Part 1 slides for projector and committee [redacted]

NICE National Institute for Health and Care Excellence

Lead team presentation

Patiromer for treating hyperkalaemia

1st Appraisal Committee meeting

Committee B, 3rd October 2018; **2nd** topic on agenda

Lead team: Chris O'Regan, Mona Johnson, Nigel Westwood

Chair: Amanda Adler

Assessment group: Warwick Evidence

NICE technical team: Jessica Cronshaw, Ross Dent

Current management of hyperkalaemia

- No randomised trial evidence for adding patiromer
- No trial evidence for patiromer for people with serum K+ ≥6.5mmol/L

Maintenance and long-term control

European Resuscitation Council definition of hyperkalaemia

Mild hyperkalaemia
5.5 to 5.9 mmol/L

Moderate hyperkalaemia
6.0 to 6.4 mmol/L

Severe hyperkalaemia
≥6.5 mmol/L

Current NHS practice

- Low potassium diet
- Adjust medicines that increase risk of hyperkalaemia (e.g. RAAS inhibitors)
- Active treatments to reduce serum K^+ (e.g. IV insulin, IV glucose, oral calcium polystyrene sulfonate [resonium])

Company positioning

Patiromer*

Company definition of hyperkalaemia differs from European Resuscitation Council definition:

- **Mild** 5.1 to <5.5 mmol/L, **Moderate-to-severe** 5.5 to <6.5 mmol/L
- **Start patiromer** >5.1 mmol/L

⊙ *Who is likely to receive patiromer in NHS practice?*
⊙ *Would patients with serum potassium 5.1 to 5.5 mmol/L be offered an active treatment in NHS practice?*

*__Note:__ **sodium zirconium cyclosilicate** has marketing authorisation for treating hyperkalaemia (separate appraisal)

Abbreviations: K^+, potassium

Overview of key clinical relationships

Impact of :	Source	RCT-based?	Use in model	Length of life	Quality of life
Hyperkalaemia events	Luo et al. (2016)	No	• Serum K^+ >5.5 • Increased probability of cardiovascular events and death	↓	↓
Renin-angiotensin-aldosterone (RAASi) use	Landray et al. (2010)	No	• 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	↑	↑
Patiromer	OPAL-HK	No	• Lower serum potassium (hazard ratio of hyperkalaemia: 0.25) Lower rate of stopping RAASi (hazard ratio: [redacted])	↑	↑

[redacted] Abbreviations: K^+, potassium; RCT, randomised controlled trial

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: 25.2 g 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)**

RAASi, serum K^+ and outcomes –

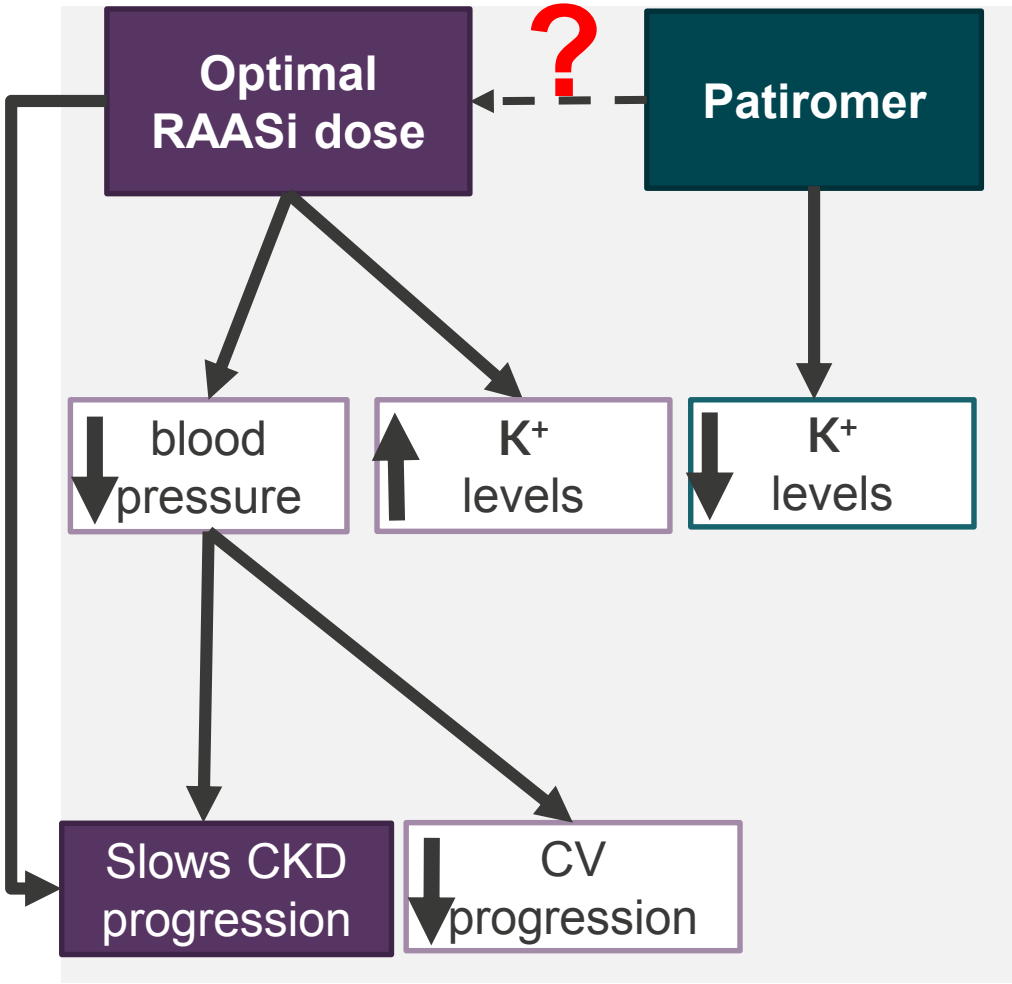
Company's conceptual role for patiromer

RAASi: (e.g. ACE inhibitors, ARBs etc.)
- **used to treat hypertension, HF, CKD**
- **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 uACR of ≥3mg/mmol
  - hypertension and uACR of ≥30 mg/mmol
  - an ACR of 70 mg/mmol or more

Because **RAASi increases serum K^+**
- do not offer RAASi if serum **K^+** >5.0 mmol/L
- **stop RAASi if serum K^+ ≥6.0 mmol/L**

Company claim about patiromer:
- An 'innovative solution' that enables patients to continue optimal RAASi dose by regulating potassium levels



⊙ *Does RAAS inhibitor drive differences in length and quality of life?*

Abbreviations: ACE, angiotensin-converting enzyme; ACR, albumin:creatinine ratio; uACR, urinary albumin:creatinine ratio; ARB, angiotensin-receptor blockers; CKD, chronic kidney disease; HF, heart failure, K^+, potassium

Patient and professional feedback

Patient perspective	• Hyperkalaemia is dangerous and distressing • Current treatments are unpalatable • Dietary restrictions are very demanding and restricts common items (bananas, coffee and chocolate) • Difficult for carers, hyperkalaemia can make a person feel sick, shake, have a racing heart and feel disoriented
Unmet need	• Current treatments ineffective and poorly tolerated • Patiromer could allow people to continue taking RAASi • Could prevent unnecessary admissions to hospital
Population	• Most suitable for people with CKD stage 3b, 4 and 5 (no-dialysing, no evidence from company) and comorbidities such as heart failure, severe hypertension, diabetes • More potential to reduce hospital admission in people with moderate hyperkalaemia 6.0mmol/L to 6.4mmol/L

Abbreviations: CKD, chronic kidney disease; RAASi, renin–angiotensin–aldosterone system inhibitors

Patient and professional feedback

Effects of patiromer	• Could optimise RAASi therapy:
	  • reduce hospitalisations for hyperkalaemia
	  • reduce cardiovascular events
	  • increase time to renal replacement therapy
	• May allow healthier diets leading to increased quality of life

Evidence base	• No evidence from a trial that patiromer:
	  • Reduces hospitalisations
	  • Increases survival
	  • Improves health related quality of life
	  • Decreases episodes of moderate hyperkalaemia (6.0 to 6.4)

Implementation	• NHS needs clear rules on duration of treatment and dose:
	  • Minimum reduction in serum potassium of 0.5 mmol/L may be reasonable
	  • Need to test for low serum magnesium (adverse event)
	  • Would expect increased effective use of RAASi and increased cost of RAASi

Abbreviations: RAASi, renin–angiotensin–aldosterone system inhibitors

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** treated with 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)
- Restriction of high potassium foods is part of current care

⊙ *What is the role of diet? Should a low potassium diet precede patiromer? Should it be a comparator?*

[redacted] Abbreviations: CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone inhibitor

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 patiromer treatment
- OPAL-HK short (12 weeks) uncontrolled trial
- OPAL-HK small trial, n=107 randomised yet relatively common condition
- Long term efficacy and safety of patiromer unknown
- OPAL-HK treatment population may not be generalisable to NHS
- 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

[redacted]

OPAL-HK summary

	Part A (4 weeks)	Part B (8 weeks)
Population	CKD 3 or 4 with K^+ >5.5 mmol/L and <6.5 mmol/L, on RAASi, no UK centres	Patients who responded to patiromer during Part A (responders: K^+ ≥5.5mmol/L start of part A; K^+ between 3.8 and 5.1mmol/L at end of part A)
Intervention	Patiromer dose adjusted to reach target range 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 8 visit, if patient's K^+ remained between ≥3.8 and <5.5 mmol/L up to the week 8 visit, or • earliest visit at which patient's K^+ was <3.8 and ≥5.5 mmol/L
Exploratory Endpoint	-	• Time to RAASi 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)

Abbreviations: K^+, potassium; RAASi, renin–angiotensin–aldosterone system inhibitors

Clinical evidence: OPAL-HK

Randomised controlled period only includes people who responded to patiromer

PART A: Single arm 'single-blind' **4 weeks**

n=243
Inclusion criteria
- Age 18 to 80 yrs
- CKD stage 3 + 4
- On RAASi

K^+ 5.1 to <5.5 mmol/L, local lab **n=92**
4.2 g patiromer 2x/day
2% discontinued early

K^+ 5.5 to <6.5 mmol/L. local lab
n=151
8.4g patiromer 2x/day
5% discontinued early

n=15

n=92

PART B: Randomised 'single blind' withdrawal phase **8 weeks**
(economic model based on part B)

n=107
Inclusion criteria
- People who **responded** to patiromer in part A
- People still having patiromer and RAASi

Patiromer n=55
18% discontinued early

Placebo n=52
42% discontinued early

ERG: trial was not designed to examine all-cause mortality or cardiovascular events
- investigators were unblinded this would introduce bias

- *In OPAL-HK were RAASi stopped only because of elevated K+? If not, is it a relevant endpoint?*
- *Does the endpoint of the study, target K^+ 3.8 to <5.1 mmol/L reflect clinical practice?*

Baseline characteristics: OPAL-HK and AMETHYST

- AMETHYST-DN: single-arm study n=306, CKD3+4, type 2 diabetes, mild hyperkalaemia, on RAASi therapy.
  - Outcomes: change in serum K+, proportion with target serum K+
- Company use AMETHYST data in economic model for patiromer discontinuation

	OPAL-HK			AMETHYST-DN
Mean (SD) or n, %	Part A	Part B (responders)		Overall
	Overall (n=243)	Placebo (n=52)	Patiromer (n=55)	Patiromer (n=304)
Age, years	64 ± 11	65 ± 9	66 ± 9	66 ± 9
White race, n	239 (98%)	52 (100%)	55 (100%)	304 (100)
Type 2 diabetes, n (%)	139 (57%)	33 (63%)	34 (62%)	304 (100)
CHF, 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 K+ (mmol/L)	5.6 ± 0.5	5.9 ± 0.4	5.9 ± 0.6	5.3 ± 0.4
eGFR ml/min/1.73m^2	35 ± 16	39 ± 20	38 ± 20	41 ± 16

⊙ *Would patients with diabetes respond differently to treatment with patiromer?*

Abbreviations: EGFR, estimated glomerular filtration rate; K^+, potassium

Generalisability of OPAL-HK to NHS practice

ERG:

- Trial doesn't reflect UK population compared with Clinical Practice Research Database (primary care date on people with CKD stage 3-4 or heart failure and/or diabetes with hyperkalaemia, on ≥ 1 RAASi)
  - patients in OPAL-HK more likely to be female, younger, have fewer comorbidities (heart failure, diabetes, hypertension)
- Majority (65%) of patients from Eastern Europe, no UK sites
- EU/US subgroup more generalisable to NHS
  - overall population data in model may overestimate the benefit of patiromer in UK
- 100% white patients, no evidence for other ethnic groups
- No description of how hypertension managed or if low K+ diet followed before trial
- **% of patients had CKD stage 2

NICE CG127 Hypertension in adults: diagnosis and management

Step 1 treatment:

- age <55: RAASi (ACE inhibitor or ARB)
- age >55 or black person of African or Caribbean family origin: **calcium channel blocker**

Step 2 treatment:

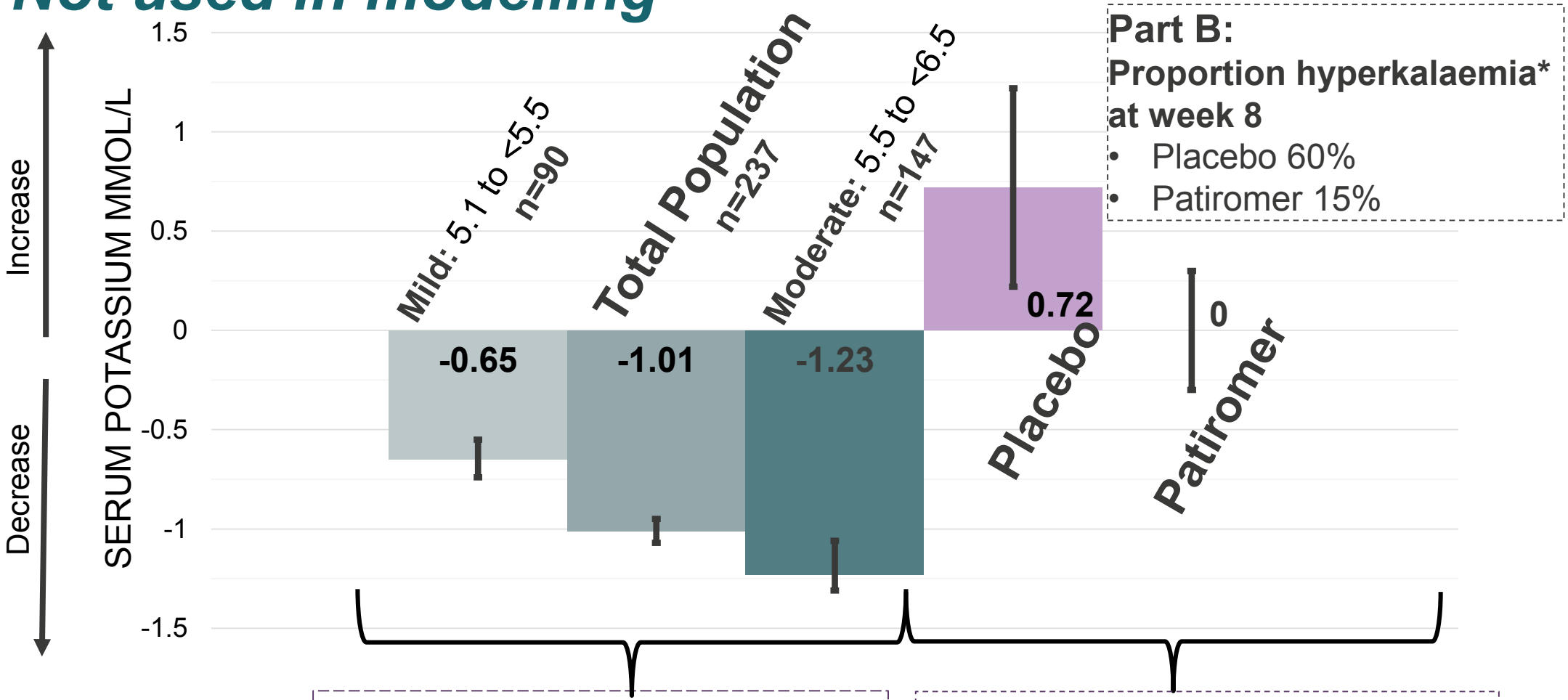
- RAASi + calcium channel blocker for all

⊙ *Is OPAL-HK Part B generalisable to NHS practice?*

Abbreviations: ACE, angiotebsin-converting-enzyme; ARB, angiotensin receptor blockers

Results OPAL-HK: change in serum potassium

Not used in modelling



Part B:
Proportion hyperkalaemia* at week 8
- Placebo 60%
- Patiromer 15%

Part A:
Average serum K^+ at start:
- **5.6** mmol/L
- **76%** had normal serum potassium at week 4 (3.8 to <5.1)

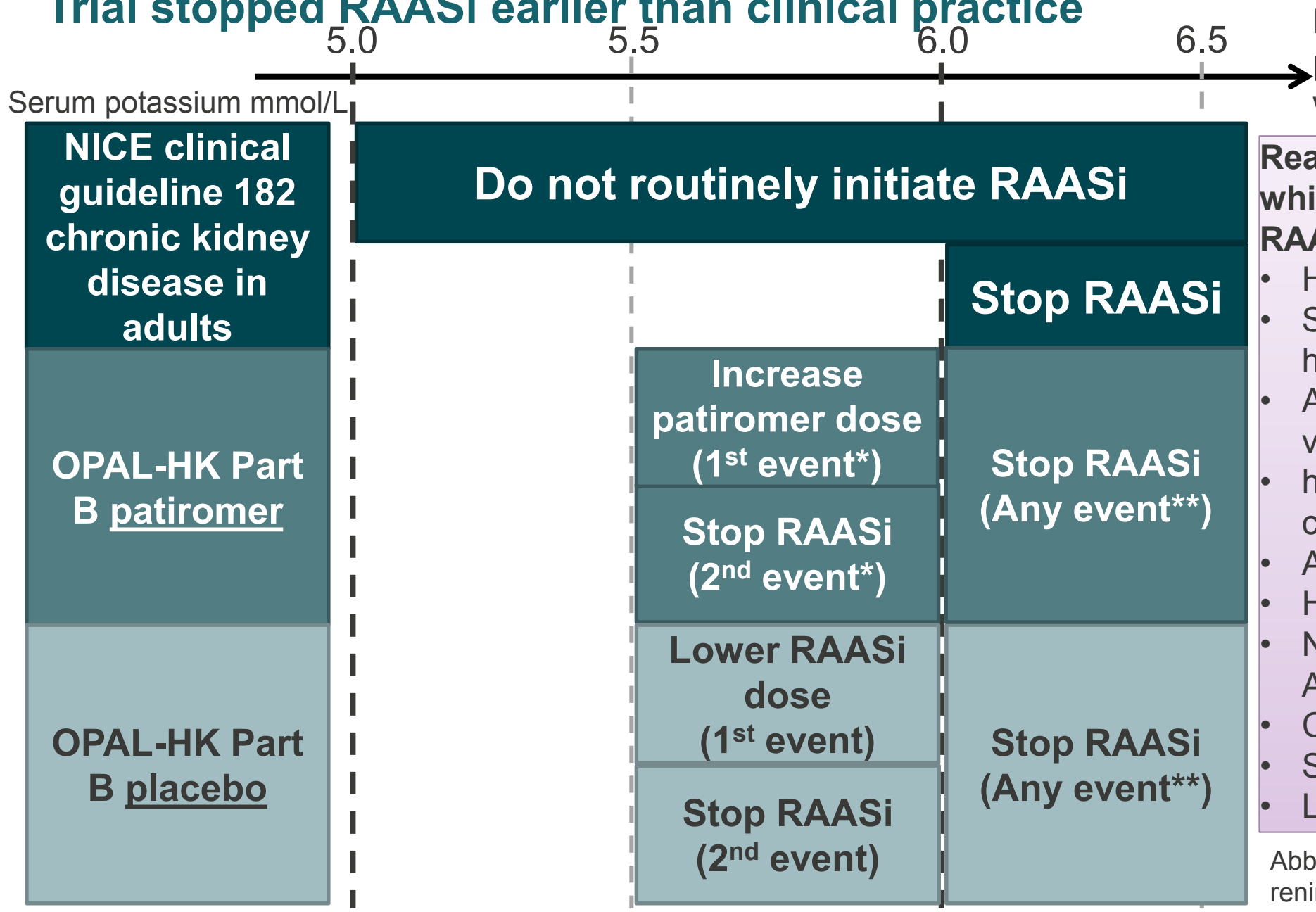
Part B:
Average serum K^+ at end:
- placebo: **5.2** mmol/L
- patiromer: **4.5** mmol/L

[redacted]

*at least one serum potassium value of ≥5.5mmol/L

Clinical criteria for stopping RAASi: trial vs. NHS

Trial stopped RAASi earlier than clinical practice



Reasons for which people stop RAAS inhibitors:

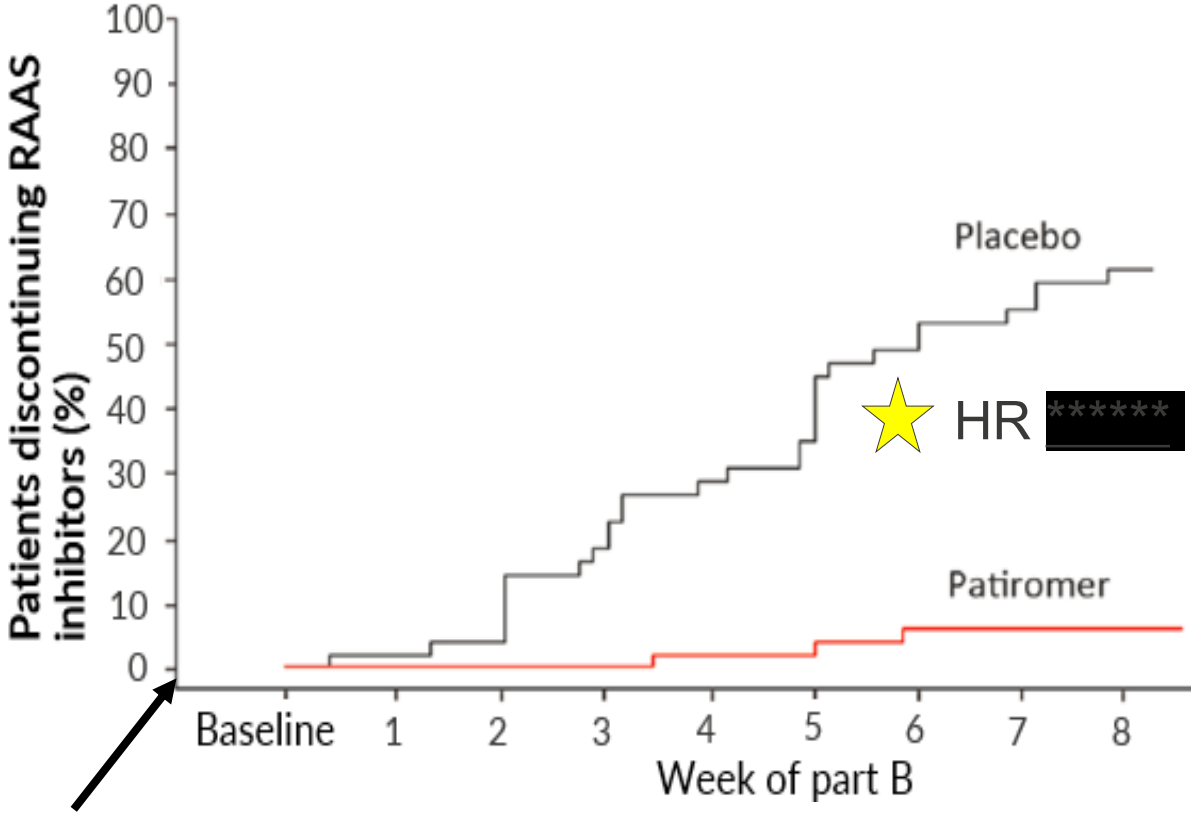
- Hyperkalaemia
- Symptomatic hypotension
- Aortic and mitral valve stenosis
- hypertrophic cardiomyopathy
- Angioedema
- Hepatic failure
- Neutropenia/ Agranulocytosis
- Cough
- Surgery
- Lithium

⊙ *Does the protocol for stopping RAASi reflect clinical practice?*

Abbreviations: RAASi, renin–angiotensin–aldosterone system inhibitors

* Event: serum potassium >5.5 mmol/L **Event: serum potassium >6.0 mmol/L

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



40% on max RAASi dose at start of part B

44% placebo arm on RAASi at week 8

ERG: Higher rates of stopping than in the NHS. Difference **may be due to protocol** in part B for stopping RAASi being more aggressive for the placebo arm than the patiromer arm (previous slide)

94% patiromer arm on RAASi at week 8

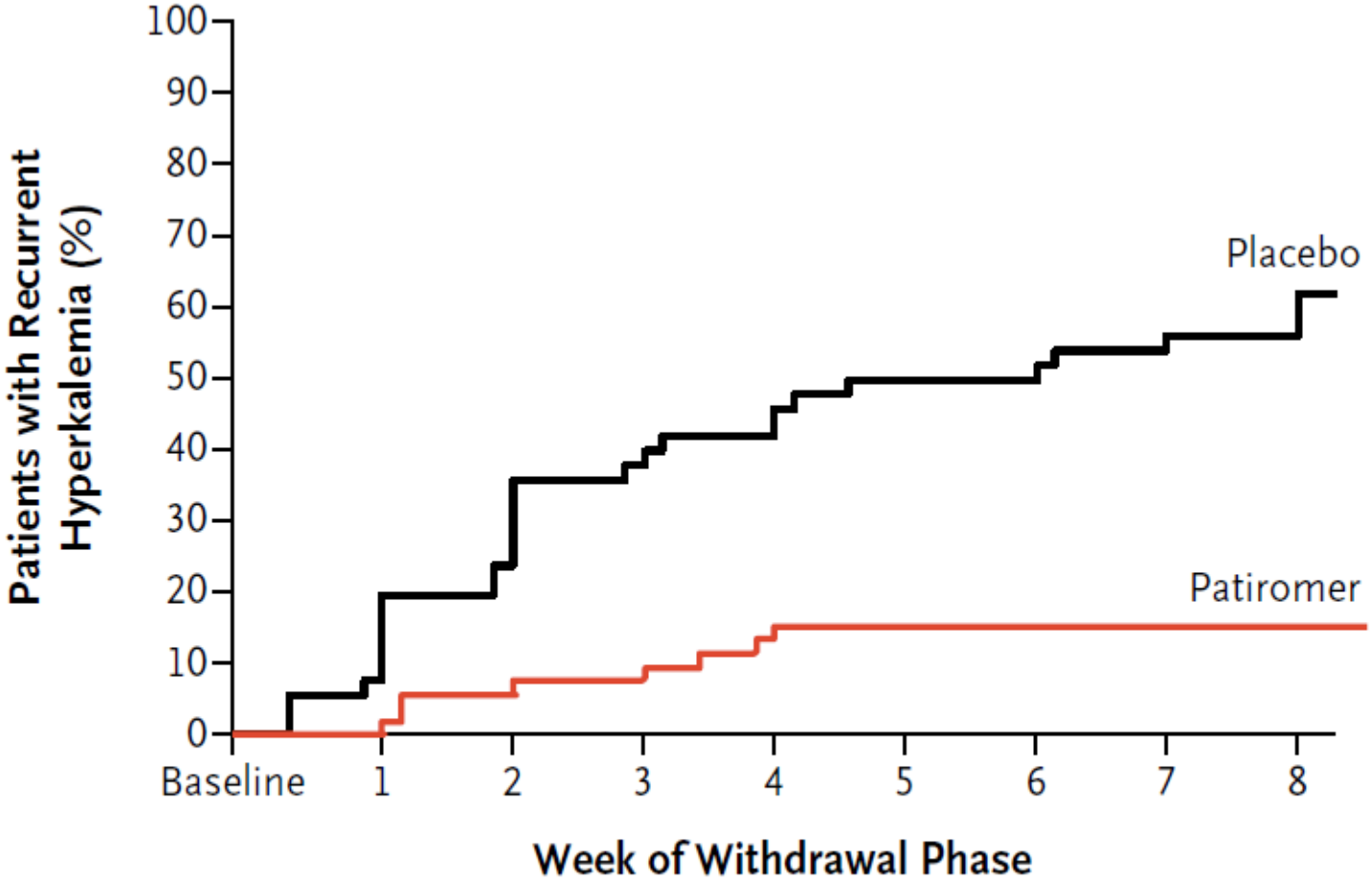
	Placebo (n=52)	Patiromer (n=55)
RAASi discontinuation for any reason	MODEL 52%	MODEL 5%

⊙ *Do rates of stopping RAAS inhibitors from the OPAL part B (responders who included mild hyperkalaemia) reflect NHS clinical practice?*

Abbreviations: RAASi, renin–angiotensin–aldosterone system inhibitors

OPAL-HK Part B: hyperkalaemia events *in economic model*

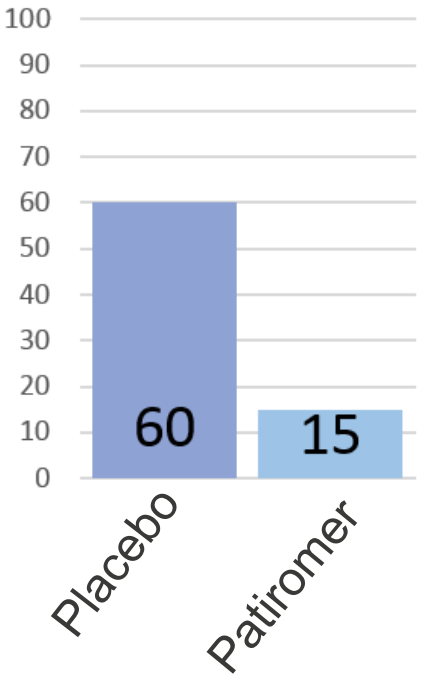
Time to first occurrence of hyperkalaemia ≥5.5 mmol/L



No. at Risk

Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32

% hyperkalaemia reoccurrence at the end of part B ≥5.5 mmol/L



⊙ *Is a serum K+ of 5.5 mmol/L cause for concern in NHS practice?*

Adverse events – pooled data

Not used in economic model

- Hypomagnesaemia more common in patiromer than placebo - serum magnesium should be monitored for at least 1 month after initiating treatment
- **Company:** systemic toxicities not expected because patiromer is not absorbed
- **ERG:** pooling OPAL-HK and AMETHYST-DN safety data inappropriate because of different: designs, primary endpoints, patiromer doses, inclusion criteria
  - safety findings inconclusive, short duration of study, low numbers of patients, high proportion with adverse events

[redacted]

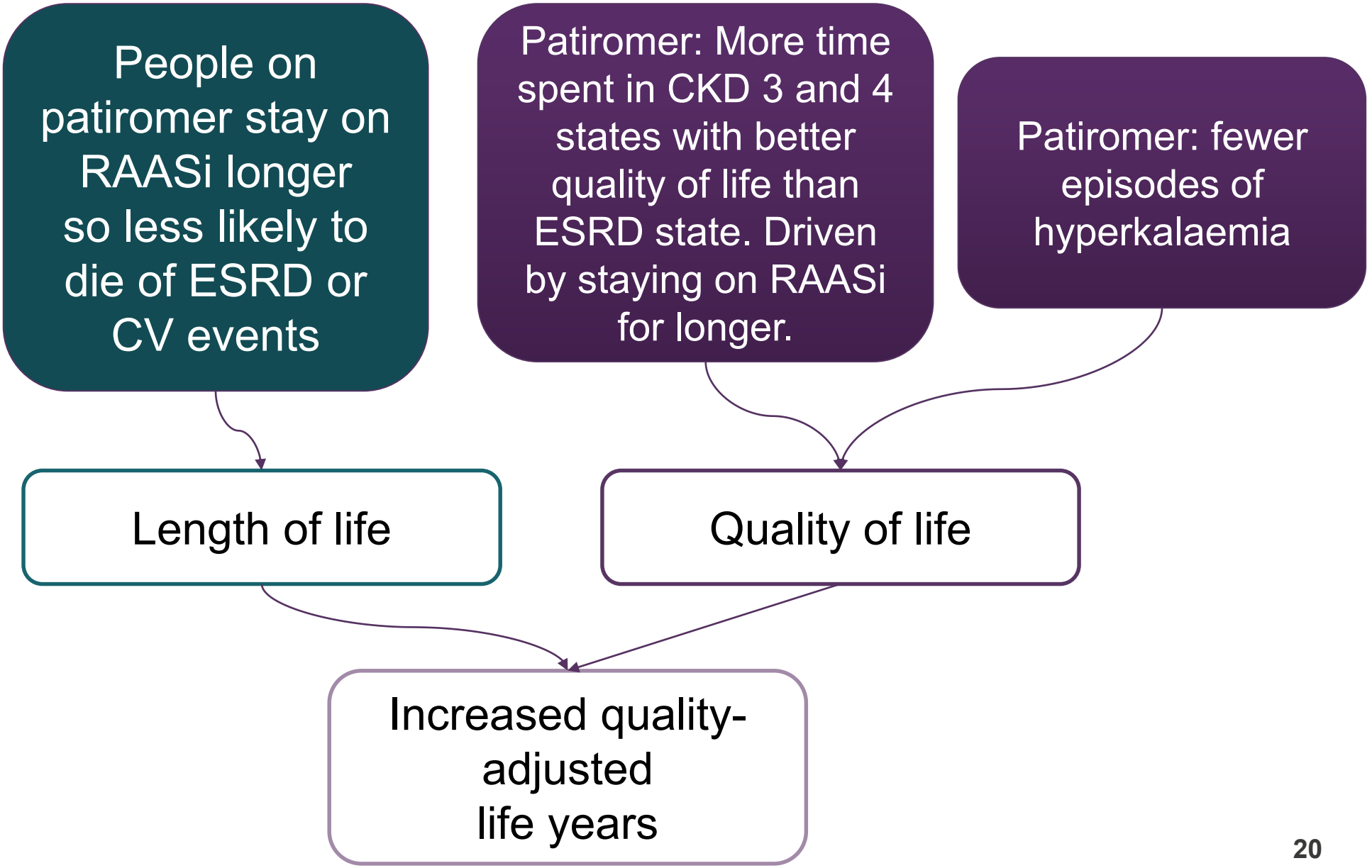
Key issues: cost effectiveness

- Company's economic model:
  - Assumes RCT results showing that taking RAASi extends life can be interpreted as stopping RAASi shortens life
  - Assumes patients not on RAASi have no active treatment for hypertension
  - Applies stopping rates for RAASi and hazard ratio from the 8 week OPAL-HK trial, extrapolates using epidemiological NHS data over a life time horizon
    - but a greater proportion of patients stopped RAASi in the placebo arm of OPAL-HK than expected in NHS practice
  - May overestimate the risk of developing end stage renal disease, 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 progression to end stage renal disease
  - Sensitive to changes in data source for patiromer discontinuation

[redacted]

How QALYs accrue

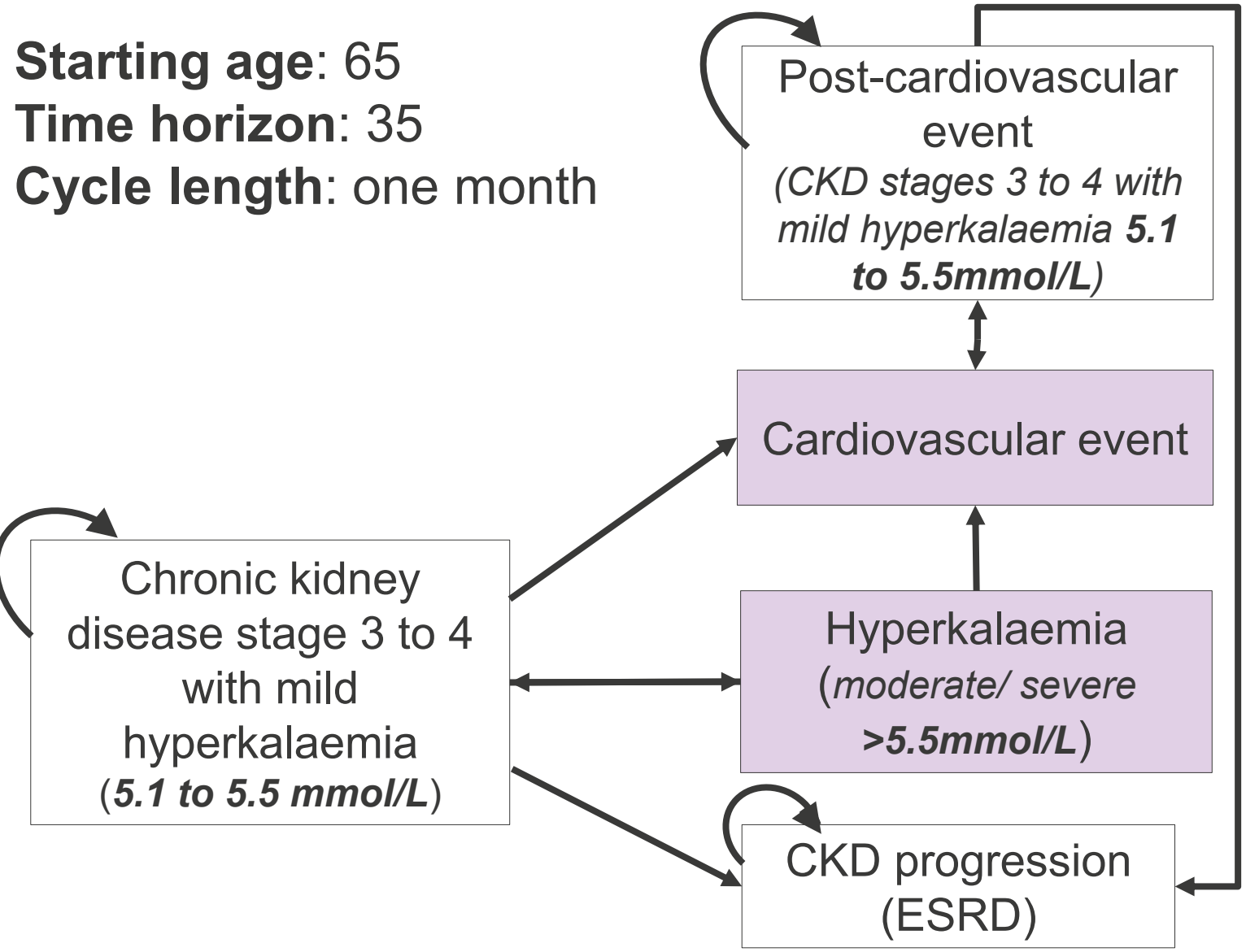
More time spent in health states with better quality of life for patients on patiromer



Company's model

Same risk of ESRD from CKD 3 or 4 does not reflect evidence

Starting age: 65
Time horizon: 35
Cycle length: one month



Key assumptions:

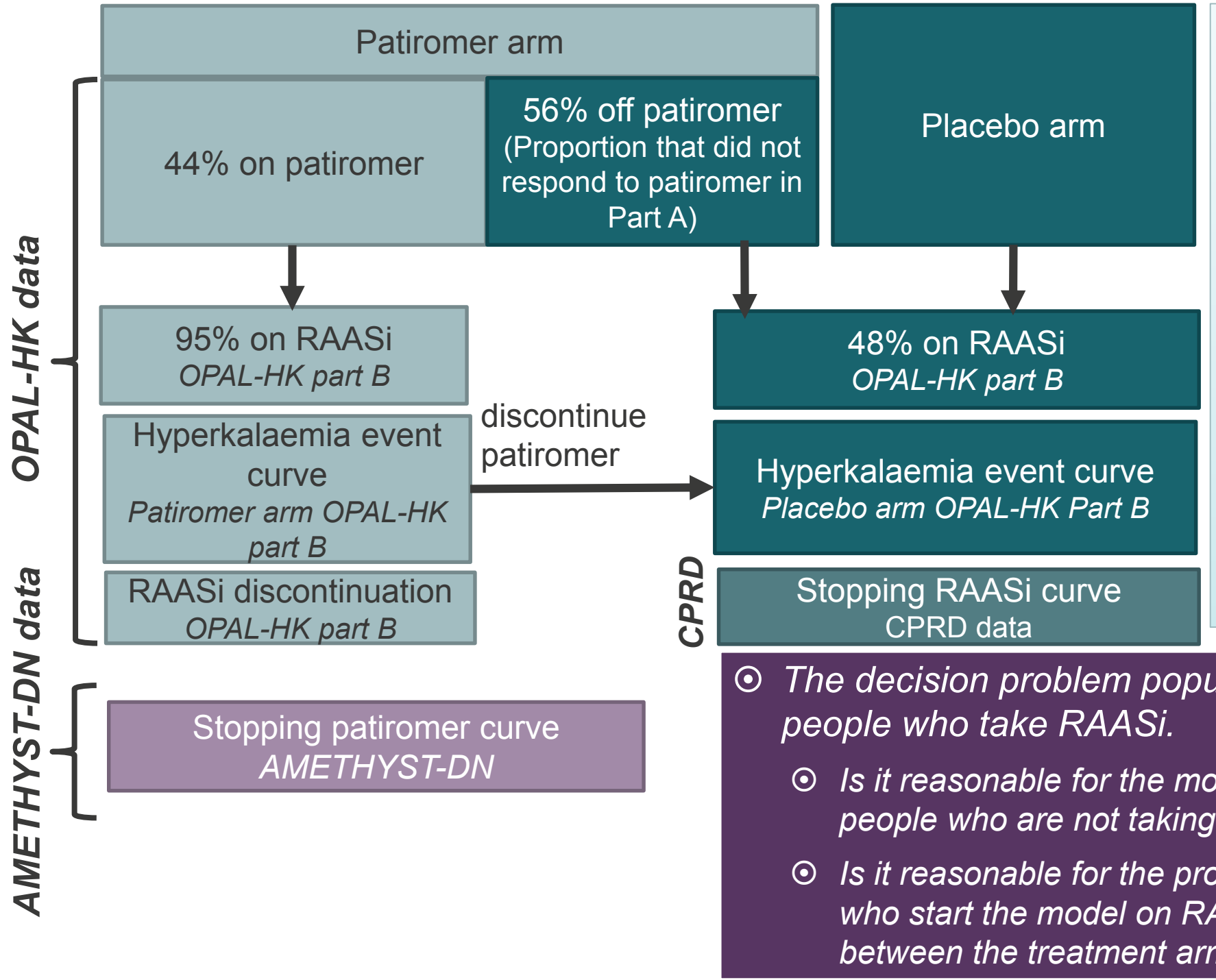
- Chronic kidney disease health state is grouped (stage 3 and 4 same health state, assumes people with stage 3 to 4 CKD transition to ESRD at similar rate)
- CV and hyperkalaemia events are tunnel states – duration 1 month

Death
(can transition from any state to death)

⊙ *Is the modelled population appropriate (K+ 5.1 to 5.5 mmol/l)?*

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease

Company's model and data sources



Assumption:
Patients that do not start on RAASi do not restart RAASi

Model uses data from different sources with different populations and does not adjust the data to account for differences in patient characteristics

- *The decision problem population includes people who take RAASi.*
  - *Is it reasonable for the model to include people who are not taking a RAASi?*
  - *Is it reasonable for the proportions of people who start the model on RAASi to be different between the treatment arms?*

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 (CPRD) • 56% on placebo discontinued in 8 wks vs. 25% over 3 yrs (CPRD) • CPRD data better reflects NHS • 100% should start on RAASi, as in trial ⊙ *Which is more appropriate?*
Stopping RAASi	• Placebo arm: CPRD data extrapolated using Weibull curve	
	• Patiromer arm: Hazard ratio applied to **CPRD** data from **OPAL-HK** [redacted] company: OPAL-HK only data in CKD 3-4)	• Patiromer arm: Calculate HR of [redacted] • Explore scenario analyses looking at waning of treatment effect on RAASi discontinuation

⊙ *Is using the hazard ratio for the entire model duration plausible, given that it is based on 8 weeks of data?*

[redacted]

Abbreviations: CPRD, clinical practice research datalink; HR, hazard ratio; RAASi, renin–angiotensin–aldosterone system inhibitors

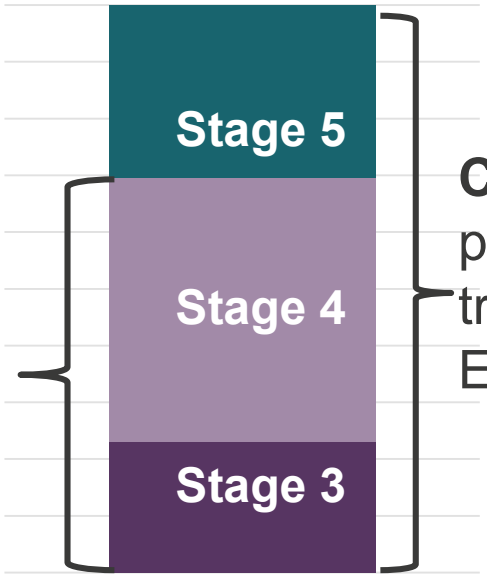
Key model inputs and assumptions (2)

Parameter	Company approach	ERG comment
Hypertensive treatment after stopping RAASi	Company assume no anti-hypertensive treatment after stopping RAASi	• Unlikely to reflect NHS • People get another antihypertensive ⊙ *Which is more appropriate?*
Stopping patiromer	• AMETHYST data extrapolated using **lognormal** (best statistical fit) • All patients in AMETHYST have diabetes vs. 63% in OPAL-HK and 23% in CPRD	• Prefer AMETHYST extrapolated using **lognormal*** with linear trend from day 113 Results are sensitive to changes in data source, scenario analysis using data from OPAL-HK provided ⊙ *Discuss at slide 28*
Adverse events	Not included in model	No long term safety data ⊙ *Should adverse events be included in the model?*
Quality of life	ESRD quality of life decrement ⊙ *Discuss at slide 29*	Company overestimates decrement for ESRD, ERG base case **-0.263** Clarke et al.

Abbreviations: CPRD, clinical practice research datalink; ESRD, end stage renal disease
*corrected after committee meeting

Key model inputs: Baseline risk of events: off RAASi

Proportion of patients with CKD by stage



ERG model: probability of transitioning to ESRD **0.39%**

Company model: probability of transitioning to ESRD **1.4%**

ERG comment:

- Company overestimated baseline risk of moving from CKD to ESRD
  - no adjustment 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 changes the monthly probability from 1.4% to **0.39%** because rate from CKD 5 to ESRD much higher than other stages

- ERG correction: company used daily probabilities for hyperkalaemia events but 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

⊙ *Should the ESRD estimate be based on CKD stage 3 to 5 or stages 2 to 4 to reflect participants in the OPAL-HK trial?*

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease

* ERG assumed transition probability from stage 2 to ESRD of 0

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 comparing RAASi (ACE and ARBs) with placebo or active controls
  - 119 trials, ~65,000 patients, patients with chronic kidney disease (any stage)

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

ERG: Including relative risks for all cause mortality introduces double counting
  - already includes benefit of being on RAASi by avoiding death from cardiovascular events and end stage renal disease - **ERG set to 1.00**
- Patients with chronic kidney disease would receive another treatment for hypertension when discontinuing RAASi,

- *Is it reasonable to interpret trial results showing starting RAASi extends life as stopping RAASi shortens life?*
- *Would patients have active treatment after stopping RAASi?*
- *Would RAASi have any additional effect on mortality, other than through slowing progression of CKD and lowered risk of CV events?*

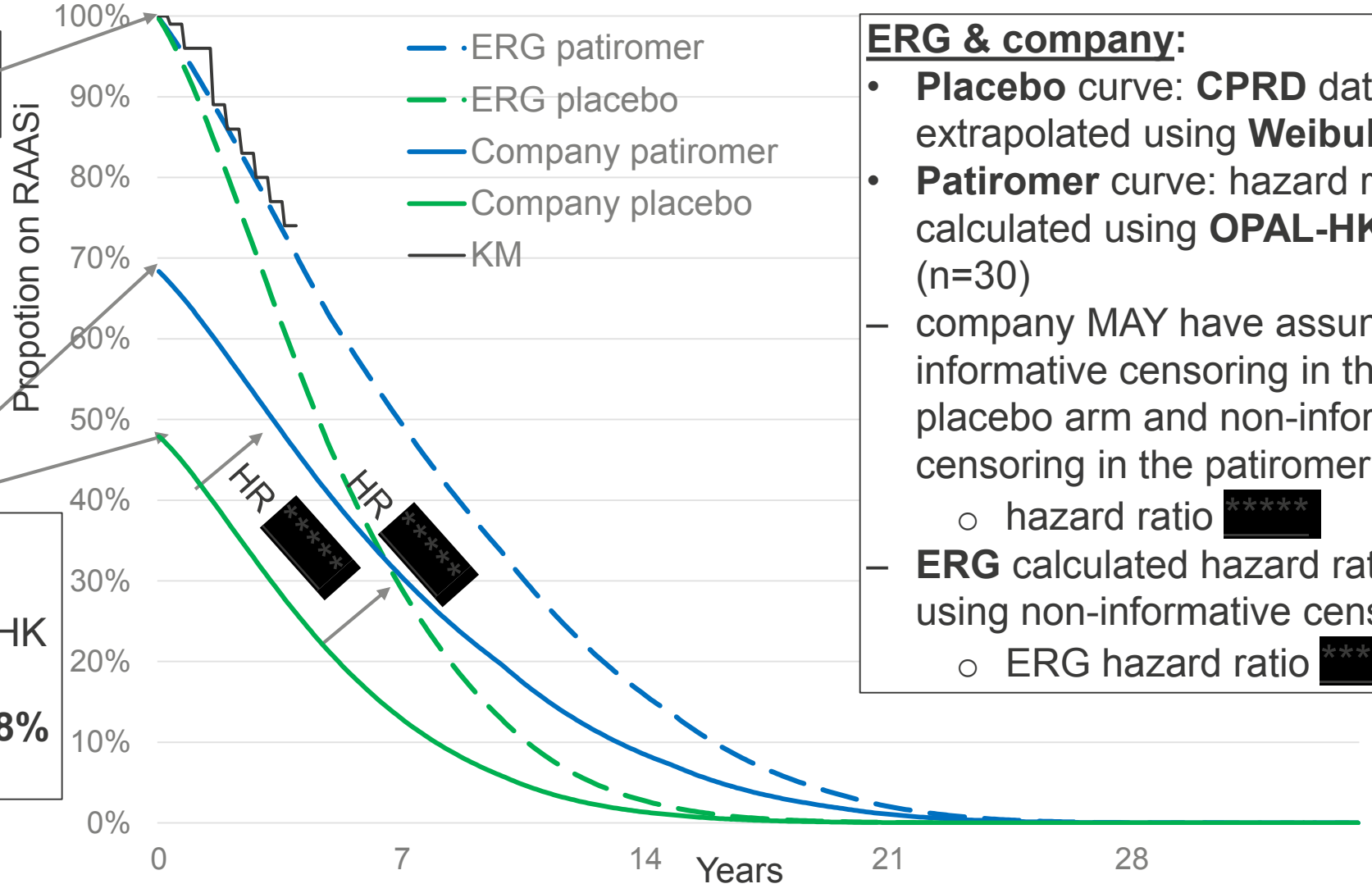
ARB, angiotensin receptor blockers; CV, cardiovascular; ESRD, end stage renal disease

RAASi discontinuation

Key driver of cost effectiveness

ERG: **100%** start on RAASi

Company: % starting RAASi same as OPAL-HK part B **69%** patiromer and **48%** placebo



ERG & company:

- **Placebo** curve: **CPRD** data extrapolated using **Weibull**
- **Patiromer** curve: hazard ratio calculated using **OPAL-HK** (n=30)
  - company MAY have assumed informative censoring in the placebo arm and non-informative censoring in the patiromer arm
    - hazard ratio *****
  - **ERG** calculated hazard ratio using non-informative censoring
    - ERG hazard ratio *****

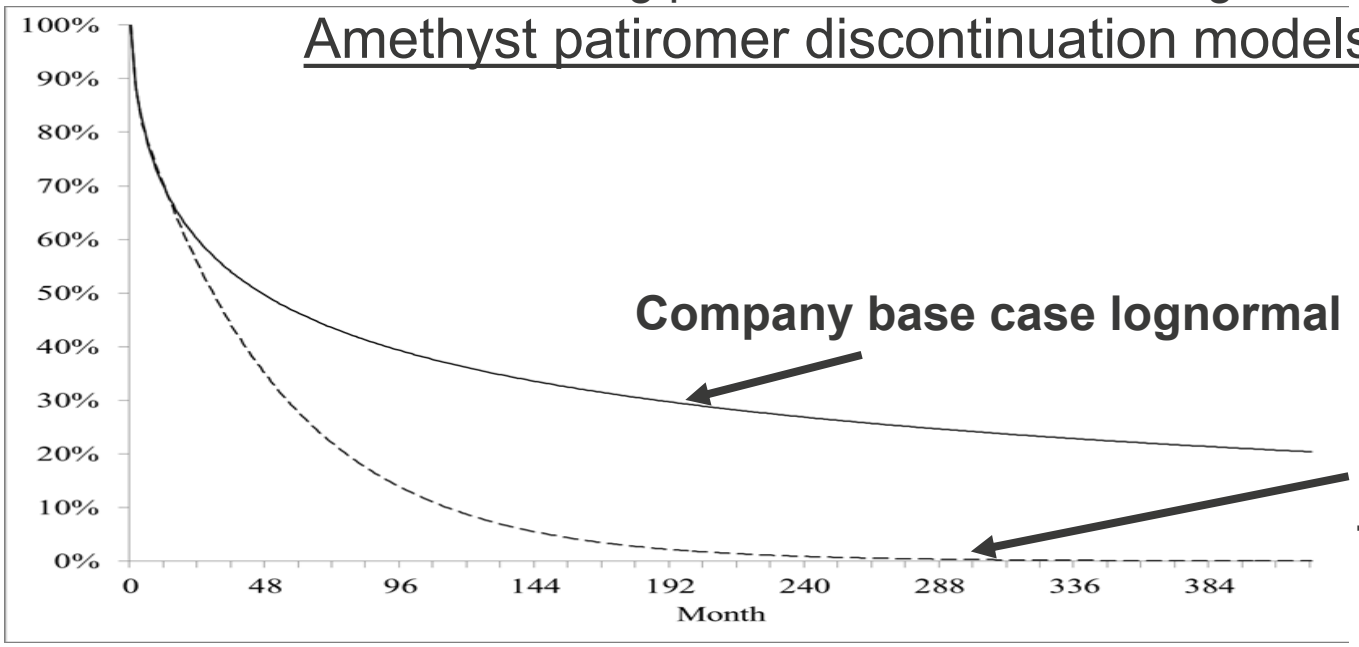
⊙ *Which hazard ratio is more appropriate, the ERGs (*****) or the company's (*****)?*

[redacted]

Abbreviations: RAASi, renin–angiotensin–aldosterone system inhibitors

Patiromer discontinuation

- Company uses AMETHYST-DN instead of OPAL-HK for patiromer discontinuation because:
  - larger number of patients, longer follow up
- **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, because discontinuation was worse in OPAL-HK than AMETHYST-DN
  - substantial number continue taking patiromer until death using the lognormal model



- *Which discontinuation curve is most clinically plausible?*
- *Would patients continue treatment with patiromer as long as they were benefiting?*
- *Is it more appropriate to use data from AMETHYST-DN or OPAL-HK?*

*ERG preferred curve updated after committee meeting – typo identified in ERG report during factual accuracy check.

Utilities

Company utility values are not standardised for a single population

- Quality of life data not collected in OPAL-HK - company uses values from a variety of different literature 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, TA390, TA336, TA315, TA288, TA151)

	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%)

⊙ *Prefer utility values from a common source (ERG approach) or a range of sources (company approach)?*

Resource use

Company assumes all hyperkalaemic events result in hospitalisation

- Company 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) 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

⊙ *Is it reasonable to assume that 24.3% of people with hyperkalaemic events will require hospitalisation?*

[redacted]

Company base case (deterministic)*

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

**Errors:

1) Company discounted patiromer price twice for the proportion of non responders (56%)

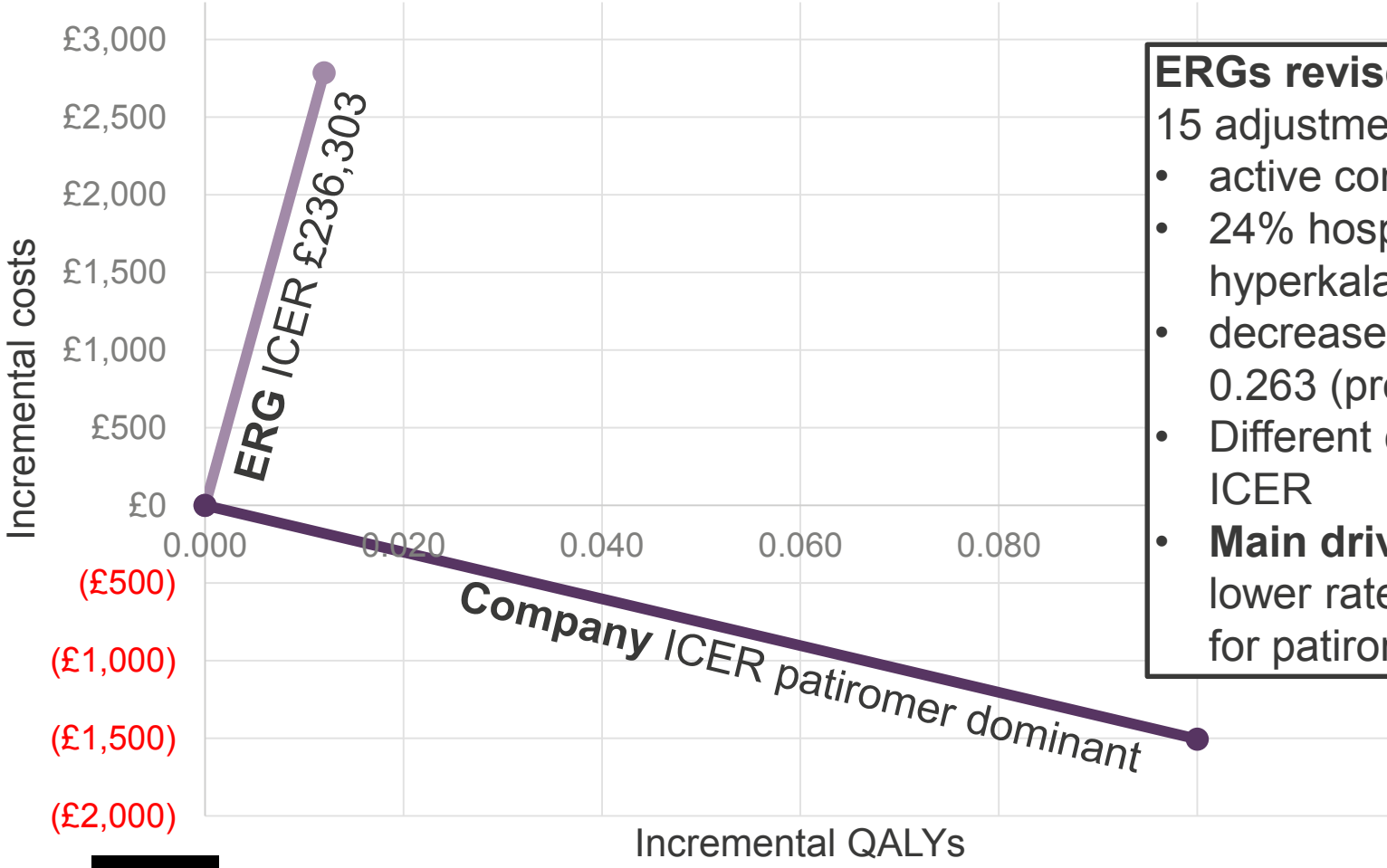
2) Probabilities applied for hyperkalaemia incorrect (daily applied instead of monthly)

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

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

ERG base case (deterministic)

	Treatment	Incremental			ICER (£/QALY)
		LYG	Cost	QALY	
ERG base case	Placebo	-	-	-	**£236,303**
	Patiromer	0.009	£2,787	0.01	



ERGs revised base case:
15 adjustments including:

- active control after stopping RAASi
- 24% hospitalised from hyperkalaemic events (from 100%)
- decreased ESRD decrement to -0.263 (previously -0.321)
- Different curves – minimal impact on ICER
- **Main driver of ERG base case** – lower rate of RAASi discontinuation for patiromer relative to placebo arm

[redacted]

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

ERG's base case adjustments (deterministic)

Scenario	Δ QALYs	Δ Costs	ICER
Company base case (corrected for 2 major errors)	0.10	-£572	Dominant
1) Active control after stopping RAASi	0.12	£2,310	£18,659
2) RAASi discontinuation: ERG's HR	0.10	-£565	Dominant
3) RAASi does not impact 'other cause' mortality	0.07	-£1,285	Dominant
4) Baseline probability of ESRD reflects stage 2 to 4	0.09	£1,092	£11,796
5) Proportion hospitalised for hyperkalaemia = 24.3%	0.10	-£62	Dominant
6) ESRD quality of life decrement to -0.263	0.09	-£572	Dominant
7) Quality of life values relative to general population	0.10	-£572	Dominant
All the above revisions (plus 6 other revisions relating to errors in event probabilities, CKD and ESRD costs and prescribing cost for patiromer)	0.07	£2,594	£38,905
Apply ERG curves*	0.06	£640	£10,520
Proportion on RAASi at start of model = 100%*	0.02	£4,806	£246,862
ERG base case (all above revisions)	0.01	£2,787	£236,303

[redacted]

*includes revisions from above

Abbreviations: HR, hazard ratio; RAASi, renin–angiotensin–aldosterone system inhibitors

ERG scenario analyses (deterministic)

ERG scenarios:

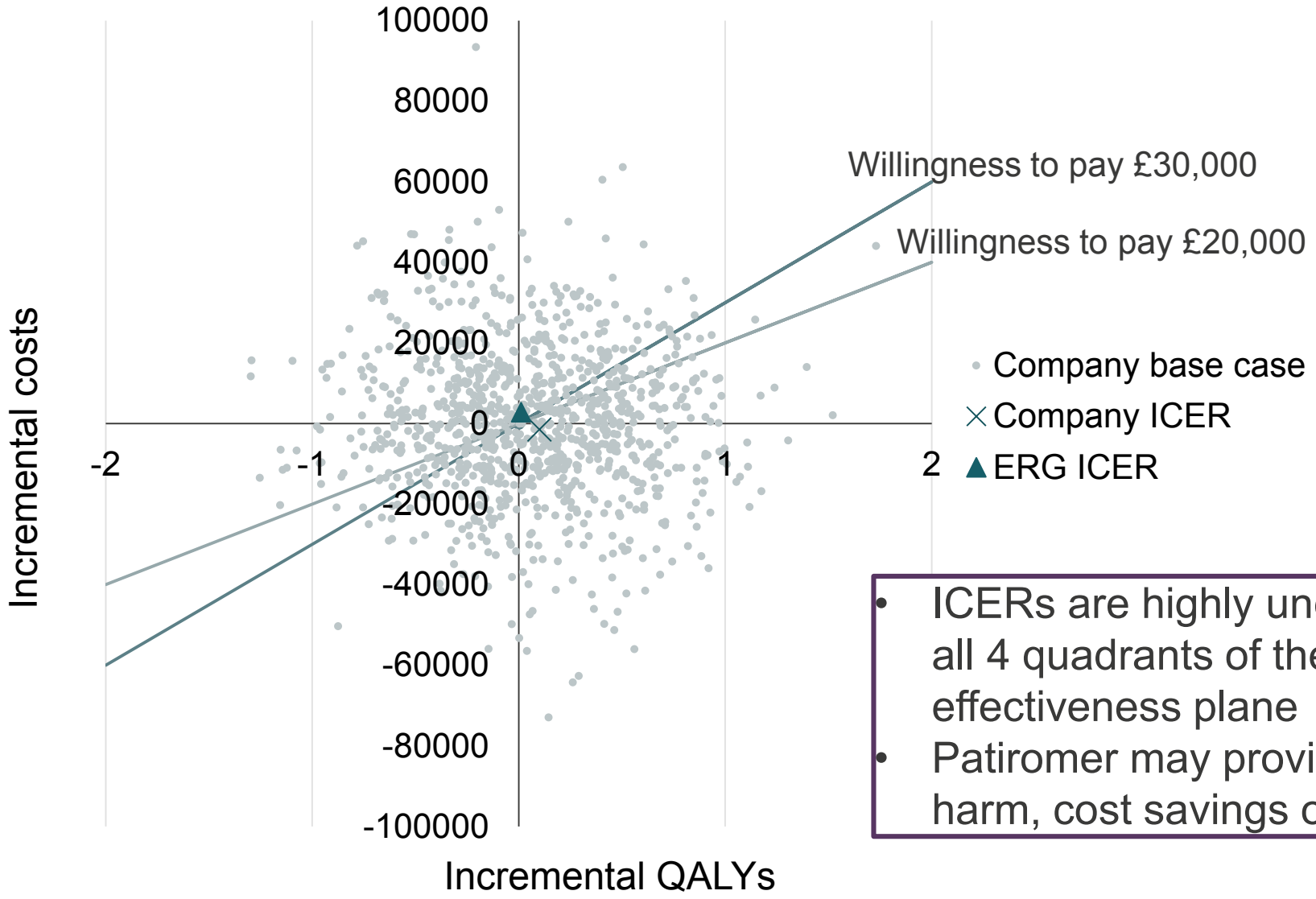
1. RAASi discontinuation curves based on OPAL-HK (previously CPRD)
2. Patiromer discontinuation curve based on OPAL-HK (previously AMETHYST)
   - reduces benefit from patiromer because reduces time on patriomer
3. ERG: unreasonable to apply hazard ratio for RAASi discontinuation from 8 week trial to 35 year time horizon, 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 over 3 years	0.01	£3,712	£371,095
3b) Waning of treatment effect on hyperkalaemia over 5 years	0.01	£3,466	£330,461

[redacted]

Abbreviations: RAASi, renin–angiotensin–aldosterone system inhibitors

Probabilistic results company and ERG base case



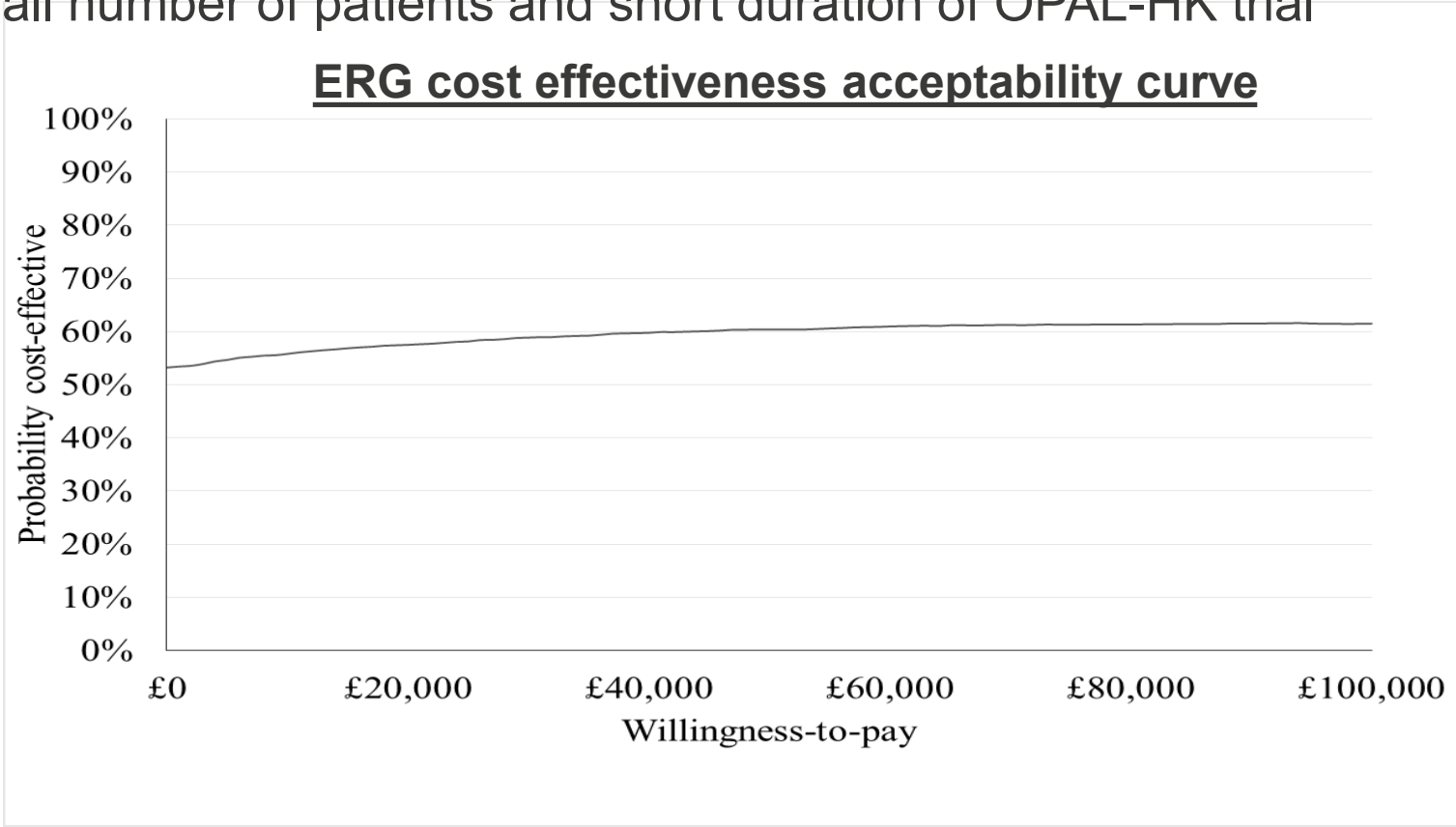
- ICERs are highly uncertain and span all 4 quadrants of the cost-effectiveness plane
- Patiromer may provide benefit or harm, cost savings or additional costs

[redacted]

Cost effectiveness acceptability curve

ERG

- Cost effectiveness acceptability curves are extremely flat and do not vary significantly from 50% likelihood of patiromer being cost effective at any threshold
  - Unusually high degree of uncertainty in model in part because of:
    - sampling of quality of life values and costs
    - small number of patients and short duration of OPAL-HK trial



[redacted]

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

[redacted]