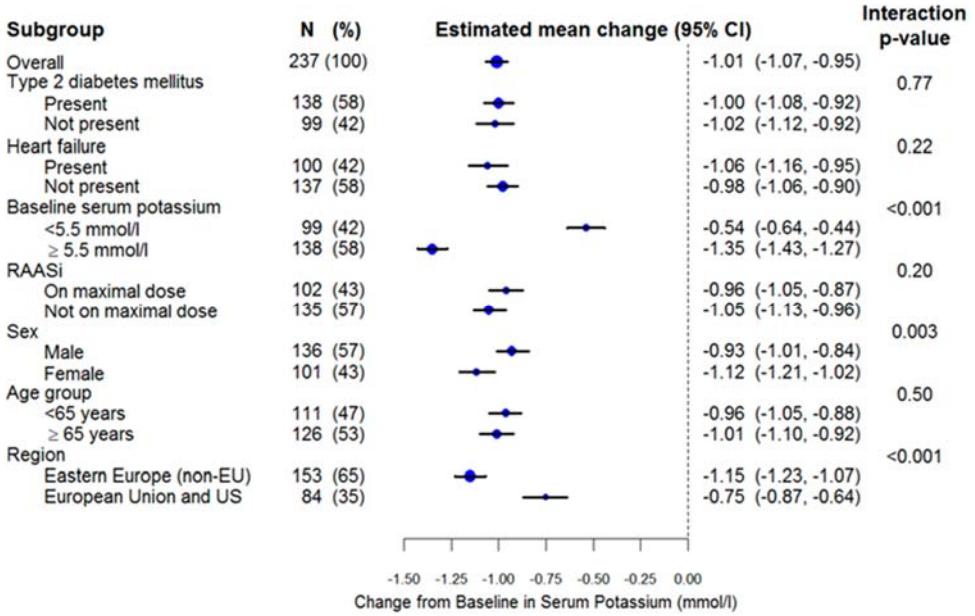
4.2.11 Subgroup analyses

The CS stated that pre-planned subgroup analyses were undertaken on the primary outcome K^+ to investigate the effect of Patiromer in patients with comorbidities of CKD and other potential risk factors. The protocol specified subgroup analysis for the primary outcome included patients: with vs. without chronic heart failure, with vs. without diabetes, K^+ levels 5.5 to < 5.8 vs. ≥ 5.8 (mmol/l), phase A RAASi therapy maximum dose vs. non-maximum dose.

Additional subgroup analysis carried out by the company on the primary outcome included: male vs. females, < 65 vs. ≥ 65 (years of age), Europe & US vs. Eastern Europe. Forest plots presented by the company are presented in Figure 1. For subgroups by region, there was a significant difference in K^+ levels at the end of phase A. Eastern European patients had significantly reduced K^+ levels (mean difference -15, 95% CI -1.23 to -1.07, 153 patients) when compared to Europe and US (-0.75, 95% CI -0.87 to –0.64, 84 patients). The two subgroups had a different baseline profile in terms of K^+ levels, RAASi dose, eGFR levels, diabetes and cardiovascular disease. A lower proportion of Eastern European patients were on

a maximal RAASi dose in comparison to Europe and US [redacted], and eGRF levels [redacted], type 2 diabetes [redacted] and heart failure rates [redacted] were higher in Eastern European patients. The ERG notes that the trial contained a majority (65%) of Eastern European patients who had a different health profile to Europe and US and showed a significantly higher reduction in K^+ levels.

Figure 1: Change in serum potassium from baseline to week 4 of the initial treatment phase, by pre- specified subgroup (CS Appendix E, p47)



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

Indirect comparison not included in the CS.

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

Indirect comparison not included in the CS.

4.5 *Additional work on clinical effectiveness undertaken by the ERG*

4.5.1 Network Meta Analysis of RAAS inhibition in CKD (Xie et al)

Xie et al. [5] conducted a systematic review and Bayesian network meta-analysis (NMA) to evaluate the effect of RAAS inhibitors (ACE and ARBs compared to placebo or active controls upon kidney disease and cardiovascular outcomes in individuals with CKD.

Hyperkalaemia was captured as drug-related adverse event in the NMA. The review included 119 trials with 64,768 patients randomized. The ERG assessed the quality of the NMA [5] following the ISPOR-AMCP-NPC checklist [55].

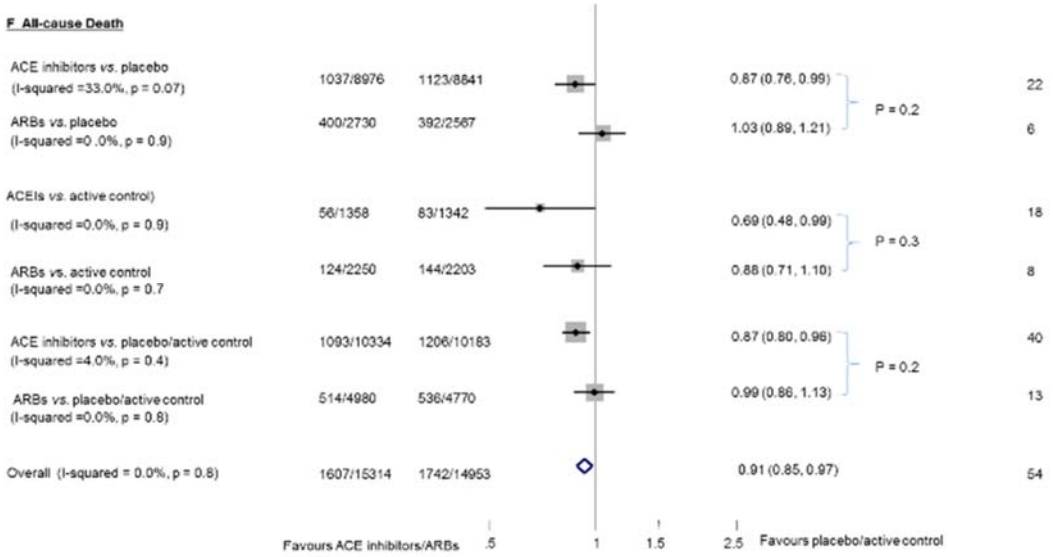
The NMA population included patients with CKD while the CS included patients with CKD stage 3 and 4. The NMA addressed the value of RAAS inhibitors in the general CKD population, providing estimates of the value of treatment in this population. Thus it is directly relevant assuming it reflects a non-hyperkalaemic population, and assuming that its findings are valid for patients managed by Patiromer to be normokalaemic.

The NMA attempted to identify all relevant RCTs by systematically searching key multiple databases and contacting authors. The search included RCTs of CKD patients treated with ACE inhibitors or ARBs. The quality of the included trials was assessed and they were mainly scored low/unclear for random sequence generation, incomplete outcomes, and other sources of bias. A number of studies were judged at high risk for blinding issues in terms of participants, personnel and outcome assessors. There are no obvious issues for selective reporting, judged at low risk of bias across included studies. The review did not provide clear evidence on effect modifier differences across the different treatment comparisons of the network.

The statistical preserved within-study randomization. Inconsistency was estimated by using the loop-specific and node splitting approach and there was no significant inconsistency within closed loops in the network that could threaten the validity of the results. However, there was some visual variation between the NMA results and meta-analysis for CVD events. Random effects models were used and heterogeneity, multiple-treatment meta-regression analysis and subgroup analyses were explored to estimate the effect of baseline covariates and were incorporated into the network meta-analysis. Overall, the NMA had good reporting quality and transparency. The beneficial effect of ACE inhibitors in patients with poor renal function was consistent with Blood Pressure Lowering Treatment Trialists Collaboration review (HR for patient with eGFR < 60 mL/min/1.73m^2: 0.81, 95% CI 0.73 to 0.89) [56].

All-cause death findings (figure 4) suggested some inconsistency since RAASi performed better against active control than placebo, implying placebo was better than active control at reducing all-cause mortality.

Figure 4: RAAS inhibitors for all-cause mortality [5]



The NMA (119 RCTs, 64,768 patients) included RCTs for CKD populations including five intervention comparisons: ARBs vs placebo, ACEi vs. placebo, ARBs vs. ACEi, ACEi vs. "active controls" and ARBs vs "active controls". Studies of placebo vs. "active controls" were not included, however the NMA allowed an indirect comparison of "active controls" vs. placebo using included studies. Active controls were defined as "other active anti-hypertensive drugs", i.e. excluding ACEi and ARBs (caption to Xie. Fig 4). "Active control" RCTs employed mostly either CCBs or beta-blockers or both in the active control arm. The ERG considers that patients with CKD would largely by managed for hypertension: when discontinuing RAASi typically they would receive some other active treatment (rather than no treatment as implied in placebo arms of trials). Therefore a more appropriate comparator is provided by active controls than placebo. Xie et al reported Bayesian odds ratios for treatment comparisons together with number of events (n), number of patients at risk (N) and mean follow up for trials for several outcomes including kidney failure. For major cardiovascular events no events data (n/N) from ARBs vs ACEi RCTs were provided. Some of these data were used in the company submission in order to populate the economic model and the values presented in CS Table 33. The Table below summarises data found in Xie et al.

Table 6: NMA odds ratios and mean follow up times

RCTs	OR kidney failure vs. PBO	OR kidney failure vs. AC	OR major CV event vs. PBO	OR major CV event vs. AC	OR CV death vs. PBO	OR CV death vs. AC	OR all cause death vs. PBO	OR all cause death vs. AC	Mean follow up (months) PBO /AC
ARBs	0.70	0.75	0.76	0.86	1.12	0.97	0.99	0.81	39.6 / 37.2
ACEi	0.61	0.65	082	0.94	0.88	0.77	0.87	0.72	48 / 44.4
	kidney failure		major CV event		CV death		all cause death		Mean follow up
ACEi vs ARBs	0.85		1.09		0.80		0.90		48

PBO = placebo; AC = active control. ACEi vs ARBs trials compared two different RAAS inhibitors

4.5.2 Risk of ESRD and death in CKD patients (Landray et al)

The Chronic Renal Impairment in Birmingham (CRIB) [57] study used a prospective cohort to quantify and compare the risks of death and ESRD in a cohort of patients with CKD stages 3-5 (not receiving renal replacement therapy). Patients were recruited between 1997 and 1999, all-cause mortality was recorded until to 2006 and development of ESRD was tracked to the end of 2007.

Patients with a serum creatinine level > 1.5 mg/dL (not receiving renal replacement therapy) attending a single large UK renal clinic in Birmingham were invited to participate in the CRIB study. The study included a total of 382 patients, 88 (23%) had stage 3 CKD (mean eGFR, 37.0 mL/min/1.73 m^2), 178 (47%) had stage 4 CKD (mean eGFR, 21.9 mL/min/1.73 m^2) and 116 (30%) had stage 5 CKD (mean eGFR, 10.1 mL/min/ 1.73 m^2). Mean age of participants was 61.5±14.3 years and 64% were male patients. The majority of patients were white (88%) while those remaining were either black (5.8%) or Asian (6.3%). Patients had co-morbidities that included vascular disease (44.8%), diabetes (17.3%) and left ventricular disease (20%). Baseline characteristics by CKD stage are presented in table 6.

See 5.3.2.2 for a discussion of the findings and use of the CRIB study.

Table 6: Baseline characteristics of the CIRB study by CKD stage [57]

	CKD stage 3	CKD stage 4	CKD stage 5
No of patients	88	178	116
Age (years)	59.3 ±14.6	62.8 ±14.6	61.1 ±3.3
Men (%)	83.0	60.7	57.8
Disease history (%)			
Vascular disease	50.0	41.6	45.7
Diabetes mellitus	17.0	14.6	21.6
Left ventricular hypertrophy	12.8	21.2	23.9
Medication (%)			
Any antihypertensive	77.3	80.9	90.5
Aspirin	30.7	28.7	22.4
Vitamin D	9.1	28.1	66.4
Calcium	4.5	16.3	43.1
Iron	6.8	20.8	45.7
Erythropoietin	1.1	3.9	24.1
Folic acid/B vitamins	8.0	10.7	17.2
Ethnicity (%)			
White	85.2	90.4	86.2
Black	10.2	2.2	7.8
Asian	4.5	7.3	6.0
Clinical measures			
SBP (mm Hg)	151.3 ±22.6	152.3 ±23.9	150.9 ±19.9
DBP (mm Hg)	86.6 ±12.0	84.5 ±11.9	81.0 ±11.1
Total cholesterol (mg/dL)	221 ±42	222 ±55	207 ±42
HDL cholesterol (mg/dL)	49 ±15	50 ±16	46 ±16

4.5.3 RAASi Discontinuation (CPRD analysis)

In their economic model the company used data from a CPRD analysis (N = [redacted], maximum follow up 4 years) to represent RAASi discontinuation (RD) in CKD Stage 3 and 4 patients not in receipt of Patiromer. In CS Figure 12 Weibull, Gompertz and exponential models based on this data were presented with extrapolation to 34 years. Because no "observed" plot was presented that might allow assessment of visual goodness of fit of the models the ERG requested in clarification a revised version of CS Figure 12 to include "observed" data: the company supplied a revised Figure 12 shown below. The ERG noted odd features in the time axis of the original CS Figure 12 in that years 4, 13, 22, 31 were omitted from the sequence

(the same was seen in CS Figure 15). In the revised Figure 12 there were no missing years but years 9 and 27 were duplicated.

Figure 2: Revised CS Figure 12 "Kaplan-Meir and parametric functions for time to RAASi discontinuation, no Patiromer (CPRD)"

While the goodness of fit for Weibull and Gompertz models appears reasonable the exponential model bears little relationship to the observed data and appears to be based on a different data set. The underlying data supplied in clarification aggregated events and censorings data to 3 years in 150-week intervals (Appendix A1): there were 338 events and 1577 censorings. Using the supplied numerical and graphical data the ERG replicated the generated Weibull, Gompertz and exponential models plus two further models (gamma and flexible) with superior AIC and BIC values (Table 7). Model results are shown in Figure 3 with extrapolation to 30 years.

Figure 3 ERG Parametric models of CPRD RAASi discontinuation

Weibull and Gompertz models were essentially identical to the CS models, the ERG exponential model aligns reasonably with the observed plot (but differs greatly from the CS exponential model), while the two exploratory ERG models both predict less RD than seen in the three company models (revised figure 12). There were differences between CS and ERG information criteria values, the reason for this is uncertain, the higher values in CS analysis may be based on more (3830) observations.

Table 7: Information criteria scores for parametric models of CPRD RAASi discontinuation

Distribution	CS AIC	CS BIC	ERG Obs	ERG df	ERG AIC	ERG BIC
Weibull	4068	4079	1915	2	2046.306	2057.421
Exponential	4104	4110	1915	1	2121.068	2126.625
Gompertz	4093	4105	1915	2	2078.712	2089.827
Flexible			1915	4	2022.866	2045.096
Gamma			1915	3	2024.927	2041.599

Although information criteria favour flexible and gamma models, their long-term extrapolation implies a decreasing or stable hazard which seems less plausible than the increasing hazard found for Weibull model (Appendix A2); on the balance of plausible

extrapolation and information criteria the ERG agree with the company that the Weibull model is appropriate.

Although RD was monitored in OPAL-HK this data was not employed directly in the economic modelling of RD. As described above, CPRD analyses were used for non-Patiromer recipients while RD for Patiromer recipients was generated using a RD HR for Patiromer vs. placebo derived from analysis of the OPAL-HK trial randomised phase (HR = [redacted]; in clarification [redacted] was stated to be used) and applying this to the parametric models shown in CS Figure 12 (the resulting extrapolations are shown in CS Figure 15).

Both CS Figures 9 (p62) and Figure 13 p(93) present KM analysis of RD during the 8 weeks post-randomisation in OPAL-HK. RD was implemented according to a prespecified algorithm for management of HK. The analysis delivered a Cox HR of [redacted]. Because CS Figures 9 and 13 differed in "numbers at risk" shown, the ERG requested clarification and the underlying data. The company response attributed differences in numbers at risk to the use of different software for the two analyses. In deriving the HR of [redacted] the company assumed proportional hazards between Patiromer and placebo arms. This was tested statistically and graphically in CS Figure 14. The null hypothesis that PH is not violated was not rejected ([redacted]). With only three events in the Patiromer arm the ERG consider the data rather underdeveloped for meaningful assessment of PH. The ERG undertook Schoenfeld residuals analysis to further investigate the PH assumption: unsurprisingly the results (Appendix A3) imply some variation in HR through time. While PH may hold over a brief eight-week period the ERG considers it is a considerable assumption that this applies over a lifetime; for example in Figure 15 there is a 220-fold extrapolation in the evidence of PH from 8 weeks to 34 years.

The ERG analysed RD data from OPAL-HK supplied in clarification; a Cox HR of [redacted] was obtained coinciding with the CS value. Because the company employed Weibull, Gompertz and exponential parametrics to model RD in CPRD the ERG generated these models for OPAL-HK data; in the case of Weibull and Gompertz parametrics, in one analysis treatment was employed as a covariate (ratio of scale parameter = HR, common shape parameter) and in a second was not (arm dependent scale and shape parameters). The results are shown in

Figure 4 (solid lines: each arm modelled independently, dashed lines: with treatment as a covariate).

Figure 4 KM plots and parametric models of RAASi discontinuation in OPAL-HK

Across the two arms, differences in IC scores were lower for Weibull models but IC differences between models were small. Over 8 weeks in the placebo arm nearly 60% discontinued RAASi. This contrasts greatly with the "no Patiromer CPRD" analysis in which about 25% discontinue over four years. It is clear that the frequency of testing and the algorithm for management of hyperkalaemia (CS doc B Appendix) and the consequent RAASi discontinuation implemented in the OPAL-HK trial bears no resemblance to UK real world practice. For the HR from OPAL-HK to be applied meaningfully to the CPRD models, congruence is needed between the OPAL-HK placebo and CPRD observed data and also between their respective parametric models. Except for the exponential model of the OPAL

Patiromer arm all models for both OPAL-HK arms suggest RAASi discontinuation is complete by 2 to 3 years. This contrasts starkly with the RD for Patiromer and no-Patiromer recipients depicted in CS Figures 12 and 15, employed for economic modelling. CS Table 15 implies (bottom row in Table) that in addition to 3 RAASi discontinuers in the Patiromer arm a further 6 patients discontinued prior to week eight. For reasons unclear to the ERG these were not included as events in the company analysis while the corresponding 3 placebo RAASi discontinuers in this bottom row were included. If, in a correct ITT analysis either the 3 placebo cases are excluded or the 6 Patiromer cases are included as events then the estimated HR of [redacted] would be biased in favour of Patiromer. Informative censoring of 3 events in the PBO arm (reducing from 30 to 27 events) generates a HR of [redacted]; alternatively introducing 6 events informatively into the Patiromer arm (increasing from 3 to 9 events) generates a HR of [redacted].

To summarise the ERG has the following concerns about the company approach to RAASi discontinuation (RD):

1] The CS exponential model for CPRD RD may be erroneous; the CPRD models explored by the company do not necessarily represent available models with the lowest AIC/BIC scores.

2] For non-Patiromer recipients there is a huge difference between RD seen in OPAL-HK and the CPRD analysis; it is evident that the hyperkalaemia management algorithm used for implementing RD in the OPAL trial is unlikely to reflect UK clinical practice RD, so the former is not well aligned with the decision problem. Monitoring of mild/moderate hyperkalaemia is probably far less frequent in practice than in OPAL-HK.

3] The company have derived a HR from patients whose RAASi discontinuation was based on a within-trial algorithm for management of hyperkalaemia and has applied this to patients whose RD management and experience is different.

4] There were only three RD events included in the Patiromer arm of OPAL-HK. The PH assumption and derived HR based on this eight-week data of RD, using the trial hyperkalaemia management algorithm, have been assumed constant beyond eight weeks to a life time horizon, a 220x extension.

5] The modelling of RD in Patiromer recipients using CPRD data for non-Patiromer recipients is only valid if an appropriate HR is employed and if the PH assumption reasonably applies over an extended period; in the opinion of the ERG these conditions fail to apply for

the RD modelling employed by the company, and therefore the results of these models should be viewed with caution.

4.5.4 Patiromer discontinuation in AMETHYST-DN

The company's economic modelling of Patiromer discontinuation (PD) used data from the uncontrolled AMETHYST-DN trial rather than from the randomised phase of OPAL-HK. While the company acknowledged the significant differences in study populations this was considered to be overridden by the benefit from the greater number of patients and longer follow up in AMETHYST-DN. In AMETHYST-DN, PD appears to be a patient reported outcome and is described as follows: "*Study staff will assess compliance at every study visit after dispensation to confirm that the patient is taking investigational product, losartan, and spironolactone according to the protocol. Compliance will be determined as the ratio of the number of sachets the subject actually took to the number of sachets the subject should have taken prior to discontinuation of study medication RLY5016*". CS Figure 16 displayed the KM plot for AMETHYST-DN PD; this indicated that after about 110 days the plot trajectory becomes almost perfectly linear, implying that a near constant hazard may apply over this period. The company explored five parametric models of discontinuation. Of these the lognormal model was identified as having the best statistical fit according to AIC and BIC scores (Table 8).

Table 8 AIC BIC scores for parametric models of Patiromer discontinuation in AMETHYST

Model	CS AIC	CS BIC	ERG Obs	ERG df	ERG AIC	ERG BIC
exponential	590.24	593.86	274	1	590.2433	593.8564
Weibull	570.57	577.80	274	2	570.5735	577.7997
loglogistic	569.19	576.41	274	2	569.1884	576.4147
Gompertz	***571.09***	***578.32***	274	2	571.0921	578.3184
lognormal	***565.48***	***572.70***	274	2	565.4784	572.7046
gamma			274	3	565.9301	576.7695
bathtub			274	3	567.0158	577.8552
flexible			274	4	566.3363	580.7888

CS Figure 17 displays the extrapolation of the models to 2500 days (~ 6.8 years) rather than over the lifetime horizon of the economic model. The ERG used data supplied in clarification to explore parametric models over a 50-year horizon (Figure 5).

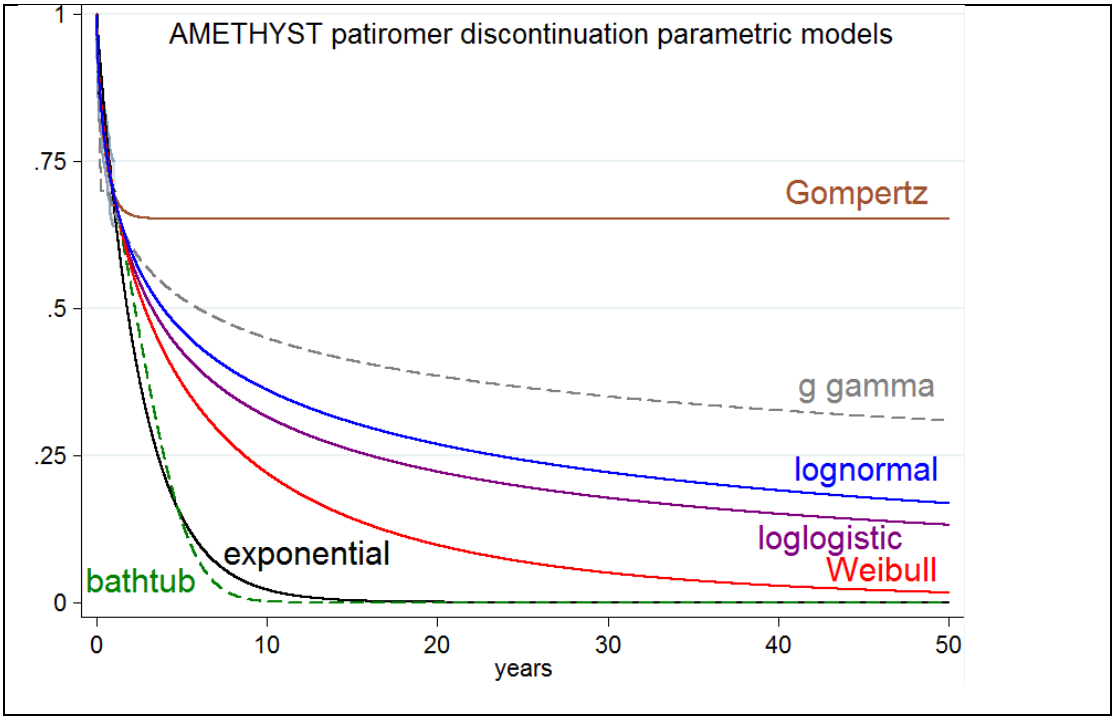


Figure 5 Parametric models of Patiromer discontinuation in AMETHYST

The lowest information criteria (AIC/BIC) scores (Table 8) were found in lognormal, gamma and bathtub models. The exponential model had poor AIC/BIC scores. Except for the bathtub and exponential parametrics, the models predict that some individuals remain on Patiromer almost indefinitely should they remain alive. Long-lived compliance to Patiromer (a preventative medication requiring daily administration) lacks evidence and may be implausible. For the lognormal model a substantial proportion of patients continue taking Patiromer until death. By contrast the bathtub model predicts all have discontinued by about ten years and applies an increasing hazard in extrapolation.

The ERG note that observed KM survival plot has an initial curved phase followed with a linear trajectory from about 100 days (Figure 6, right) ; this is also reflected in a plot of cumulative hazard (CH= -(ln(St)) versus a linear regression fit from 113 to 385 days (Figure 6 , left). The ERG therefore explored implications of a linear trend model. This was extrapolated to the model time horizon and corresponding survival was estimated as S= exp(-CH); the model is rather similar to application of a constant hazard in extrapolation. Over the time frame of the 113 to 385 days it provides an equal or better visual fit to the survival data than the lognormal model (Figure 6, right) .

[redacted]

Figure 6 Models of Patiromer discontinuation in AMETHYST

On extrapolation to a lifetime horizon the ERG judges the linear fit produces more plausible discontinuation than the lognormal model or the severe discontinuation of the bathtub model.

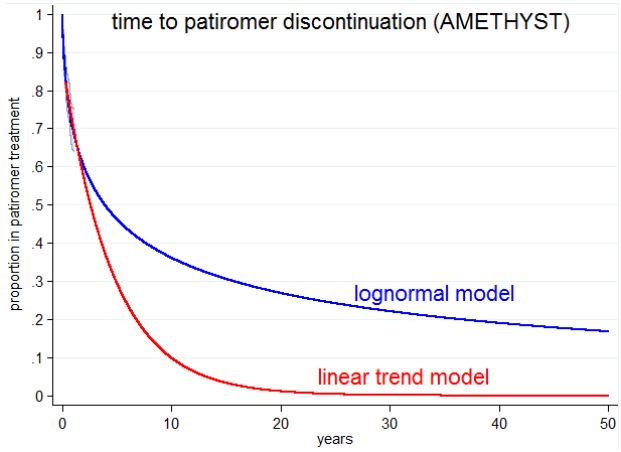


Figure 7 Extrapolation of models of Patiromer discontinuation in AMETHYST

4.5.5 Patiromer discontinuation (PD) in OPAL-HK

Instead of using AMETHYST-DN, it is possible to model Patiromer discontinuation within OPAL-HK using data supplied in clarification. Information criteria for parametric models fit separately for Patiromer and placebo arms are summarised in Table 9.

Table 9 AIC/BIC values for discontinuation of Patiromer and placebo in OPAL-HK

arm	model	obs	df	AIC	BIC
Patiromer	exponential	55	1	73.51184	75.51917
Patiromer	lognormal	55	2	74.61606	78.63073
Patiromer	loglogistic	55	2	75.26805	79.28272
Patiromer	Weibull	55	2	75.44312	79.45778
Patiromer	Gompertz	55	2	75.45464	79.46931
Patiromer	gamma	55	3	75.79136	81.81336
placebo	lognormal	52	2	106.2216	110.1241
placebo	loglogistic	52	2	106.227	110.1295
placebo	Weibull	52	2	106.3281	110.2305
placebo	Gompertz	52	2	107.3988	111.3013
placebo	exponential	52	1	107.9892	109.9405
placebo	gamma	52	3	108.1099	113.9636

Extrapolation of these models is summarised in Figure 8 . For Patiromer discontinuation the exponential model has superior AIC/BIC score and implies cessation of treatment by 5 years, all models except the Gompertz and gamma models, which generate implausible extrapolations, imply almost complete cessation of treatment by ~ 20 years. Discontinuation of placebo occurs rapidly in all the models and appears complete by 2 to 3 years.

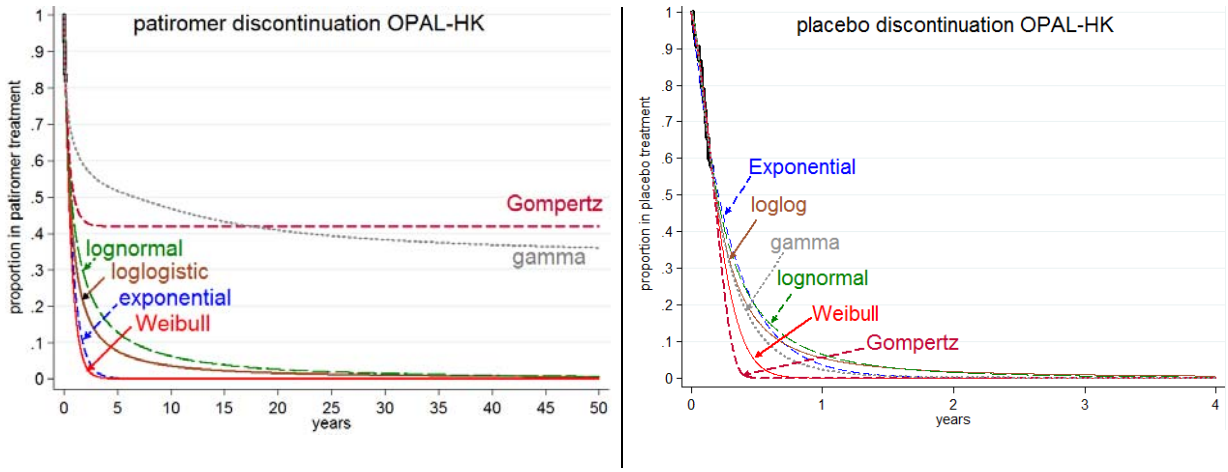


Figure 8 Parametric models of discontinuation in OPAL-HK

If Patiromer treatment is discontinued according to OPAL-HK (rather than AMETHYST-DN) this would reduce the benefit from Patiromer (through reduced RAASi continuation)

4.5.6 Time to hyperkalaemia.

CS Figures 6a and 18 present KM plots for time to hyperkalaemia (HK ≥ 5.5 mmol/l) during the 8 week randomised phase of OPAL-HK. CS Figures 19 and 20 present parametric models

for each arm extended to 34 years follow up. Data supplied in clarification documents indicated that there were 8 and 30 events respectively in Patiromer and placebo arms and that the last event time in the placebo arm occurred at 57 days (two events) and in the Patiromer arm at 29 days, and the last censorings at 59 and 61 days respectively. The CS states "*parametric functions were generated for each arm in order to allow extrapolation to the model lifetime horizon*". The ERG interpret this to mean each arm was modelled separately. Using data supplied in clarification ERG and CS parametric models exactly correspond (Appendix A4). Table 10 and Table 11 show the CS and ERG AIC/BIC scores. The ERG is unclear how differences have arisen: it is possible that the company have used treatment or other variables as covariates. Differences in IC between most models are trivial however, for ERG AIC/BIC scores, the exponential model is slightly superior to the lognormal for the Patiromer arm while these extrapolated models are distinctly different.

Table 10 AIC/BIC values for models of time to HK > 5.5 mmol/l for the Patiromer arm of OPAL-HK

Parametric model;	CS AIC	CS BIC	ERG obs	ERG df	ERG AIC	ERG BIC
Exponential	245.31	247.31	55	1	66.2872	68.29453
Weibull	244.83	248.84	55	2	68.06354	72.07821
Loglogistic	243.08	247.10	55	2	67.78357	71.79824
Gompertz	239.91	243.93	55	2	65.84692	69.86159
Lognormal	***240.92***	***244.94***	55	2	66.7033	70.71797

Table 11 AIC/BIC values for models of time to HK > 5.5 mmol/l for the Placebo arm of OPAL-HK

Parametric model;	CS AIC	CS BIC	ERG obs	ERG df	ERG AIC	ERG BIC
Exponential	376.09	378.03	52	1	142.9971	144.9483
Weibull	377.95	381.85	52	2	144.9629	148.8654
Loglogistic	369.95	373.86	52	2	142.5441	146.4466
Gompertz	377.19	381.09	52	2	143.8032	147.7057
Lognormal	***368.37***	***372.27***	52	2	140.6771	144.5796

In extrapolation the parametric models are likely to be quite strongly influenced by the long flat tail in the Patiromer KM plot and the two late events (at 59 days) in the placebo KM plot. A Cox HR of 0.187 was reported but proportional hazards was not tested for (ERG PH test: P = 0.7744; Schoenfeld residuals Appendix A5).

4.5.7 Time to hyperkalaemia according to region

Data supplied in clarification indicate that most patients in the OPAL-HK randomisation phase were located in non-EU/US centres ([redacted], 79%). The ERG investigated the possible impact on HK of these regional differences. AIC / BIC scores for parametric models by region and treatment are summarised in Table 12. Across the four groups, exponential models offered the best IC statistics, and also reasonable fit to KM plots (

Figure 9).

Table 12 AIC BIC scores for models according to region and treatment

Population	Model	Obs	df	AIC	BIC
Patiromer non EU/US	exponential	45	1	44.1691	45.97577
Patiromer non EU/US	weibull	45	2	46.11889	49.73221
Patiromer non EU/US	gompertz	45	2	45.18068	48.794
Patiromer non EU/US t	lognormal	45	2	45.39105	49.00437
Patiromer non EU/US	loglogistic	45	2	45.99736	49.61068
Placebo non EU/US	exponential	40	1	103.2613	104.9502
Placebo non EU/US	weibull	40	2	105.251	108.6288
Placebo non EU/US	gompertz	40	2	104.9551	108.3328
Placebo non EU/US	lognormal	40	2	103.2918	106.6696
Placebo non EU/US	loglogistic	40	2	104.4619	107.8396
Placebo non EU/US	gamma	40	3	104.6172	109.6839
Patiromer EU/US	exponential	10	1	22.13086	22.43344
Patiromer EU/US	weibull	10	2	23.96334	24.56851
Patiromer EU/US	gompertz	10	2	22.67039	23.27556
Patiromer EU/US	lognormal	10	2	23.24793	23.8531
Patiromer EU/US	loglogistic	10	2	23.69681	24.30198

Placebo EU/US	exponential	12	1	32.84949	33.3344
Placebo EU/US	weibull	12	2	34.03842	35.00823
Placebo EU/US	gompertz	12	2	34.83607	35.80588
Placebo EU/US	lognormal	12	2	32.22736	33.19717
Placebo EU/US	loglogistic	12	2	32.31462	33.28443
Placebo EU/US	gamma	12	3	34.09697	35.55169

Figure 9 Time to HK exponential and KM plots by region (left) parametric models for EU/US right

Figure 10 shows the extrapolation of exponential models and illustrates the difference between regional subgroups according to treatment. For Patiromer recipients, a considerable difference in time to HK is seen according to region, with EU/US patients experiencing more rapid HK than those enrolled at non EU/US centres. The apparent benefit from Patiromer (in increasing time to HK) appears to be much greater for patients from non-EU/US centres than for those from EU/US centres (Figure 11).

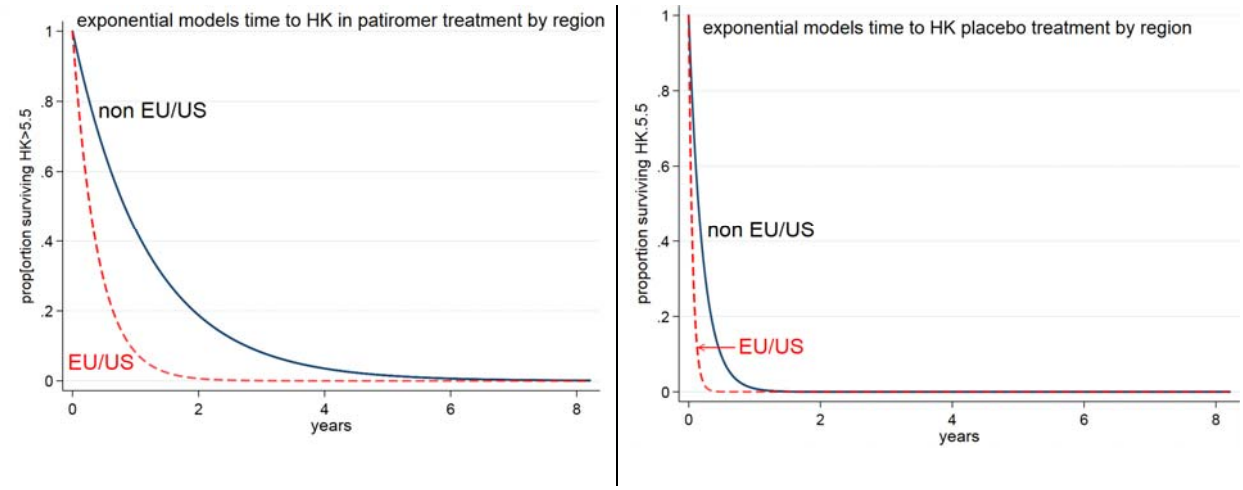


Figure 10 Extrapolation of exponential models of time to HK according to treatment received.

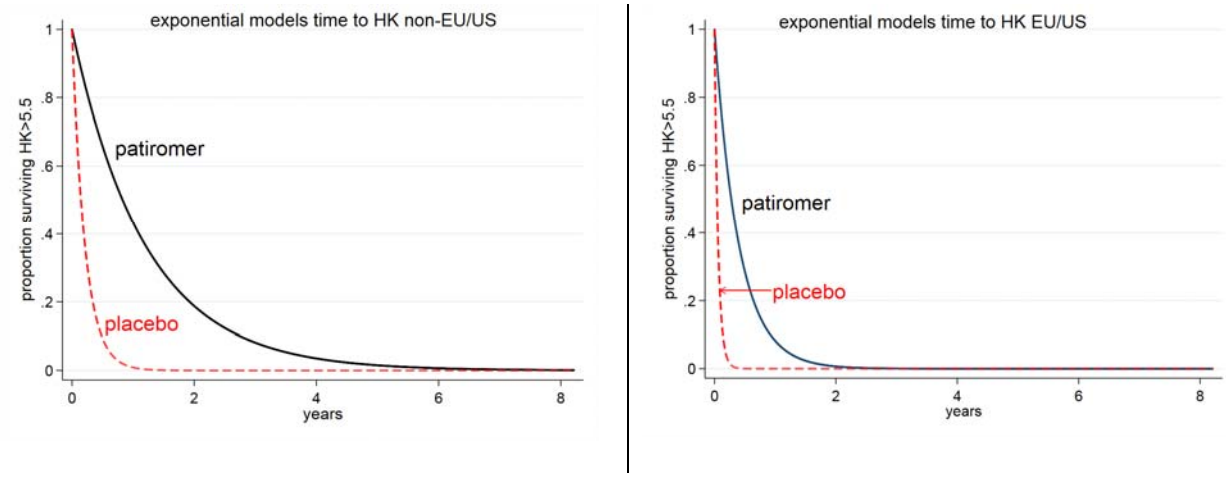


Figure 11 Extrapolation of exponential models of time to HK according to treatment region.

However, the ratio of scale parameters (Patiromer vs no Patiromer) is similar across regional populations inferring that the relative effectiveness of Patiromer is likely to be similar across populations and that the absolute differences seen reflect differing demographics between the populations. This being the case the ERG consider the EU/US subgroup may be more generalizable to the UK, and the use of average trial results in the company model an overestimate of benefit from Patiromer. Because of differences by subgroup, any models for a "whole" population will be influenced by the proportion of non-EU/US patients relative to EU/US patients.

4.5.8 Progression from CKD to ESRD

The CS performed systematic reviews (detailed in CS Appendices) to identify studies to populate their economic model; the CS then used specified studies to determine transition probabilities and relative risks for particular events such as CKD progression. The quality of these reviews is difficult to assess within time constraints. It is worth bearing in mind that: "*The framing of the question, the choice of eligible studies, the selection of comparisons, populations, and outcomes of interest, the types of data extracted, and the statistical methods used, along with many other factors, allow for substantial diversity in the final results. More importantly, the interpretation of even the same results can differ*" [58].

CS Table 33 provides monthly transition probabilities (TPs) and Relative Risks (RRs) for important events used in the economic model. For further details the CS refers the reader to Appendices included in the submission. However these cross references fail to provide insight into how the TPs and RRs were estimated from the selected data sources: the submission's description of how these inputs were calculated was opaque. The ERG therefore requested clarification on these model parameters, and undertook independent analyses to obtain some of the TP and RR values listed in CS Table 33. The methods employed by the ERG are described in Appendix A6.

The large NMA of international studies by Xie et al. [5] was used in the CS to estimate several of the TPs and RRs listed in CS Table 33. CS Appendix B Table 58 provides details of the Xie study. The ERG provide a summary of Xie et al in 4.5.1. Because of its impact on cost effectiveness estimates the most important of the events is CKD to CKD progression. The CS used Landray et al. data (382 patients, see 4.5.2 for a summary) for estimating a TP (= 0.0139) and the NMA paper by Xie et al. (~64,000 patients) for RR (= 0.64). The ERG looked for consistency in CKD progression between the Landray et al.[57] and Xie studies. The method employed by the company to estimate the value of 0.0139 was supplied in clarification (Appendix A7) and was replicated by the ERG but employing data from Xie et al. with TP results of 0.001776 and 0.008977 for ACEi and ARBs trials respectively; if these are combined in the ratio 0.71:0.29 as suggested in the CS a single value of 0.003864 is obtained. The ERG estimates based on Xie et al produces a monthly probability of 0.0043 for placebo and of 0.0040 for active controls. For consistency and because of the numbers involved, the ERG argue it would be better to use the TP based on Xie et al rather than Landray et al. Additionally, the ERG consider it probable that CKD patients who discontinue RAASi typically would typically receive alternative active treatment (rather than no treatment as implied in placebo arms of trials and used in the company model). The ERG prefer

consistent use of Xie et al. for incidence of events and applying the active control comparison to RAAS inhibition.

The study by Kovesdy et al [59] reports even lower values of CKD progression for patients in the UK PSP-CKD cohort (Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease) of 16,828 patients. Only 0.64% developed ESRD during 2.0 years up, an annualised rate of ~0.0032 and the monthly probability approximately 0.000265. This finding contrasts greatly with the estimate based on Landray et al. These various TP estimates for CKD progression are summarised in Table 13.

Table 13 Estimates of monthly TP CKD to CKD progression

Source	Monthly TP placebo	Monthly TP active control
CS method based on Landray	0.0139	NR
CS method based on Xie	0.003864	
ERG method based on Xie	0.0043	0.0040
Based on UK PSP-CKD cohort	0.000265	

4.5.9 CKD to CKD progression, CV events, CV mortality and all cause mortality

Table 14 summarises the ERG estimates for monthly transition probabilities derived using data from Xie et al. and Table 15 the ERG estimates of relative risk.

Table 14 Transition probabilities estimated from data in Xie et al.

	Risk	Risk LCI	Risk UCI
CKDprog AC	0.003992611	0.003405167	0.0046314
CKDprog PBO	0.004260026	0.00363338	0.004941387
CVevent AC	0.005081268	0.004772357	0.005400455
CVevent PBO	0.005798885	0.005446586	0.006162872
CV death AC	0.001289636	0.001020041	0.001597266
CVdeath PBO	0.001125274	0.000890008	0.001393752
All cause death AC	0.002282405	0.00194861	0.002647872
All cause death PBO	0.00188341	0.00160787	0.00218512

Table 15 Relative risks estimated from data in Xie et al.

Outcome	Comparison	RR	RR LCI	RR UCI
CKD prog	RAASi vs AC	0.678	0.619	0.743
CKD prog	RAASi vs PBO	0.636	0.581	0.696
CV event	RAASi vs AC	0.916	0.876	0.958
CV event	RAASi vs PBO	0.803	0.769	0.838
CV death	RAASi vs AC	0.824	0.679	0.999
CV death	RAASi vs PBO	0.944	0.773	1.152
All cause death	RAASi vs AC	0.745	0.656	0.847
All cause death	RAASi vs PBO	0.903	0.791	1.032

4.6 *Conclusions of the clinical effectiveness section*

The OPAL-HK trial provides evidence that Patorimer is effective in reducing hyperkalaemia and RAASi discontinuation in CKD patients. However the ERG has a number of concerns about the trial:

- There was no initial sequential testing to establish CKD diagnosis in accordance with guidelines (about [redacted]% of screened eligible patients had stage 2 disease [eGFR 60+ ml/min/ per minute/1.73m^2] at baseline, contravening trial inclusion criteria).
- There was no formal test of a potassium reducing diet before recruitment, as recommended in guidelines and the ERG's clinical experts.
- There was no formal review of hypertension management before recruitment (e.g. optimising the use of diuretics as potassium-depleting drugs). Also [redacted]% of patients were on dual blockade with ACEi and ARB, now contraindicated.
- The specified OPAL-HK population was limited to patients with stage 3-4 CKD on RAAS inhibitor therapy with hyperkalaemia: value in the broader hyperkalaemia population is not addressed.
- Longer term efficacy and safety outcomes are not clear because of the short duration of the trial. The CS includes evidence from AMETHYST-DN to augment safety evidence: an uncontrolled dose-ranging study of Patiromer with 1-year follow-up in patients with diabetes and mild to moderate hyperkalaemia.
- OPAL-HK includes 100% white patients in the withdrawal phase, thus the trial provides no evidence of efficacy or safety for other ethnic groups. AMETHYST-DN similarly recruited 100% white patients.
- OPAL-HK was conducted in the US, EU and Eastern Europe (not the UK) with the majority of patients from Eastern Europe (65%). It is unclear if these populations, or the care they receive, are representative of the UK.
- During the withdrawal phase the management protocol for dose reduction or discontinuation of RAAS inhibitor therapy was more aggressive in the placebo than Patiromer arm, which may may contributed to the difference in RAAS inbitor discontinuation rates.
- Patients responding in the treatment phase and included in the withdrawal phase had initial serum K^+ 5.5 to <6.5 mmol/l and achieved the target range 3.8 to <5.1 mmol/l while receiving Patiromer and RAAS inhibitors over 4 weeks. Thus no randomised

evidence is offered for the patients included in the treatment phase with mild hyperkalaemia at baseline (5.1 to <5.5 mmol/l) or non-responders. These two groups constitute 56% of recruitment. The value of Patiromer in mild hyperkalaemia is not established by the CS.

With respect to the first three concerns, effective management of patients in accordance with guidelines might have altered the population eligible for and recruited to OPAL-HK. It is unclear how a more difficult-to-treat population would have responded to Patiromer

Patiromer is licenced to treat hyperkalaemia (HK). However, the company submission to NICE is restricted to patients with chronic kidney disease (CKD) stages 3 and 4. CKD is unique in that RAAS inhibition substantially reduces progression to ESRD over and above other active antihypertensive treatments, while RAAS inhibition is no better than other antihypertensives at preventing CV disease. The value proposition rests on Patiromer, by treating hyperkalaemia, keeping patients from RAASi discontinuation or dose reduction. An epidemiological model then predicts reduction in disease progression with consequent affect upon costs and quality of life. The model is populated from a wide range of epidemiological sources (the most important of which are discussed in 4.5 above) which appear selected and potentially biased. The restriction to the CKD population by the company appears entirely driven by the needs of the model.

The company provide a CPRD (English GP database) analysis of CKD patients to provide their model with representative estimates of RAASi discontinuation. This analysis shows that CKD patients in primary care are different to the OPAL-HK trial population. CPRD patients were more likely to be female (54% vs 42%), on average [redacted] years younger ([redacted] vs 65.0), less severe CKD (eGFR 45.7 vs 39.0), considerably less likely to have diabetes (23% vs 63%), hypertension (82% vs 96%), heart failure (18% vs 42%) or previous myocardial infarction (14% vs 27%). Thus, the trial population are not representative of the UK population.

5 COST EFFECTIVENESS

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

The CS (Appendices G, H, I and L) provides detailed reports of 4 systematic reviews undertaken in 2018, aimed at identifying; a) cost-effectiveness and HRQoL studies; b) health state utilities for CKD and CVD; c) cost and resource use; d) relationship between hyperkalaemia and major adverse cardiac events or mortality in a CKD population. A further

non-systematic search of secondary data (economic evaluations and systematic reviews of economic evaluations) on RAASi v placebo in CKD or diabetic retinopathy undertaken in 2016 is also reported.

The search strings and sources used for the 4 systematic reviews appear to be adequate. Lists of excluded studies at full-text are not provided. As noted above in section 4.5.8, the quality of these reviews is difficult to assess within time constraints. It is worth bearing in mind that: "*The framing of the question, the choice of eligible studies, the selection of comparisons, populations, and outcomes of interest, the types of data extracted, and the statistical methods used, along with many other factors, allow for substantial diversity in the final results. More importantly, the interpretation of even the same results can differ*" [58].

5.1.1 Conclusions

Table 23 on page 78 of Document B provides a reasonable summary of the results of the cost-effectiveness studies of Patiromer.

- Sutherland et al [60] conclude that Patiromer results in gains of 0.33 to 0.54 QALYs and net gains, taken by the ERG to mean net savings, of £9,540 to £9,950.
- Little et al [61] estimate a net QALY gain from Patiromer of only 0.0004 QALYs, a net cost in 2011 prices of US$10,690 and so an ICER of US$26 million per QALY

The company omits to mention that Sutherland et al is authored by staff of the European Center of Pharmaceutical Medicine at the University of Basel and staff of Vifor. It appears that Vifor commissioned the model of the current submission from the European Center of Pharmaceutical Medicine. As a consequence, the results of Sutherland et al are likely to be subject to exactly the same critique as the ERG critique of the current company submission.

Little et al is authored by staff of the Department of Medicine, Walter Reed National Military Medical Center, Bethesda, MD, USA who declare that they have no conflicts of interest. The cost results of Little et al are of less relevance to the UK setting, but very small QALY gain that is estimated from use of Patiromer is noteworthy. The time horizon of the model of Little et al is only 1 year, while in the current submission the main benefits of Patiromer arise from avoiding ESRD over a number of years. Further, a broader group of patients than CKD patients is included, compared to the current submission.

The literature review identifies a number of cost-effectiveness studies of sodium polystyrene sulphate (SPS) for hyperkalaemia. Little et al note that this is often usual standard of care in the US and estimates the cost effectiveness of Patiromer relative to SPS.

5.2 *Summary of company's submitted economic evaluation*

5.2.1 NICE reference case checklist

Table 16: NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice. The scope specifies "*Standard care, including a low-potassium diet with or without agents that reduce the level of potassium in the body*".	Patiromer is compared with placebo. The main effect of Patiromer is to reduce RAASi discontinuations. Those who discontinue RAASi are assumed to not receive any further active hypertensive treatment. This is unlikely to reflect routine NHS practice.
Patient group	As per NICE scope: "*Adults with hyperkalaemia*".	Based on the OPAL-HK trial, the patient group is limited to CKD patients with initial moderate hyperkalaemia The 1st cycle of the model relies upon data from OPAL-HK. The hazard ratio of RAASi discontinuation for those on Patiromer compared to those on placebo is also drawn from OPAL-HK. Extrapolation of Patiromer discontinuations relies upon AMETHYST-DN, the trial of Patiromer among patients with hyperkalaemia and diabetic kidney disease. Extrapolation of RAASi discontinuations for placebo relies upon a company analysis of CPRD data, restricted to patients with hyperkalaemia subsequent to a diagnosis of CKD or a co-diagnoses of heart failure and/or diabetes.
Perspective costs	NHS & Personal Social Services	Largely, but adverse events are not included.
Perspective benefits	All health effects on individuals	Largely, but adverse events are not included.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	35 years, which given the baseline age of 65 years is effectively a lifetime horizon.
Synthesis of evidence on outcomes	Systematic review	Phase A of OPAL-HK provides the proportion who respond to Patiromer at 4 weeks.

		Phase B of OPAL-HK provides the proportions who discontinue RAASi at 12 weeks for Patiromer and for placebo. Phase B of OPAL-HK provides the hazard ratio for RAASi discontinuation for those receiving Patiromer compared to those receiving placebo. Analysis of CRPD data provides estimates of RAASi discontinuation for placebo. The AMETHYST-DN trial provides the data used to estimate long term Patiromer discontinuation. The baseline probabilities of events for those who discontinue RAASi are drawn from values taken from a review of the literature. The odds ratios of events for RAASi vs no RAASi that are applied to the baseline probabilities of events for those who discontinue RAASi are taken from Xie et al [5], a systematic review identified by the company in its literature search.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The quality of life value for CKD event free survival of 0.744 is drawn from Jesky et al [62], which is based upon the EQ-5D-3L. The quality of life values that are applied for events are derived from a variety of disparate sources. The quality of life values are further conditioned the usual EQ-5D UK age related norms of Ara and Brazier [63].
Benefit valuation	Time-trade off or standard gamble	Jesky et al [62] and Ara and Brazier [63] use the UK population tariff based upon time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Jesky et al [62] and Ara and Brazier [63] use the UK population tariff based upon time trade off among a representative sample of the UK general public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.

Probabilistic modelling	Probabilistic modelling	Yes. The result of this are unusual in that the CEAC is extremely flat, indicating an unusually high degree of uncertainty around the cost effectiveness estimates despite the company central estimate being dominance for Patiromer. This is in part due to the sampling of quality of life values and costs, but may also be due in part the relatively patient numbers in OPAL-HK and also the degree of extrapolation beyond the trial period.
Sensitivity analysis		A range of univariable sensitivity analyses are included.

5.2.2 Model structure

The model structure is as per figure 10 of the company submission document B, as reproduced below (see Figure 12).

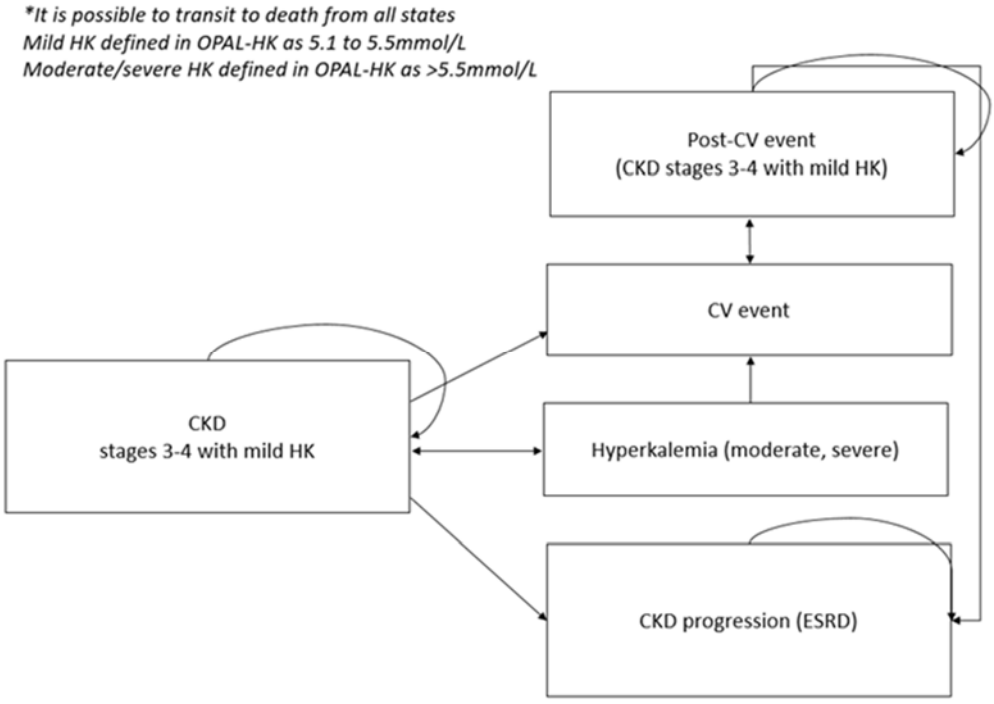


Figure 12: Company model structure

The implementation of this model structure is quite unusual. Each arm is split into four sub-cohorts:

- A: On Patiromer and on RAASi at baseline
- B: On Patiromer and off RAASi at baseline
- C: Off Patiromer and on RAASi at baseline
- D: Off Patiromer and off RAASi at baseline

The above model structure is applied independently to each of the four sub-cohorts. Patients cannot move between these sub-cohorts. A patient in sub-cohort A who discontinues Patiromer does not transfer to sub-cohort C.

For both the independent sub-cohorts C and D the probabilities of hyperkalaemia events are taken from a placebo specific hyperkalaemia event parameterised curve. For the both the independent sub-cohorts A and B the situation is more complex because not all those on Patiromer at baseline will remain on it. Weighted average probabilities of hyperkalaemia are calculated based upon a Patiromer discontinuation parameterised curve being applied to a Patiromer specific hyperkalaemia event parameterised curve, coupled with the residual of the Patiromer discontinuation parameterised curve being applied to a placebo specific hyperkalaemia event parameterised curve. The combination of the three parameterised curves provides the time specific probability of hyperkalaemia for both the independent sub-cohorts A and B.

The main treatment effects depend upon whether a patient is on or off RAASi. For both the independent sub-cohorts B and D who are off RAASi at baseline constant monthly probabilities of the events are applied as tabulated below. For the independent sub-cohorts A and C who are on RAASi at baseline, on-RAASi relative risks derived from the literature are applied to derive the baseline probabilities of events as outlined below.

But in sub-cohorts A and C patients will discontinue RAASi over time. For sub-cohort C, off Patiromer and on RAASi at baseline, a placebo RAASi discontinuation parameterised curve is derived from CPRD patient level data. This placebo RAASi discontinuation parameterised curve conditions the relative risks, and so determines the implied the time dependent monthly event probabilities. The placebo RAASi discontinuation curve converges to unity and by the end of the time horizon the probability of events for those in sub-cohort C have converged with those in sub-cohorts B and D.

For sub-cohort A, on Patiromer and on RAASi at baseline, a hazard ratio of [redacted] for Patiromer RAASi discontinuations is derived from OPAL-HK Kaplan Meier data. This [redacted] hazard ratio is applied to the placebo CPRD RAASi discontinuation parameterised curve to derive a markedly superior RAASi discontinuation curve for those on Patiromer. The RAASi

discontinuation curve for sub-cohort A is calculated as the sum of the Patiromer specific RAASi discontinuation curve conditioned by the Patiromer discontinuation curve and the placebo specific RAASi discontinuation curve conditioned by the residual of the Patiromer discontinuation curve. The RAASi discontinuation curve for sub-cohort A then conditions the relative risks and probabilities of events as per sub-cohort D. But the RAASi discontinuation curve for sub-cohort A does not converge to unity, and the probabilities of events in this sub-cohort remain below those of the other sub-cohorts throughout the time horizon of the model.

The Patiromer arm is differentiated from the placebo arm according to the proportions of patients in each of the four independent sub-cohort, A, B, C and D. For the Patiromer arm the proportion of patients going on to receive maintenance Patiromer is based upon the OPAL-HK Phase A response percentage, i.e. week 4 of OPAL-HK, of 107 / 243 = 44%.

Table 17: Distribution of patients across independent sub-cohorts for Patiromer arm

	Patiromer	Placebo
OPAL-HK Part A	243	
OPAL-HK Part B	107 (44%)	
Randomised to	55	52
Of whom hyperkaliaemic On RAASi Off RAASi	[redacted]	[redacted]
Of whom non-hyperkaliaemic On RAASi Off RAASi	[redacted]	[redacted]
Pooled On RAASi Off RAASi	 52 (95%) 3 (5%)	 25 (48%) 27 (52%)

The 44% proportion responding during Phase A is divided between sub-cohorts A and B according to the proportion of the 55 patients randomised to Patiromer during OPAL-HK Phase B who remained on RAASi at the end of Part B, i.e. week 12[1] of OPAL-HK. This was [redacted] of the [redacted] patients who were hyperkaliaemic at week 12 and [redacted] of the patients who were not hyperkaliaemic at week 12 to yield a total of 52 / 55 = 95%. Hence 95% * 44% = 42% start in sub-cohort A and 5% * 44% = 3% start in sub-cohort B.

In a similar manner the 56% of OPAL-HK Phase A non-responders is divided between sub-cohorts C and D according to the proportion of the 52 patients who were randomised to

[1] Based upon figure 11 of Document B

placebo during OPAL-HK Phase B who remained on RAASi at week 12. This was 20 of the 47 patients who were hyperkaliaemic at week 12 and all 5 of the patients who were not hyperkaliaemic at week 12 to yield a total of 25 / 52 = 48%. Hence 48% * 56% = 27% start in sub-cohort C and 52% * 56% = 29% start in sub-cohort D.

In the above it can be noted that the distribution of patients on RAASi pools those on RAASi with hyperkalaemia and on RAASi without hyperkalaemia. These patients are treated identically in the modelling in terms of the likelihoods of hyperkalaemia, RAASi discontinuation and other events. Similarly, the model pooled patients off RAASi regardless of whether they were with or without hyperkalaemia.

For the placebo arm, no patients are assigned to sub-cohorts A or B and all patients are divided between sub-cohorts C and D. OPAL-HK does not provide a placebo subgroup from baseline, so the company assumes that the distribution between sub-cohorts C and D for the placebo arm will be proportionately the same as that among those randomised to placebo during OPAL-HK Part B: 48% and 52%.

Table 18: Distribution of patients across independent sub-cohorts by arm

	Patiromer	**Placebo**
Sub-cohort A: On PATR, On RAASi	42%	..
Sub-cohort B: On PATR, Off RAASi	3%	..
Sub-cohort C: Off PATR, On RAASi	27%	48%
Sub-cohort D: Off PATR, Off RAASi	29%	52%

The above (Table 18) is not immediately intuitive. A simpler presentation of it is to consider 100 patients being modelled, for which [redacted] in sub-cohort C and [redacted] in sub-cohort D are common to both arms and so cancel out between the arms. Taking these [redacted] patients out of both arms results in the following distribution of patients between the arms.

Table 19: Effective distribution of patients across independent sub-cohorts by arm

	Original distribution		**Common removed**		**Effective distribution**	
	Patiromer	Placebo	Patiromer	Placebo	Patiromer	Placebo
Sub-cohort A	42	..	42	..	95%	..
Sub-cohort B	2	..	2	..	5%	..
Sub-cohort C	27	48	..	21	..	48%
Sub-cohort D	29	52	..	23	..	52%
Total	100	100	44	44	100%	100%

The effective distribution model compares Patiromer and placebo arms, taking the OPAL-HK Phase B RAASi discontinuation rates without reference to Phase A.

OPAL-HK does not provide a comparator arm from baseline and a randomised comparison is only available among those randomised at the start of Phase B. The company model assumes that the experience of those who do not receive Patiromer will be the same as that of the patients entering Phase B of OPAL-HK and were randomised to receive placebo. As a consequence, key unwritten modelling assumptions are that among those who have never received Patiromer:

- At baseline the same proportion will be on RAASi as the proportion of those who during Phase B of OPAL-HK were randomised to placebo who were on RAASi at the end of Part B
- The proportion who are on RAASi will have the same experience as those who during Phase B of OPAL-HK were randomised to placebo and who were on RAASi at the end of Part B.
- The proportion who are off RAASi will have the same experience as those who during Phase B of OPAL-HK were randomised to placebo and who were off RAASi at the end of Part B.

5.2.3 Population

The population modelled by the company centres around that of the OPAL-HK trial which is limited to patients with hyperkalaemia and CKD. Additional data is drawn from a variety of sources including the AMETHYST-DN trial, the CPRD database and papers within the literature. Similarly, these are not as aligned with the population of the scope: patients with hyperkalaemia.

5.2.4 Interventions and comparators

Patiromer is compared with placebo.

The main effect of Patiromer is to slow RAASi discontinuations. Those who discontinue RAASi are assumed to receive placebo for their hypertension rather than an alternative active control treatment.

5.2.5 Perspective, time horizon and discounting

The perspective and discounting is as per the NICE reference case. The time horizon is 35 years which given the baseline age of 65 years is effectively a lifetime horizon.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Mortality

CKD stage 3 patients have age banded SMRs of 3.1, 2.0 and 2.2 for those aged under 70, 70 to 79 and 80 plus respectively, taken from the Norwegian study of Eriksen et al [64]. A mortality multiplier CKD stage 4 patients of 2.56 taken from Sud et al [65] is applied to these SMRs, resulting in pooled age banded SMRs of 5.2, 3.4 and 3.7 for those aged under 70, 70 to 79 and 80 plus respectively

ESRD patients have age banded annual mortality risks taken from Steenkamp et al [66], in bands of 5 years from age 65 of 114 per 1,000, 143 per 1,000, 200 per 1,000, 258 per 1,000 rising to 371 per 1,000 for those aged 85 plus.

It can be noted that due to the CKD mortality risks calculated using SMRs increasing with the general population all-cause mortality risks as patients age, the increased mortality risk from ESRD relative to CKD declines with age. By age 85 the mortality risks in the model for CKD and ESRD are the same. This may suggest that the application of the CKD SMRs for those who are very old may exaggerate the effects of CKD due to the SMRs that are applied to general population all-cause mortality risks being too high.

5.2.6.2 Baseline probabilities of events and RAASi relative risks

(See also 4.5.1) The main effects of Patiromer are not direct but rather indirect. The model estimates that Patiromer enables more patients to remain on RAASi. RAASi is in turn effective in reducing the probabilities of:

- Developing ESRD, baseline annual probability for no RAASi of 17% sourced from Landray et al [57],
- Having a cardio-vascular event, baseline annual probability for no RAASi of 7.8% sourced from Xie et al [5],
- Having a cardio-vascular related death, baseline annual probability for no RAASi of 1.8% sourced from Parving et al [67], and
- CKD mortality, SMRs for CKD patients taken from Eriksen et al [64] and Sud et al [65] and ESRD mortality taken from Steenkamp et al [66], as outlined above

The relative risks for RAASi of these events are taken from the NMA of Xie et al [5]. This lists relative risks for RAASi relative to an active control and relative to placebo. The company uses those relative to placebo:

- CKD to ESRD relative risk of 0.64,
- CKD to CV event relative risk of 0.82,
- CV event being fatal relative risk of 0.88, and
- All-cause mortality relative risk of 0.87.

RAASi discontinuation curve placebo and Patiromer hazard ratio of RAASi discontinuation

In the model the proportions on RAASi at baseline are determined by those on RAASi at the end of OPAL-HK:

- 69% for Patiromer, and
- 48% for placebo.

Thereafter the risk of discontinuing RAASi in the placebo arm is calculated from RAASi discontinuation data among those having a hyperkalaemia event in the UK CRPD database.

Figure 13: CPRD RAASi discontinuation subsequent to hyperkalaemia curves

The Weibull has the lowest AIC and BIC and is selected for the base case. Something appears to have gone wrong with the exponential as it bears no relation to the Kaplan Meier data, but it is not used for the company modelling. The company also estimates log-normal and log-logistic curves but does not present these or their information criteria on the apparent grounds that applying a hazard ratio to them is invalid, in that it will not result in a log-normal or a log-logistic curve resulting for Patiromer.

For Patiromer, the OPAL-HK Phase B RAASi discontinuation curves are used to estimate a hazard ratio of RAASi discontinuation of [redacted]. Note that this data is only over 8 weeks, and relates to only [redacted] events in the Patiromer arm compared to [redacted] events in the placebo arm.

[redacted]

Figure 14: OPAL-HK RAASi discontinuation Kaplan Meier data: S(t) and N at risk

This results in the following proportions being modelled as being on RAASi.

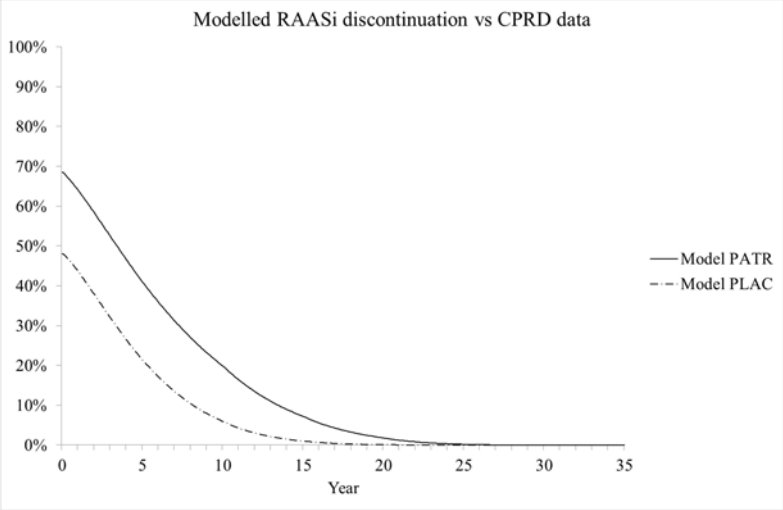


Figure 15:Modelled proportions on RAASi by arm

Note that the company collected anti-hyperintensive discontinuation data during AMETHYST-DN. But at clarification the company stated that this data only related to anti-hyperintensives as a whole, implying that RAASi discontinuation data could not be extracted from the subset of patients on RAASi, and so was not useful for current purposes.

5.2.6.3 Hyperkalaemia curves

(See also: 4.5.6). Parameterised curves were independently fitted to the 8 week OPAL-HK Phase B data for placebo and Patiromer; i.e. proportionate hazards was assumed not to apply and no treatment effect was applied within an analysis pooling data between the arms. Hyperkalaemia was defined as K^+ of at least 5.5 mmol/l. It is not known whether the company

explored proportionate hazards, why it was rejected as an approach or what effect this would have had, and the ERG did not ask about this at clarification.

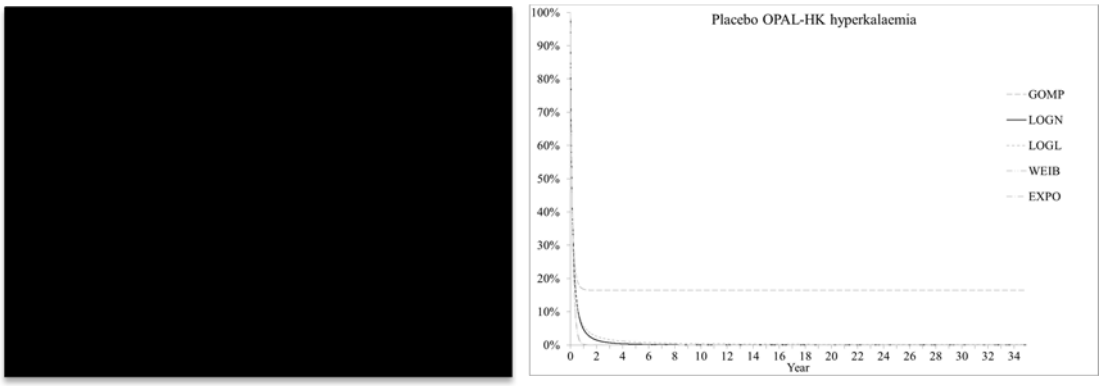


Figure 16: OPAL-HK placebo hyperkalaemia curves

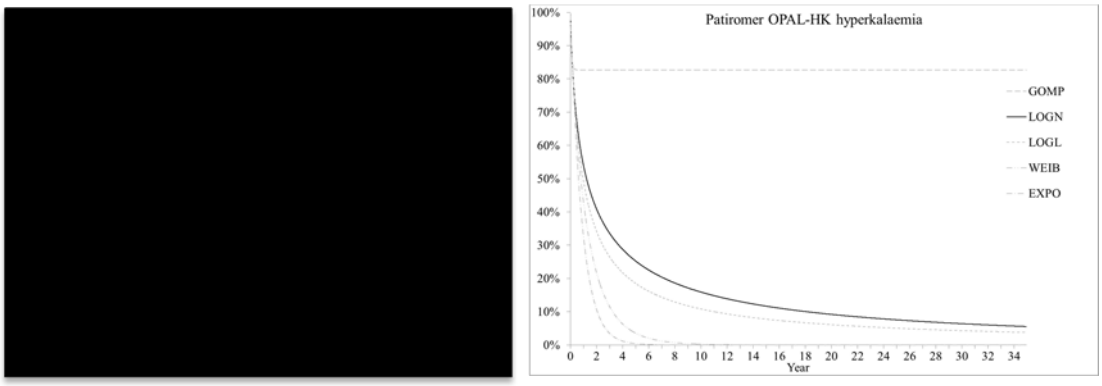


Figure 17: OPAL-HK Patiromer hyperkalaemia curves

For both arms there may be the suggestion of a steeper initial Kaplan Meier curve with some levelling off thereafter. It is not clear that the smooth curves that have been fitted necessarily reflect this pattern. Any levelling off would tend to cause less hyperkalaemia to be extrapolated in both arms.

The log-normal had the lowest information criteria for both Patiromer and placebo so was used for both.

5.2.6.4 Patiromer discontinuation curves

(see also: 4.5.4and 4.5.5). Due to the somewhat longer follow-up during AMETHYST-DN than during OPAL-HK the company fitted curves to the AMETHYST-DN Kaplan Maier Patiromer discontinuation data.

Figure 18: OPAL-HK and AMETHYST Patiromer discontinuations and fitted curves

There may be some suggestion that Patiromer discontinuation during OPAL-HK was worse than during AMETHYST-DN during the same period. All the curves fitted to the AMETHYST-DN data are a poor visual fit to the OPAL-HK data.

The exponential and gamma curves provide a relatively poor visual fit to the AMETHYST-DN data. The other curves appear to be reasonable fits, but the log-normal curve has the best information criteria and the company selects it on this basis. As is common, the curves mainly diverge during the period of extrapolation.

5.2.6.5 Application of the various curves within the model and resulting probabilities

What follows provides an account of how the above curves are applied within the model to qualify the relative risks and so the probabilities of events within the four model sub-cohorts. Those not interested in the technical details might move forward to section 5.2.7 on quality of life.

Calculation of sub-cohort hyperkalaemia monthly event probabilities

Monthly probabilities of hyperkalaemia events are calculated for Patiromer from the Patiromer parameterised hyperkalaemia curve and for placebo from the placebo parameterised hyperkalaemia curve.

Both the independent sub-cohorts C and D are modelled as being off Patiromer at baseline, so have the monthly placebo hyperkalaemia probabilities applied. Both the independent sub-cohorts A and B are modelled as being on Patiromer at baseline, so have the monthly Patiromer hyperkalaemia probability applied at baseline. But they discontinuing Patiromer according to the Patiromer discontinuation curve that is derived from the AMETHYST-DN Kaplan Meier discontinuation data. As a consequence, for these patients each subsequent monthly probability of hyperkalaemia is a weighted average of the monthly Patiromer hyperkalaemia probability and the monthly placebo hyperkalaemia probability, weighted by the proportion of patients on and off Patiromer respectively.

The following figure is based upon the monthly hyperkalaemia probabilities, though as reviewed in more detail later the company base case has an error that causes it to apply daily hyperkalaemia probabilities to the monthly cycles of the model. The proportion on Patiromer in sub-cohorts A and B is measure on the left hand vertical axis, with the monthly probabilities being measured on the right hand vertical axis.

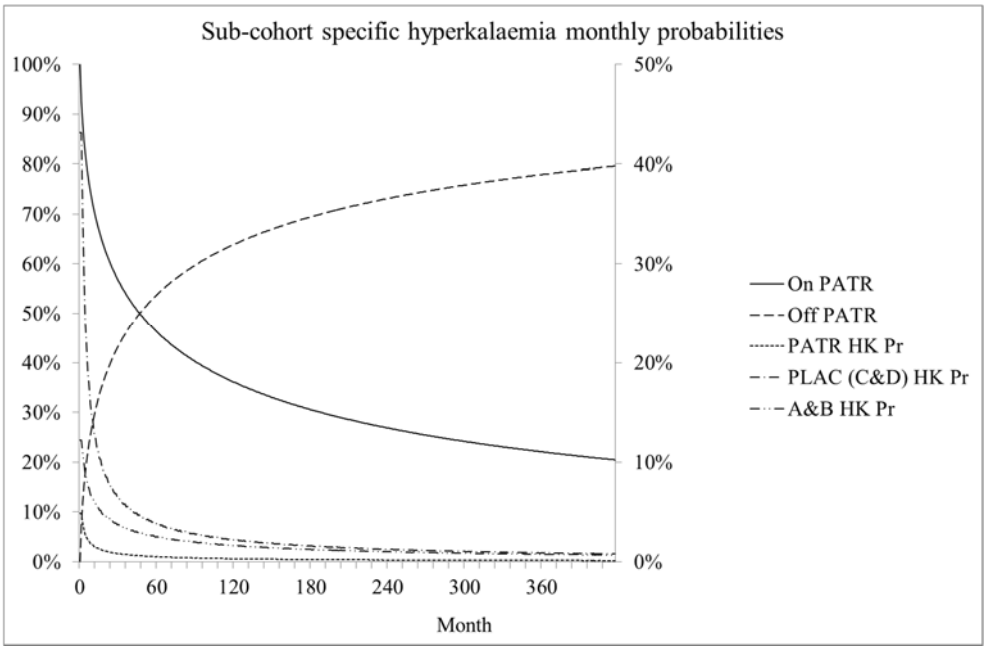


Figure 19: Sub-cohort monthly probabilities of hyperkalaemia

The above (Figure 19) shows how those not on Patiromer from baseline in sub-cohorts C and D have a very high initial monthly probability of hyperkalaemia, as high as 43% in the 1st cycle. But this probability drops off quite quickly.

Those on Patiromer have a much lower initial monthly probability of hyperkalaemia: only 10% in the 1st cycle. Those in sub-cohorts have the weighted average monthly probability applied. By month 50 half of these patients are modelled as having discontinued Patiromer. Their month 50 probability of hyperkalaemia is consequently mid-way between the 1.2% Patiromer probability and the 4.5% placebo probability: a monthly 2.8% hyperkalaemia probability. Due to 20% of patients in sub-cohorts A and B remaining on Patiromer at the end of the time horizon, the probability of hyperkalaemia in these sub-cohorts is always below that in sub-cohorts C and D.

The above also illustrates another unwritten assumption. Those discontinuing Patiromer are assumed to have the contemporaneous placebo probability of hyperkalaemia. It can be argued that those discontinuing Patiromer should be assumed to have the placebo hyperkalaemia curve appended from that point, with its very much higher initial probabilities of hyperkalaemia. If this should apply or should apply to some degree, the model structure is biased in favour of Patiromer in this respect.

5.2.6.6 Calculation of sub-cohort RAASi event probabilities and relative risks

For the sub-cohort of patients who are off Patiromer but on RAASi in the first cycle, the sub-cohort relative risk of ESRD is conditioned by the placebo RAASi discontinuation curve. This cycle specific sub-cohort relative risk is then applied to the 1.39% monthly off-RAASi probability of ESRD to derive the cycle specific sub-cohort monthly probability of ESRD. This is most easily seen graphically as below. This shows the proportion of patients modelled as being on and off RAASi and the resultant ESRD relative risks as measured on the left vertical axis. The resulting monthly probabilities of ESRD are measured on the right vertical axis, which has been scaled so that the off RAASi monthly probability of 1.39% lies in the middle of the axis.

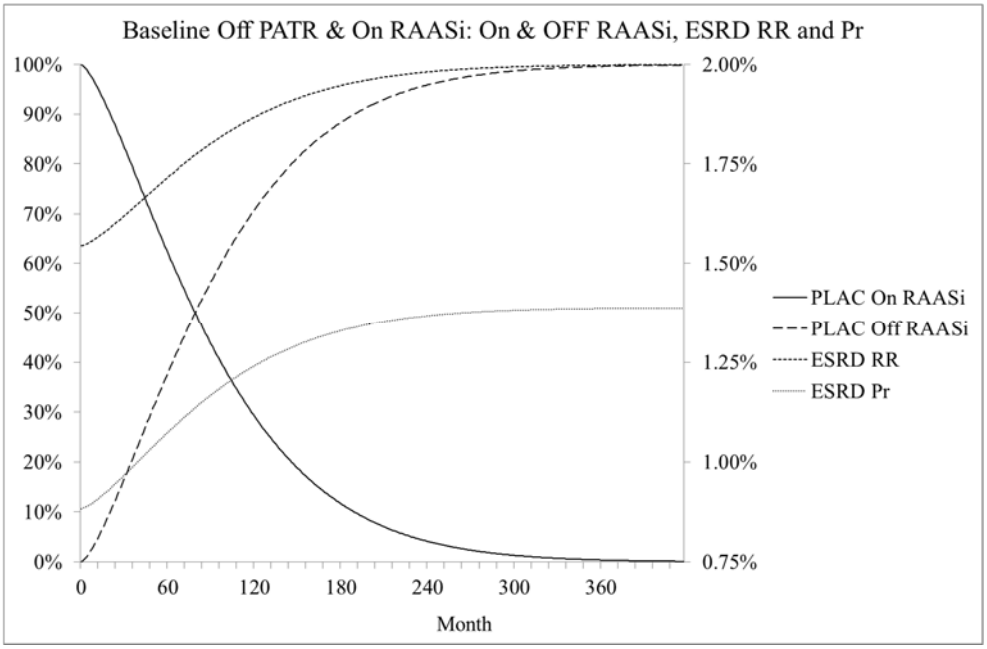


Figure 20: Initially off Patiromer but on RAASi: On & Off RAASi curves, ESRD RR and Probabilities

Initially, all are on RAASi and the relative risk of ESRD is 64%. The monthly probability is consequently 64% * 1.39% = 0.88%. By month 82 half are on RAASi and half are off RAASi. The relative risk is consequently half way between the 64% of those on RAASi and the 100% of those off RAASi, 82%. The 82% relative risk results in in a monthly ESRD probability of 82% * 1.39% = 1.14% which is half way between the 0.88% of those on RAASi and 1.39% of those off RAASi. As the proportion remaining on RAASi falls over time the ESRD relative risk tends towards 100% and the monthly ESRD probability tends towards 1.39%.

The situation is more complicated for the sub-cohort who are on Patiromer and on RAASi in the first cycle. There is a RAASi discontinuation curve for those remaining on Patiromer and a RAASi discontinuation curve for those on placebo. But there is not a RAASi discontinuation curve for those who are initially on Patiromer and on RAASi. This is constructed as the sum of:

- The Weibull RAASi discontinuation curve for those remaining on Patiromer multiplied by the proportion modelling as remaining on Patiromer, as per the log-normal Patiromer discontinuation curve.
- The Weibull RAASi discontinuation curve for those remaining on placebo multiplied by the proportion modelling as having discontinued Patiromer.

This constructed pooled RAASi discontinuation curve is then used to condition the ESRD relative risk and calculate the resulting cycle specific relative risk and monthly probability for the sub-cohort. Again, this is most easily seen graphically as below. The first figure immediately below (Figure 21) shows the construction of the RAASi discontinuation curve, while the subsequent figure (Figure 22) shows how the RAASi discontinuation curve leads to the ESRD relative risk and monthly probability curves.

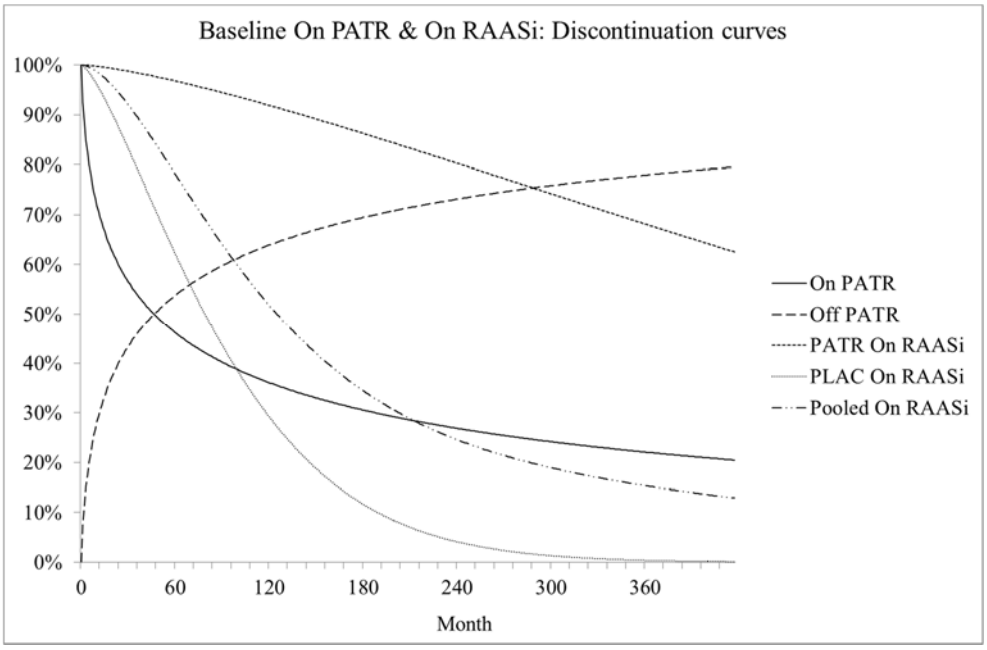


Figure 21: Initially On Patiromer and on RAASi: Discontinuation curves

As an example, in the above curves the proportion remaining on Patiromer has fallen to 50% by month 50. Among those on Patiromer the proportion remaining on RAASi at month 50 is 98% while for those on placebo it is 72%. As a consequence, the constructed on RAASi proportion is mid-way between these two values at 85%.

Within the construction of the sub-cohort RAASi curve is should be noted that among those discontinuing Patiromer and moving onto placebo at, say, month 50 the proportion remaining on RAASi is assumed to be the same as the proportion remaining on RAASi who have received placebo from baseline. This may not be realistic. It may be more realistic to assume that those discontinuing Patiromer would take time to discontinue RAASi to the same extent as those who had only ever received placebo. If so, this will bias the model against Patiromer. Given the sub-cohort specific RAASi discontinuation curve, this conditions the ESRD relative risk and monthly probabilities as previously outlined and as below.

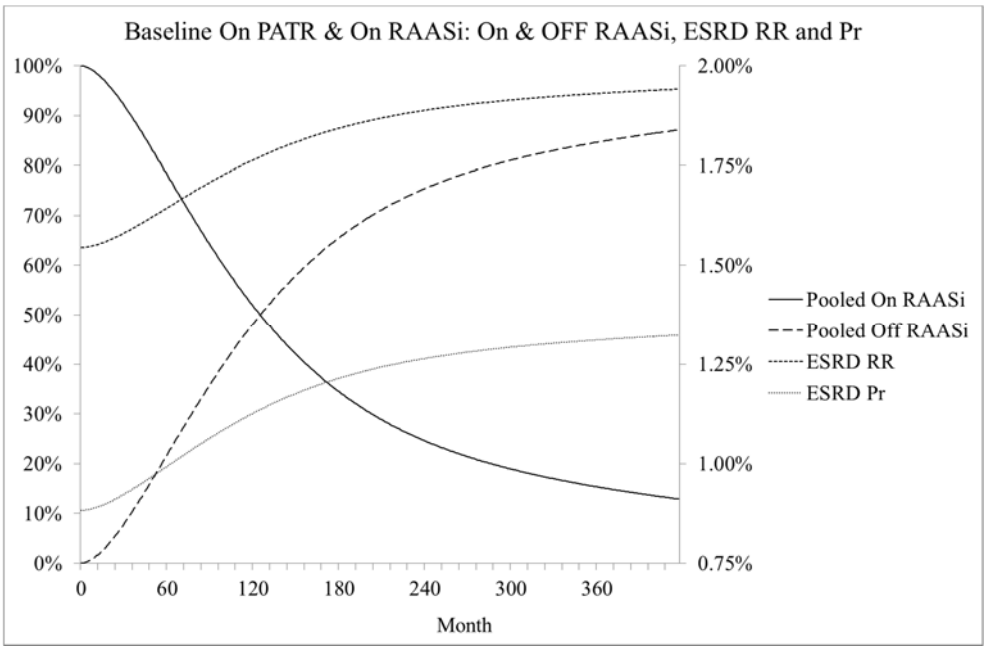


Figure 22: Initially On Patiromer and on RAASi: On & Off RAASi curves, ESRD RR and Probabilities

With all in the sub-cohort being on RAASi at baseline the relative risk of ESRD is 64% and the monthly probability is 64% * 1.39% = 0.88%. But due to a proportion of patients being modelled as remaining on RAASi throughout the relative risk never converges to unity and tends to converge at 95% which results in the monthly probability of ESRD tending to converge at 95% * 1.39% = 1.32%.

The above considerations result in the following sub-cohort specific ESRD relative risks, measured against the left hand axis, and ESRD monthly probabilities, measured against the right hand axis.

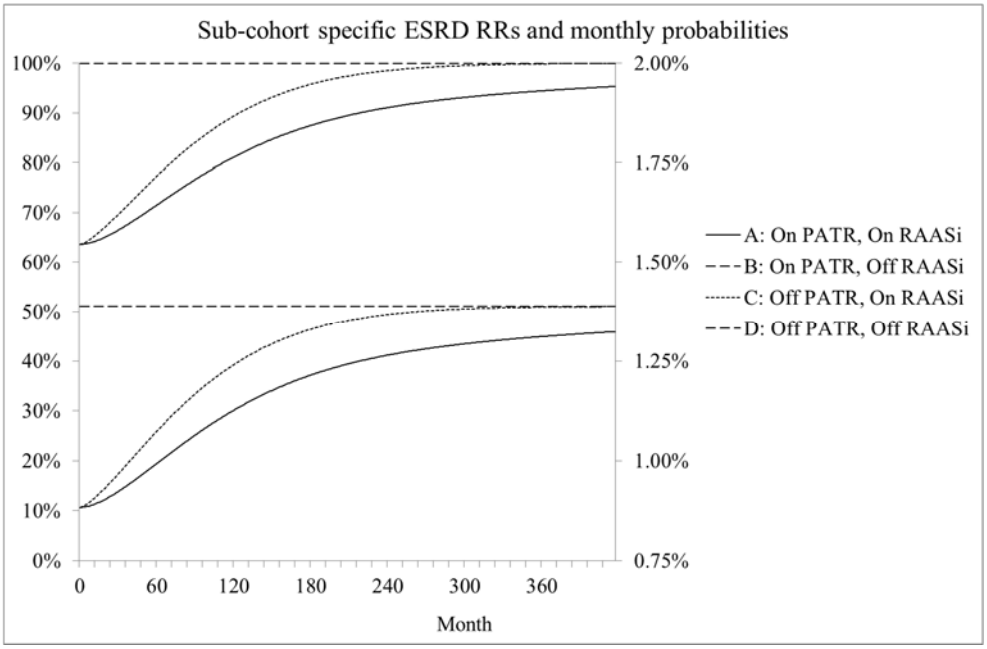


Figure 23: Sub-cohort specific ESRD relative risks and monthly probabilities

The relative risks for both sub-cohort B and sub-cohort D are 100% throughout due to all patients in these sub-cohorts having ceased RAASi at baseline by assumption. As a consequence, the monthly probability of ESRD for these patients is 1.39% throughout.

The baseline relative risk for sub-cohort C, those not on Patiromer but on RAASi at baseline, is 64%, resulting in a baseline monthly probability of ESRD of 64% * 1.39% = 0.88%. But the proportion on RAASi falls and as a consequence the relative risk converges to unity, causing the monthly probability of ESRD for these patients to converge to 1.39%.

The baseline relative risk for sub-cohort A, those on Patiromer and on RAASi at baseline, is 64%, resulting in a baseline monthly probability of ESRD of 64% * 1.39% = 0.88%. But while the proportion on RAASi falls it never falls to zero, and the relative risk converges to around 95%. As a consequence, the monthly probability of ESRD for these patients converges at around 1.32%.

The above describes the derivations of the sub-cohort specific CKD to ESRD relative risks and monthly probabilities. The same method is applied to derived the sub-cohort specific relative risks and monthly probabilities of:

- CKD to cardio-vascular events,
- CKD to all-cause mortality, and
- cardio-vascular events to death.

5.2.7 Health related quality of life

Quality of life within the model is measured relative to the UK population age specific norms as defined by the equation of Ara and Brazier [63]. This results in a mean quality of life for the UK population age 65 of 0.821, with a smooth annual decline thereafter. For instance, at age 70 it declines to 0.805, at age 75 declines to 0.789 and continues to decline thereafter.

Quality of life data was not collected during OPAL-HK. As a consequence, the company relies upon the quality of life values reported in Jesky et al [62] for its baseline quality of life value, a prospective observational study among 745 UK patients in pre-dialysis CKD. This collected EQ-5D-3L data and values it using the standard UK social tariff. Jesky et al report quality of life values of 0.80, 0.80 and 0.74 for stages 3a, 3b and 4 respectively which when weighted by the OPAL-HK baseline proportions of 24%, 32% and 44% result in a CKD event free baseline quality of life value of 0.774. This 0.774 quality of life value is 94% of the UK population norm of 0.821 for those age 65. For event free CKD the model applies this 94% quality of life ratio to the age specific UK population norms over the period of the model.

The quality of life values for events are taken from a variety of disparate sources.

- Hyperkalaemia is assigned a quality of life of 0.816 based upon Wyld et al [68].
- Stroke and MI are assigned quality of life values of 0.519 and 0.605 in the year of the event, based upon Sullivan et al [69]. A balance between stroke and MI of 35:65 is taken from Lee et al [70], yielding a mean quality of life for the year of a cardiovascular event of 0.574.
- Stroke and MI are assigned quality of life values of 0.525 and 0.672 subsequent to the year of the event, drawn from Pockett et al [71]. Coupled with the proportions of Lee et al this yields a mean quality of life post cardiovascular event of 0.620.
- Peritoneal dialysis, haemodialysis and kidney transplant are assigned mean quality of life values of 0.530, 0.443 and 0.712 based upon Lee et al [70]. A balance between peritoneal dialysis, haemodialysis and kidney transplant of 19:73:8 is taken from the UK Renal registry to yield an ESRD average quality of life of 0.480.

Quality of life ratios relative to the UK population norm for those age 65 of 0.821 are calculated for the above quality of life values. These quality of life ratios are then applied to the cycle specific CKD event free quality of life value to yield the cycle specific quality of

life values for events. For the 1st cycle of the model this implies the following quality of life values.

Table 20: 1st cycle quality of life values

	CKD no event	HK	CV	Post CV	ESRD
UK Norm Age 65			0.821		
QoL Ratio to UK Norm	0.774 94%	0.816 99%	0.574 70%	.. 0.620	0.480 59%
Formulae Final QoL Value	0.821 * 94% 0.774	0.774 * 99% 0.769	0.774 * 70% 0.541	0.774 * 62% 0.480	0.774 * 59% 0.453

Within the above the Post-CV quality of life ratio is not calculated, the correct ratio being 0.821 / 0.620 = 76%. Instead the Post-CV quality of life value of 0.620 or 62% has been used as the ratio. This tends to depress the applied quality of life value for Post-CV and so increases the benefits from avoiding CV events.

The key point to note in the above is that the events' quality of life ratios relative to the UK population norm of 0.821 are not applied to the UK population norm. Instead, the company applies them to the quality of life value of 0.774 for CKD event free. This tends to depress the quality of life values for events and so increases the benefit from avoiding them.

Hyperkalaemia events and cardiovascular events are tunnel health states, so are assumed to last for one month.

5.2.8 Adverse events

Adverse events and their quality of life effects are not considered within the model.

5.2.9 Resources and costs

5.2.9.1 Patiromer direct drug and administration costs.

Patiromer is available in 30-sachet packs of either 8.4g sachets or 16.8g sachets. It is assumed that the larger sachets cannot be split in half for those on the lower dose. Flat list pricing applies with a 30 day pack costing £300 so an annual cost of £3,652 per patient. A simple PAS of [redacted] applies, which reduces the pack cost to [redacted], or an annual cost of [redacted] per patient.

As reviewed in more detail in section 5.2.11 below in addition to the PAS the company applies a further 56% discount to the Patiromer costs. This effectively reduces the annual cost of Patiromer from [redacted] to [redacted] per patient.

Patients in the Patiromer arm start the Markov model at week 12 of OPAL-HK. One month's Patiromer costs are applied to account for Patiromer use during the 12 weeks of OPAL-HK. Thereafter the Patiromer monthly costs are conditioned by the Patiromer discontinuation curve. A half cycle correction is applied rather than using the start of cycle patient numbers, so drug wastage is underestimated.

No prescribing costs are applied. Being an oral formulation no administration costs are applied. It is assumed that there are no additional monitoring costs associated with Patiromer.

5.2.9.2 RAASi direct drug and administration costs

A monthly direct drug cost of £3.60 is applied[2].

No prescribing costs are applied. No administration costs are applied. It is assumed that there are no additional monitoring costs associated with RAASi.

5.2.9.3 Ongoing CKD costs

There is no allowance for the costs of routine monitoring of CKD.

CKD medication costs for vitamin D, ESA and phosphate binders of £600 per year or £50 per monthly cycle are applied.

It is assumed that CKD patients are hospitalised on average for 6.78 days each year at a daily cost of £225, based upon 2009 data from the NHS Institute of Innovation and Improvement. This is inflated to £1,949 in 2018 prices, or £162 per monthly cycle.

5.2.9.4 Hyperkalaemia event costs

All hyperkalaemia events are assumed to result in hospitalisation, with an average inpatient cost of £1,386.

5.2.9.5 ESRD costs

End stage renal disease costs are based upon annual costs in 2009 prices of £20,078 for peritoneal dialysis, £24,043 for haemodialysis and £2,792 for transplant are taken from Kerr et al [72]. The cost of transplant assumes a post-transplant survival of 5 years. A split between

[2] Note that this is also broadly in line with ERG estimates of the monthly cost of CCBs of £3.63 though a lower cost could be argued for if only amlodipine is considered. It is for this reason that the ERG considers it reasonable to apply the RAASi cost to all patients when it is modelling patients ceasing RAASi as having another active treatment and not placebo.

the three costs of 19:73:8 is taken from UK Renal Registry data, resulting in an average annual cost of £23,471. This is inflated to £31,448 in 2018 prices, or £2,621 per monthly cycle.

5.2.9.6 Cardiovascular event costs

Annual costs in 2009 prices of £12,200 for stroke and £7,734 for MI are taken from Kerr et al [72] and weighted 35:65 based upon Kerr et al [72] to yield an average event cost of £9,311. Inflating this to 2018 prices increases it to £11,894.

5.2.9.7 Post cardiovascular event costs

These are assumed to be the same as for CKD, but with an additional clopidogrel monthly cost of £1.16, hence £164 per monthly cycle.

5.2.9.8 In hospital deaths

A £4,580 cost in 2014 prices per hospital death is taken from Georghiou and Bardsley [73] and inflated to £4,884 in 2018 prices. It is assumed that half of deaths are in hospital based upon data taken from the website of the Marie Curie Organisation. This has minimal impact on results.

5.2.9.9 Adverse events

Adverse events and their costs are not considered within the model.

5.2.10 Cost effectiveness results

The company deterministic base case estimates the following disaggregate discounted medication costs.

Table 21: Company deterministic base case disaggregate medication costs

	Patiromer	RAASi	CKD	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	[redacted]

The company deterministic base case estimates the following disaggregate discounted event costs.

Table 22: Company deterministic base case disaggregate event costs

	CKD	ESRD	CV	Post-CV	HK Hosp	Hospdeath	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£3,258

The company deterministic base case estimates the following disaggregate discounted QALYs.

Table 23: Company deterministic base case QALYs

	CKD	ESRD	CV	Post-CV	HK	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.133	-0.053	0.000	0.024	-0.002	0.103

The company deterministic base case estimates the following aggregate undiscounted life years and discounted life years, QALYs, costs and resulting ICER.

Table 24: Company deterministic base case

		Discounted			
	LYs	LYs	QALYs	Costs	ICER
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	
Net	0.154	0.108	0.103	-£1,505	Dominant

The costs of Patiromer are more than offset by the reductions in ESRD costs and savings of £1,505 are anticipated from Patiromer. Coupled with gains of 0.103 QALYs this results in Patiromer dominating placebo.

The company probabilistic model as reported in the company submission has central discounted estimates as below.

Table 25: Company reported probabilistic base case central estimates

	QALYs	Costs	ICER
Patiromer	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	
Net	0.10	-£146	Dominant

These differ from the ERG rerun of the PSA over 10,000 iterations which results in central discounted estimates as below.

Table 26: ERG re-run probabilistic base case central estimates

	QALYs	Costs	ICER
Patiromer	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	
Net	0.100	-£1,412	Dominant

The model supplied by the company had 100 iterations specified. This does not imply that the company PSA was only run over 100 iterations. But given the uncertainty around PSA estimates a smaller number of iterations could account for the difference between the company PSA central estimates and both the deterministic estimates and the ERG PSA re-run central estimates. The deterministic estimates and the ERG PSA re-run central estimates are broadly aligned.

The scatter plot and CEAC from the ERG re-run over 10,000 iterations are as below.

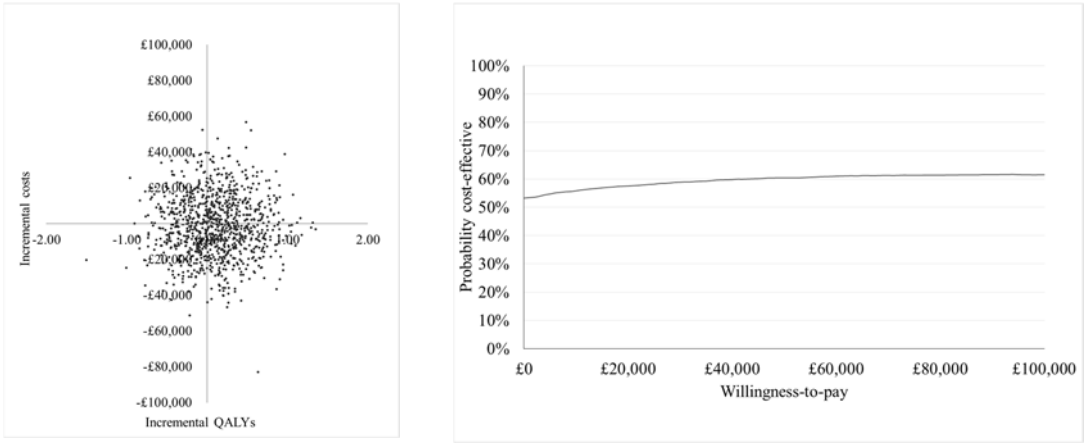


Figure 24: Probabilistic scatter plot and CEAC

There is apparently enormous uncertainty about the net costs and net QALYs. The scatterplot provides sampled estimates of the net costs and the net QALYs for the population as a whole. The CEAC reflects this uncertainty, being flat between 50% and 60%. Across the 10,000 iterations, there is only a 53% likelihood of Patiromer being cost saving and a 47% likelihood of Patiromer resulting in higher costs. Across the 10,000 iterations there is a 61% likelihood of patients benefitting from Patiromer and a 39% likelihood of patients being harmed by Patiromer.

Table 27: Uncertainty around the PSA estimates

	Net QALYs		Net Costs	
Mean	+0.100		-£1,412	
Median	+0.101		-£1,360	
Interquartile range	-0.156	+0.354	-£12,305	+£9,258
95% range	-0.658	+0.868	-£34,902	+32,235
Min-Max range	-1.500	+1.626	-£93,139	+£70,635

5.2.11 Sensitivity analyses

The company conducts a wide range of univariate sensitivity analyses, typically varying parameters through their 95% confidence interval or where this was not available by ±10%. The full tornado diagram is presented as figure 26 on page 127 of Document B. The sensitivity analyses for the variables that results are most sensitive to are tabulated below.

Table 28: Company sensitivity analyses

	Values			ICER	
	Base	Low	High	Low	High
RR CKD to CKD progression - RAASi	64%	47%	79%	-£24,433	£1,644
RR CKD to death (non-CV) - RAASi (all cause)	87%	74%	101%	-£5,986	-£30,588
RR CKD progression to death - RAASi	100%	90%	110%	-£4,170	-£27,102
% ESRD - Haemodialysis	73%	66%	80%	-£11,380	-£18,155
Monthly costs ESRD - Haemodialysis	£2,857	£2,571	£3,142	-£11,772	-£17,529
Discount rate - utilities	3.5%	1.0%	6.0%	-£12,076	-£17,471
SMR for mortality with CKD 4 vs CKD 3	256%	175%	375%	-£12,566	-£17,608
Discount rate - costs	3.5%	1.0%	6.0%	-£16,020	-£13,159

The values compare with a base case ICER of -£14,651 per QALY; i.e. there are savings per QALY. The ERG has not rerun the company sensitivity analyses and assumes that the company negative ICERs all relate to cost savings and QALY gains. In short, the company finds results show some sensitivity to the relative risks taken from Xie et al [5], the costs of haemodialysis and the proportion of ESRD patients incurring these costs and the SMR for CKD Stage 4 versus CKD Stage 3.

5.2.12 Model validation and face validity check

The main determinants of the cost effectiveness of Patiromer are the direct costs of Patiromer, the cost offsets and survival benefits from avoiding ESRD and to a lesser extent the cost offsets from avoiding hospitalisations associated with hyperkalaemia. The differential rates of ESRD by arm depend upon the proportion modelled as receiving RAASi, the baseline probability of ESRD and the relative risk of RAASi on this probability.

Some simple sensitivity analyses can be undertaken to explore the model structure around RAASi discontinuations, net ESRD costs, net total costs, net total QALYs and the ICER. Three scenario analyses can be performed and combined:

- the Patiromer hazard rate for RAASi discontinuations can be set to unity,
- the RAASi relative risk of moving from CKD to ESRD can be set to unity,
- all within the model can be assumed to be on RAASi at baseline rather than applying the OPAL-HK Phase B 8 week proportions.

These scenarios also apply the ERG corrections to monthly hyperkalaemia probabilities and avoiding the additional 56% discount to Patiromer costs as summarised in section 5.3.1 below, which results in net gains of 0.100 QALYs and a net cost saving of only £572.

Table 29: Scenario analyses exploring RAASi discontinuations and ESRD

	Base	Scen1	Scen2	Scen3	Scen4
PATR HR RAASi disc. = 1	×	✓	×	×	✓
RAASi RR ESRD = 1	×	×	✓	×	✓
Baseline RAASi = 100%	×	×	×	✓	✓
Net ESRD costs	-£3,716	-£2,768	£535	-£1,006	-£4
Net total costs	-£572	£112	£2,594	£1,622	£1,990
Net total QALYs	0.100	0.075	0.025	0.023	-0.003
ICER	Dom.	1,499	£102k	£70,644	Dom'td
Dom: dominant, Dom'td: dominated					

Scenario 1 sets the Patiromer hazard ratio for RAASi discontinuation to unity, and so applies the same CPRD RAASi discontinuation curve for Patiromer as for placebo. Despite this, there are still very considerable cost offsets from avoiding ESRD. This is because the RAASi discontinuations are still hugely differentiated by arm due to the OPAL-HK Phase B Patiromer and placebo RAASi discontinuation rates being applied prior to appending the CPRD RAASi discontinuation curves to these.

Scenario 2 sets the RAASi relative risk of ESRD to unity. This causes there to be some additional ESRD costs in the Patiromer arm. This appears to arise due to the model still applying a RAASi relative risk of death from CKD of 0.87, which results in a higher survival in the Patiromer arm and so more time to develop ESRD.

Scenario 3 which assumes all patients are on RAASi when diagnosed with hyperkalaemia, and then applies the CRPD RAASi discontinuation curve for those receiving placebo and the Patiromer hazard ratio conditioned CRPD RAASi discontinuation curve for those receiving Patiromer dramatically reduces the ESRD cost savings. The net patient gain is also much reduced.

It is only when all three scenarios are combined that the model estimates essentially the same ESRD costs in both arms, and also essentially the same QALYs in both arms.

The company analyses RAASi discontinuation from the UK CRPD data of patients receiving at least one prescription of RAASi in the 90 days prior to a diagnosis of hyperkalaemia. RAASi discontinuation was defined as no RAASi prescription within 90 days after the expected termination of the pre-hyperkalaemia RAASi prescription. The CPRD Kaplan Meier data and the company parameterised RAASi discontinuation curves for placebo are presented below. The modelled proportions remaining on RAASi are superimposed upon this.

Figure 25: CPRD RAASi parameterised curves versus modelled RAASi

Even allowing for the 3 month duration of OPAL-HK and a horizontal movement of the modelled curves by this amount, there is effectively no alignment between the model curve for placebo and the CPRD Kaplan Meier data. The model also shows no alignment with any of the CPRD RAASi discontinuation curves, let alone the company preferred Weibull.

It is possible that RAASi discontinuation rates during Phase B of OPAL-HK were protocol driven and may not reflect likely clinical practice. Additionally, different rates of RAASi discontinuation by arm during Phase B of OPAL-HK may also be at least in part protocol driven, with the trial being only single blinded in part to allow for this. The RAASi discontinuation and down titration protocol during each 4 week period of Phase B of OPAL-HK is summarised below.

Table 30: OPAL-HK Phase B protocol for RAASi discontinuation and down titration: 4 weekly

Serum K+	HK Event	Patiromer	Placebo
< 5.5	..	No change	No change
5.5-6.0	1st	No change	Decrease each RAASi medication by 50% or to next available dose strength below 50%
	2nd	Discontinue RAASi	Discontinue RAASi
6.0+	Any	Discontinue RAASi	Discontinue RAASi

A decrease in dose of RAASi could be a discontinuation if patients were on a RAASi starting dose and dose titration had not been managed. Weir et al [4] report that in OPAL-HK only 44% of patients were receiving the investigator-determined optimal dose.

Testing of serum K^+ during OPAL-HK Phase B may also have tended to be more frequent than would occur in clinical practice, so might have detected number of what would otherwise be transient hyperkalaemia events.

For these reasons the Patiromer hazard ratio for RAASi discontinuation of [redacted] estimated from Phase B of OPAL-HK may not apply in practice during the 1st 8 weeks of Patiromer treatment. There are also major concerns about applying this 8 week hazard ratio over a time horizon of 35 years. The NICE methods guide specifies that scenario analyses limiting the duration of treatment benefit to the duration of the trial and other scenarios limiting the duration of treatment benefit should be conducted. The ERG will conduct scenario analyses around the extrapolation of benefit.

The company appends the parameterised CRPD RAASi discontinuation curves to the end of the OPAL-HK trial period. Within the CPRD data the RAASi discontinuation rate is initially high as would be expected and then declines over time. Appending this data to the discontinuation data of Phase B of OPAL-HK may double count the initial large effects of hyperkalaemia on RAASi discontinuation rates.

In the opinion of the ERG, if the CPRD RAASi discontinuation data is felt to be more reflective of probable UK practice than OPAL-HK the natural assumption is to assume all are on RAASi when diagnosed with hyperkalaemia and then to model the placebo arm using the CPRD RAASi discontinuation curves. Those receiving and remaining on Patiromer should then be modelled by applying the Patiromer RAASi discontinuation hazard ratio to the placebo curve for however long is felt to be plausible. This choice between whether the RAASi discontinuations for the control arm should be modelled using the UK CRPD RAASi discontinuation data or should be modelled using the OPAL-HK proportions at 12 weeks with the CPRD risks appended thereafter is the key assumption that needs to be considered by Committee. Which is most likely to reflect current UK clinical practice?

5.2.12.1 Proportion of patients on Patiromer at baseline

The Markov model in a sense starts at the end of Phase B of OPAL-HK, hence the on-RAASi proportions assumed by the company. But the company model assumes that 100% of Patiromer Phase A responders will remain on Patiromer at the Markov model baseline 8 weeks later. This may not be reasonable and it may be better to assume the end of Phase B proportion remain on Patiromer at the baseline of the Markov model: 45 / 55 = 82%. But as reviewed in more detail in section 5.3.4 when considering the Phase A responder percentage, this seems likely to have relatively little effect upon the ICER.

5.2.12.2 Probabilistic modelling and CEAC

It unusual to find an economic model with a "dominant" central estimate, but with a CEAC which virtually flat lines a little above 50%. The ERG has re-run the PSA for the model corrected for the two major company errors as outlined below in section 5.3.1 and presents the associated CEAC for this analysis, which again largely flat lines.

To explore the source of this uncertainty, the ERG has rerun the PSA of the model corrected for the two major company errors another eight times, each over 10,000 iterations, with the sampling of the Phase B proportions turned off and sequentially turning off sampling of the following variables:

1. The Patiromer hazard ratio of RAASi discontinuation
2. The RAASi relative risk of ESRD
3. The RAASi relative risk of hyperkalaemia
4. The RAASi relative risks of events excluding hyperkalaemia
5. The placebo probability of ESRD
6. The placebo probabilities of events excluding hyperkalaemia
7. The parameters of the fitted curves
8. The quality of life values and costs taken from the literature

Somewhat surprisingly, the first seven analyses all result in a scatterplot and CEAC much as per the corrected base case. It is only the eighth analysis which tightens the scatterplot and CEAC as below. It remains the case that there is only a 53% likelihood of Patiromer resulting in cost savings. But the likelihood of it resulting in QALY gains increases. Across the 10,000 iterations there is a 68% likelihood of patients benefitting from Patiromer and a 32% likelihood of patients being harmed by Patiromer.

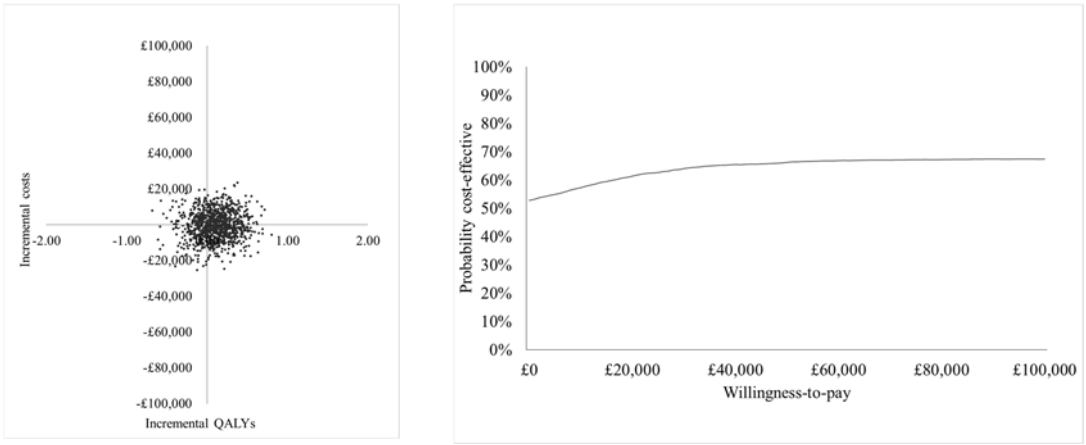


Figure 26: Probabilistic modelling: no sampling of quality of life values or costs

5.3 *ERG cross check and critique*

5.3.1 Base case results

5.3.1.1 ERG rebuild of company 4 independent sub-cohorts model

The ERG has rebuilt the company deterministic base case using the company segmented 4 independent sub-cohorts approach. The results of this are near identical to those of the company model. But the ERG rebuild has uncovered two major errors in the company model.

5.3.1.2 Application of the probabilities of hyperkalaemia: Major error

There is a major error in the estimates of the monthly probabilities of hyperkalaemia that are applied to each monthly cycle of the model. Daily probabilities are applied. For a given set of inputs this considerably underestimates the monthly probabilities of hyperkalaemia. Correcting this error improves the model estimates from the base case net saving of £1,505 to a net saving of £2,318, but marginally worsens the net gains from 0.103 QALYs to 0.100 QALYs.

5.3.1.3 Costing of Patiromer: Major error

The direct drug cost of Patiromer is based upon the number of patients receiving Patiromer in each cycle. The model cohort flow separates the overall patient cohort into one of four sub-cohorts:

- On Patiromer and on RAASi in the 1st model cycle
- On Patiromer and off RAASi in the 1st model cycle

- Off Patiromer and on RAASi in the 1st model cycle
- Off Patiromer and off RAASi in the 1st model cycle

These four sub-cohorts are modelled separately and do not interact with one other. The sub-cohorts of the first two bullets taken together amount to the Phase A Patiromer response proportion of 44%.

For a given cycle the number of patients incurring the cost of Patiromer is estimated as

- the sum of patients in the first two on Patiromer sub-cohorts, 44% of patients
- minus those modelled as having ESRD or having died in these sub-cohorts
- multiplied by the cycle specific Patiromer discontinuation curve proportion; e.g. 93% in the 1st cycle
- multiplied by the Phase A Patiromer response proportion of 44%

The 44% Phase A proportion responding who remain on Patiromer is conditioned by a second application of the Phase A Patiromer response proportion of 44%. In the 1st model cycle this results in a proportion who incur the costs of Patiromer of 44% * 93% * 44% = 18%.

More simply, the double application of the Phase A responder proportion in the costing of Patiromer means that the Patiromer drug costs from the 1st model cycle onwards are underestimated by 56%. Correcting this error worsens the model base case estimates from a net saving of £1,505 to a net cost of £241.

5.3.1.4 Revised company model base case results

Given the seriousness of the above errors the company base case corrected for these errors is presented below. The revision of the probabilities of hyperkalaemia to some extent cancels out the company giving itself an additional 56% discount on price, but the net effect is to lower both the cost savings and the QALY gains.

Table 31: Company deterministic base case corrected for major model errors

		Discounted			
	LYs	**LYs**	**QALYs**	**Costs**	**ICER**
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	
Net	0.154	0.108	0.100	-£572	Dominant

The central probabilistic estimates over 10,000 iterations are a net gain of 0.101 QALYs and are a net saving of £391 with the following scatterplot and CEAC.

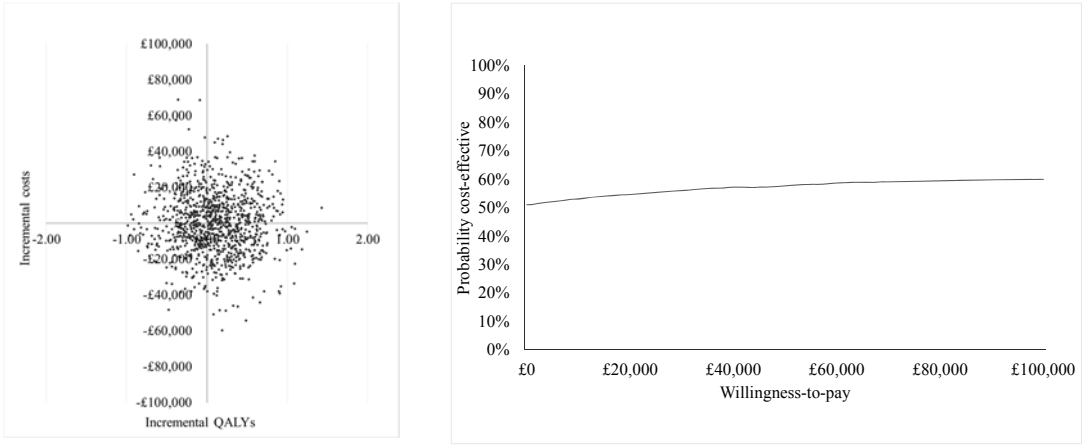


Figure 27: Company probabilistic scatterplot and CEAC corrected for major model errors

The likelihood of Patiromer being cost saving is 51%. The likelihood of it resulting in patient gains is 60%, and of patient harm 40%.

5.3.1.5 Company revisions at clarification

In its clarification response the company suggests that the base case should be revised along the following lines:

- For consistency the quality of life for stroke and MI of 0.519 and 0.605 in the year of the event should not be based upon Sullivan et al [69] but should rather be 0.495 and 0.690 based upon Pockett et al [71].
- The quality of life value for post-MI from Pockett et al [71] should be revised from 0.672, which relates to pooled events, to the value for MI patients of 0.702.
- The costs of CKD should be revised from £162 to £237 per month to account for routine primary care and OP visits.
- The survival post kidney transplant should be reduced from 5 years to 3.5 years based upon the 19th report of the Renal Association, [74] which increases the annual cost of ESRD from £31,448 to £31,767.
- The balance in ESRD between peritoneal dialysis, haemodialysis and transplant could be revised from the ESRD incident proportions of 19:73:8 to the ESRD prevalent proportions of 20:71:9.

The ERG revises the quality of life values for stroke and MI as outlined in its review of quality of life values below. The ERG applies the other company corrections in its revised base case.

5.3.2 Correspondence between written submission and cited sources

5.3.2.1 Mortality

The SMRs for CKD stage 3 relative to an age matched general population of Eriksen et al [64] and the SMR for those progressing beyond CKD stage 3 relative to CKD stage 3 of Sud et al [65] cross check, as do the ESRD mortality rates taken from Steenkamp et al [66]. But the ERG note that the model pooled SMRs of 5.2, 3.4 and 3.7 for those aged under 70, 70 to 79 and 80 plus respectively while initially below the SMRs for ESRD patients reported in Steenkamp et al, rise above the Steenkamp et al SMR for ESRD patients of 2.6 for those over 85.

It seems likely that there are two elements to this.

- All-cause mortality risks rise substantially with age. In Steenkamp et al the SMR for ESRD patients consequently falls off for those 85+. This does not happen with the SMR data for CKD stage 4 relative to CKD stage 3 as taken from Sud et al.
- The SMR data of Sud et al is for those progressing beyond CKD stage 3 and so may encompasses some CKD stage 5 patients. It does not appear to be specific to CKD stage 4 patients.

The above implies that the mortality benefits of avoiding ESRD may be underestimated among the very old in the model which may bias the model against Patiromer.

5.3.2.2 Baseline probability of developing ESRD

The company estimate of the probability of developing ESRD is based upon Landray et al [57]. This uses data from the UK Chronic Renal Impairment in Birmingham study. Table 3 of Landray et al sets out the following data.

Table 32: Table 3 of Landray et al

	CKD Stage 3	CKD Stage 4	CKD Stage 5	Pooled
Patients N	88	178	116	382
ESRD				
Patient years	560	837	173	1,571
ESRD n	9	80	101	190
Annualised	1.7%	11.9%	74.6%	15.4%
Monthly	0.1%	1.1%	10.8%	1.4%

The company model suggests a balance of 56:44 between CKD stages 3 and 4. Despite this the company applies the pooled monthly probability of 1.4%, which is skewed by the high probability of developing ESRD when CKD stage 5. Weighting the patient numbers by the company CKD stage proportions suggests a somewhat lower monthly probability of ESRD of 0.59%.

The Weir et al [4] supplement suggests a balance of 11:48:41 between CKD stages 2, 3 and 4 during Phase B of OPAL-HK. Assuming a zero probability of ESRD for stage 2 patients and the same mean duration of follow-up of 6.4 years as was observed for stage 3 patients suggests a monthly probability of ESRD of 0.39%. The ERG have revised the monthly probability of ESRD when sourced from Landray et al to 0.39%, and performed scenario analyses using 1.4%.

5.3.2.3 Baseline probability of a cardio-vascular event

The company submission reports that it derives a baseline annual probability of cardio-vascular events of 7.8% from Xie et al [5] which is converted to a monthly probability of 0.64%. This is based upon the number of events for the pooled placebo arms of the Xie et al meta-analysis, 1,720 MACE events among 8,357 patients. This is converted to the annual rate based upon the unweighted mean years of follow-up of the studies of 2.65 years. Xie et al do not report what MACE events include, but it can be noted that the company applies MI and stroke costs and quality of life values to cardiovascular events within the model.

The ERG has not had time to review the inputs to the figures that underlie the 1,720 MACE events among 8,357 patients over a mean of 2.65 years, or what constituted MACE within these figures. However, the ERG derives its own baseline probability of an event from Xie et al, using active controls as the comparator for RAASi.

5.3.2.4 Baseline probability of death once having had a cardio-vascular event

The company submission reports that it derives a baseline annual probability of death post cardio-vascular events of 3.6% from Xie et al [5] which is converted to a 0.30% monthly probability. This is calculated in a similar manner to the probability of cardiovascular events, with 792 deaths among 8,301 placebo patients. This probability is the probability of cardiovascular death. It does not appear to be particularly related to the probability of death in the months subsequent to having had a cardiovascular event.

The model puts a floor on the probability of mortality from an event of the SMR adjusted all-cause mortality, which is 0.43% in the 1st cycle and rises thereafter. As a consequence, the company derived monthly probability of 3.6% is not applied.

5.3.2.5 Baseline probability hyperkalaemia resulting in a cardiovascular event

The company estimate of the probability of a 1st cardio-vascular event is based upon Luo et al [75]. This was a study of 55,266 US CKD patients, where MACE events included arrhythmia, MI, stroke and heart failure exacerbation. The study reports crude MACE event rates per patient year, and estimates the incident rate ratio for hypokalaemia and hyperkalaemia, by eGFR category. Given the concentration on mild and moderate hyperkalaemia, Table 4 of Luo et al can be summarised as below.

Table 33: Luo et al MACE events and incident rate ratios

Serum K^+ (mmol/l)	4.5-4.9 rate	5.0-5.4 IRR	5.5-5.9 IRR
eGFR < 30 ml/min/1.73m^2	5.65	1.01	1.14
eGFR 30-39 ml/min/1.73m^2	4.20	1.02	1.16
eGFR 40-49 ml/min/1.73m^2	3.10	1.07	1.14
eGFR 50-59 ml/min/1.73m^2	2.53	0.97	1.12

The company ignores the annual rates and take a simple average of the IRRs and divides by 100 to yield 0.011 or 1.1%, which it takes to be an annual rate. This is then converted to a monthly probability of 0.09%.

The model applies costs and quality of life values that are based upon MI and stroke, and does not include heart failure or arrhythmia. As a consequence, either the event rate is too high for the costs and quality of life decrement that are applied, or the cost and quality of life decrement are too large for the event rate.

In the light of the above, the ERG has applied a relative risk of 1.1 to the CKD to cardiovascular event probability to calculate the probability for the HK transition to a cardiovascular event. This results in a higher probability than the company calculations.

5.3.2.6 Baseline probability hyperkalaemia resulting in death

The company also uses Luo et al [75] to calculate the probability of dying from hyperkalaemia.

Table 34: Luo et al deaths and incident rate ratios

Serum K^+ (mmol/l)	4.5-4.9 rate	5.0-5.4 IRR	5.5-5.9 IRR
eGFR < 30 ml/min/1.73m^2	0.09	1.01	1.11
eGFR 30-39 ml/min/1.73m^2	0.04	0.73	0.98
eGFR 40-49 ml/min/1.73m^2	0.03	1.18	1.68
eGFR 50-59 ml/min/1.73m^2	0.02	1.02	0.99

As with the probability of HK to MACE (above), the company ignores the event rates and averages the IRRs to yield 1.09, divides this by 100 and then converts this average to a monthly probability of 0.09%.

But the model sets a floor to the probability of death, based upon the CKD SMR adjusted mortality rates. As a consequence, this probability is not applied in the model. The company average of the IRRs of 1.09 is perhaps not that different from unity, and the IRRs display some unusual patterns. Hyperkalaemia is also a tunnel state with patients only remaining in for one model cycle. As a consequence, the ERG has not made any revisions to the company model.

5.3.2.7 Baseline probability of another cardiovascular event

The company estimate of the probability of having another cardio-vascular event is based upon Ariyaratne et al [76]. This is a study of an Australian registry data among CKD patients of cardio-vascular readmissions during the 12 months following a PCI. These readmissions included hospitalisations for: elective angiogram, heart failure, arrhythmia, unstable angina pectoris, stroke, MI, PCI and CABG. Among the 2,648 patients with moderate CKD there were 113 readmissions for heart failure, 23 for stroke and 133 for MI. From this 12-month data the company derives a monthly probability of having another cardio vascular event of 0.8%.

The data also only relates to readmissions during the 12 months after a PCI. The data does not exactly correspond to what would ideally be required. The probability of an event seems likely to decline after the 1st 12 months following a PCI. The model does not easily permit a waning of this probability, and the only real alternative is to set it to zero.

The ERG has revised the monthly probability of having another cardio-vascular event to 0.5%, and have performed a scenario analysis which sets it to zero.

5.3.2.8 Baseline probability of dying subsequent to a cardiovascular event

The company derives the probability of cardiovascular death from CKD from the placebo arm of the RCT of Aliskiren among T2DM patients, as reported in Parving et al [67]. The 215 cardiovascular related deaths among the 4,287 placebo patients and a median follow up of 32.9 months results in a monthly probability of 1.8%. But these deaths are among T2DM patients as a group and have little obvious relationship to the probability of interest, that of a cardiovascular event among CKD patients resulting in a death. Time constraint mean that the ERG has not identified an alternative estimate.

5.3.2.9 Baseline probability of hospitalisation from a hyperkalaemia event

The company derives a probability of hospitalisation from a hyperkalaemia event of 48% from Thomsen et al [77]. This reports the results of an analysis of 157,766 Danish CKD patients, with 28% of these experiencing a 1st hyperkalaemia event. Event rates rose with CKD severity, 119, 239 and 333 for per 1,000 person years for stages 3b, 4 and 5 respectively. Across all patients the proportion who were hospitalised in the 6 months prior to a hyperkalaemia event was 33.8%, compared to 57.1% in the 6 months after a hyperkalaemia event. The authors estimate an adjusted relative risk of 1.72.

The company applies the adjusted relative risk to the 6-month 33.8% hospitalisation rate prior to the hyperkalaemia event to derive a 6-month post rate of 58.1%. As a consequence, the company estimates an increase in the proportion hospitalised as a result of hyperkalaemia of around 24%. The company then simply doubles this to yield an "annualised" probability of 48%.

The ERG views the doubling of the probability of hospitalisation as invalid. It seems likely that any effects of a hyperkalaemia event upon hospital admissions will have been observed within 6 months, the 6-month window presumably being chosen by Thomsen et al for this very reason. It is also invalid in the context of a model where a hyperkalaemia event is a tunnel health state that last for one month.

But the company does not apply this probability. Rather it assumes that 100% of hyperkalaemia events result in an inpatient stay at a cost of £1,386. The ERG has applied the 24.3% probability of hospitalisation to the hyperkalaemia hospitalisation costs[3].

5.3.2.10 Baseline probabilities: unquantifiable bias

The company has misrepresented some of the main baseline probabilities, and used values that are obviously too high from even a cursory read of the papers. This raises concerns that the company may also have preferentially selected the references it uses to provide unduly high baseline risks.

As an example, there are other possible sources of the monthly probability of developing ESRD. This probability and its associated RAASi odds ratio are key to the cost offsets estimated within the model. ERG work on the papers that underlie Xie et al [5] suggests that the monthly probability of developing ESRD from CKD could be as low as 0.045%, and at least

[3] The ERG also includes the ongoing costs of CKD for those who are not hospitalised for this tunnel health state

an order of magnitude less than the 1.4% derived by the company and the 0.4% derived by the ERG from Landray et al [57].

The company at clarification notes that "targeted literature searches … were necessary as the scope of the mandatory systematic literature reviews (clinical, HRQL, economics and resource use) were not broad enough to cover all inputs needed for the economic model. The nature of these targeted searches was to identify literature which could provide data for populating the economic model rather than to identify all possible data sources. While there may be alternative sources available, the above sources were considered appropriate for the inputs for which they were used."

The ERG does not have the time or resource to conduct a systematic literature review for the many inputs to the company model. The biases identified by the ERG in the company data extraction from the company selected source papers raises the possibility of further unquantifiable company bias in its selection of the source papers. For instance, it is readily apparent when reading Landray et al [57] that the pooled incidence of ESRD is in large part driven by CKD stage 5 patients. The company identifies the systematic review of Wyld et al but does not mention the ESRD quality of life values within this systematic review, instead selecting the somewhat lower values of Lee et al [70]. In addition to these selection issues, the ERG has quality concerns. For example the company model, by incorporating an additional unwarranted 56% discount on the price of Patiromer, resulted in just 18% of patients incurring the costs of Patiromer during the 1st cycle. The ERG is curious to have sight of the company model underlying Sutherland et al [60] to see if it also incorporates this discount to the Patiromer costs, but because the ERG had not identified the discount prior to clarification did not request a model copy.

In the opinion of the ERG it is reasonable to assume that some degree of selection is likely to have occurred during the company choice of inputs from the range of possible sources.

5.3.2.11 Quality of life: CKD event free

The quality of life values for CKD stage 3a, 3b and 4 of 0.80, 0.80 and 0.74 cross check with the values reported in Jesky et al [62]. This is a UK study surveying all 745 CKD patients recruited to the Renal Impairment In Secondary Care study to the end of March 2014, with quality of life being estimated using the EQ-5D-3L. It can also be noted that a value of 0.73 was estimated for stage 5 patients.

5.3.2.12 Quality of life: Cardio-vascular events

Pockett et al [71] provide the company preferred source for the quality of life estimates for stroke and MI. This is a study of the quality of life effects among patients within 1 month of discharge from three UK hospitals after MI, stroke or unstable angina, and is sponsored by Roche. 1,176 post-MI patients, 898 unstable angina patients but only 29 stroke patients were enrolled in the study, with a mean age of 68 and 24% being diabetic. Quality of life was assessed through the EQ-5D-3L with an overall response rate of 62% at baseline, the response rate actually rising over the 6, 12 18 and 24-month follow-up period to 68%. The values for stroke and MI are reported below, with the company preferred quality of life values as revised at clarification for incident events and post event being highlighted.

Table 35: Pockett et al Quality of Life values

	MI			**Stroke**		
	n	QoL	(s.e.)	n	QoL	(s.e.)
Baseline	702	0.690	(0.011)	20	0.496	(0.081)
6 months	733	0.702	(0.014)	13	0.525	(0.118)
12 months	817	0.708	(0.011)	21	0.498	(0.082)
18 months	844	0.692	(0.012)	17	0.448	(0.103)
24 months	888	0.706	(0.011)	16	0.527	(0.101)

Key in the above is that there is no anchoring value for being event free or pre-event. This makes it difficult to use as a source to assess the proportionate effect of events upon quality of life other than to assess quality of life immediately after an event relative to some time after the event. The authors conclude that quality of life falls following an event based upon a comparison with general population norms, and that although some improvements occur in the next 24 months these patients' quality of life remains lower than general population age-related values.

The company argues for using the 6-month values for extrapolating post event quality of life because the "*other time points available in Pockett were considered too far post-event to be appropriate*". The ERG note that this is an unusual justification given the 35-year time horizon of the model and the conclusions of Pockett et al., though it can also be noted that these values are only a little worse than those at 24 months. The ERG has revised the post cardio-vascular quality of life values to be the 24-month values, as these seem the most appropriate for long term extrapolation

The probability of cardio-vascular events is calculated from data taken from Ariyaratne et al [76], a study of Australian hospital readmissions among CKD patients who have receive PCI. The balance between stroke and MI in Ariyarante et al is 15:85. But the company disregards this data and chooses to use data from Kerr et al [72]which uses modelling to suggest an excess number of stroke among UK CKD patients of 6,734 and an excess number of MIs of 12,334. But these are not secondary events. In the opinion of the ERG it is better practice to source the probability of events and the balance between these events from the same source, so the ERG has applied a balance of 15:85 between stroke and MI for the quality of life of secondary cardio-vascular events.

5.3.2.13 Quality of life: Hyperkalaemia

Hyperkalaemia is assigned a quality of life of 0.816 based upon a 'data on file' document supplied by the company in the reference pack accompanying the CS (Prevalence Assessment of Hyperkalaemia, Associated Treatment Patterns and Healthcare Outcomes in Germany, 2016) and Wyld et al [68]. It can be noted that this value is above the baseline value of 0.774 for CKD and is little different from the age adjusted UK population norm of 0.821. This may be the reason for the company assuming the hyperkalaemia decrement should be calculated relative to the UK population norm rather than relative to the CKD baseline utility.

Wyld et al provide a systematic review of CKD quality of life values among studies either directly reporting the quality of life values or where these values could be inferred from the SF-36 or SF-12 reported values. The ERG has not been able to source the 0.816 value for hyperkalaemia in Wyld et al., so have conducted a scenario analysis setting the hyperkalaemia quality of life decrement to zero. The ERG understands that many individuals with hyperkalaemia may be asymptomatic, and that when present, symptoms are nonspecific and not easily differentiated from common comorbidities such as CKD, diabetes and heart failure.

5.3.2.14 Quality of life: ESRD

The values of 0.530, 0.443 and 0.712 cross check with those reported for peritoneal dialysis, haemodialysis and kidney transplant in Lee et al [70]. This is UK study which surveyed 1,251 ESRD patients using the EQ-5D, with a response rate of 33%.

As noted above, the company cites Wyld et al [68] for the estimate of quality of life for hyperkalaemia. The systematic review of Wyld et al also reports in Table 3 the quality of life comparison for the directly reported EQ-5D data and their inferred quality of life from SF-36 data in the same paper. This table only reports values for ESRD, but it can be noted that the EQ-5D values of Lee et al [70] of 0.53 for peritoneal dialysis and 0.44 for haemodialysis are

considerably less than those of the three papers of Manns et al [78-80] of 0.56 for peritoneal dialysis and a range of 0.58 to 0.71 for haemodialysis. Wyld et al in Table 2 estimate a mean quality of life for peritoneal dialysis of 0.72 and a haemodialysis effect of -0.03, suggesting a value of 0.69.

The company also ignores the Jesky et al [62] estimate for quality of life for CKD Stage 5 patients despite using Jesky et al estimates for CKD stage 3 and CKD stage 4 patients. There is a strong consistency argument for using the Jesky et al CKD stage 5 estimate, and the company has should explain why this approach has been rejected.

Why the company uses the values of Lee et al rather than the results of the systematic review of Wyld et al, which encompasses the results of Lee et al, is unclear. But the choice results in considerably lower quality of life values for ESRD.

The balance of 19:73:8 between peritoneal dialysis, haemodialysis and kidney transplant cross check with the UK Renal Registry 2017 report[74].

Quality of life decrements, values inferred for events and the UKPDS study

Denoting the age-related general population quality of life as U_P, and supposing that the quality of life for CKD has been taken from the same population with a quality of life U_{CKD}. The quality of life for CKD is taken to be:

$$U_{CKD}^{Applied} = U_P . \frac{U_{CKD}}{U_P}$$

However, supposing that the quality of life for hyperkalaemia has been taken from a separate population where those with hyperkalaemia have U_{HK} and those without U_{NoHK}, the company method applies the following

$$U_{HK}^{Applied} = U_P . \frac{U_{CKD}}{U_P} . \frac{U_{HK}}{U_{NoHK}}$$

To see why the company method may be biased, suppose that all the quality of life values came from the same study so that $U_P = U_{NoHK}$. The above then becomes:

$$U_{HK}^{Applied} = U_P . \frac{U_{CKD}}{U_P} . \frac{U_{HK}}{U_{NoHK}} = U_P . \frac{U_{CKD}}{U_P} . \frac{U_{HK}}{U_P} = U_{CKD} . \frac{U_{HK}}{U_P}$$

As a consequence, the quality of life value applied for hyperkalaemia is below the quality of life value that was observed for hyperkalaemia by the proportion that the quality of life for CKD falls below the quality of life of the general population, in this case an estimated 94%. It would seem more appropriate to apply:

$$U_{HK}^{Applied} = U_P . \frac{U_{CKD}}{U_P} . \frac{U_{HK}}{U_{CKD}} = U_P . \frac{U_{HK}}{U_P} \; or \; U_{CKD} . \frac{U_{HK}}{U_{CKD}}$$

Since the assumed ratio of the quality of life of CKD without events to the quality of life of the general population is around 95%, the quality of life decrements for events may have been overestimated by around 5%. But which ratios should be applied depends very much upon having both a quality of life value for the event and a quality of life value for no event from the same source, and knowing whether this source is more relevant to the general population or to a CKD population.

The above argument demonstrates the desirability for quality of life values with the event and without the event coming from a common source. The company method simply combines absolute values from disparate sources. For the adverse events there is no assessment of their proportionate effect upon quality of life relative to the quality of life values prior to the event. A possible route around this or means of assessing the reasonableness of the quality of life decrements for the events within the model is to note that around two thirds of OPAL-HK were diabetic. This may mean that the UKPDS quality of life values of Clarke et al [81] are relevant. This estimates quality of life decrements for a variety of events from pooled UKPDS EQ-5D quality of life data.

Table 36: UKPDS Quality of life decrements compared to company estimates

		Company	
	UKPDS	**Event**	**Post-event**
No event	0.785	0.774	0.774
Decrements			
MI	-0.055 (-7%)	-0.204 (-26%)	-0.140 (-18%)
Stroke	-0.164 (-21%)	-0.285 (-37%)	-0.279 (-36%)
ESRD	-0.263 (-34%)	-0.321 (-41%)	-0.321 (-41%)

The UKPDS EQ-5D data suggests a smaller absolute and relative quality of life impact for ESRD. In the light of the results of the systematic review of Wyld et al, the ERG has applied the UKPDS event proportionate ESRD effect to the no event CKD quality of life. The ERG has also conducted scenario analyses that apply the values of Wyld et al and Lee et al.

5.3.2.15 CV costs

The CV costs cross check with those of Kerr et al [72] for MI and stroke. The costs of heart failure are not considered in the model. The pooled inflated cost of a CV event in the model is £11,894.

Given the high proportion of diabetics in OPAL-HK it can be noted that Alva et al [82] provide UKPDS estimates of annual hospital and outpatient costs in 2012 prices for diabetics without complications of £992. The additional annual cost of fatal strokes and fatal MIs in the year of event are only £1,054 and £3,485, or £1,186 and £3,920 in current prices. Similarly, the additional annual cost of non-fatal stroke and non-fatal MI in the year of incidence in 2012 prices are only £7,109 and £7,732. The ERG has explored applying the latter two amounts in a scenario analysis.

5.3.2.16 Post-CV costs

The costs following a cardio-vascular event in the model are only an additional £14 to the routine care costs of CKD, to allow for the cost of clopidogrel.

Given the high proportion of diabetics in OPAL-HK it can be noted that Alva et al [82] provide UKPDS estimates of net annual hospital and outpatient costs in 2012 prices for diabetics for non-fatal stroke and non-fatal MI subsequent to the year of event of £897 and £838 respectively, which when inflated increase to £1,009 and £943 respectively. While these estimates only relate to diabetics, the Post-CV costs do appear to be too low which biases the model against Patiromer. In the absence of better estimates the ERG has applied the UKPDS estimates of £1,009 and £943 in additional to the ongoing costs of managing CKD in a sensitivity analysis.

5.3.2.17 ESRD costs

The main cost offset of the model arises due to the high costs of ESRD. The values of the model cross check with those given in Kerr et al [72]. When inflated to current prices the annual cost estimate of £31,448 is reasonably similar to the default value used in the UKPDS OM1 model of £30,000, though this appears to be in 2009 or 2010 prices so if inflated would rise to £38,321. The ERG has applied the £38,321 in a sensitivity analysis.

5.3.3 Correspondence between the written submission and electronic model

There is broad agreement between the written submission and the electronic model.

5.3.3.1 End of OPAL-HK on RAASi proportions

One difference between the written submission and the electronic model may relate to the proportion of patients modelled as having discontinued RAASi by the end of OPAL-HK Part B. The Kaplan Meier data supplied by the company suggests that 3 of the 55 patients in the Patiromer arm discontinued, 5%, compared to 30 of the 52 patients in the placebo arm, 52%. Table 15 of document B appears to suggest that 3 of the 30 modelled as discontinuing RAASi

in the placebo arm were not observed discontinuing RAASi but were actually censored, and an additional 6 patients in the Patiromer arm were not observed discontinuing RAASi but were censored.

When calculating the hazard ratio it appears that the company may have assumed informative censoring for the placebo arm Kaplan Meier data, with censoring being equivalent to RAASi discontinuation, but non-informative censoring for the Patiromer arm. If the ERG similarly assumes informative censoring for the Patiromer arm Kaplan Meier data and that the 6 patients censored in the Patiromer arm discontinued RAASi the hazard ratio increases from [redacted] to [redacted]. If the ERG assumes non-informative censoring and that 3 of the 30 patients modelled as discontinuing RAASi in the placebo arm were censored, the hazard ratio increases from [redacted] to [redacted].

For its revised base case the ERG has applied the hazard ratio calculated assuming non-informative censoring. A scenario analysis has explored applying the hazard ratio calculated assuming informative censoring.

5.3.4 ERG commentary on model structure, assumptions and data inputs

5.3.4.1 Part A Patiromer response percentage

As reviewed in the clinical section above, the design of OPAL-HK is unusual in that Phase A enrolled a number of patients with mild hyperkalaemia. But these patients were excluded from Part B. The model calculates the Phase A response percentage using the total number of patients enrolled in Phase A as the denominator.

Denote the total QALYs modelled for each of the independent sub-cohorts as Q_A, Q_B, Q_C and Q_D, the proportion responding to Patiromer during Phase A as R_{SA}, the proportion of those randomised to Patiromer during Phase B who remain on RAASi at the end of Phase B as Ri_{PT}, and the equivalent among those randomised to placebo during Phase B as Ri_{PL}.

The total QALYs in the placebo arm is:

$$Q_{PL} = (Ri_{PL}.Q_C + (1 - Ri_{PL}).Q_D)$$

The total QALYs in the Patiromer arm is:

$$Q_{PT} = R_{SA}.(Ri_{PT}.Q_A + (1 - Ri_{PT}).Q_B) + (1 - R_{SA}).(Ri_{PL}.Q_C + (1 - Ri_{PL}).Q_D)$$

$$Q_{PT} = R_{SA}.(Ri_{PT}.Q_A + (1 - Ri_{PT}).Q_B) + \left(1 - R_{StageA}\right).Q_{PL}$$

Net QALYs are consequently:

$$Q_{NET} = R_{SA}.(Ri_{PT}.Q_A + (1 - Ri_{PT}).Q_B) - R_{SA}.Q_{PLAC}$$

$$Q_{NET} = R_{SA}.(Ri_{PT}.Q_A + (1 - Ri_{PT}).Q_B - Q_{PLAC})$$

By a similar token the net costs are:

$$£_{NET} = R_{SA}.(Ri_{PT}.£_A + (1 - Ri_{PT}).£_B - £_{PLAC})$$

Both net QALYs and net costs of the Markov model are proportionate to the Phase A response percentage. But for the ICER = $£_{NET}/Q_{NET}$ the Phase A response percentage cancels out and the ICER is invariant to it.

However, the model includes some Patiromer costs for Phase A and Phase B which are prior to the Markov model, call them $£_{PT}$. The true ICER is consequently:

$$ICER = \frac{R_{SA}.(Ri_{PT}.Q_A + (1 - Ri_{PT}).Q_B - Q_{PLAC})}{£_{PT} + R_{SA}.(Ri_{PT}.£_A + (1 - Ri_{PT}).£_B - £_{PLAC})}$$

This causes the ICER to be slightly affected by the initial Phase A response percentage, this effect increasing as net costs of the Markov model fall relative to the Patiromer costs included for Phase A and Phase B of OPAL-HK.

In the light of this and the conduct of the OPAL-HK trial, the ERG has revised the Phase A response percentage as the patients included in Part B, n=107, divided by the number at Phase A baseline with serum K^+ of at least 5.5mmol/l, n=151, rather than the total n=243 enrolled in Part A. The higher response proportion slightly improves the ICER due to the pre-Markov Patiromer costs being spread across a larger proportion of patients which reduces the cost per patient.

5.3.4.2 Probabilities of hyperkalaemia among those discontinuing Patiromer

Those on Patiromer have the monthly Patiromer probability of hyperkalaemia until they discontinue, from which point they have the monthly placebo probability of hyperkalaemia. To illustrate this consider a patient initially on Patiromer who discontinues and crosses over to the placebo probabilities at month 30, as below. The hyperkalaemia S(t) curves of the company base case are measured against the left-hand vertical axis, and the monthly probabilities of hyperkalaemia against the right-hand vertical axis.

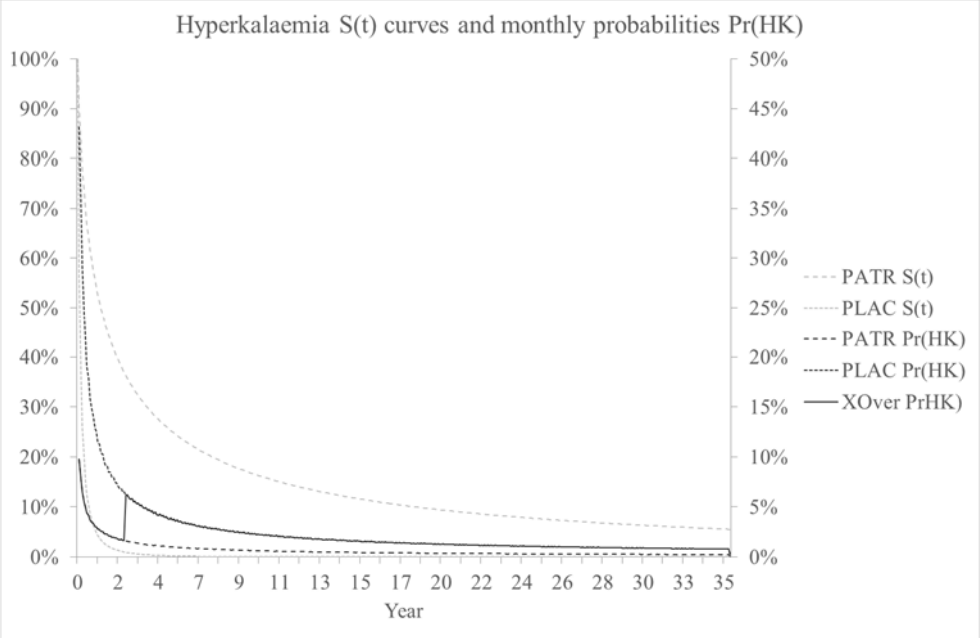


Figure 28: Company hyperkalaemia curves and probabilities of hyperkalaemia

The placebo curve has an initially very high probability of hyperkalaemia, which then tails off, whereas the Patiromer curve has a much lower probability of hyperkalaemia throughout, but particularly initially.

What may be of concern are the probabilities applied to a Patiromer patient who discontinues at, say, month 30 as shown above. This patient avoids the initial very high placebo probabilities of hyperkalaemia and only goes on to receive the placebo probabilities of hyperkalaemia from month 30 by which time they are very much reduced. There may be a question as to whether this patient should be modelled as having the high probabilities of the start of the placebo curve when they cross over to placebo. If so, the effect of Patiromer on hyperkalaemia will have been exaggerated.

5.3.4.3 Waning of treatment effect on hyperkalaemia

As discussed elsewhere the ERG is sceptical that it is reasonable for a hazard ratio for RAASi discontinuations derived from 8 weeks data of a relatively small trial should be extended to 35 years' effect. The ERG has performed scenario analyses that wanes the treatment effect on RAASi discontinuations.

Given ERG model revisions hyperkalaemia comes more to the fore in terms of cost offsets. Applying the hyperkalaemia curves outlined above or the ERG hyperkalaemia curves derived from 8 weeks data of a relatively small trial over 35 years may tend to exaggerate the likely treatment effect of Patiromer on hyperkalaemia. There is no simple means of applying a

waning of effect within the company curves. But given the selection of the ERG exponential hyperkalaemia curves waning of the effect upon hyperkalaemia is relatively simple to implement due to their constant probability of an event over time. The lower probability of hyperkalaemia for Patiromer can be increased linearly over a period to time to equalise with the probability of hyperkalaemia for placebo. In the absence of anything obvious that could inform this, the ERG has performed two scenario analyses that wane the Patiromer treatment effect from month 3 of the model, one over 3 years and the other over 5 years.

5.3.4.4 Xie et al odd ratios

The RAASi odds ratios reported by Xie et al [5] are transformed into relative risks. These are applied to the baseline risks for no RAASi as reported in section 5.2.6 above to derive the risks of events for those receiving RAASi. The company uses the relative risks implied by the Bayesian odds ratios for RAASi relative to placebo.

For the RAASi relative risk of ESRD the company pools the ACEI and ARB relative risks, roughly weighting these by the proportions on ACEIs and ARBs during OPAL-HK of 71:29. For the other RAASi relative risks the company applies the ACEI value. It is unclear why the company has not pooled the other relative risks. As reviewed in greater detail in the clinical effectiveness section of Chapter 4 above, it is questionable whether the comparator should be placebo. For UK practice it seems reasonable to assume an active comparator. The following table reports the central estimates of the RAASi relative risks of the company, and as recalculated by the ERG pooling ACEI and ARB relative risks 71:29.

Table 37: Company and ERG RAASi relative risks of events from Xie et al

		ESRD	CV Event	CV Death	Death
CS	vs Placebo	0.64	0.82	0.88	0.87
ERG	vs Placebo	0.64	0.80	0.94	0.90
	vs Active	0.68	0.92	0.82	0.74

The comparison with active treatments suggests a lesser effect for RAASi upon ESRD and CV events. The picture is more mixed for CV deaths, and RAASi is estimated to have a greater effect relative to active treatment than relative to placebo upon other deaths. As reviewed elsewhere, the ERG does not have confidence in the relative risks for 'other mortality' (non CV-related or ESRD-related mortality), see 4.5.1.

5.3.4.5 Baseline risks of events

The ERG review of correspondence between the submission and cited references highlights a number of changes that the ERG will make to the baseline risks of events when taken from

the company cited papers. But for the ERG revised base case, for consistency the ERG has derived the baseline risks from Xie et al [5] as below.

Table 38: ERG baseline monthly risks of events from Xie et al

		ESRD	CV Event	CV Death	Death
ERG	Placebo	0.43%	0.58%	0.11%	0.19%
	Active	0.40%	0.51%	0.13%	0.23%

5.3.4.6 Double counting of ESRD mortality effects

Preventing ESRD will reduce the number of ESRD deaths, due to ESRD being associated with a higher probability of death as is appropriate. But the effects of RAASi are estimated to reduce both ESRD and all-cause mortality.

This may be double counting. RAASi is estimate to reduce ESRD and so to reduce ESRD related deaths. But these ESRD related deaths may be the main determinant of the increased risk of all-cause death among the non-RAASi CKD patients reported by Xie et al [5]. Further conditioning the all-cause mortality of the model by the Xie et al relative risk of all-cause mortality will apply the mortality benefits of avoiding ESRD twice. For this reason alone it may be most reasonable to set this relative risk to unity. The ERG also views this relative risk as unreliable for the reasons previously summarised (see 4.5.1).

There is a similar argument around the cardio-vascular event relative risk, the cardio-vascular death relative risk and the all-cause mortality risk. But the main clinical drivers of the model are avoiding ESRD and avoiding hyperkalaemia.

5.3.4.7 OPAL-HK Patiromer cost

The model applies one month's cost of Patiromer to account for Patiromer use during OPAL-HK. But this only accounts for Patiromer use during Phase A of OPAL-HK. In the opinion of the ERG the model should account for Patiromer use during Phase A and Phase B of OPAL-HK, before extrapolating using the Markov model. This suggests applying an additional 2 month's Patiromer costs among the OPAL-HK Phase A responders. The ERG has increased the Patiromer costs accordingly.

It should also be noted that the company assumes that ESRD patients will cease Patiromer, which reduces Patiromer costs in the model. The ERG has not found reference to this in the SmPC but the company may argue that this is a reasonable assumption in the absence of appropriate safety data.

5.3.4.8 Patiromer wastage

The direct drug costs are based upon half cycle corrected values rather than the start of cycle patient numbers. This will underestimate Patiromer wastage. The ERG has applied the start of cycle values when calculating drug costs.

5.3.4.9 Prescription costs

No prescription costs are included. A community pharmacy would only amount to an additional £1.25 per script, but ERG expert opinion indicates that Patiromer would be dispensed from a hospital pharmacy. Assuming 10 minutes of pharmacist time costed using PSSRU unit costs of healthcare for a Band 6 hospital based scientific member of staff suggests adding perhaps around £5 to the pack cost of Patiromer. This is relatively minor given the pack cost, but the ERG has included it for completeness.

5.3.4.10 Hyperkalaemia costs

ERG expert opinion suggests that perhaps two additional outpatient visits will be required for hyperkalaemia events which are not managed through hospitalisation. The ERG has added the costs of two nephrology outpatient appointments, each costed at £153 from 2017 NHS reference costs WF10A, consultant led.

5.3.4.11 Probabilistic modelling

The company model samples the proportions remaining on RAASi at the end of Phase B using a beta distribution, as is appropriate. But the proportion of Phase A responders to Patiromer is not sampled. This will underestimate the uncertainty within the company base case by a considerable degree due to the costs of Patiromer within the company base case being incorrectly conditioned by a double application of the proportion of Phase A responders. Correcting this modelling error reduces the importance of sampling the proportion of Phase A responders, but in the opinion of the ERG this should still be sampled using a beta distribution.

The probabilistic modelling also assumes a large number of variables are log-normally distributed with a standard error that is 10% of the mean value, μ. But the sampling of these on the log scale, prior to exponentiating to arrive at a value in natural units, samples using the standard error in natural units; i.e. the PSA sampled value in Excel is Exp(NormInv(Rand(),ln(μ),10%*μ)). This consequently applies a much larger standard error. It also causes problems within the modelling. For instance, the sampled quality of life for Stage 3 CKD is estimated to be superior to the general population age weighted quality of life in 37% of the PSA iterations. There will be similar problems in the sampling of quality of life

values for the event decrements. This could account for some noise in the probabilistic modelling. Time constraints mean that the ERG has not attempted to correct this aspect of the model.

The deterministic modelling also assumes that the RAASi relative risk of hyperkalaemia is unity. The probabilistic modelling samples it based upon the distribution of the odds ratio reported in Xie et al [5] of 2.16 (1.24-3.68). This causes some misalignment of the probabilistic modelling and the deterministic modelling. But as outlined earlier in this chapter, not sampling this variable has little effect upon the probabilistic estimates.

The sampling of the balance between CKD stages is not restricted to sum to unity. But visual inspection suggests that this sum typically sums to an amount not substantially different from unity.

The RAASi relative risks are assumed to be log-normally distributed. The probabilistic sampling sets any sampled values that are above unity to unity. This skews the sampled distributions and causes the mean of the distributions to be lower than the inputted mean and deterministic value. This biases the probabilistic modelling in favour of Patiromer. It should also be noted that the RAASi relative risks which are assumed to be unity in the base case are also sampled probabilistically. The distribution for these relative risks typically assumes an arbitrary 95% confidence interval of (0.9-1.1). Setting any sampled values that are above unity to unity for these distributions results in very obvious bias. These biases are trivial for the RAASi relative risks of CKD to ESRD and CKD to CV, and relatively inconsequential for the RAASi relative risk of CKD to death. Around 10% of the sampled values of RAASi relative risk for CV event to death are restricted to unity, but the mean value of restricted sampling is only around 1% less than the mean value of unrestricted sampling. Given the assumed 95% confidence interval of (0.9-1.1) for the RAASi relative risk of ESRD to death, half of the values sampled are restricted. But the mean value of restricted sampling is still only around 2% less than the mean value of unrestricted sampling.

The sampling of the parameters of the parameters of the log-normal TTE HK curves assumes the parameters are independent and does not apply any variance-covariance structure upon them.

5.4 *Exploratory and sensitivity analyses undertaken by the ERG*

The ERG makes a number of revisions to the company base case. Firstly, it discards the company submission estimates due to the two major errors in the company model implementation.

- Applying daily probabilities of hyperkalaemia to a model with a monthly cycle
- Applying an additional 56% price discount to Patiromer drug costs in addition to the PAS.

All subsequent ERG analyses include correction for the above errors.

The ERG makes the following initial corrections and revisions to the company model.

1. Assuming that those ceasing RAASi have another active control rather than placebo with relative risks and baseline risks taken from Xie et al [5], costing this active control at the same level as RAASi.
2. Assuming non-informative censoring for the placebo censoring events in Table 15 of Document B and applies the resulting Patiromer hazard ratio of RAASi discontinuation.
3. Assuming an effect from RAASi upon cardio-vascular and ESRD deaths but not upon other deaths.
4. Revising ongoing CKD costs, ESRD balance and post kidney transplant survival as per the company clarification response.
5. Revising the company probability of ESRD to reflect the OPAL-HK patient balance, in particular removing the CKD stage 5 patients from this estimate.
6. Revising the probability of a cardio-vascular event from hyperkalaemia to reflect the cited paper.
7. Revising the probability of an initial cardio-vascular event to be for MI and stroke, and of a subsequent cardio-vascular event to reflect the cited paper.
8. Revising the probability of hyperkalaemia resulting in hospitalisation from 100% to reflect the cited paper with non-hospitalised patients incurring an additional two outpatient appointments, and including the ongoing CKD costs for those with hyperkalaemia.
9. Revising the quality of life for ESRD to be taken from the UKPDS values of Clarke et al [81] rather than Lee et al [70].
10. Revising the quality of life values for cardio-vascular events to reflect the values in the cited paper.

11. Revising the quality of life calculations such that the relative effects of events are consistent with the hypothetical situation of all the quality of life values being measured among a coherent single population[4].
12. Revising the Patiromer drug costs to allow for OPAL-HK Phase B use, to be based upon start of cycle rather than half cycle corrected values and including a £5 prescribing cost.
13. Applying the Phase A response percentage among those with moderate hyperkalaemia at Phase A baseline.

Prior to turning to the ERG preferred base case, the effect of each of these revisions on the company base case discounted results, corrected for the two major error, can be explored in turn followed by the results of their collective application. Note that their collective application overrides the company estimated probabilities of events with those estimated by the ERG from Xie et al [5].

Table 39: ERG revisions effect upon company base corrected for 2 major errors

	Δ QALYs	**Costs**	**ICER**
Base case correct for the two major errors	0.100	-£572	Dominant
Rev01: Active control	0.124	£2,310	£18,659
Rev02: HR RAASi discontinuation censoring	0.100	-£565	Dominant
Rev03: No RAASi effect upon other mortality	0.072	-£1,285	Dominant
Rev04: CKD and ESRD cost revisions	0.099	-£328	Dominant
Rev05: Company probability of CKD to ESRD	0.093	£1,092	£11,796
Rev06: Company probability of HK to CV	0.104	-£608	Dominant
Rev07: Company probability of CV events	0.100	-£588	Dominant
Rev08: Proportion HK hospitalised	0.100	-£62	Dominant
Rev09: ESRD QoL UKPDS	0.093	-£572	Dominant
Rev10: CV QoL values	0.101	-£572	Dominant
Rev11: QoL calcs all relative to general population	0.097	-£572	Dominant
Rev12: Patiromer drug costs	0.100	-£250	Dominant
Rev13: Phase A response proportion	0.161	-£1,060	Dominant
All the above revisions	0.067	£2,594	£38.905

The above findings show that the company model is sensitive to the following:

[4] Note that this

- Applying an active control reduces the cost offsets from ESRD and also reduces the anticipated QALY gain. Patiromer ceases to be cost saving and has an ICER of £18,659 per QALY.
- If RAASi has no effect on 'other mortality' the patient gain is less but net savings increase due to patients in the Patiromer arm not living that much longer and so not incurring more ongoing costs of CKD and events.
- The main sensitivity of results to the baseline probabilities is to the probability of ESRD. If this is revised to the value implied by Landray et al [57] rather than the value calculated by the company from Landray et al Patiromer ceases to be cost saving and has an ICER of £11,796 per QALY.
- Reducing the proportion of hyperkalaemia events that require hospitalisation also results in Patiromer effectively ceasing to be cost saving.
- The UKPDS quality of life values for ESRD moderately reduce the anticipated QALY gain, the other quality of life values matter less and revising the quality of life calculations to all be relative to the general population quality of life has only a limited effect.
- Further revising the Patiromer drug costs reduces the cost savings but does not reverse them.
- Revising the Phase A response proportion affects net costs and net QALYs quite considerably, but these change in reasonable proportion to one another. For instance, removing this change but retaining all other changes only worsens the ICER from £38,905 per QALY to £41,037 per QALY. In a similar vein, if the end of Part B proportion remaining on Patiromer is applied, as can be argued for as part of the base case, the ICER worsens from £38,905 per QALY to £39,683 per QALY.

Revisions together result in the anticipated gain being more than halved to only 0.067 QALYs, the net savings reversing to a net cost of £2,513 and the ICER worsening to £38,905 per QALY.

The above modelling retains all the parameterised company curves. More critically, it also retains the assumption that the UK clinical practice of RAASi discontinuation is better reflected by the OPAL-HK trial data than by the UK CPRD data. The ERG disagrees with this and views the most reasonable base case as one that applies the UK CRPD RAASi discontinuation data for placebo.

In addition to the 13 revisions outlined above, the ERG revised base case:

- Applied the ERG estimated Weibull CPRD RAASi discontinuation curve for placebo
- Applied the ERG revised OPAL-HK Patiromer hazard ratio of RAASi discontinuation to the UK CRPD RAASi discontinuation data to derive the probability of RAASi discontinuation among those on Patiromer.
- Applied the ERG estimated exponential OPAL-HK hyperkalaemia curves for Patiromer and placebo.
- Applied the ERG estimates Weibull AMETHYST-DN Patiromer discontinuation curve.

5.4.1 ERG revised base case

The ERG revised base case reflects changes to the company base case detailed in 5.4. The impact of these changes upon medication, events, quality-of-life and ICER is presented below

The ERG revised deterministic base case estimates the following disaggregate discounted medication costs.

Table 40: ERG deterministic base case disaggregate medication costs

	Patiromer	BP meds	CKD	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	£5,013

The ERG revised deterministic base case estimates the following disaggregate discounted event costs.

Table 41: ERG deterministic base case disaggregate event costs

	CKD	ESRD	CV	Post-CV	HK	Hospdeath	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£2,226

Within the above it may seem peculiar for the costs of CKD to be somewhat higher for Patiromer than for placebo. Some arises from longer survival. But more probably arises from more patients in the placebo arm passing through the one month tunnel health of hyperkalaemia, which also includes the routine costs of CKD management for these patients.

The ESRD cost offsets are much reduced compared to the company base case. The reduction in the costs of hyperkalaemia are around half the Patiromer drug costs.

The ERG revised deterministic base case estimates the following disaggregate discounted QALYs.

Table 42: ERG deterministic base case QALYs

	CKD	ESRD	CV	Post-CV	HK	Total
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net	0.226	-0.010	0.000	0.002	-0.206	0.012

The QALY gains from avoiding ESRD are much reduced compared to the company base case. As for costs, the differences in total QALYs for CKD and hyperkalaemia in large part balance out. The total QALY gains are very much reduced compared to the company base case.

The ERG revised deterministic base case estimates the following aggregate undiscounted life years and discounted life years, QALYs, costs and resulting ICER.

Table 43: ERG deterministic base case

		Discounted			
	LYs	LYs	QALYs	Costs	ICER
Patiromer	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	
Net	0.013	0.009	0.012	£2,787	£236,303

The ERG revised deterministic base case suggests a cost effectiveness estimate of £236k per QALY. Given the small QALY gain and the resulting instability of the ICER, the central probabilistic estimate of the model run over 10,000 iterations of £209k per QALY is actually quite closely aligned to the deterministic estimate of £236k per QALY.

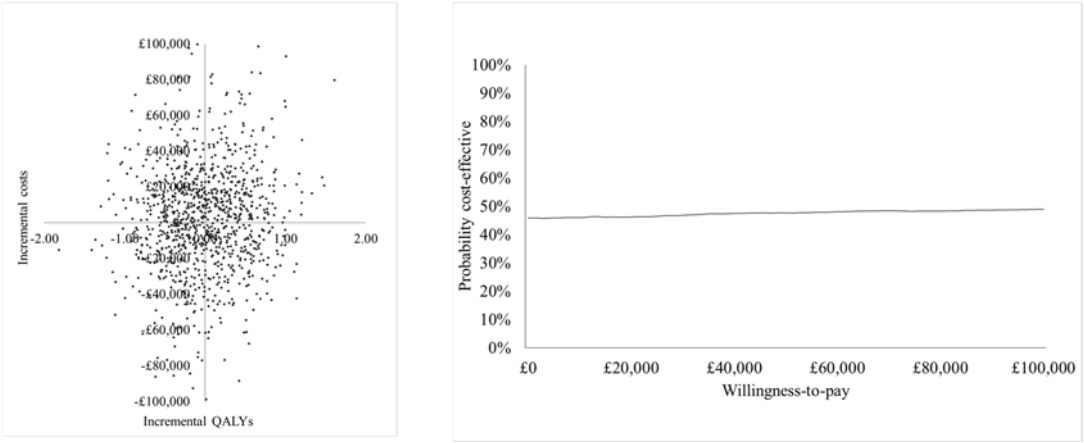


Figure 29: Probabilistic modelling: ERG revised base case

The ERG notes that the probabilistic modelling still estimates a 46% likelihood of Patiromer being cost saving, and still has concerns around the probabilistic modelling. The model estimates likelihoods of Patiromer being cost effective at £20k, £30k, 50k and £100k per QALY of 46%, 47%, 48% and 49% respectively.

5.4.2 ERG Scenario analysis

Additionally, the ERG conducted the following scenario analyses:

- SA01: Applying the ERG estimated OPAL-HK RAASi discontinuations curves for placebo and for Patiromer. Note that this analysis no longer applies the Patiromer hazard ratio of RAASi discontinuation to the placebo curve.
- SA02: Applying the ERG estimated OPAL-HK Patiromer discontinuations curve.
- SA03: For the effects of RAASi, assume placebo rather than active control
- SA04: Retaining the company curves.
- SA05: Assuming informative censoring for the Patiromer RAASi discontinuation hazard ratio from the data in Table 15 of document B, which increases the number of events in the Patiromer arm and worsens the hazard ratio.
- SA06: Company Patiromer RAASi discontinuation hazard ratio.
- SA07: Since the Patiromer hazard ratio for RAASi discontinuations from OPAL-HK may be protocol driven to a degree, and it may be optimistic to extrapolate a hazard ratio derived from 8 week's data over a lifetime, waning the hazard ratio from the third month. This waning assumes that the hazard ratio is proportionate to the number

of patients remaining on Patiromer. In other words, it is assumed that the relative effect of Patiromer on RAASi discontinuations among those remaining on Patiromer tends to reduce, this reduction being related to how many patients cease to find Patiromer beneficial and so discontinue its use. While imperfect, it is not obvious to the ERG what other waning scenario could have been reasonably justified. Note that this only wanes the effect on RAASi discontinuations, it retains the benefits in terms of the hyperkalaemia curves.

- SA08: Waning the treatment effect upon hyperkalaemia from month 3 linearly over 3 years and over 5 years.
- SA08: Setting the probability of a 2nd cardio-vascular event to zero.
- SA09: Assuming no quality of life decrement for hyperkalaemia.
- SA10: Assuming the Lee et al quality of life decrement for ESRD.
- SA11: Assuming the Wyld et al quality of life decrement for ESRD.
- SA12: Applying UKPDS costs for ESRD and cardio-vascular events.

The ERG scenario analyses result in the following.

Table 44: Scenario analyses around ERG revised base case

	Δ QALYs	**Costs**	**ICER**
ERG revised base case	0.012	£2,787	£236,303
SA01: OPAL-HK RAASi discontinuation curves	0.012	£2,761	£227,403
SA02: OPAL-HK Patiromer discontinuation curve	0.002	£1,074	£681,235
SA03: RAASi relative to placebo control	0.015	£2,746	£183,888
SA04: Company curves	0.019	£4,806	£246,862
SA05: Informative RAASi censoring	0.011	£2,860	£272,094
SA06: Company HR RAASi discontinuation	0.012	£2,783	£234,333
SA07: Waning of HR RAASi discontinuation	0.008	£3,006	£371,271
SA08a: Waning of Pr(HK) effect over 3 years	0.010	£3,712	£371,095
SA08b: Waning of Pr(HK) effect over 5 years	0.010	£3,466	£330,461
SA09: No 2nd CV events	0.012	£2,786	£236,223
SA10: No HK QoL decrement	0.011	£2,787	£265,125
SA11: ESRD QoL Lee et al	0.012	£2,787	£226,573
SA12: ESRD QoL Wyld et al	0.008	£2,787	£342,327
SA13: UKPDS Costs ESRD and CV	0.012	£2,660	£225,505

The ERG revised base case is most sensitive to the following:

- If Patiromer discontinuations are more in line with the faster discontinuation observed during OPAL-HK the cost effectiveness of Patiromer is much worse.
- If patients who discontinue RAASi do not receive an alternative active treatment for their hypertension.
- If the effect of Patiromer on the likelihood of discontinuing RAASi among those remaining on Patiromer wanes over time.
- If the effect of Patiromer on the likelihood hyperkalaemia wanes over time.
- Using the quality of life estimates for ESRD from the Wyld et al [68] systematic review.

5.5 *Conclusions of the cost effectiveness section*

The company model contains two major errors.

- Applying daily probabilities of hyperkalaemia in the context of a monthly model cycle.
- Applying an additional unwarranted 56% discount to Patiromer costs.

The first error partially cancels out the second, but the main effect of them is to cause the total cost saving within the company base case to be overestimated.

In the opinion of the ERG, the company submission shows further bias in terms of:

- Not considering the Patiromer discontinuation data of OPAL-HK.
- Its choice of RAASi hypertensive treatment comparator and its associated relative risks.
- Its calculations of baseline risks of events, most notably the probability of developing ESRD.
- In some instances the selection of papers from which to derive inputs, and,
- There is no consideration of adverse events, which may be of secondary importance but sets the general tenor of the submission, in the absence of longer term safety data.

The ERG does not have the time or resources to systematically review all the inputs to the company model, and has concentrated upon those that seem the most important. It is possible that that the company may also have been selective in its choice of papers for other inputs.

The company estimates that Patiromer dominates placebo whereas ERG estimates an ICER of £236k per QALY. This discordance reflects different approaches to the use of evidence to

model the unobserved life-time cost-effectiveness of Patiromer with small numbers of patients and short term RCT data. The company model extrapolates effects estimated from the 8 weeks' data of Phase B of OPAL-HK over a 35 year time horizon. RAASi discontinuations were protocol driven in OPAL-HK with a different protocol for the placebo arm than the Patiromer arm, potentially biasing the hazard ratio for discontinuation, while CPRD and OPAL-HK RAASi discontinuation rates differed significantly. ERG illustrative scenarios that wane the treatment effect upon RAASi discontinuations and hyperkalaemia probabilities considerably worsen the ICER. It is unclesr whether restriction of the company submission to people with CKD is driven by the need to demonstrate cost-effectiveness rather than the needs of people with hyperkalaemia.

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

The ERG initially provides a set of analyses that retain the main modelling assumption of the company, that the proportions on RAASi in the placebo arm at the end of Phase B of OPAL-HK is the most reasonable estimate for current UK clinical practice and that the RAASi discontinuation risks of the UK CPRD data should only be appended to this. Correcting two major errors, assuming that those discontinuing RAASi would not be left untreated but would receive another active anti-hypertensive treatment and revising the ESRD baseline risk to that implied by the company preferred reference results in a cost effectiveness estimate of £20,654 per QALY.

Retaining the company parameterised curves and the main modelling assumption of the company but applying the other ERG preferred revisions results in a cost effectiveness estimate of £37,691 per QALY.

The final ERG revised base case assumes that the most reasonable estimate for RAASi discontinuations for placebo, or current UK practice, are those derived from the UK CPRD data. The ERG applies the Patiromer hazard ratio of RAASi discontinuation estimated from OPAL-HK to the CRPD curve to estimate the risks of RAASi discontinuation among those receiving Patiromer. The ERG applies the ERG curves for:

- Hyperkalaemia, estimated from Phase B of OPAL-HK.
- Placebo RAASi discontinuations, estimated from the CRPD data, the ERG curve being similar to that of the company.

- Patiromer discontinuation, estimated from AMTHYST-DN, though again the ERG curve is similar to that of the company.

The ERG also assumes that those discontinuing RAASi would receive an alternative antihypertensive treatment such as a calcium channel blocker. Other less important revisions are summarised in section 5.4. These changes result in an estimated net gain of 0.012 QALYs, net costs of £2,787 and an ICER of £236k per QALY.

In part due to the small QALY gains that are estimated, these results are sensitive to:

- Applying the Patiromer discontinuation curve estimated by the ERG from OPAL-HK, which worsens the ICER to £681k per QALY.
- Assuming no active antihypertensive treatment after discontinuing RAASi, which improves the ICER to £184k per QALY.
- Assuming informative censoring when estimating the Patiromer hazard ratio for RAASi discontinuation, which worsens the ICER to £272k per QALY.
- Waning of the treatment effect, which worsens the ICER to well over £300k per QALY.
- Applying the company parameterised curves, which worsens the ICER to £247k per QALY.
- Assuming no quality of life effect from hyperkalaemia, which worsens the ICER to £265k per QALY.
- Applying the ESRD quality of life estimates of the company identified systematic review, which worsens the ICER to £342k per QALY.

7 END OF LIFE

End of life does not apply.

8 OVERALL CONCLUSION

Assuming that the company agrees that the two main errors of the submitted model should be corrected, within the economics the main differences of opinion between the ERG and the company are:

- What Patiromer discontinuation data should be applied?
    - OPAL-HK, or

- AMETHYST-DN

The company base case applies the AMETHYST-DN Patiromer discontinuation data, as does the ERG revised base case. But the ERG is ambivalent about this. At a minimum there is a strong argument for exploring the effects of applying the OPAL-HK Patiromer discontinuation data. This greatly worsen the cost effectiveness of Patiromer within the ERG revised base case.

- What modelling of RAASi discontinuations for those who never receive Patiromer is most likely to reflect current UK clinical practice?
    - Applying the UK CRPD data as per the ERG revised base case, or
    - Applying the OPAL-HK Part-B placebo RAASi discontinuation data and subsequently appending the UK CRPD risks of discontinuation as per the company base case.
- What treatment do patients receive when discontinuing RAASi?
    - Another active treatment such as a calcium channel blocker, or
    - No treatment or placebo.
- Given the OPAL-HK trial protocol and 8 weeks' Kaplan Meier data, how reliable is the estimated Patiromer hazard ratio for RAASi discontinuations, has censoring been correctly applied in its calculation and for how long is it reasonable to extrapolate this treatment effect?
- Given the OPAL-HK trial 8 weeks' Kaplan Meier data, how long is it reasonable to extrapolated the hyperkalaemia treatment effect?
- What is the most reasonable source for the baseline risks of events?
    - Values calculated from a variety of papers within the literature, or
    - Values taken from the NMA among CKD patients that also provides the relative risk estimates for RAASi.
- If the most reasonable source of baseline risks of events is papers within the literature what is the most reasonable baseline risk for developing ESRD?
    - The company calculated value from Landray et al [57], or
    - The ERG calculated value from Landray et al, or

- An estimate from other sources which could be somewhat less than both of the above.

- What is the most reliable source of quality of life values for ESRD?
  - The Lee et al [70] values as per the company base case, or
  - The Clarke et al [81] values from the UKPDS which have been used in number previous NICE assessments and are as per the ERG revised base case, or
  - The Wyld et al [68] systematic review values.

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10 APPENDICES

Appendix A1 Data supplied to ERG for RAASi discontinuation in CPRD

The supplied data is shown in the Table below; event times have been aggregated to 150 week intervals which do not coincide with event times in the KM plot supplied in clarification; individual patient times were not provided.

T (Day)	N Risk	Event	Censored	S(t)
[redacted]				

Appendix A2 Hazard plot for models of RAASi discontinuation in CPRD

The g gamma curve exhibits decreasing hazard in extrapolation, the extrapolation of the flexible model is strongly influenced by number and position of knots selected, the Gompertz model (not shown) exhibits a very steeply rising hazard.

Appendix A3 Schoenfeld residuals plot OPAL-HK RAASi discontinuation (CS Fig 13)

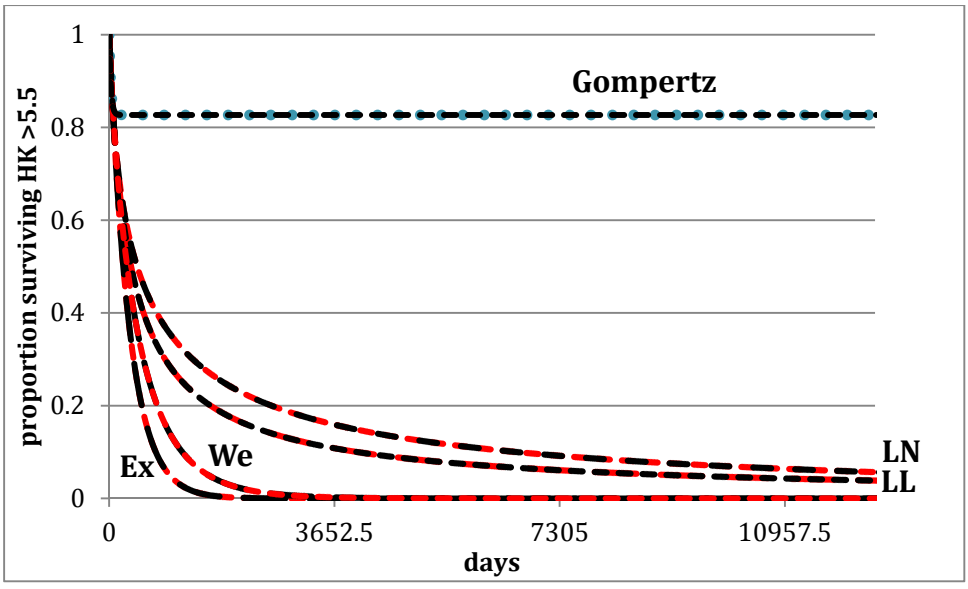
The resulting plot (red line) deviates from a straight line, but 95% CIs are large and the HR line is almost completely encompassed within these for the whole duration (a hypothetical example in which PH holds perfectly and HR = 1 is indicated on the right).

[redacted]

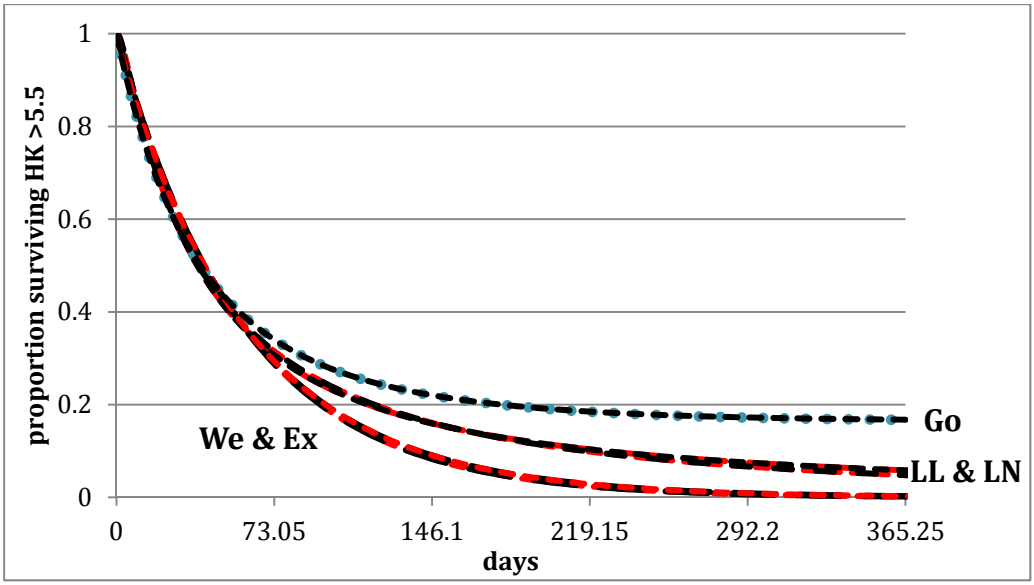
Appendix A4 Comparison of CS and ERG models for time to HK >5.5 mmol/l

The dashed lines for models indicated overlaying ERG and CS model extrapolations

Patiromer arm



No-Patiromer arm



CS submission models and ERG models exactly correspond. LN= lognormal, LL = loglogistic, We =Weibull, Ex=exponential.

Appendix A5 Schoenfeld residuals plot OPAL-HK time to HK >5.5 mmol/l

Appendix A6 ERG method for using Xie data for Kidney Failure and other outcomes

1] Extract RAASi data for: n events in N patients at risk over mean follow up in months (FU), and calculate monthly risk as (n/N)/FU. Because Xie examined two RAASi (ACEi & ARBs) in three sorts of trial (RAASi vs PL, RAASi vs AC and RAASi (ACE) vs RAASi (ARB)) this procedure results in multiple values for an outcome. For CV events no data was available from RAASi vs RAASi trials resulting in four values whereas for Kidney Failure (KF) event data was also available from ACEi vs ARBs trials resulting in six values.

2] Convert risk from 1] to odds: oddsRAASi = riskRAASi / (1 –riskRAASi); giving four (CV) or six (KF) values.

3] Extract the NMA OR for the outcome for RAASi vs PL and for RAASi vs AC; this yields four OR values: ACEi vs PL, ARBs vs PL, ACEi vs AC and ARBs vs AC.

4] Calculate odds of event/patient /month for PL and for AC by applying the appropriate OR to the appropriate odds value from 2] above). This yields four or six values for PL and four (CV) or six (KF) values for AC.

5] Weight the log of the odds values derived in 4] using weightings allocated in the company submission (see XX below). For PL and for AC this yields in each case four (CV) or six (KF) weighted values: i] from ACEi versus PL studies, ii] from ACEi versus AC studies, iii] from ARBs vs PL studies, iv] from ARBs vs AC studies.

6] Derive single values for ln odds (for PL, AC, and RAASi) using the sums of weighted ln odds divided by the sum of weights: $\sum [w*(\ln \text{odds})] / \sum w$.

7] Exponentiate the resulting values to provide the odds of event/month for PL for AC and for RAASi.

8] Convert odds to risk: risk = odds/(1+odds)

9] Estimate TP for PL and AC using: TP = 1 – (exp (-risk).

Estimation of RRs

Monthly risk of events and of no-events in each arm (RAASi, PBO, active controls) were estimated from data in Xie using NMA ORs as described above. The resulting RRs were pooled using the relative weighting suggested in the CS for ACE : ARB derived data of 0.71 : 0.29.

Appendix A7 CS method for estimating TP for CKD to CKD progression

In clarification the ERG requested an explanation of how the CKD to CKD progression transition probability (CS Table 33, value 0.0139) had been calculated using data from Landray et al. Below reproduces the calculation provided:

Annual CKD progression was 12.1%. The observed period was 4.1 years giving a cumulative incidence of 12.1 * 4.1 = 49.61%. There were 382 patients, so the total events observed was 49.61% of 382 = 190.

Rate = 190/382 over 4.1 years. The following equations were then used:

Annual rate = -Ln(1-(events/patients))/years

Annual rate = - ln(1-(190/382))/4.1 = 0.168

Monthly probability = 1- Exp (-rate*t)

Monthly probability =1- exp(-.168*(1/12)) = 0.0139

This high monthly probability derives from Landray et al. from which the CS estimated that 49.1% of patients progress over 4.1 years.

Using Xie source data and the CS method for CKD to CKD progression

In Xie the data for PBO trials was:

RAASi type	PBO events	N	Months follow up	Monthly probability
ACE_pbo	299	3337	48	0.001776
ARB_pbo	727	2421	39.6	0.008977

Using the CS method we have PBO rates of 299/3337 over 4.4 years and 727/2421 over 3.3 years (ACE and ARB trials respectively), giving annual rates of = -Ln(1-(299/3337))/4.4 = 0.021335 and = -Ln(1-(727/2421))/3.3 = 0.108209 respectively, and monthly probabilities of:

1- exp(-.021335*(1/12)) = 0.001776, and 1- exp(-0.108209*(1/12)) = 0.008977 respectively.

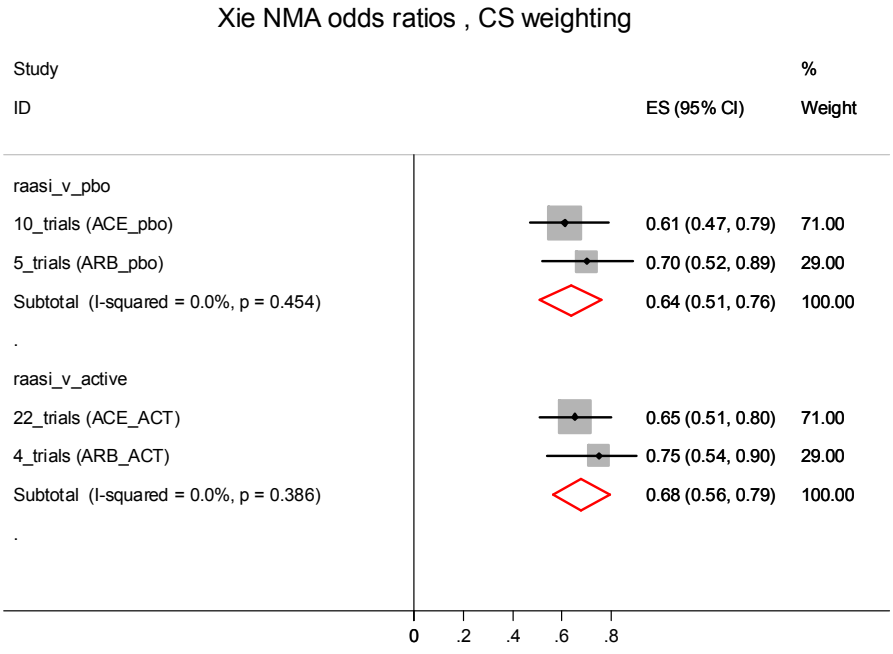
These values are appreciably lower than the CS estimates based on Landray et al. The company weighting has not been used in the above calculation (the company gives more weight to ACEi studies than to ARBs studies).

The ERGs estimates based on Xie and undertaken prior to clarification response from the company developed a monthly probability (after weighting) of 0.0043 for PBO and 0.0040 for active controls.

The study by Kovesdy et al [59] reports low values of CKD progression for UK patients in a UK CKD cohort of 16,828 patients in the PSP-CKD cohort (Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease). Only 0.64% developed ESRD, follow up averaged across studies was 4.0 years. With an assumed follow up of only 1 year for PSP-CKD the p.a. rate would be ~0.0064 and the monthly probability ~0.00053.

Relative Risk of CKD progression using odds ratios from Xie et al

CS Table 33 provides a relative risk (RR) for CKD to CKD progression of 0.64 (RAASi vs PBO) based on Xie et al. The ERG are unclear how this was estimated. Using NMA odds ratios data from Xie (Figure 2) and relative weighting of ACE to ARB studies specified in the CS the ERG obtain a pooled OR corresponding to the Table 33 entry (0.64); for active controls the corresponding OR is 0.68.



Using the expression: Relative risk=odds ratio/(1−p0+(p0×odds ratio)) (where p0 = baseline risk, = risk in control arm) to convert these ORs to RRs provides RR estimates of 0.67 and 0.68.

Using the conventional meta-analysis OR reported by Xie slightly different pooled ORs are obtained:

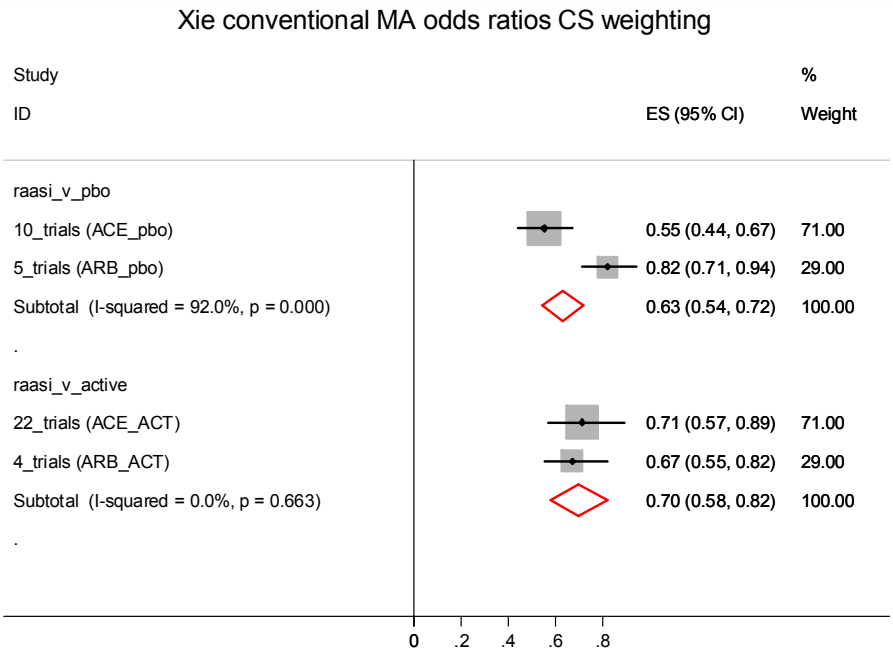


Table 33 CKD to CKD prog RR = 0.64. This may in fact be an OR; obtained by pooling the NMA ORs for ACE and for ARB trial (data in Xie Suppl. FIG 4)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Patiromer for treating hyperkalaemia [ID877]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm on 14 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Page numbering

Description of problem	Description of proposed amendment	Justification for amendment
Many page number references to the submission are incorrect (usually out by one) as the references are made to the first version of the submission.	Please use correct page number references to the latest documents submitted to NICE.	Accuracy

Issue 2 Sutherland et al original model

Description of problem	Description of proposed amendment	Justification for amendment
Page 63 states “the company omits to mention that Sutherland et al is authored by staff of the European Center of Pharmaceutical Medicine at the University of Basel and staff of Vifor. It appears that Vifor commissioned the model of the current submission from the European Center of Pharmaceutical Medicine. As a consequence, the results of Sutherland et al are likely to be subject to exactly the same critique as the ERG critique of the current company submission”.	Replace with “The Sutherland et al model is authored by staff of the European Center of Pharmaceutical Medicine at the University of Basel. Vifor commissioned the model of the current submission from the European Center of Pharmaceutical Medicine. As a consequence, the results of Sutherland et al are likely to be subject to similar critique as the ERG critique of the current company submission.”	The company was upfront regarding the current model being an adaptation of Sutherland et al. Page 80 of Document B states “the current economic model is based on a model developed by Sutherland et al”. In addition, the title page of the MS Excel model states that “The model structure was first developed for UK (Scotland), prepared by the Institute of Pharmaceutical Medicine at the University of Basel, in 2017, with inputs verified by Vifor Ltd. It was then adapted to Wales and England by incorporating time-to-event data, healthcare costs, utilties, and age-related mortality of CKD patients, as well as discounting factors, by IQVIA in collaboration with Vifor Pharma Ltd”.

Issue 3 Comparators

Description of problem	Description of proposed amendment	Justification for amendment
Page 68 states: Hence 95% * 44% = 42% start in sub-cohort A and 5% * 44% = 3% start in sub-cohort B.	5% * 44% = 2.2%	Accuracy

Issue 4 Parametric extrapolation

Description of problem	Description of proposed amendment	Justification for amendment
Page 72: The company also estimates log-normal and log-logistic curves but does not present these or their information criteria on the apparent grounds that applying a hazard ratio to them is invalid, in that it will not result in a log-normal or a log-logistic curve resulting for Patiromer.	Remove the word “apparent”.	The company would like to clarify that log based curves were not used given that the proportional hazards assumption cannot be assumed.

Issue 5 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
The graph on P72 is no longer AIC.	Please remove marking.	Updated post request from NICE

Issue 6 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 73, Figure 15 should be AIC.	Please mark as AIC.	As per latest documents provided to NICE.

Issue 7 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 74 Figures 16 and 17 do not need to be AIC marked. Page 77, Figure 18 the fitted curves do not need to be AIC marked (KM curves should remain marked).	Please remove marking.	As per latest documents provided to NICE.

Issue 8 Utilities

Description of problem	Description of proposed amendment	Justification for amendment
Stroke and MI are assigned quality of life values of 0.519 and 0.605 in the year of the event, based upon Sullivan et al. A balance between stroke and MI of 35:65 is taken from Lee et al, yielding a mean quality of life for the year of a cardiovascular event of 0.574.	"…yielding a mean quality of life for the year of a cardiovascular event of 0.6996".	Incorrect calculation; the sum product of these utilities should be 0.549, providing a relative utility of 0.6996.

Issue 9 Deterministic basecase results

Description of problem	Description of proposed amendment	Justification for amendment
P85 Table 21. Labelling error.	Please re-label table heading which states "CKD" with "concomitant medication".	Accuracy

Issue 10 Hazard ratio

Description of problem	Description of proposed amendment	Justification for amendment
Pg 108 “When calculating the hazard ratio it appears that the company may have assumed informative censoring for the placebo arm Kaplan Meier data, with censoring being equivalent to RAASi discontinuation, but non-informative censoring for the Patiromer arm.”	Please remove this text as the company can confirm that non-informative censoring was used in both arms.	Keeping this in the report would be misleading.

Issue 11 Target population

Description of problem	Description of proposed amendment	Justification for amendment
Pg 25 states “The CS did not clearly justify the rational for restricting the population to patients with chronic kidney disease.” Pg 62 states “The restriction to the CKD population by the company appears entirely driven by the needs of the model.” Pg 123 states “It is unclesr whether restriction of the company submission to people with CKD is driven by the need to demonstrate cost-effectiveness rather than the needs of people with hyperkalaemia.”	Please replace the sentence from pg 25 with “The CS justified the rationale for restricting the population to patients with chronic kidney disease on the basis that the best available evidence for patiromer comes from the OPAL-HK trial, which includes this population”. Please remove the sentences on page 62 and page 123.	The company would like to clarify that as stated in section B1.1 of the submission, the “patient population is narrower than the marketing authorisation because the evidence base on patiromer is focused on this population” i.e. OPAL-HK.

Issue 12 Discrepency

Description of problem	Description of proposed amendment	Justification for amendment
Page 28: "The ERG noted some discrepancy for the number of included studies between document B (p24) and Appendix D (table 8, p35 -38). In the CS document B, clinical effectiveness and safety data were drawn from two studies while in the supplementary material table 8 lists a total of 27 included records."	Please remove.	Document B does not contain a statement about the number of included studies in the clinical trial. In the appendices, 27 studies were found which relate to 4 trials; OPAL-HK, AMETHYST, TOURMALINE and PEARL-HF. The company provide rationale for discarding TOURMALINE and PEARL-HF in Document B section B.2.1, leaving two studies which provide clinical and safety data (OPAL-HK and AMETHYST).

Issue 13 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 119, Table 42, incremental disaggregated QALYs not marked as CIC	Please mark as per as CIC as per Table 40 and 41 of Document B5 (Appendices)	As per latest documents provided to NICE.

Issue 14 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 119, Table 43., incremental outcomes are not marked as CIC	Please mark as CIC as per Table 43 of Document B (PAS price results)	As per latest documents provided to NICE.

Issue 15 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 121 Table 44 incremental costs and QALYs not CIC.	Please mark as CIC.	As per latest documents provided to NICE.

Issue 16 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment
Page 38: "CPRD patients were more likely to be female, on average [redacted] years younger, not on dual blockade and considerably less likely to have diabetes, hypertension, …"	CPRD patients were more likely to be female, on average [redacted] years younger, not on dual blockade and considerably less likely to have diabetes, hypertension, …"	Please mark age difference as AIC, consistent with P63 of the ERG report.

Issue 17 Dietary advice in OPAL-HK

Description of problem	Description of proposed amendment	Justification for amendment
Page 25: "Both Patiromer-treated and untreated patients are assumed to receive the same advice on potassium diet and general clinical care for related conditions."	Replace with: "Both Patiromer-treated and untreated patients are assumed to receive the same advice on potassium diet and general clinical care for related conditions in OPAL-HK. Patients were counselled at each visit to restrict their intake of high K foods (>250mg per 100g) and maintain a low-potassium diet >3g per day".	These additions would provide a more complete reflection of the response the company provided the ERG at clarification.

1 Critique of company's definition of decision problem

1.1 *Population*

The NICE final scope reflects the licenced indication for Patiromer: adults with hyperkalaemia. However, the CS restricted the population to hyperkalaemia patients with stage 3-4 chronic kidney disease (which may include other co-morbidities such as heart failure and diabetes) treated with RAAS inhibitors. The CS did not clearly justify the rational for restricting the population to patients with chronic kidney disease. Given its therapeutic indication, the ERG questions the restricted population of the submission, since no value proposition is presented for other populations.

1.2 *Intervention*

The CS intervention matches that in the NICE final scope: Patiromer (8.4 to 16.8 g/day).

1.3 *Comparators*

Both Patiromer-treated and untreated patients are assumed to receive the same advice on potassium diet and general clinical care for related conditions in OPAL-HK. Patients were counselled at each visit to restrict their intake of high K foods (>250mg per 100g) and maintain a low-potassium diet >3g per day, although the extent and clinical compliance with counselling is not reported. The comparator in the decision problem is 'standard care', with RAAS inhibition discontinued or reduced in patients where hyperkalaemia is uncontrolled. The ERG asked the company (clarification question A1) to provide a rational for excluding from standard care low-potassium diet with or without agents that reduce levels of potassium in the body. In response the company stated: "…a low potassium diet restricts consumption of healthy foods and that there is limited evidence on the efficacy of and adherence to a low potassium diet". The ERG disagrees with this statement: the company provided no evidence for its assertion either in its original submission or in its clarification response to the ERG's request for evidence. CS evidence includes: a website giving advice about how to maintain a low potassium diet [26]; findings from an unpublished company survey of Scottish GPs (data on file), which found that the majority of GPs would recommend diet change (numbers not provided); reference to the EPAR Report for Veltassa [18], which provides an unreferenced opinion that dietary modification is difficult due to the ubiquitous presence of potassium in foods.

The NICE guideline on CKD states:

"1.4.7 Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD.

For the placebo group, RAAS inhibitor was decreased by 50% or the next dosage below at the first occurrence of hyperkalaemia. RAAS inhibitor was discontinued on the second occurrence of hyperkalaemia.

Participants were enrolled from February 2013 from 10 different countries (Eastern Europe, Europe and US sites), none from the UK. The last study visit was in August 2013. There was some discrepancy in the number of sites reported in the CS and the trial publication, however the conduct of the trial was fairly presented in the CS.

1.3.1 Selection of participants

The CS reported the key inclusion criteria in table 5 p34-35 and Appendix D (table 9); in summary (phase A) these were patients 18 to 80 years of age, had stage 3 or 4 chronic kidney disease (estimated glomerular filtration rate [eGFR] 15 to < 60 ml per minute per 1.73m^2 of body-surface area) at screening, had serum K^+ levels of 5.1 to > 6.5 mmol/l at two screening (hyperkalaemia), and had been receiving a stable dose of one or more RAAS inhibitors for at least 28 days. For phase B: patients were eligible if they had a serum K^+ level of ≥ 5.5 mmol/l at baseline of phase A, had a serum K^+ level at the end of phase A within the target range (3.8 - < 5.1 mmol/l) while receiving Patiromer and RAAS inhibition. Thus the randomised trial evidence only relates to subjects with serum K^+ level of ≥ 5.5 mmol/l who respond to Patiromer in the target range, the company offer no value proposition for mild hyperkalaemia (serum K^+ levels of 5.1 to <5.5 mmol/l) or non-responders.

Mild hyperkalaemia was defined as K^+ levels 5.1 to < 5.5 mmol/l and moderate to severe hyperkalaemia was defined as 5.5 to < 6.5 mmol/l. The ERG notes that the definition of hyperkalaemia can vary, for example The National Institute for Health and Care Excellence (NICE) 'Treatment summary for fluids and electrolytes' defines acute severe hyperkalaemia as > 6.5 mmol/l [8].

Hyperkalaemia (K^+ level) was determined using local and central laboratory results (CS p36).

- Central laboratory: phase A baseline values
- Local laboratory: phase A post baseline values
- Both central and local laboratory: phase B withdrawal

During each phase patients could have dose adjustments based on the local laboratory serum potassium values and according to titration algorithms. The ERG asked the company how well the measures (central vs. local) correlated (clarification question A4) and the company provided correlation analysis and visual figures. The concordance between local and central laboratory serum K^+ for phase A baseline and post-phase A baseline was provided in

hypertension, RAAS inhibitor use or diuretic use; Clarification A6.2). Therefore the ERG is not clear that RAAS inhibitor therapy or blood pressure management more generally is consistent across regions. The majority of the sample was from Eastern Europe (total = [redacted], Patiromer = [redacted], placebo = [redacted]); fewer patients were from the US and Europe (total = [redacted], Patiromer = [redacted], placebo = [redacted]). Patients recruited to the OPAL-HK [4] trial had mild-moderate hyperkalaemia ($K^+ \geq 5.1$ to less than 6.1 mmol/l).

The ERG notes that the trial did not include any UK centres and asked the company to supply supporting evidence to demonstrate the generalisability of the OPAL-HK [4] population to the UK population (clarification question A5). The company referred to CS table 27 on page 91 where the placebo group of phase B was compared to the Clinical Practice Research Datalink (CPRD) database [54]. CPRD is governmental non-profit research service (funded by the NHS and NIHR) that provides anonymised primary care records for public health research. The company assertion that baseline characteristics between the cohorts were broadly comparable is not supported (Table 1). CPRD patients were more likely to be female, on average [redacted] years younger, not on dual blockade and considerably less likely to have diabetes, hypertension, heart failure or previous myocardial infarction. The ERG did not find the OPAL-HK [4] patients comparable to the CPRD population [54].

Table 1: Patient characteristics in OPAL-HK Part two (B) and CPRD England [4, 54]

	OPAL-HK Placebo (N=52)	**OPAL-HK Patiromer (N=55)**	**CPRD (N=[redacted])**
Male, % (*n*)	58% (30)	51% (28)	[redacted]
Mean age, mean±SD	65.0 (55)	65.5 ± 9.4	[redacted]
Mean eGFR, mean±SD	39.0± 20.4	38.6 ± 20.7	[redacted]
RAASi (ACE), % (*n*)	73% (38)	67% (37)	[redacted]
RAASi (ARB), % (*n*)	31% (16)	44% (24)	[redacted]
RAASi (aldosterone), % (*n*)	8% (4)	7% (4)	[redacted]
Mean serum K^+ mmol/l, mean±SD	5.9 ± 0.4	5.9 ± 0.6	[redacted]
Myocardial infarction, % (*n*)	27% (14)	33% (18)	[redacted]
Hypertension, % (*n*)	96% (50)	98% (54)	[redacted]
Diabetes mellitus, % (*n*)	63% (33)	62% (34)	[redacted]
Heart Failure, % (*n*)	42% (22)	49% (27)	[redacted]

economic evaluations) on RAASi v placebo in CKD or diabetic retinopathy undertaken in 2016 is also reported.

The search strings and sources used for the 4 systematic reviews appear to be adequate. Lists of excluded studies at full-text are not provided. As noted **Error! Reference source not found.** in section 4.5.8, the quality of these reviews is difficult to assess within time constraints. It is worth bearing in mind that: "*The framing of the question, the choice of eligible studies, the selection of comparisons, populations, and outcomes of interest, the types of data extracted, and the statistical methods used, along with many other factors, allow for substantial diversity in the final results. More importantly, the interpretation of even the same results can differ*" [58].

1.3.2 Conclusions

Table 23 on page 79 of Document B provides a reasonable summary of the results of the cost-effectiveness studies of Patiromer.

- Sutherland et al [60] conclude that Patiromer results in gains of 0.33 to 0.54 QALYs and net gains, taken by the ERG to mean net savings, of £9,540 to £9,950.
- Little et al [61] estimate a net QALY gain from Patiromer of only 0.0004 QALYs, a net cost in 2011 prices of US$10,690 and so an ICER of US$26 million per QALY

The Sutherland et al model is co-authored by both staff of the European Center of Pharmaceutical Medicine at the University of Basel and staff of Vifor. Vifor commissioned the model of the current submission from the European Center of Pharmaceutical Medicine. As a consequence, the results of Sutherland et al are likely to be subject to a similar critique as the ERG critique of the current company submission. It should be noted that the estimates of Sutherland et al are very much more favourable to patiromer in terms of both the net QALYs and the net costs than those of the current submission, despite the current submission including the effects of the patiromer PAS. The reason for these differences is unknown. Little et al is authored by staff of the Department of Medicine, Walter Reed National Military Medical Center, Bethesda, MD, USA who declare that they have no conflicts of interest. The cost results of Little et al are of less relevance to the UK setting, but very small QALY gain that is estimated from use of Patiromer is noteworthy. The time horizon of the model of Little et al is only 1 year, while in the current submission the main benefits of Patiromer arise from avoiding ESRD over a number of years. Further, a broader group of patients than CKD patients is included, compared to the current submission. The literature review identifies a number of cost-effectiveness studies of sodium polystyrene sulphate (SPS) for hyperkalaemia. Little et al note that this is often usual standard of care in the US and estimates the cost effectiveness of Patiromer relative to SPS.

discontinuation curve for sub-cohort A is calculated as the sum of the Patiromer specific RAASi discontinuation curve conditioned by the Patiromer discontinuation curve and the placebo specific RAASi discontinuation curve conditioned by the residual of the Patiromer discontinuation curve. The RAASi discontinuation curve for sub-cohort A then conditions the relative risks and probabilities of events as per sub-cohort D. But the RAASi discontinuation curve for sub-cohort A does not converge to unity, and the probabilities of events in this sub-cohort remain below those of the other sub-cohorts throughout the time horizon of the model.

The Patiromer arm is differentiated from the placebo arm according to the proportions of patients in each of the four independent sub-cohort, A, B, C and D. For the Patiromer arm the proportion of patients going on to receive maintenance Patiromer is based upon the OPAL-HK Phase A response percentage, i.e. week 4 of OPAL-HK, of 107 / 243 = 44%.

Table 2: Distribution of patients across independent sub-cohorts for Patiromer arm

	Patiromer	**Placebo**
OPAL-HK Part A	243	
OPAL-HK Part B	107 (44%)	
Randomised to	55	52
Of whom hyperkaliaemic On RAASi Off RAASi	[redacted]	[redacted]
Of whom non-hyperkaliaemic On RAASi Off RAASi	[redacted]	[redacted]
Pooled On RAASi Off RAASi	52 (95%) 3 (5%)	25 (48%) 27 (52%)

The 44% proportion responding during Phase A is divided between sub-cohorts A and B according to the proportion of the 55 patients randomised to Patiromer during OPAL-HK Phase B who remained on RAASi at the end of Part B, i.e. week 12[1] of OPAL-HK. This was [redacted] of the [redacted] patients who were hyperkaliaemic at week 12 and [redacted] of the patients who were not hyperkaliaemic at week 12 to yield a total of 52 / 55 = 95%. Hence 95% * 44% = 42% start in sub-cohort A and 5.5% * 44% = 2.4% start in sub-cohort B.

In a similar manner the 56% of OPAL-HK Phase A non-responders is divided between sub-cohorts C and D according to the proportion of the 52 patients who were randomised to

[1] Based upon figure 11 of Document B

- CKD to ESRD relative risk of 0.64,
- CKD to CV event relative risk of 0.82,
- CV event being fatal relative risk of 0.88, and
- All-cause mortality relative risk of 0.87.

RAASi discontinuation curve placebo and Patiromer hazard ratio of RAASi discontinuation

In the model the proportions on RAASi at baseline are determined by those on RAASi at the end of OPAL-HK:

- 69% for Patiromer, and
- 48% for placebo.

Thereafter the risk of discontinuing RAASi in the placebo arm is calculated from RAASi discontinuation data among those having a hyperkalaemia event in the UK CRPD database.

Figure 1: CPRD RAASi discontinuation subsequent to hyperkalaemia curves

The Weibull has the lowest AIC and BIC and is selected for the base case. Something appears to have gone wrong with the exponential as it bears no relation to the Kaplan Meier data, but it is not used for the company modelling. The company also estimates log-normal and log-logistic curves but does not present these or their information criteria on the grounds that applying a hazard ratio to them is invalid, in that it will not result in a log-normal or a log-logistic curve resulting for Patiromer.

For Patiromer, the OPAL-HK Phase B RAASi discontinuation curves are used to estimate a hazard ratio of RAASi discontinuation of [redacted]. Note that this data is only over 8 weeks, and relates to only [redacted] events in the Patiromer arm compared to [redacted] events in the placebo arm.

Table 3: Uncertainty around the PSA estimates

	Net QALYs		Net Costs	
Mean	+0.100		-£1,412	
Median	+0.101		-£1,360	
Interquartile range	-0.156	+0.354	-£12,305	+£9,258
95% range	-0.658	+0.868	-£34,902	+32,235
Min-Max range	-1.500	+1.626	-£93,139	+£70,635

1.3.3 Sensitivity analyses

The company conducts a wide range of univariate sensitivity analyses, typically varying parameters through their 95% confidence interval or where this was not available by ±10%. The full tornado diagram is presented as figure 26 on page 128 of Document B. The sensitivity analyses for the variables that results are most sensitive to are tabulated below.

Table 4: Company sensitivity analyses

	Values			ICER	
	Base	Low	High	Low	High
RR CKD to CKD progression - RAASi	64%	47%	79%	-£24,433	£1,644
RR CKD to death (non-CV) - RAASi (all cause)	87%	74%	101%	-£5,986	-£30,588
RR CKD progression to death - RAASi	100%	90%	110%	-£4,170	-£27,102
% ESRD - Haemodialysis	73%	66%	80%	-£11,380	-£18,155
Monthly costs ESRD - Haemodialysis	£2,857	£2,571	£3,142	-£11,772	-£17,529
Discount rate - utilities	3.5%	1.0%	6.0%	-£12,076	-£17,471
SMR for mortality with CKD 4 vs CKD 3	256%	175%	375%	-£12,566	-£17,608
Discount rate - costs	3.5%	1.0%	6.0%	-£16,020	-£13,159

The values compare with a base case ICER of -£14,651 per QALY; i.e. there are savings per QALY. The ERG has not rerun the company sensitivity analyses and assumes that the company negative ICERs all relate to cost savings and QALY gains. In short, the company finds results show some sensitivity to the relative risks taken from Xie et al [5], the costs of haemodialysis and the proportion of ESRD patients incurring these costs and the SMR for CKD Stage 4 versus CKD Stage 3.